Clinical Effects and Mechanisms of Actions of the Chinese Herbal Formula (RCM-104) for Weight Management: Literature Reviews and Computational Analysis

A thesis submitted in fulfilment of the requirements for the degree of

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Declaration

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Table of Contents

List of Tables

List of Figures

Summary

Background

Overweight and obesity is a major global health issue, characterised by higher dietary energy intake than energy expenditure. Statistics from the World Health Organisation (WHO) indicated that in 2016, more than 1.9 billion adults were overweight and 650 million of them were obese (WHO, 2021). Apart from being a disease in itself, obesity is a major risk factor for a number of other conditions such as type-2 diabetes, high blood pressure, heart diseases, stroke, certain types of cancer, sleep apnoea, osteoarthritis, fatty liver disease, kidney diseases and pregnancy problems (NIDDK, 2018).

Currently, pharmacotherapy is being used as the first line of treatment for patients with overweight and obesity. However, anti-obesity pharmacotherapies have been unsafe and minimally efficacyious, and some anorectics were withdrawn from the market due to severe adverse side effects (Marcus & Wildes, 2013; Pi-Sunyer, 2009). Therefore, there is a need to seek solutions outside the regime of current pharmacotherapy. Thus, more and more patients are seeking alternatives for weight management, such as Chinese herbal medicine (CHM) (Xiao & Luo, 2018; Yeh et al., 2017).

Aim

RCM-104 is a weight management CHM formula developed in RMIT University (Lenon et al., 2012) which comprises three Chinese herbs: Jue ming zi (JMZ, Cassiae Semen), Lu cha ye (LCY, Green tea, Camellia Sinensis leaf), and Huai hua (HH, Sophora Flos). The clinical effects of RCM-104 were evaluated with a 12-week randomised controlled trial (RCT) with placebo as control. The results of the RCT have shown that RCM-104 is effective in reducing

weight, body mass index and body fat content in obese individuals. However, the pharmacological and molecular mechanisms of actions of the RCM-104 ingredients are still unknown.

The aim of this research project was to investigate the clinical effects and mechanisms of actions of RCM-104 for the treatment of simple obesity, through systematic reviews of classic and modern literatures, as well as computational analysis.

Methods

This research project contains three phases: Phases I and II are review of classical and modern literature respectively and Phase III is computational analysis.

A comprehensive review of classical literature was conducted in phase I to understand the interpretation of obesity in ancient China and to collect information concerning properties, actions and indications of the ingredients of weight-loss CHM formula RCM-104. A two-stage process was used in the classical literature search: A CD-ROM database named *Zhong Hua Yi Dian* (ZHYD; Encyclopaedia of Traditional Chinese Medicine) was first used to locate any related citations. This was then followed by cross-referencing to hardcopy authenticated editions of the books in *Zhong Guo Ben Cao Quan Shu* (ZGBCQS; The Complete Collection of Traditional Texts on Chinese Materia Medica) to verify the retrieved information.

Phase II was divided into IIa and IIb. Phase IIa was to investigate the phytochemistry, pharmacological profiles and clinical applications of the herbal ingredients in formula RCM-104. Comprehensive searches were performed on seven English databases and three Chinese databases for publications on original experiments related to phytochemistry, pharmacology, and toxicology of the herbs from their earliest available records to 30 April 2020.

Phase IIb was to identify the required data as input for next phase, computational analysis. The possible anti-obesity targets were identified through online database search including Herb Ingredients' Targets (Ye et al., 2011), Traditional Chinese Medicine Systems Pharmacology database (Ru et al., 2014), the Protein Data Bank (Berman et al., 2000) and DrugBank (Wishart et al., 2008; 2018). Known drugs for weight management were searched through the online database Monthly Index of Medical Specialities for drugs available in Australia, and DrugBank and the Metabolomics Innovation Centre for drugs available in the United States, Canada and the European Union. Herbal compounds of RCM-104 were identified through (1) *Encyclopaedia of Traditional Chinese Medicine* (Zhou et al., 2012), (2) textbooks (Bensky et al., 2004; Chen et al., 2004), (3) an open chemistry database: *PubChem*, and (4) a database of systems pharmacology for drug discovery from herbal medicines—Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform. Keywords overweight and obesity were used in the screening process. Additionally, literature search was conducted to identify any compounds missed from books and online databases and new compounds discovered through *in vitro* experiments.

Computational molecular docking and analysis approaches were used in phase III. The objectives were: (1) to understand the anti-obesity pathways of the individual herbs of RCM-104; (2) to evaluate the synergistic effects of the individual herbs of RCM-104 through pharmacological network analysis; (3) to identify active herbal compounds of RCM-104 which could have potential therapeutic effects on weight management; and (4) to understand the interactions of the identified compounds with the relevant anti-obesity targets. Current anti-obesity agents were used as control ligands for comparison with the herbal compounds in the computational analysis.

Key findings

The findings in review of classic literature show that JMZ may assist in maintaining a healthy body weight due to its actions in nourishing the Liver and clearing Liver heat. LCY may assist in maintaining a healthy body weight by eliminating the fat, purging the Gallbladder and reducing the damp-heat and pathogenic fire. HH may assist in weight loss by cooling the Large Intestine, clearing the Liver fire, disperse wind-heat and cooling the blood. Therefore, RCM-104 can help to prevent overeating by reducing the heat from Stomach and Large Intestine, because all the three herbs of RCM-104 are cool in nature with JMZ and HH entering the Yang Ming meridians. In addition, all three herbs enter the Liver channel which are beneficial to the free flow of Qi in the body and clear Liver Qi Stagnation.

The modern literature review on the phytochemistry, pharmacology and toxicity of the herbal ingredients of formula RCM-104 has demonstrated a profound influence of these herbs and their chemical compounds on various diseases and health conditions apart from overweight and obesity. The results of the search found that JMZ and nine of its active chemical compounds are identified to have weight reduction effects. It was found that JMZ compounds may exert anti-obesity effects via inhibiting amylases and lipases and suppress appetite by 5-HT2C receptor activation. LCY plays a role in weight loss by reducing food intake, interrupting lipid emulsification and absorption, suppressing adipogenesis and lipid synthesis and increasing energy expenditure via thermogenesis, fat oxidation and faecal lipid excretion. HH and its bioactive compounds have demonstrated various potentials to against major obesity-related health risks such as diabetes. In summary, the main pathways of weight loss effect of RCM-104 are reducing food intake through appetite suppression and reducing lipid absorption through inhibition of digestive enzymes.

Through extensive search on multiple databases, seven anti-obesity drugs/agents, 38 anti-obesity protein target structures and a total of 147 herbal compounds of formula RCM-104 were identified for the molecular docking of the next phase of the project.

In Phase III computational analysis, the output of the docking process consisted of the binding affinity scores of protein-target pairs and the top 10 most energetically favourable 3D models of each pair. A pharmacological network detailing the interactions between the formula, herbs, chemical compounds and targets was established. This visual presentation has provided insights on the mechanisms of actions of formula RCM-104 towards its specific targets. Further analysis on the interaction of these targets and their selected herbal compounds discovered that a major mechanism of action of formula RCM-104 is to supress appetite by influencing the serotonergic and dopaminergic systems. On the other hand, through analysing the docking results and protein-ligand interactions, it was established that each herb of RCM-104 contains chemical compounds which are effective in inhibiting pancreatic lipase and thus achieve weight-loss by suppressing the absorption of lipids.

Conclusion

In conclusion, the goal of this research has been achieved. The results from this research project suggested that formula RCM-104 is indicated for overweight or obese patients of Stomach Heat syndrome with or without Liver Qi Stagnation. And this project deduced that the two major mechanisms of actions of the formula RCM-104 are suppressing appetite by influencing the serotonergic and dopaminergic systems and suppressing lipid absorption by inhibiting pancreatic lipase activities.

Chapter 1 General introduction

This chapter describes the background, rationale, aims and objectives of this research project. It also outlines where the research was conducted and how this thesis was organised.

1.1 Background

Overweight and obesity is a major global health issue (AIHW, 2017). It is defined by the World Health Organisation (WHO) as abnormal or excessive fat accumulation that presents a risk to health and characterised by higher dietary energy intake than energy expenditure (WHO, 2019).

The prevalence of obesity is expected to rise due to increased fatty food intake and decreased exercise worldwide. At the beginning of the 21st century, obesity has become the leading global metabolic disease (Formiguera & Cantón, 2004). In the period between 2014 and 2015, nearly two-thirds (63%) of Australian adults were overweight or obese (Khan & Mukhtar, 2018). Statistics from the World Health Organisation (WHO) revealed that in 2016, more than 1.9 billion adults were overweight; out of them 650 million were obese (WHO, 2021). In 2017-18, two-thirds (67.0%) of Australians 18 years and over were overweight or obese. Slightly more than one third (35.6%) were overweight and slightly less than one third were obese (31.3%) (Australian Bureau of Statistics [ABS], 2019).

Prevalence of overweight and obesity is relatively lower in Asian countries (Ramachandran & Snehalatha, 2010). However, as economic interchange increases, it is predicted that the current mean BMI trends depicted in developing nations will surpass even the maximum mean BMI values reported in developed countries (Bhurosy & Jeewon, 2014).

The report from the Australian Burden of Disease Study (ABDS) 2011 (Al-Yaman, 2017) found that 7.0% of the total health burden in Australia was due to overweight and obesity. The Study also found that 53% of the diabetes burden and 45% of the osteoarthritis burden were

also due to overweight and obesity (Australian Institute of Health and Welfare [AIHW], 2017a). It was noted that around 14% of disease burden due to overweight and obesity could be avoided if the population's body mass dropped slightly (AIHW, 2017).

Apart from being a disease in itself, obesity is a major risk factor for a number of other conditions such as type-2 diabetes, high blood pressure, heart diseases, stroke, certain types of cancer, sleep apnoea, osteoarthritis, fatty liver disease, kidney diseases and pregnancy problems (NIDDK, 2018). The top 5 diseases highlighted in the Study as a result of being overweight or obese were: coronary heart disease, diabetes, osteoarthritis, stroke and breast cancer (AIHW, 2017). As the level of excess weight increases, so does the risk of developing these conditions (AIHW, 2018a).

Obese individuals may experience day-to-day health problems such as breathlessness, increased sweating, snoring, inability to cope with sudden physical activity, daily fatigue, back and joint pains, low confidence and self-esteem and feelings of isolation (Scotland's National Health Information Service [NHS inform], 2019).

1.2 Research rationale

The worldwide prevalence of obesity nearly tripled between 1975 and 2016 and the rates of overweight and obesity continue to grow in adults and children (WHO, 2021). Therefore, interventions to manage and prevent overweight and obesity are urgently required to reverse the current trends.

The current main treatment options with sufficient evidence-based support are lifestyle, intervention, pharmacotherapy and bariatric surgery (Apovian et al., 2015; Heymsfield & Wadden, 2017; Robinson, 2009).

Pharmacotherapy is currently used first line of intervention for patients with overweight and

obesity if they are unable to manage their weight with lifestyle changes. Although these pharmaceutical approaches may prevent symptoms or reduce their severity, the unpleasant and negative side-effects (Chen, Y. 2016; Lucas & Kaplan-Machlis, 2001; Rodgers et al., 2012) are not tolerable to some users. Historically, anti-obesity pharmacotherapies have been unsafe and minimally efficacious (Colon-Gonzalez et al., 2012) and some anorectics, such as fenfluramine and dexfenfluramine, were withdrawn from the market due to severe adverse side effects (Demos et al., 2006). Therefore, there is a need to seek solutions outside the regime of current pharmacotherapy.

Modern studies have revealed that some CHMs had similar effects to Western anti-obesity drugs with fewer side-effects (Lenon, et al., 2012; S. Luo, et al., 2019a; Xu et al., 2012).

Chinese herbal medicine (CHM) has a long history of use for metabolic disorders (Shennong-shi, 250–200 B.C.). Discussion concerning the issues of being overweight and obesity in Traditional Chinese Medicine (TCM) can be traced back more than 2,000 years ago to the earliest Chinese medicine book *Huangdi Neijing* (HDNJ, The Yellow Emperor's Classic of Internal Medicine) (Huangdi Emperor of China et al., 1972). In chapter 28 of the text 'The Book of Plain Questions', HDNJ, it states: 'If excess body weight occurs in the nobleman and rich people, they must be over consuming heavy and greasy foods.' (Huangdi Emperor of China et al., 1972). The use of CHM in China for the management of obesity can be traced back to the 16th century. For example, Jue ming zi was mentioned in *Bencao Pinhui Jingyao* (The Collected Essentials of Herbal Species) that it could help to reduce body weight by nourishing the Liver and Kidney (LIU Wentai, 1505).

RCM-104 is a weight management CHM formula which significantly reduced body weight and BMI compared with placebo (Lenon et al., 2012) in 12-week randomised controlled trial (RCT). The formula RCM-104 comprises three Chinese herbs: Jue ming zi (JMZ, Cassiae

Semen), Lu cha ye (LCY, Green tea, Camellia Sinensis leaf), and Huai hua (HH, Sophora Flos).

Although the results of the RCT have shown that RCM-104 effectively reduces weight, BMI, and Body fat composition (BFC) in obese individuals, the mechanism of its action is unknown. Therefore, there is a need for a deeper understanding of how RCM-104 and its component herbs contribute to weight management.

To generate a full spectrum of knowledge for the understanding of formula RCM-104, it is necessary to examine its herbal ingredients in classical and modern literature for both traditional and modern evidence and further explore the mechanisms of actions using up-to-date computational techniques. This approach can also identify chemical compounds from RCM-104 with therapeutic potential for weight management.

1.3 Aims and objectives

The overall aims of this research project were to investigate the clinical effects and mechanisms of the actions of CHM formula RCM-104 for the treatment of simple obesity through systematic reviews of classical Chinese medicine and modern literature, as well as computational analysis.

The objectives of 'Phase I: Review of classical literature' were to understand how the ancient Chinese identified the issues of excess body weight, the maintenance of a healthy weight and the properties, actions and indications of the three herbs in formula RCM-104.

The objectives of 'Phase II: Reviews of modern literature' were to explore the phytochemistry, pharmacological profiles and clinical applications of the three herbal ingredients in formula RCM-104 and to identify chemical compounds and protein targets for further studies in computational analysis.

The objectives of ‘Phase III: Computational analysis’ were to evaluate the binding activities between the chemical compounds in RCM-104 and the targets, in order to understand the mechanisms of the actions and pathways.

1.4 Location of the research project

The reviews of both classical literature and modern literature and the analyses of the computational docking results were conducted at the RMIT University (RMIT). The molecular docking process was performed using the Intel Xeon Sandy Bridge 2.6 GHz Broadwell nodes of the Raijin cluster (decommissioned in December 2019) high performance computing cluster located at the National Computational Infrastructure (Canberra, Australia).

1.5 Organisation of the thesis

This thesis is organised into 10 chapters. A brief outline of each chapter is provided below. Chapter 1 provides a general introduction of this research project. The background, rationale, aims, objectives and location of the project and the organisation of this project are presented in this chapter.

Chapter 2 describes the various aspects of obesity from Western medicine perspective, including its diagnosis and assessment, risk factors manifestation and pathology. Different regimes of the current management of obesity are also presented in this chapter.

Chapter 3 introduces obesity from Chinese medicine perspective, including the Chinese medicine theory of obesity, aetiology, pathogenesis, syndrome differentiation and treatment of obesity. The chapter compares the understanding of obesity from Chinese and Western medicine perspectives.

Chapter 4 details the methods adopted by this research project, namely, Phase I: Review of classical literature; Phase IIa: Review of modern literature; Phase IIb: Identification of targets and ligands; Phase III: Computational analysis.

Chapter 5 reports the results from the classical literature review of the three Chinese herbs contained in formula RCM-104, which include their properties, actions and indications.

Chapter 6 presents the results of modern literature review, which include the data of the phytochemistry, pharmacology and toxicology of the individual ingredients of formula RCM-104. Chapter 7 covers the results of identification of targets and ligands, which include anti-obesity targets, anti-obesity agents and the herb's chemical compounds of the individual ingredients of formula RCM-104.

Chapter 8 and Chapter 9 report the results of molecular docking between RCM-104 active compounds and anti-obesity target proteins. Chapter 8 states the predicted binding affinities and ligand-protein network of the three herbs in formula RCM-104. Chapter 9 focuses on selection of the proteins and ligands for analysis and discusses the interactions between the selected proteins and ligands. The proposed the synergistic effects of RCM-104 based on the docking results are reported in Chapter 9**.**

Chapter 10 summarises the key findings of the project, identifies the strengths and limitations and discusses the implications for current clinical practice and future research.

Chapter 2 Understanding of obesity from Western medicine perspective

This chapter outlines the advanced knowledge accumulated through a literature review concerning obesity from Western medicine perspectives. The following areas are discussed: definition, diagnosis and assessment; manifestation; pathogenesis; current management and new directions in the treatment of obesity.

2.1 Definition, diagnosis and assessment of obesity

2.1.1 Definition of obesity

The World Health Organisation (WHO, 2019) defines overweight and obesity as abnormal or excessive fat accumulation that presents a risk to health.

The most common way to determine if a person is overweight or obese is to calculate the body mass index (BMI). However, individuals with the same BMI may have very different body shapes depending on the distribution of fat, for instance, visceral fat in the abdominal region is associated with greater metabolic abnormalities. Therefore, different techniques can be used in order to assess body fatness—each with its own advantages and disadvantages (Hawkesworth, 2013; National Institute of Health [NIH], 2016).

2.1.2 Body Mass Index

Body Mass Index (BMI) is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults (World Health Organisation [WHO], 2021). It is defined as the weight in kilograms divided by the square of the height in metres (kg/m^2) (Nuttall, 2015). For example, an adult who weighs 75kg and whose height is 1.76m has a BMI of 14.2 (BMI = 75 kg / ($1.76\ m^2$) = 14.2). It is used by most healthcare practitioners

in order to make an initial diagnosis of overweight and obesity because the calculation used is simple and no special equipment is required (Hawkesworth, 2013).

BMI provides a useful and convenient measure of overweight and obesity as it is the same for both sexes and adults of all ages. However, it is characterised as a rough guide since it may not correspond to different individuals with the same degree of obesity. If a person, for example, a prime athlete has increased muscle mass rather than fat, then this person runs the risk of being incorrectly diagnosed as obese when, in fact, the person is not (Haththotuwa et al., 2020). BMI also does not provide accurate information for pregnant women and athletes (Centers for Disease Control and Prevention, USA, 2020).

Childhood obesity is assessed according to age, weight and a comparison with children of similar age and gender instead of simple index of weight-for-height. The amount of fat at different ages and differences between gender are taken into account. (Atkinson, 1998; Esposito et al., 2013).

In Asia-Pacific region, people develop negative health consequences at a lower BMI than Caucasians (Kanazawa et al., 2005). Therefore, individuals begin to be considered overweight, pre-obese and obese at lower BMIs in the Asia-Pacific population (Hawkesworth, 2013). The international standard and region-specific BMI cut-off points as shown in Table 2.1.

Chinese people experienced greater odds of comorbidities than Caucasians for a given BMI after standardising for age and sex. It is proposed that the cut-off for overweight and obesity for Chinese should be 22.5 and 25.9 kg m^2 in men, and 22.8 and 26.6 kg m^2 in women after both fat and fat distribution are taken into account (He et al., 2015).

Table 2.1: Classification of underweight, overweight and obesity according to body mass index

Classification	BMI (kg/m^2)	
	International, the (principal) BMI cut-off points	In Asia-Pacific Region, the BMI cut-off points
Underweight	**<18.50**	**<18.50**
Severe thinness	<16.00	<16.00
Moderate thinness	16.00-16.99	16.00-16.99
Mild thinness	17.00-18.49	17.00-18.49
Normal range	**18.50-24.99**	**18.50-22.99**
Overweight	**≥25.00**	**≥23.00**
Pre-obese	25.00-29.99	23.00-24.99
Obese	**≥30.00**	**≥25.00**
Obese Class I	30.00-34.99	25.00-29.99
Obese Class II	35.00-39.99	≥30.00
Obese Class III	≥40.00	≥40.00

Note: Adapted from Hawkesworth (2013).

2.1.3 Other assessment techniques

Other measurements for assessing overweight and obesity (Hu, 2008; Hawkesworth, 2013; NIH, 2016) are listed below:

- Measurement of waist circumference (WC)
- Calculation of waist-to-hip circumference ratio (WHR)
- Skinfold thickness which measures the thickness of a skinfold by pinching some skin and fat with a calliper

- Imaging techniques such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) and
- Bioelectric impedance analysis (BIA)

WC is a measurement taken around the abdomen at the level of the umbilicus. Health experts use WC to screen patients for possible weight-related health problems. It is an indicator of health risk associated with excess fat around the waist (Bagchi& Preuss, 2007), especially for metabolic syndrome (Lee et al., 2007; Proietto & Baur, 2004) and obesity-related cardio-metabolic disease (Misra et al., 2005). Regular aerobic exercise may cause a reduction in both WC and cardio-metabolic risk without a change in BMI. Therefore, measuring WC instead of BMI is more helpful on monitoring the outcome of diet and exercise treatment. (Lin et al., 2012).

As with the WC, the WHR is also used to measure abdominal obesity. It's calculated by first measuring the waist circumference (the smallest measurement of the torso) and the hip circumference (the largest measurement of the buttocks) and then dividing the waist measurement by the hip measurement (Hu, 2008). WHR is not commonly used because the measurement using WC alone, or in combination with other metabolic measures, is a much better indicator of risk (AIHW, 2005). In addition, WHR is prone to measurement error because it requires the use of two measurements (Hu, 2008).

Skinfold thickness measures the amount of subcutaneous fat obtained by inserting a fold of skin into the jaws of a specialised calliper (Medical Dictionary, 2009). Skinfold measurements are generally taken at the right upper arm, right thigh, and upper abdomen. Two measurements of skinfold thickness in millimetres are recorded and then the results are then averaged (Rostami et al., 2013). This technique is widely used in clinical and field studies because it is relatively easy to administer to large groups of individuals and the equipment is inexpensive (Sowers & Tisch, 2000).

CT and MRI scans are considered the most accurate methods for measuring tissue, organ, and whole-body fat mass as well as lean muscle mass and bone mass (Hu, 2008). They are typically only used for this purpose in research settings.

BIA is a special scale to measure body fat. The equipment measures resistance by sending out a small, imperceptible, safe electric current through the body. The current experiences more resistance when passing through body fat than when passing through lean body mass and water. Equations are then used to estimate the body fat percentage and the fat-free mass (Hu, 2008). BIA is safe, portable and easy to use. However, its accuracy is diminished due to the possibility of a change in the ratio of body water to fat if a subject is ill or dehydrated. It is not as accurate as other methods–especially in individuals with a BMI of 35 or higher (Hu, 2008).

2.2 Manifestations of obesity

2.2.1 Signs and symptoms

The major signs and symptoms of obesity are excessive weight gain and overgrown of fatty tissue (Salem et al., 2014). Obesity induces chronic inflammation in the adipose tissue, the liver, the skeletal muscles and the vascular system (Sato & Mukai, 2020) and causes day-to-day health problems (J. Zhou, Ho, et al., 2019) such as breathlessness, increased sweating, snoring, inability to cope with sudden physical activity, extreme daily fatigue, back and joint pains, low confidence and self-esteem, and feelings of isolation.

2.2.2 Obesity-related health risks and complications

Obesity can be considered as a chronic disease which is characterised by pathophysiological processes resulting in increased adipose tissue mass resulting in both increased morbidity and mortality (Garvey et al., 2014; Haththotuwa et al., 2020).

The risk of comorbidities rises with an increasing BMI, with a mild rise in the overweight range. Apart from body fat percentage, distribution is important to the incidence of comorbidities. Central abdominal fat, particularly visceral fat, is a risk factor for metabolic syndrome.

Obesity causes a significant increase in morbidity, disability and mortality and seriously impairs quality of life (Jarolimova et al., 2013). It gives rise to several secondary medical conditions (Salem et al., 2014) and is associated with an increased risk of death from both cardiovascular diseases and certain cancers, particularly with higher levels of obesity. The specific levels of risk vary with age, gender, ethnicity and social conditions (Tsigos et al., 2008). The major medical comorbidities associated with childhood obesity in the current literature are metabolic risk factors, asthma, and dental health issues. Major psychological comorbidities include internalising and externalising disorders, attention-deficit hyperactivity disorder, and sleep problems (Pulgarón, 2013). Table 2.2 lists the obesity-related health risks and complications (Adams et al., 2006; Banegas et al., 2003; Flegal et al., 2007; Linde et al., 2004; Renehan et al., 2008; Roberts et al., 2003; Stevens et al., 2002).

Table 2.2: Obesity-related health risks and complications

	Obesity-related health risks and complications
Metabolic complications	Diabetes, insulin resistance Dyslipidaemia Metabolic syndrome Hyperuricaemia, gout Low-grade inflammation

	Obesity-related health risks and complications
Cardiovascular disorders	Hypertension Congestive heart failure Coronary heart disease Stroke Venous thromboembolism
Respiratory disorders	Asthma Sleep apnoea syndrome Obesity hypoventilation syndrome
Cancers	Oesophagus, small intestine, colon, rectum, liver, gallbladder, pancreas, kidney, leukaemia, multiple myeloma, and lymphoma In women: endometrial, cervix uteri, ovary, breast cancer after menopause In men: prostate
Gastrointestinal disorders	Gallbladder disease Non-alcoholic fatty liver disease Gastroesophageal reflux Hernia
Reproductive disorders	Menstrual irregularity, infertility, hirsutism, polycystic ovaries Miscarriage Gestational diabetes, hypertension, preeclampsia, Macrosomia, foetal distress, malformation (i.e. neural tube defect) Dystocia and primary caesarean section
Musculoskeletal disorders	Osteoarthritis (knee) Back pain Increased in pain in the weight bearing joints
Psychological and social consequences	Low self-esteem Anxiety and depression Stigmatisation Discrimination in employment, higher education acceptance, job renumeration
Miscellaneous	Idiopathic intracranial hypertension Proteinuria, nephrotic syndrome Skin infections Lymphoedema Complications from anaesthesia Periodontal disease

Note: Adapted from Adams et al. (2006), Banegas et al. (2003), Flegal et al. (2007), Linde et al. (2004), Renehan et al. (2008), Roberts et al. (2003) & Stevens et al. (2002).

2.3 Pathophysiology of obesity

Obesity pathophysiology includes two main processes: sustained positive energy balance (energy intake > energy expenditure) and the resetting of the body weight 'set point' at an increased value (Schwartz et al., 2017).

Positive energy balance is indicated by an increase in the mass of adipose tissue. There are two main types of adipose tissues in the body, namely, white adipose tissue and brown adipose tissue. White adipose tissue stores energy in the form of triglycerides and plays an important role in balancing energy and lipid homeostasis. Brown adipose tissue is responsible for thermoregulation and heat production through non-shivering thermogenesis. An increase in the mass of adipose tissue can arise by increasing cell size (hypertrophy), cell number (hyperplasia or adipogenesis) or both (Feng et al., 2016).

The 'set point' process explains why weight-loss through changes of diet and/or lifestyle tends to be regained over time posing a major obstacle to effective obesity treatment (Schwartz et al., 2017).

The underlying factors involved in the cause and development of obesity are described below in detail.

2.3.1 Hereditary factors

Hereditary factors are basically related to genetics, family history and racial/ethnic difference (Hruby & Hu, 2015). In general, obesity heritability is estimated to be between 40% and 70% (McPherson, 2007). Studies have shown that parental overweight/obesity is associated with increased obesity risk in offspring (Mathillas, 2010; Schwartz et al., 2017).

Over 60 relatively common genetic markers have been implicated in elevated susceptibility to obesity (Hindorff et al., 2009; Speliotes et al., 2010). Genes that may contribute to obesity susceptibility can be considered in four broad areas (McPherson, 2007), as shown in Figure 2.1.

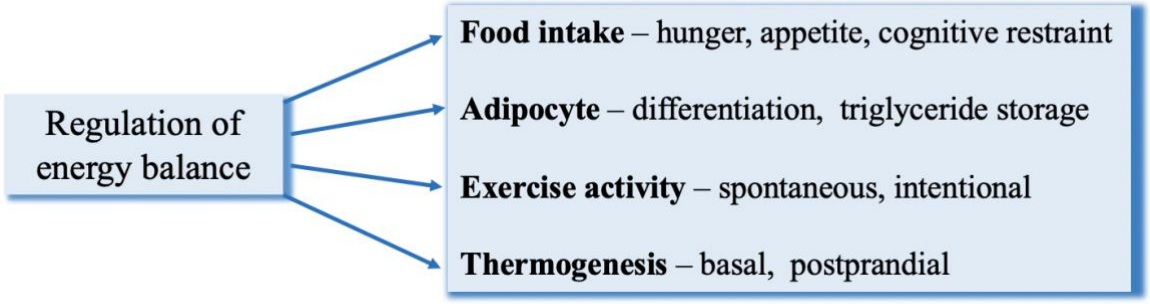


Figure 2.1: Four areas of energy balance regulation

Note: Adapted from McPherson (2007).

Although the importance of genes in influencing appetitive traits has been demonstrated in different studies, it is still unclear which genes are responsible for this (Carnell & Wardle, 2009). Besides this, the 32 most common genetic variants are thought to account for only less than1.5% of the overall inter-individual variation in BMI (Speliotes et al., 2010). This relatively small difference in BMI, coupled with the dramatic rise in obesity over the last half century in developed and developing nations alike point to obesity risk factors far beyond genetics (Hruby et al., 2015).

2.3.2 Dietary and eating behavioural factors

Research from animal and clinical studies, from both controlled trials and from epidemiologic and ecologic analyses provides strong evidence that dietary fat plays a crucial role in the development and treatment of obesity (Bray & Popkin, 1998; Golay & Bobbioni, 1997). High-fat diets produce obesity by enhancing passive over-consumption of energy and increasing the energy density of the diet. The thermic effect of food is defined as the increase in metabolic

rate after the ingestion of a meal. Due to the lower thermic effect of fat and the higher energy cost of converting carbohydrates to fatty acids, fat is more readily stored in the adipose tissue than is carbohydrate (Bray & Popkin, 1998).

A study on dietary factors associated with overweight and body adiposity in Finnish children aged 6–8 years found that protein intake was directly associated with body fat percentage, waist circumference and hip circumference, whereas intakes of other nutrients were not related to measures of adiposity (Eloranta et al., 2012).

Consumption of added sugars has been implicated in an increased risk of obesity (Rippe & Angelopoulos, 2016). The results of a systemic review have shown a positive association between greater intakes of sugar-sweetened beverages and weight gain and obesity in both children and adults (Malik et al., 2006).

The results of some studies suggest that eating main meals—especially breakfast—is important in the prevention of overweight and obesity in children and adolescents (de Gouw et al., 2010; Lehto et al., 2011; Toschke et al., 2009). According to the result of a cross-sectional electronic health survey, skipping breakfast is reported to be a risk factor for weight gain (Croezen et al., 2009).

Fast eating (or ‘gorging’) is also a risk factor for weight gain (Granér et al., 2006; Kral et al., 2009). The result of a study in Korea showed that the eating rate appeared to correlate with overeating, as almost 60% of children in the study who ate rapidly also engaged in overeating (Lee et al., 2011).

2.3.3 Lifestyle factors

While many factors may influence the body weight, overweight and obesity occur mainly because of an imbalance between the energy intake from the diet and the corresponding energy expenditure.

The human body expends energy in three ways: resting energy expenditure, the thermic effect of feeding and non-resting energy (Leibel et al., 1995). Physical activity is the most variable component of energy expenditure, and it contributes to about 20% of the daily energy expenditure for a normally active person (AIHW, 2018b).

As the living standard rises over the past few decades, people are used to more comfortable living conditions with reduced physical activities including labour works, sports and exercises. Ecological analyses imply that the increase in the prevalence of obesity is more strongly related to lower levels of physical activity than higher energy intakes (Jebb & Moore, 1999).

Sleep is an important lifestyle factor on weight gain. Markwald et al. (2013) demonstrated that sleep plays a key role in energy metabolism and insufficient sleep may contribute to overweight and obesity by affecting the physiological and behavioural mechanisms. Sleep loss has been shown to result in alterations of metabolic and endocrine, including decreased glucose tolerance, insulin sensitivity and leptin level, increased ghrelin level, hunger and appetite and increased BMI (Beccuti & Pannain, 2011; Taheri et al., 2004). Evidence from both laboratory and epidemiological studies has shown that inadequate sleep is a high-risk factor that can contribute to overweight and obesity (Beccuti & Pannain, 2011; Bobak et al., 2003; Theorell-Haglöw et al., 2010; Jean-Louis et al., 2014).

Stress is another factor affecting body weight. In acute stressful situation, the body releases catecholamines in order to blunt the appetite and to mobilise glucose from hepatic glycogen. If

the stress levels increase, another hormone called cortisol is released. Cortisol increases appetite and can cause overeating (Kral et al., 2009)

For some time, it has been presumed that alcohol consumption may contribute to weight gain due to increased energy intake. However, it is relatively unclear whether this can be considered as a risk factor because studies have equally reported a positive, negative or no association on the effect of alcohol intake on obesity risk (Croezen et al., 2009; Lahti-Koski et al., 2002; Sayon-Orea et al., 2011; Traversy & Chaput, 2015; Wannamethee & Shaper, 2003; Yeomans, 2004).

2.3.4 Social factors

Obesity prevalence is significantly associated with sex, racial ethnic identity, and socioeconomic status. Environments experiencing deprivation, disorder, or high crime have been shown to be associated with higher odds of obesity which may appear more frequently in individuals of low socioeconomic status (Lee et al., 2019). In the United States, non-Hispanic black, non-Hispanic Asian, and Hispanic women all have a significantly higher prevalence of obesity than men with the same racial ethnic identity (Hales et al., 2017). The reasons of variation in obesity prevalence by race and ethnicity are not very clear, but some evidence points to the differences in genetic backgrounds affecting body composition and fat distribution (Cardel et al., 2011; Fernández & Shiver, 2004), and to the differences in cultural body image standards (Kronenfeld et al., 2010).

The prevalence of obesity increases with lower income and educational attainment (Ogden et al., 2017). The correlation between obesity prevalence and years of education has been shown

in a study undertaken in Spain. A lower rate of obesity was found among individuals who had completed a technical college degree or above (Martín et al., 2008).

Higher socioeconomic status is generally associated with healthy lifestyle behaviours which are often the first line of prevention or treatment for obesity. On the other hand, low socioeconomic status may be associated with less leisure time for physical activity (O'Donoghue et al., 2018) and consumption of energy-dense diets that are nutrient poor (Darmon & Drewnowski, 2008) which are the main risk factors for weight gain.

2.3.5 Physiological factors

When the human body is in a state of equilibrium, all the energy intake from the ingested food and drink is metabolised for the maintenance of basic metabolic rate, thermogenesis, and muscle action. Any excess energy is stored for later use (Lenard & Berthoud, 2008). Therefore, lipid accumulation is the major casual factor of overweight and obesity (van Herpen & Schrauwen-Hinderling, 2008). In homoeostatic regulation, the hypothalamus has a central role in integrating signals regarding food intake, energy balance and body weight (Greenway, 2015). Figure 2.2 illustrates the major mechanisms and factors of homoeostatic regulation (Greenway, 2015).

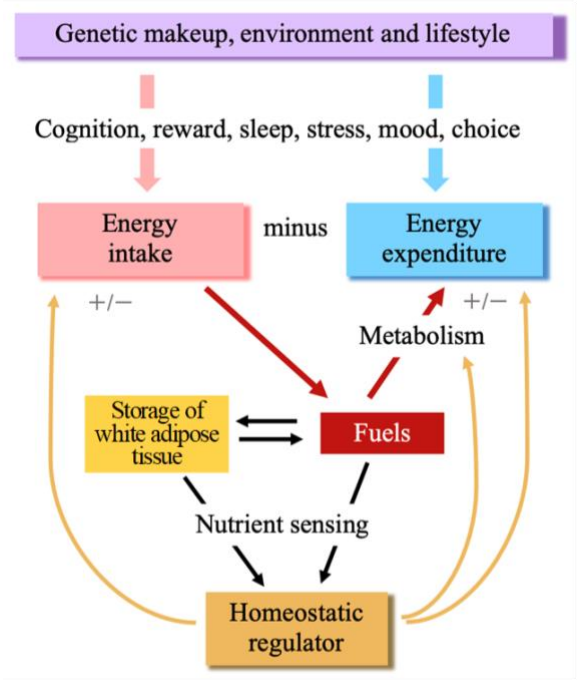


Figure 2.2: Major mechanisms and factors of homeostatic regulation

Note: Adapted from Greenway (2015).

Energy homeostasis consists of a two-way communication between the brain—particularly the hypothalamus, and the peripheral tissues. Chemical signals, such as cholecystokinin (CCK), are released from the digestive system to inform the brain of feelings of fullness as the food is being digested. On the other hand, a gastric hormone, ghrelin, is produced to stimulate the appetite during the fasting state (Penny & Carryer, 2011; van der Lely et al., 2004).

When the homeostasis state is interrupted and the obligate nutritional requirements are overridden, pathological chronic overnutrition may occur (Kral et al., 2009). Obesity occurs when most of the excess calories are converted into triglycerides which are then stored in the adipose tissue (Chen & FareseJr, 2005; Jensen et al., 2011).

2.3.6 Medication factors

Whilst medications are intended to be used for improving health conditions, they can also be associated with a wide variety of adverse effects including weight gain (Leslie et al., 2007;

Rotermann et al., 2014). Drugs often associated with weight gain include antidiabetic agents, neurologic agents and psychiatric agents. (Malone, 2005; Yogaratnam et al., 2013). Evidence suggests that pharmaceutical-induced weight gain is a vital contributor to the obesity epidemic (Malone, 2005; McAllister et al., 2009).

Long-term usage (≥3 months) of corticosteroids, hormonal contraceptives and some antidiabetic and neurologic agents are also known to result in significant weight gain (Malone, 2005; Wharton et al., 2018).

2.4 Current management of obesity

Currently, there are four levels of interventions for weight management which are summarised in Table 2.3 (National Institute for Health and Care Excellence, 2014). Details of the interventions are discussed in the following sub-sections.

Table 2.3: Levels of intervention for weight management

Level of intervention	Description of intervention
1	General advice on healthy weight and lifestyle
2	Lifestyle intervention
3	Lifestyle intervention; pharmacotherapy
4	Lifestyle intervention; pharmacotherapy; surgery

Note: Adapted from National Institute for Health and Care Excellence (2014).

2.4.1 Lifestyle intervention

The goal of lifestyle intervention for weight management is to establish a negative energy balance. The readiness and enthusiasm of the patients is important (Proietto & Baur, 2004). The three principal components of lifestyle intervention are: dietary management, physical activity, and behavioural therapy (Webb & Wadden, 2017).

2.4.1.1 Dietary management

Dietary management plays an important role in maintaining energy balance because obesity occurs when energy intake, through drinks and food, exceeds energy expenditure.

Intake of fat and sugar should be limited to avoid unhealthy weight gain (Food and Agriculture Organization of the United Nations, 2010; Hooper et al., 2012). The optimal diet for prevention of weight gain and obesity is a diet which is fat-reduced, fibre-rich and high in low-energy density carbohydrates (such as fruit, vegetables, and whole grain products) with a restricted intake of energy-laden drinks (Smethers & Rolls, 2018). Reducing soft drink and fruit juice intake is also important (Ludwig et al., 2001).

The Australian Dietary Guidelines (2013) (Australia National Health and Medical Research Council, 2013) indicates that the estimated acceptable macronutrient distribution ranges related to reduced risk of chronic disease are: 20–35% of total energy intake from fats, 45–65% from carbohydrates, and 5–25% from proteins.

In order to achieve a nutritious and balanced diet, the Australian Dietary Guidelines recommend the number of 'standard serves' to be consumed daily from the five-core food groups: grain foods, vegetables/legumes/beans, lean meats/poultry/fish/eggs, milk/yoghurt/ cheese and fruits. (Nutrition Australia, 2021).

Some randomised controlled trials have shown that low-carbohydrate, high-protein diets produce short-term weight-losses (Foster et al., 2003; Sacks et al., 2009). A randomised parallel-group trial for two years demonstrated that successful weight-loss could be achieved with either a low-fat or low-carbohydrate diet when coupled with behavioural intervention (Foster et al., 2010).

2.4.1.2 Physical activities

The National Health and Examination Survey (2022) reported that people who engage in limited recreational activity were more likely to gain weight than more active people (Centers for Disease Control and Prevention, USA, 2022). Other studies have shown that inactive people gain more weight than those who engage in regular assertive activities (Webb & Wadden, 2017). Weight management programs typically prescribe aerobic activities, such as brisk walking or other types of moderate-intensity aerobic exercise for between 150 and 180 minutes per week (Sacks et al., 2009).

Physical activity alone, however, has a minimal impact on weight-loss. Individuals who combine physical activities and caloric restriction achieve better outcomes (Barry et al., 2014; Webb & Wadden, 2017).

2.4.1.3 Behavioural therapy

The basis of behavioural change for weight management is the self-monitoring of food and caloric intake, along with the recording of physical activity and weight (The Diabetes Prevention Program Research Group, 2002; Wadden et al., 2007). Behavioural therapy for weight management generally consists of the following essential elements (van Dorsten & Lindley, 2011):

- Objective treatment goals;
- Self-monitoring of diet and exercise behaviours;
- Making changes to the environment in order to support positive changes;
- Using stimulus control techniques to cue the occurrence of desired behaviours; and
- Relapse-prevention planning.

Behaviour often contributes to an overeating episode (van Dorsten & Lindley, 2011). Monitoring assists obese individuals to identify behavioural patterns, target areas for change, and track progress towards goals. Individuals who engage in frequent self-monitoring of eating and exercising achieve better results in weight management (Steinberg et al., 2015; Wadden et al., 2005; Wing et al., 2006).

2.4.2 Pharmacotherapy

When lifestyle interventions do not achieve the weight-loss goal, pharmacotherapy may be considered (Cannon & Kumar, 2009; Gadde & Pritham Raj, 2017). Anti-obesity drugs are indicated for patients with a BMI of ≥30 kg/m^2 and also for those with a BMI of at least 27 kg/m^2 in the presence of obesity-related diseases or risk factors as an add-on to lifestyle modification (Jensen et al., 2014). The two main catalogues of Western weight-loss drugs are: 1) appetite suppressants which minimize food intake; and 2) lipase inhibitors which reduce the absorption of dietary fat. Although there is evidence supporting that pharmacotherapy can enhance weight-loss combined with lifestyle interventions, (Anderson et al., 2002; Wadden et al., 2005), experts are concerned that, in some cases, the side effects of prescription medications that treat overweight and obesity may outweigh the benefits (NIH, 2022). Table 2.4 lists the weight management medications approved by Food and Drug Administration of United States and their common side effects (NIH, 2022).

Table 2.4: Common side effect of approved weight management medication

Weight Management Medication	Common Side Effects
orlistat (Xenical)	• diarrhea • gas • leakage of oily stools • stomach pain
phentermine-topiramate (Qsymia)	• constipation • dizziness

	• dry mouth • taste changes, especially with carbonated beverages • tingling of your hands and feet • trouble sleeping
naltrexone-bupropion (Contrave)	• constipation • diarrhea • dizziness • dry mouth • headache • increased blood pressure • increased heart rate • insomnia • liver damage • nausea • vomiting
(Other medications that curb your desire to eat include) • phentermine • benzphetamine • diethylpropion • phendimetrazine	• dry mouth • constipation • difficulty sleeping • dizziness • feeling nervous • feeling restless • headache • raised blood pressure • increased heart rate

Note: Adapted from National Institutes of Health (2022).

2.4.3 Surgery

Bariatric surgery is a treatment option which has been increasingly used in obese patients (Cannon & Kumar, 2009; Sudlow et al., 2020). Obese adults with a BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with obesity-related comorbid conditions may be referred to an experienced bariatric surgeon for consultation and evaluation (Jensen et al., 2014).

There are many types of bariatric surgeries. The most commonly performed procedure (Sudlow et al., 2020) are listed in Table 2.5.

Table 2.5: Most commonly performed bariatric surgeries

Bariatric Surgery	Mechanism of Action
Sleeve gastrectomy	↑ GLP-1, PYY, insulin secretion, bile acid secretion and satiety ↓ Ghrelin, insulin resistance and hunger
Adjustable gastric band	↓ Hunger, meal frequency and caloric intake
Biliopancreatic diversion with duodenal switch	↑ GLP-1, PYY, insulin secretion, bile acid secretion and satiety ↓ Ghrelin, hunger, insulin resistance, hepatic glucose production and intestinal absorption
One anastomosis gastric bypass	↑ GLP-1, PYY, insulin secretion, bile acid secretion and satiety ↓ Ghrelin, hunger, insulin resistance, hepatic glucose production and intestinal absorption
Roux-en-Y gastric bypass	↑ GLP-1, PYY, insulin secretion, bile acid secretion and satiety ↓ Hunger, insulin resistance and hepatic glucose production

Note: GLP-1 = Glucagon-like peptide-1; PYY = hormone peptide YY.
Data adapted from Sudlow et al. (2020).

2.5 Discussion

This chapter has provided information about obesity from Western medicine perspectives, including diagnosis and assessment, manifestations, pathogenesis and current management of obesity. At present, pharmacotherapy is the main medical interventions for weight management, but the side effects of prescribed anti-obesity medications may outweigh the benefits for some obese individuals. Thus, more and more patients are seeking alternatives, such as Chinese herbal medicine (Xiao & Luo, 2018; Yeh et al., 2017). Traditional Chinese medicine is a medical system with rich history and clinical experiences. Next chapter provides information of obesity from Chinese medicine perspectives and its approach on weight management.

Chapter 3 Understanding obesity from Chinese medicine perspective

This chapter introduces the understanding of obesity from Chinese medicine (CM) perspective, including the Chinese medicine theory aetiology and pathogenesis, syndrome differentiation and the treatment for obesity in Chinese medicine. This chapter also compares the similarities and differences in understanding of obesity between Chinese medicine and Western medicine.

3.1 Definition of obesity in classical Chinese medicine

The classic book *Huangdi Neijing* (The Yellow Emperor's Classic of Internal Medicine) (Curran, 2008) stated that obesity is a result of overeating heavy, rich, and sweet foods. CM holds that the Spleen governs the production of vital substance, the Heart and Lung govern their movement, the Kidney governs their storage, the Liver is in the charge of 'dredge' and 'discharge' (Garvey & Lifang, 2001). Although this information is important for maintaining healthy weight, there was no detailed explanation given concerning treatment of obesity (Mullin et al., 2014). This may be because obesity was not common in ancient times. Therefore, the diagnosis and treatment for primary obesity in modern times is primarily approached by applying basic CM principles. Further details are discussed in Section 3.4.

'Fat' is called *Gao* in Chinese language. Primarily, it refers to the adipose tissue in the abdomen (in both men and women) and in the breasts (in women). It also includes the peritoneal membranes which encapsulate the organs (Maciocia, 2015). According to CM theory, Gao (adipose tissue) is the accumulation of phlegm generated by the condensation of 'thin' and thick' fluid in the body.

The Lung, Spleen and Kidney are deemed responsible for the regulation of body fluid whilst the Spleen plays the significant role in the development of obesity (Cheng & Deng, 1999; Zhu, & Wang, 2010). The main functions of the Spleen are transportation and transformation which

would decrease when Spleen Qi is chronically deficient. When the Spleen fails to move and transform liquid efficiently, humid would accumulate and eventually congeal into phlegm (Mullin et al., 2014). When phlegm is lodged, the person might feel heavy and lethargic with weakened immune system. Oedema might be developed in the body and sputum might be developed in the Lung. These might lead to less motivation and capability for physical exercises and therefore cycle of phlegm accumulation is intensified. Therefore, the primary treatment principle for obesity in CM is to strengthen the Spleen so that the phlegm in the body can be disposed efficiently (Mullin et al., 2014).

3.2 Aetiology and pathogenesis of obesity

In CM, obesity can be caused by multiple factors such as poor food choices, lack of physical activities and unstable emotions. The outcome can be exacerbated by specific types of bodily constitution and the ageing process.

3.2.1 Food

In CM, the amount and type of food intake directly affect the two organs of digestion: the Spleen and the Stomach. Eating irregularly or eating excessive amounts of fats, dairy or sugars weakens the Spleen and leads to the accumulation of dampness and phlegm. The Spleen is an organ and is susceptible to cold foods and cold beverages according to CM theory. Frequent consumption of cold foods and beverages weakens the Spleen and causes it to perform sluggishly. On the other hand, the Stomach is an organ with disposition for warm foods and beverages (Lu & Schaplowsky, 2009). However, too much heat in the Stomach leads to thermogenesis of the stomach contents which, in turn, produces hunger and encourages the person to develop a tendency to overeat (Maciocia, 2008; 2015; Mullin et al., 2014). Therefore,

excessive consumption of heavy, greasy, spicy, or fried foods should be avoided, so as not to generate excessive heat in the Stomach.

3.2.2 Physical activities

Chapter 5 of the *Huangdi Neijing* (The Yellow Emperor's Classic of Internal Medicine) (Curran, 2008), notes that: Jiǔ wò shāng qì, jiǔ zuò shāng ròu (久臥傷氣，久坐傷肉), which means that lying for too long damages the Qi; sitting too long damages the muscle.

Since muscle is associated with the Spleen according to the Five Element Theory, 'damaging the muscle' technically means 'damaging the Spleen'. Due to the interruption of the flow of the Qi and the subsequent reduction of Spleen functions, the body essence congeals to phlegm. On the other hand, physical overwork, including excessive exercise and sports, also weakens the Spleen and may lead to Spleen deficiency which, in turn, may lead to phlegm (Maciocia, 2008). Therefore, it is important to seek a balance of physical activities in order to achieve a healthy weight.

3.2.3 Emotions

Long-standing strong emotions can cause obesity in different pathways (Maciocia, 2015). Firstly, the Spleen can be weakened or damaged by unstable emotions such as anxiety and worry (Zhu, & Wang, 2010; Cheng & Deng, 1999). As explained earlier, a weak Spleen can cause obesity. Secondly, when the Liver is affected by stress, depression, anger or frustration, it fails to regulate the flow of Qi, which then, in turn, generates dampness in the body (Maciocia, 2015). Thirdly, the stagnation of the Qi in the Liver can lead to disharmony between the Spleen and the Liver giving rise to fluid retention (Zhao et al., 2018). Over time, the dampness congeals into phlegm and results in obesity.

3.2.4 Bodily constitution

In CM, the bodily constitution has a close relationship with metabolic syndrome including obesity and Type 2 diabetes mellitus (Li, et al., 2017). Studies have shown that the phlegm dampness constitution is positively associated with obesity and overweight (Wang et al., 2013; Zhao, 2018).

3.2.5 Ageing

Ageing is one of the risk factors of weight gain. When people get older, the Liver function of regulation of the flow of Qi is reduced, resulting sluggish Qi and blood flow tend to block the meridians. Therefore, dampness is likely to remain in the body more in the elderly then in younger people. Over time, the dampness will congeal into phlegm and cause overweight and obesity (Maciocia, 2015).

3.3 Syndrome differentiation of obesity

In CM, there is no physical measurement for determining the severity of obesity similar to that in Western medicine. The initial assessment of obesity in CM is mainly based on visual inspection. Further investigation of obesity is based on CM diagnosis.

According to the CM theory, the pathogenesis of simple obesity is mainly considered to be a blood vessel obstruction caused by Qi deficiency and phlegm dampness stagnation. This obstruction could be caused by various internal and external factors such as stagnation of the Liver Qi, deficiency of the Spleen, or over-consumption of, for example, greasy or spicy foods, just to name a few. The organs associated with obesity in CM refer to Spleen, Liver and Kidney (Flaws & Sionneau, 2001; L.-H. Wang et al., 2019).

Since there are multiple factors causing the occurrence of obesity, a syndrome differentiation approach is necessary in order to identify the patient's unique pattern of dysfunction and to ascertain the patient's personal history and metabolic reasons for weight gain (Mullin et al., 2014). Details of the common types of obesity syndrome are discussed in the follow sub-sections, and the signs and symptoms of the syndromes are listed in Table 3.1 (Cheng & Deng, 1999; Mullin et al., 2014; Zhu & Wang, 2010).

Table 3.1: Syndrome differentiation of obesity

Type of syndrome	Presenting signs and symptoms
Stomach heat and Spleen deficiency	Corpulence, fullness of head, vertigo, increased hunger, heavy limbs, lethargy, an increased thirst and fluid intake, constipation, slippery and rapid pulse, red tongue with slightly yellow greasy tongue coating
Deficiency of Spleen Qi	Corpulence, oedema, tiredness, body heaviness, asthenia, hypoxemia, poor appetite, abdominal fullness, loose stool, soft fresh, poor appetite, fatigue, weakness, swelling, oedema, bloating, soggy and forceless pulse, pink tongue with thin white coating, with or without teeth marks on tongue
Stagnation of Liver Qi	Corpulence, melancholy, irritability, hypochondriac, rib-side distension or abdominal distension and fullness, bitter taste, irregular menstruation, insomnia, dreaminess, thread and taut pulse, white or thin greasy tongue coating
Deficiency of Spleen and Kidney Yang	Corpulence, tiredness, asthenia, lumbar soreness and leg weakness, impotence, sensation of coldness in the genitalia, deep and thready pulse, swollen tongue with white coating
Blood Stasis	Distension of the lower belly, stabbing pain in the chest, coldness in lower body, irregular menstruation, wiry or choppy pulse, dark red or purple tongue
Retention of phlegm	Body heaviness, lassitude of limbs, tiredness, dark circles under eye, profuse phlegm, chest oppression, formation of sputum, dizziness, vomiting and lack of appetite, slippery bowstring pulse, white and greasy tongue coating.

Note: Adapted from Cheng & Deng (1999), Mullin et al. (2014) and Zhu & Wang (2010).

3.3.1 Stomach heat and Spleen deficiency

Over-indulgence of heat-producing foods is the main source of Stomach heat. Stomach heat produces hunger and a tendency to overeat, but Spleen vacuity fails to disperse and transform the essence of the food. Prolonged periods of heat in the stomach can cause heat in the intestines leading to both constipation and stagnation. The stagnation caused by heat and the failure of the transportation and transformation functions of Spleen thus facilitate the formation of phlegm and result in weight gain (Mullin et al., 2014). In a clinical setting, these patients usually describe frequent problems with their overall digestive system. They are easily hungry but also get easily full and bloated after only consuming a little food (Mullin et al., 2014).

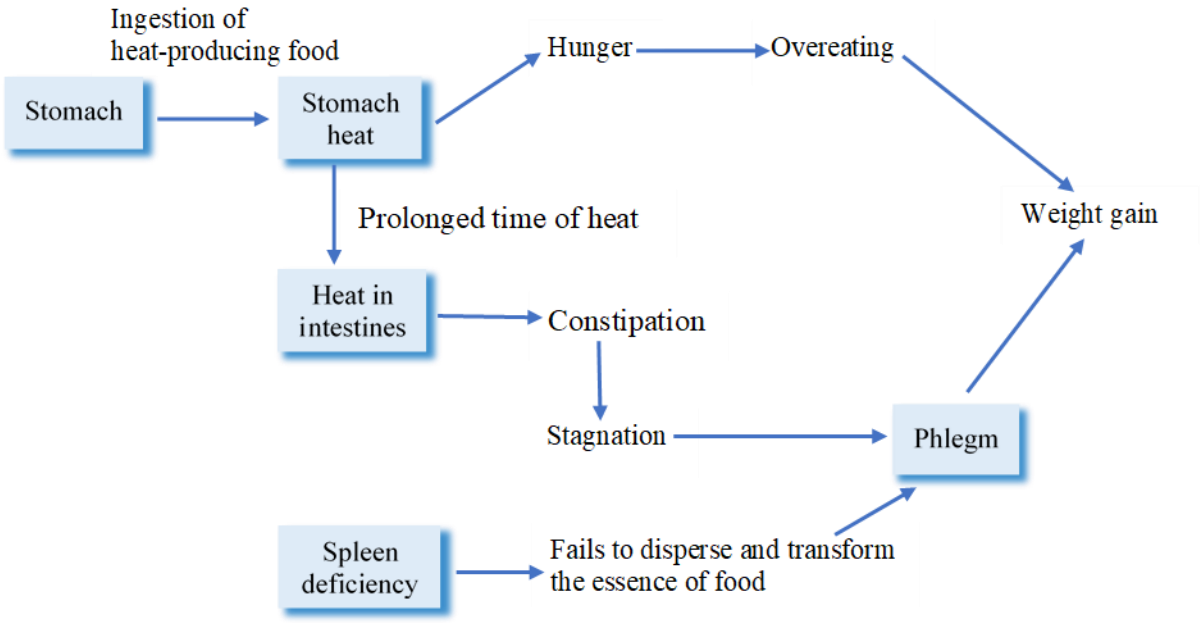


Figure 3.1: Flow chart of pathogenesis – Stomach heat and Spleen deficiency

Note: Adapted from Mullin et al. (2014).

3.3.2 Deficiency of Spleen Qi

Spleen in TCM is not synonymous with the spleen in western medicine anatomically (Wu, 1998). The main functions of Spleen in TCM are transportation and transformation. Spleen Qi deficiency may cause failing on its function of moving and transforming food and waste fluids.

The gathering of the metabolic wastes may be collected and transformed into pathogenic factors of dampness. After the pathogenic factors of dampness sustain over a period of them, they will congeal into phlegm, and become fat tissue (Maciocia, 2015). In clinical settings, these patients present with a pale complexion and lips, fatigue, loss of appetite, nausea, diarrhoea and bloating. (Gao, 2016; Mullin et al., 2014).

Obesity syndrome of Spleen Qi deficiency is generally due to dietary irregularities, frequent binges and fasting, eating too much sweet or raw foods, or subordinate causes due to some other illness (Lu & Schaplowsky, 2009; Mullin et al., 2014). Some people try to lose weight by fasting but frequent binges and fasting can, in fact, produce negative outcomes by damaging the Spleen and thereby causing deficiency of Spleen Qi (Mullin et al., 2014).

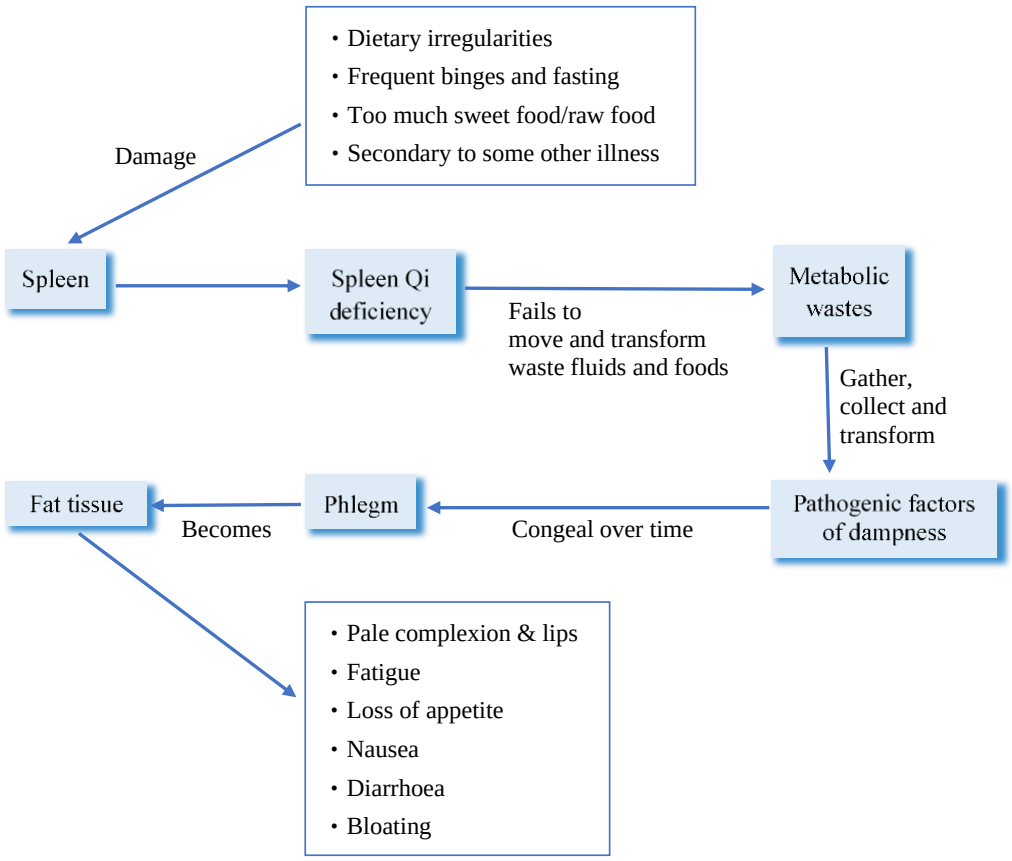


Figure 3.2: Flow chart of pathogenesis – Deficiency of Spleen Qi

Note: Adapted from Maciocia (2015), Gao (2016) and Mullin et al. (2014).

3.3.3 Stagnation of the Liver Qi

Stagnation of the Liver Qi is usually caused by prolonged emotional distress (Gao, 2016). It is observed that very emotional, anxious females or easily irritated males are more prone to stagnation of the Liver Qi (Mullin et al., 2014). Stagnation of the Liver Qi impairs the smooth flow of Qi and gives rise to fluid retention and over time results in phlegm accumulation and, finally, obesity (Maciocia, 2015). Some people with Liver Qi stagnation may lose interest in doing anything and even experience depression. The lack of Qi flow or mobility will lead to the generation of fat turbidity becoming stagnant within the body (Wiseman & Ellis, 1995).

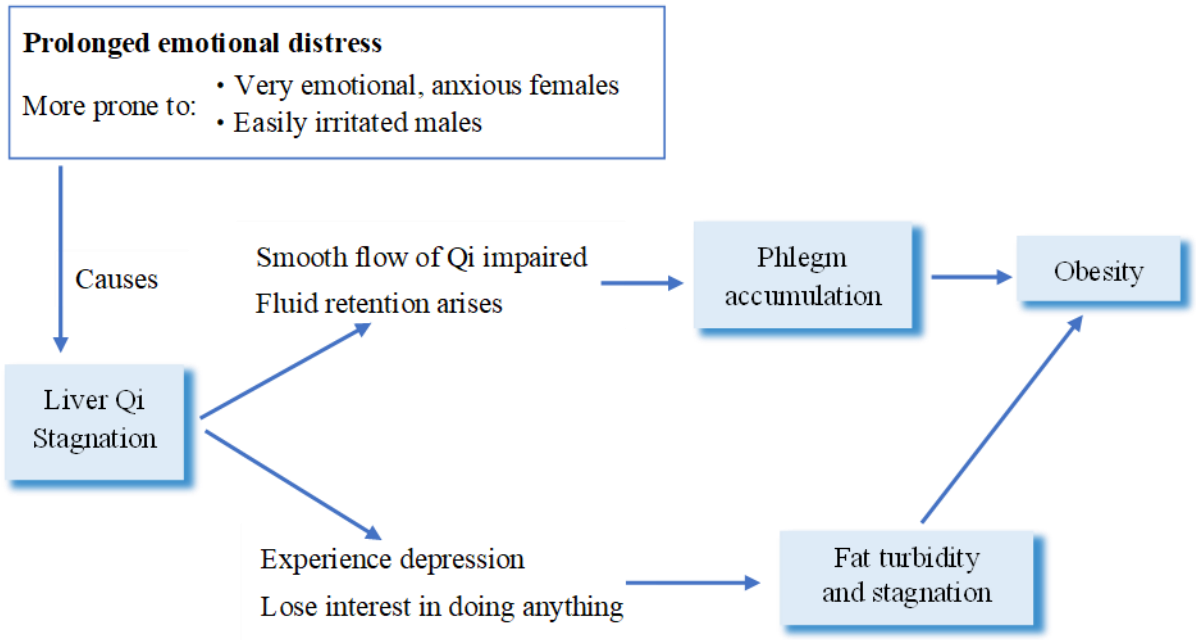


Figure 3.3: Flow chart of pathogenesis – Stagnation of Liver Qi

Note: Adapted from Gao (2016), Mullin et al. (2014), Maciocia (2015) and Wiseman & Ellis (1995).

3.3.4 Deficiency of the Spleen and the Kidney Yang

Deficiency of the Spleen and Kidney Yang can be congenital or due to overexertion (Mullin et al., 2014). The function of the Spleen and Kidney are interdependent. The Spleen provides the Kidney with Yin (nutrients) for functioning while the Kidney provides Yang (heat) to the

Spleen for carrying out the digestive process. Deficiency of the Spleen and Kidney leads to a Yang deficiency thus causing a failure in both organs to support each another and maintain normal functions. People with Spleen and Kidney Yang deficiency often feel exhausted or fatigued. They don't have enough Qi to transform or resolve the phlegm and, eventually, become obese (Wiseman & Ellis, 1995). In clinical settings, they are usually very similar in outer appearance to those with Spleen Qi deficiency but experience more from symptoms of coldness (Mullin et al., 2014).

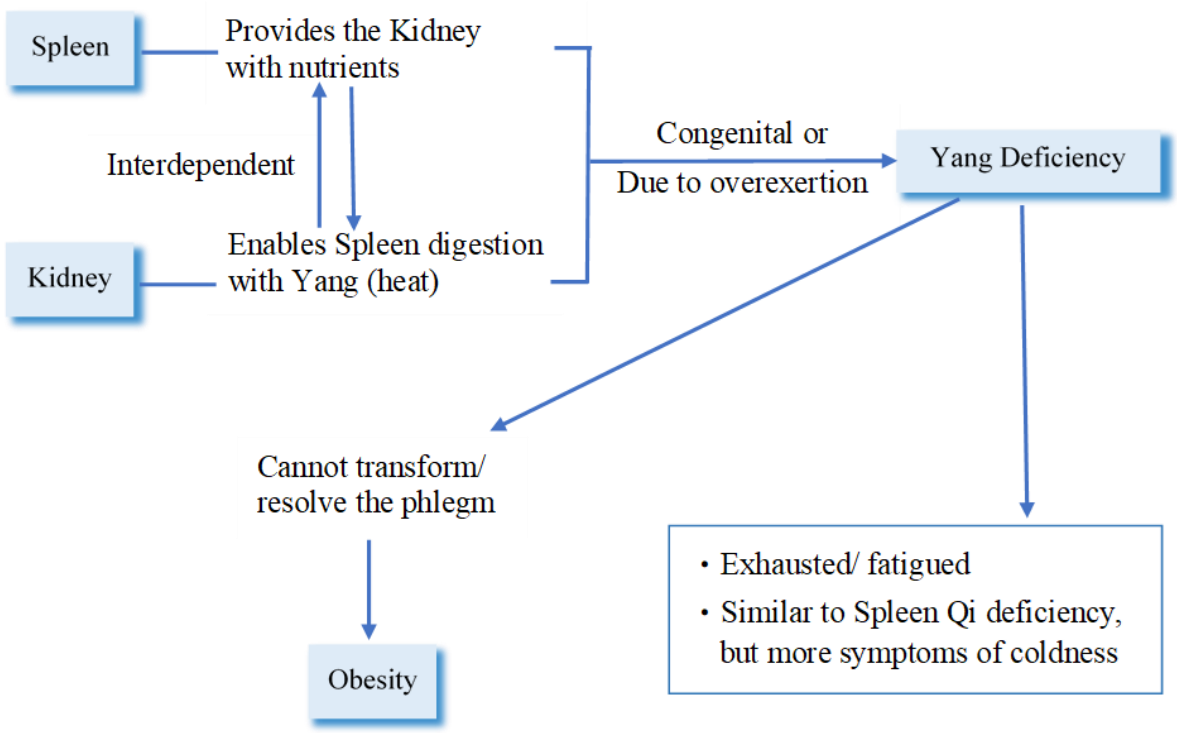


Figure 3.4: Flow chart of pathogenesis – Deficiency of Spleen and Kidney Yang

Note: Adapted from Mullin et al. (2014) and Wiseman & Ellis (1995).

3.3.5 Blood stasis

According to CM theory, Qi is the motivational force for the blood. Without Qi, the blood would be an inert substance (Maciocia, 2015). Therefore, blood stasis can be due to the stagnation of the flow of Qi and can also be induced by the corresponding stagnation of the

Liver Qi (Mullin et al., 2014). Blood stasis obstructs the blood vessels and, in turn, inhibits the Qi mechanism. Dampness and phlegm collect and accumulate inside the blood vessels, thus causing the blood to become more viscous. Gradually, obesity develops (Wiseman & Ellis, 1995). In clinical settings, these patients do not appear to be very obese but have more fat accumulated in the lower abdominal area closed to the waistline. This is frequently observed in female patients (Mullin et al., 2014).

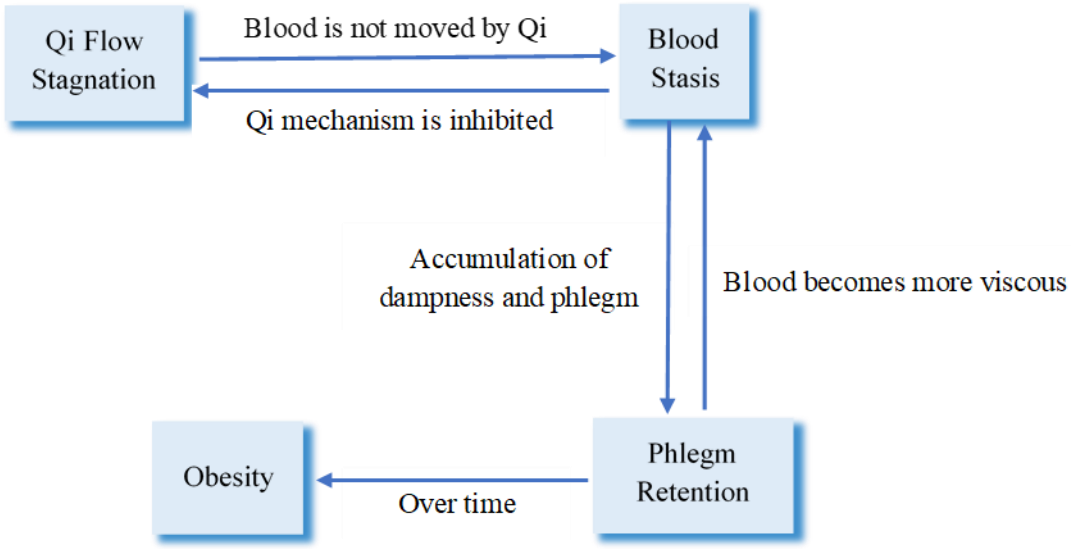


Figure 3.5: Flow chart of pathogenesis – Blood stasis

Note: Adapted from Maciocia (2015), Mullin et al. (2014) and Wiseman & Ellis (1995).

3.3.6 Retention of the phlegm

Retention of the phlegm is the type of obesity most frequently observed. It may be the actual cause on its own or an issue that arises as a complication relating to the functions of the Lung, Spleen, or Kidney (Mullin et al., 2014; Wiseman & Ellis, 1995). Enormous improvement in symptoms can be observed when such patients commence physical workouts (Mullin et al., 2014). Section 3.3 has discussed in more detail of the mechanisms of phlegm formation.

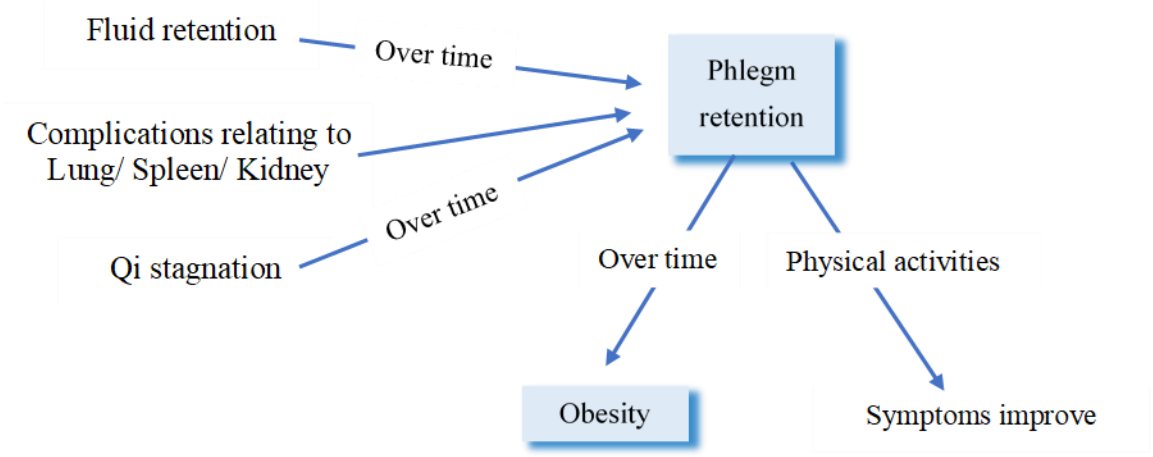


Figure 3.6: Flow chart of pathogenesis – Retention of phlegm

Note: Adapted from Mullin et al. (2014) and Wiseman & Ellis (1995).

3.4 Treatment for obesity in Chinese medicine

In CM, treatment principles are determined based of syndrome differentiation and treatment plans are tailor-made to individual patients based. The treatment modalities for obesity in CM include Chine se herbal medicine (CHM), acupuncture, dietary advice and exercise therapy. They can be administrated independently or as co-treatment. The CM treatment aims to return the systemic dynamic balance of the body so as to return patients to a state of health.

3.4.1 Chinese herbal medicine

Chinese herbal medicine (CHM) has been embedded in China's medical system for thousands of years and has produced substantial clinical experience in the treatment of various diseases (Xu et al., 2018). Traditionally, multiple herbs are prescribed as a formula in order to achieve a balanced therapeutic effect.

Traditionally, CHM formulae are prescribed to obese patients according to the patterns of the presented syndrome. For example, Qing Wei San for Stomach heat; Gui Pi Tang for Spleen Qi

deficiency; Xiao Yao San for Liver Qi stagnation and Er Chen Tang for phlegm retention. Sometimes the formula may be modified by either adding or subtracting the herbs or changing the dosage of certain herbs in order to suit the individual obese patient.

Modern research focuses more on the anti-obesity properties of single herbs and their chemical constitutions. The following Chinese herbs are shown to have potential for weight management:

- Ku gua, Momordica Charantia (bitter melon) (Fan et al., 2019)
- Qing hao, Artemisiae Annuae Herba (sweet wormwood) (Xu et al., 2018)
- Qiang huo, Notopterygii Rhizoma et Radix (Notopterygium root) (Xu et al., 2018)
- Lei gong teng, Tripterygii Radix et Rhizoma (Triptergium) (Xu et al., 2018)
- La jiao, Capsicum annuum (Chilli peppers) (Xu et al., 2018)
- Huang lian, Picrorhizae Rhizoma (Coptis chiensis) (Xu et al., 2018)
- Ren shen, Ginseng Radix et Rhizoma (Ginseng) (Xu et al., 2018)
- Lu cha, Camellia sinensis (Green tea) (Tannis M. Jurgens et al., 2012)
- Jue ming zi, Cassiae Semen (Cassia seed) (Au et al., 2003)

3.4.2 Acupuncture

Acupuncture is a central CM treatment method which has been practised for thousands of years in China. Over the last four to five decades, the practice of acupuncture has grown exponentially in the Western world (Deadman et al., 2007; O'Brien & Birch, 2009; Schnyer et al., 2005). The treatment involves inserting very thin metal needles into the skin at specific (acupuncture) points on the body (Harvard Health Publishing, 2017). It is believed that the insertion of needles in specific of the body will assist, correct, and rebalance the flow of Qi along the energy pathways, that is, the meridians (Mullin et al., 2014). As well as ancient

knowledge and traditional clinical experiences, modern scientific evidence has demonstrated the effect of acupuncture in the management of simple obesity (L.-H. Wang et al., 2019).

Table 3.2 summarises the most frequently used acupuncture points in the treatment of obesity based on syndrome differentiation. This information is based on the Chinese medicine textbook *Chinese Acupuncture and Moxibustion* (Cheng & Deng, 1999), a book on integrative weight management (Mullin et al., 2014) and two review articles (Sui et al., 2012; Zhang et al., 2017).

Table 3.2: Selection of acupuncture points for different types of obesity syndrome

Type of syndrome	Selected acupuncture points
Stomach heat and Spleen deficiency	SP4(*Gongsun*), SP6(*Sanyinjiao*), LI4(*Hegu*), LI11(*Quchi*), ST25(*Tianshu*), ST34(*Liangqiu*), ST36(*Zusanli*), ST37(*Shangjuxu*), ST40(*Fenglong*), ST44(*Neiting*), BL21(*Weishu*), BL27(*Xiaochangshu*)
Deficiency of Spleen Qi	SP4(*Gongsun*), SP6(*Sanyinjiao*), SP9(*Yinlingquan*), ST25(*Tianshu*), ST34(*Liangqiu*), ST36(*Zusanli*), ST40(*Fenglong*), CV6(*Qihai*), CV12(*Zhongwan*)
Stagnation of Liver Qi	SP6(*Sanyinjiao*), SP10(*Xuehai*), SP14(*Fujue*), BL17(*Geshu*), BL18(*Ganshu*), BL19(*Danshu*), GB31(*Fengshi*), ST25(*Tianshu*), ST26(*Wailing*), ST34(*Liangqiu*), ST36(*Zusanli*), ST37(*Shangjuxu*), TE5(*Waiguan*), TE6(Zhigou), GB26(*Daimai*), CV4(*Guanyuan*), KI3(*Taixi*)
Deficiency of Spleen and Kidney Yang	SP9(*Yinlingquan*), ST37(*Shangjuxu*), BL20(*Pishu*), BL15(*Xinshu*), CV3(*Zhongji*), CV6(*Qihai*), CV12(*Zhongwan*), KI3(*Taixi*), SP6(*Sanyinjiao*), CV4(*Guanyuan*)
Blood statis	SP6(*Sanyinjiao*), SP10(*Xuehai*), BL17(*Geshu*), BL18(*Ganshu*), BL19(*Danshu*), GB31(*Fengshi*), ST25(*Tianshu*), ST34(*Liangqiu*), ST36(*Zusanli*), ST37(*Shangjuxu*), TE5(*Waiguan*), TE6(Zhigou), GB26(*Daimai*)
Retention of phlegm	SP4(*Gongsun*), SP9(*Yinlingquan*), ST27(*Daju*), ST28(*Shuidao*), ST36(*Zusanli*), ST38(*Tiaokou*), ST39(*Xiajuxu*), ST40(*Fenglong*), ST44(*Neiting*), CV4(*Guanyuan*), CV6(*Qihai*), CV9(*Shuifen*), CV12(*Zhongwan*), TE4(*Yangchi*), LI11(*Quchi*), PC6(*Neiguan*), LR3(*Taichong*)

Note: BL: Bladder meridian; CV: conception vessel meridian; GB: Gall Bladder meridian; KI: Kidney meridian; LI: Large Intestine meridian; PC: Pericardium meridian; SP: Spleen meridian; ST: Stomach meridian; TE: Triple energiser meridian.

For example, acupuncture point SP4 refers to the 4th point of the Spleen meridian and the word in italics is the Chinese name of the acupuncture point.

Data adapted from Cheng & Deng (1999), Mullin et al. (2014), Sui et al. (2012) and Zhang et al. (2017).

3.4.3 Dietary advice

In CM, diet is an important element for health maintenance but at the same time, it is one of the major causes of disease if not appropriately managed (Maciocia, 2015). Types of food and their energetic effect are classified according to their 'energy' into cold and hot in nature and temperature. Food which is classified as 'cold' is judged in two ways: firstly, this food has a 'cold' energy, e.g., lettuce; secondly, the food is actually cold in temperature, e.g., iced water, ice-cream and so forth (Maciocia, 2015; Shyu & Leelarthaepin, 1987).

From a CM point of view, consumption of excessive cold foods (cold-energy food or raw food) may weaken the Spleen, in particular, Spleen Yang. The Spleen prefers dryness and warmth in food and dislikes any excess of fluids or coldness. An over-consumption of cold foods and beverages will overload the Spleen and weaken the Spleen-Yang thus causing diarrhoea, chilliness, cold mucus, abdominal pain and distension. Therefore, raw and cold foods should be limited especially for those who tend to have Spleen deficiency. Apart from raw and cold food, any oily and/or greasy food should also be limited for healthy weight management.

Research has shown that green tea assists metabolism and weight reduction (Hursel et al., 2009; Jurgens et al., 2012). Food types that are beneficial for weight management include bitter melon (Gao et al., 2021; Luk et al., 2008), hot pepper (Xu et al., 2018), Goji berries (Bensky et al., 2004) and hawthorn fruit (Bensky et al., 2004).

3.4.4 Exercise therapy

As discussed previously, Qi stagnation is one of the major root causes of weight gain. From the CM perspective, the purpose of physical exercise is to activate the stagnated Qi and thus improve the Qi flow in the body. Accordingly, CM recommends gentle exercises such as Tai Chi to improve the general Qi flow mechanism and specific Qigong movements to strength the organs related to the obesity pattern (Lu & Schaplowsky, 2009). The Qi activated by either Tai Chi or Qigong travels through the whole body and regulating the heart and respiration as well as strengthening the body. The activated Qi is then able to facilitate the coursing and unblocking of the meridians, harmonises with the blood stasis and calms the mind (Sancier & Holman, 2004).

In China, medical practitioners have found Qigong to be effective in the treatment of a wide variety of health conditions including drug abuse and obesity (Jette & Vertinsky, 2010; Lu & Schaplowsky, 2009).

3.5 Discussion

A comparison on Western and Chinese medicine theories the aetiology and the pathogenesis of obesity may provide a better understanding on the issue. Figure 3.7 shows the comparison of both Western and Chinese medicine theories on obesity.

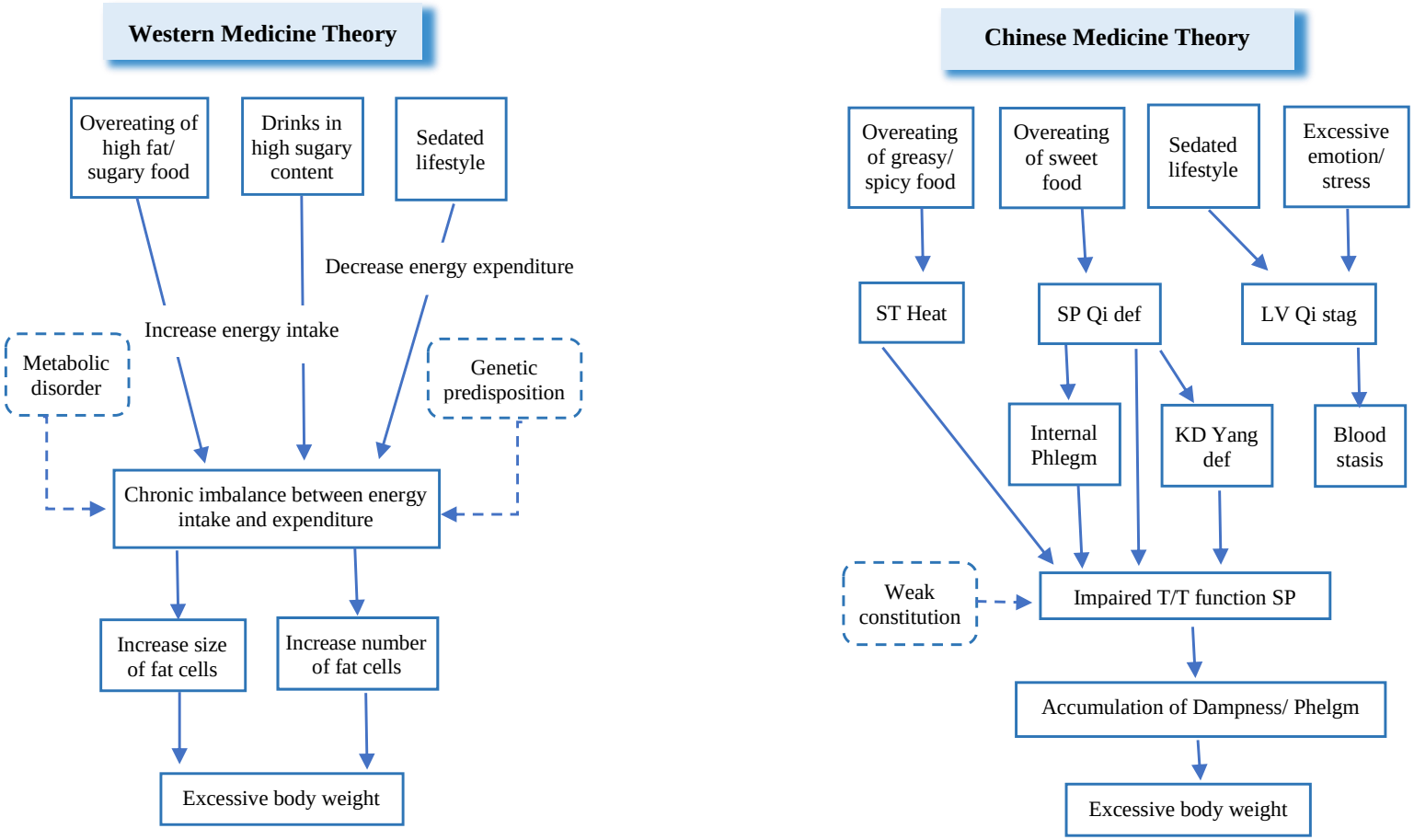


Figure 3.7: Comparison of Western and Chinese medicine theories on obesity

Note: def: deficiency; KD: Kidney; LR: Liver; SP: Spleen; ST: Stomach; T/T: transport/ transform

Both CM and Western medicine concur that lifestyle changes are essential for successful weight management. Regarding dietary advice, Western medicine focuses on the total amount of caloric intake; whilst CM can highlight more on the nature, temperature and taste of the food as well as the cooking methods employed.

Western medicine views physical exercise as a source of energy expenditure and, therefore, focuses on the intensity and amount. However, CM believes that vigorous exercises are generally not recommended for obese people who are already displaying areas of depletion in the body as vigorous exercises induce sweating and further deplete the body essence. From the CM perspective, the purpose of physical exercise is to activate the stagnated Qi and improve the Qi flow in the body but not to burn the calories as in Western medicine theory.

Pharmacotherapy is a crucial element for the treatment of obesity in both Western and Chinese medicines. The actions of Western weight-loss medications are to suppress appetite and to reduce absorption of dietary fat. The CHM prescribed for weight management vary according to syndrome differentiation (Sui et al., 2012). While SP Qi deficiency is the root cause, Liver Qi Stagnation and ST heat are the most common manifestations of overweight in modern day. CM formula generally consists of a combination of different herbs with different actions. Therefore, it is important to thoroughly study each individual herbs of the formula in order to understand its mechanisms of actions.

Chapter 4 General methodology

This chapter describes and details the general methodology used in this research project. The project was conducted at the Discipline of Chinese Medicine, School of Health and Biomedical Sciences, RMIT University. It consisted of three phases in order to address the aims and objectives including methods for reviewing classical literature and modern literature and conducting computational analysis (Figure 4.1). The methods described in Sections 4.1–4.4 contributed to the following publications:

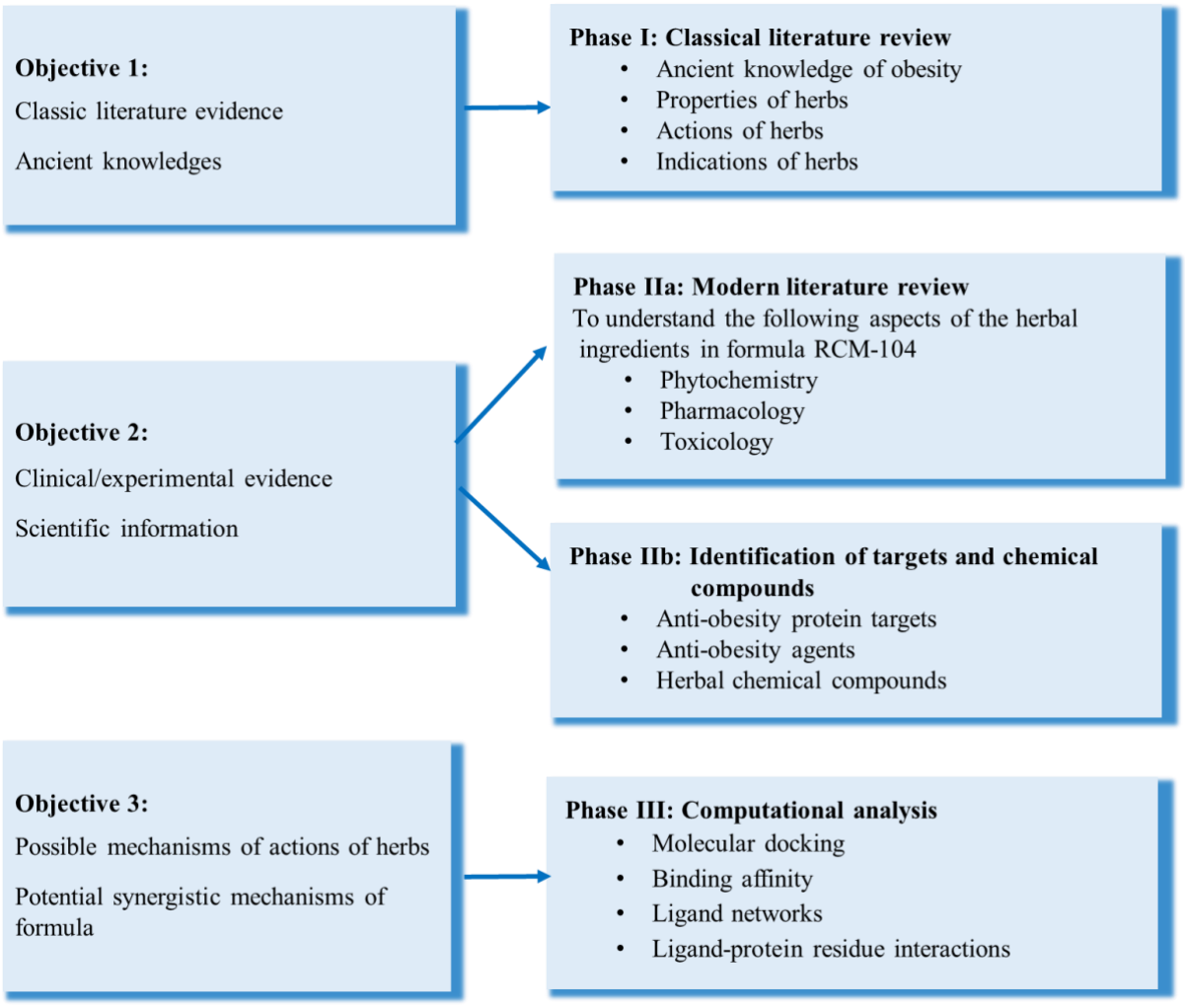


Figure 4.1: Objectives and phases of this project

4.1 Methods for Phase I: Review of classical literature

A compressive review of classical Chinese medicine literature was conducted in this phase. A data-mining and text-mining method was employed in order to both understand the interpretation of obesity in ancient China and to ascertain information, such as the properties, actions and indications, concerning the ingredients of weight-loss CHM formula RCM-104. The findings are reported in Chapter 5.

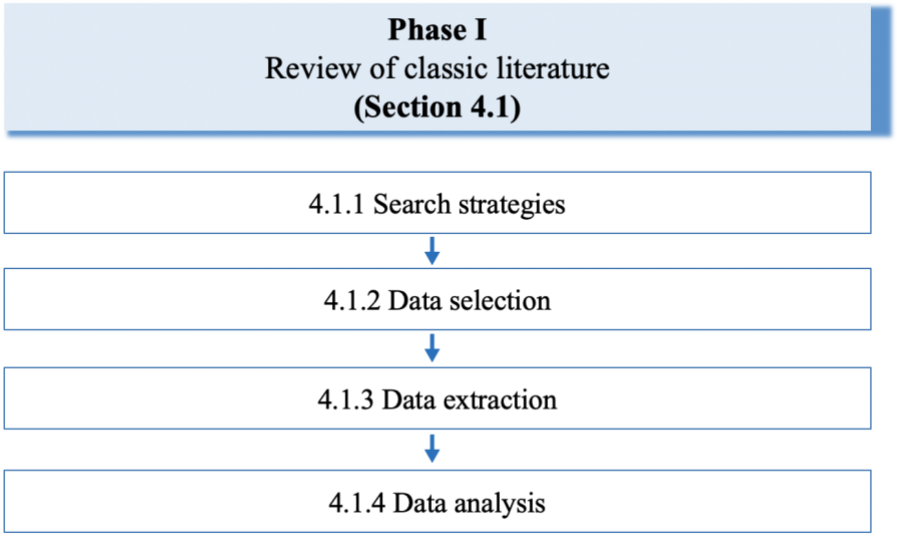


Figure 4.2: Methods for review of classical literature

4.1.1 Search strategies

A two-stage search process was used for the classical CM literature review: A CD-ROM database named *Zhong Hua Yi Dian* (ZHYD; *Encyclopaedia of Traditional Chinese Medicine*) (China Association of Chinese Medicine, 2015) was first used to locate any relevant citations. This was then followed by cross-referencing the extracted citations with hardcopy authenticated editions of the books in *Zhong Guo Ben Cao Quan Shu* (ZGBCQS; *The Complete*

Collection of Traditional Texts on Chinese Materia Medica) (China Association for Culture Studies, 1999) in order to verify the retrieved information.

The searchable database ZHYD was chosen for this project as 1,156 classical texts, written before the establishment of the People's Republic of China in 1949, are comprehensively recorded in this database. It is an electronic resource with a broad coverage of classical CM literature which facilitated the exploration of the concept of obesity in ancient times also provided information concerning the herbs comprising herbal formula RCM-104. All the classical texts in ZHYD were included in the search. The keywords used for searching the electronic database are shown in Table 4.1.

The ZGBCQS collection is the largest published full-text collections of the traditional literature on Chinese medicine with 2,027 titles (May et al., 2012). It consists of 401 volumes under 10 genre categories. The first 251 volumes, under the first 3 genre categories, were included in the search. The genre categories and the table of contents of ZGBCQS are listed in Appendix B.

Table 4.1: Keywords for electronic database search in *Zhong Hua Yi Dian*

Topic	Keywords
Obesity	Fei (肥), Pang (胖), Rou (肉)
Cassiae semen	Jue ming zi (决明子), Yang ming (羊明), Hai tong zi (還瞳子), Ma ti zi (馬蹄子)
Camellia sinensis	Yuan cha (元茶,) Ku cai (苦菜), Ming (茗), Cha ye (茶葉), Chuan (荈), Jia (檟)
Flos Sophora	Huai mi (槐米), Huai hua (槐花)

The complete book ZGBCQS is the largest collection of Materia medica texts in CHM and contains 740 complete or partial books with 2,027 titles in print form (May et al., 2012). It

provides solid resources for cross-referencing and thus enabled a thorough study of the herbs in terms of their original sources and historical evolutions, properties, actions and indications.

4.1.2 Data selection

The boundary timeline between classical and modern CM history was identified as 1950 so only the texts published before 1950 in China were considered for inclusion (May et al., 2014). Any texts related to the properties, actions or indications of the three herbs were included for the review. If a herb was listed as an ingredient of a formula without mention of its individual properties, actions or indications, it was then excluded from the review.

4.1.3 Data extraction

The electronic results extracted from ZHYD were exported to Excel files. The search results extracted from the ZGBCQS collection were then manually copied from the classical books. These two sets of data were cross-checked with each other and any duplicated data, if any, were removed. Textual data extracted from the classical books included specific details concerning classical book titles, authors, dynasties of publication, the herbal names and their properties, actions and indications. The screening and extraction of this data was performed by reviewer 1 (HY) and doubled-checked by reviewer 2 (AY). Any disagreements between these two reviewers were resolved either through mutual discussion or via the third party (GL).

4.1.4 Data analysis

The extracted data were re-organised in chronological order according to the year of publication of the identified books and all entries for each herb were assigned to three different spreadsheets in order to map out their properties, actions and indications. After the removal of irrelevant data, such as harvest seasons and cooking methods, the contents of the spreadsheets

were translated into English by researcher 1 (HY) and checked by researcher 2 (AY) for analysis of the properties, actions and indications of each herb.

4.2 Methods for Phase IIa: Reviews of modern literature

Comprehensive reviews of modern literature were conducted in this phase in order to understand the phytochemistry, pharmacology, and toxicology of the herbal ingredients in the formula RCM-104. The herbs: Jue ming zi (JMZ, Cassiae Semen), Lu cha ye (LCY, Green tea, Camellia Sinensis leaf), and Huai hua (HH, Sophora Flos) were examined in different forms such as single raw herbs, powders, granules and chemical compound extracts. CHM formulae consisting of any of these three herbs were also investigated using the same method. Figure 4.3 shows the methods of the modern literature review. The findings are reported in Chapter 6.

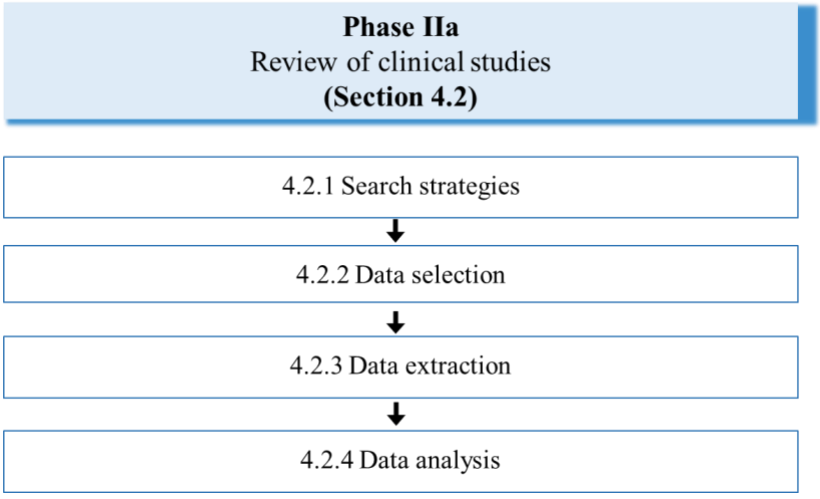


Figure 4.3: Methods for modern literature review

4.2.1 Search strategies

Comprehensive searches were performed on seven English databases and three Chinese databases for publications on original experiments related to phytochemistry, pharmacology, and toxicology of the herbs from their earliest available records up to 30 April 2020. The list of databases searched is provided in Table 4.2.

Table 4.2: Databases searched for modern literature review

English database	Chinese database
1. PubMed 2. Scopus 3. Science Direct 4. ProQuest 5. Cochrane Central Register of Controlled Trials 6. Cumulative Index to Nursing and Allied Health Literature (CINAHL) 7. Allied and Complementary Medicine Database (AMED)	1. China National Knowledge Infrastructure (CNKI) (http://www.cnki.net) 2. Wanfangdata (http://www.wanfangdata.com.cn/) 3. Chinese Biomedical Literature Database (CBM) (http://www.sinomed.ac.cn/)

The literature search of each herb was performed independently. The keywords used for the chosen herbs included the Chinese names (決明子, 綠茶, 槐花), Chinese pinyin (Jue ming zi, Lu cha, Huan hua), English names (Cassia seed, green tea and Sophora flower) and pharmaceutical names (Cassiae semen, Camellia Sinensis and Sophorae Flos). The reference lists of the review articles for potential studies were manually searched. The results were exported into an EndNote library. Duplicated data were identified and removed automatically or manually from the EndNote library.

4.2.2 Selection criteria

In this research, original experimental studies, including clinical trial, *in vivo*, *in vitro* or *in silico* studies, were included for JMZ and HH, Due to recent publications of the comprehensive reviews of LCY (green tea) (Bansal et al., 2013; Steinmann et al., 2013; Suzuki et al., 2016), the results of its pharmacological activities included in this research were based on the current published review papers instead of the original experimental studies. All the searched articles were screened and evaluated according to inclusion and exclusion criteria as follows:

The searched articles were considered for inclusion if they were:

1 published in English or in Chinese with full text availability;

2 an original experimental study, including clinical trial, *in vivo*, *in vitro* or *in silico* studies for Jue ming zi and Huai hua;

3 a review article for Lu cha ye;

4 related to the phytochemistry, pharmacology, and toxicology of any of the three herbs;

5 investigating any of the three herbs of the same species and plant part as described in the *Pharmacopoeia of the People's Republic of China* (PPRC) (Chinese Pharmacopoeia Commission, 2015), and

6 investigating the single herb or the CHM formula comprising the herb in any form (eg. decoction, granule, pill or capsule) or the chemical compounds of any of the three herbs.

The searched articles were excluded from the review if they were:

1 published in a language other than English or Chinese;

2 the full text of the study was not available for review;

3 they were in a form of a review, a report or a protocol;

4 not related to the phytochemistry, pharmacology, and toxicology of any of the three herbs;

5 not investigating any of the three herbs of same species or plant part as described in *Pharmacopoeia of the People's Republic of China* (PPRC) (Chinese Pharmacopoeia Commission, 2015).

4.2.3 Data extraction

After the included studies were screened, the relevant data were extracted from the screened articles and assigned to a predesigned Excel template by reviewer 1 (HY). If the herb was listed as an ingredient of a formula without reference to its individual properties, actions or indications, it was then excluded. The extracted data included: pharmacological effects, study types, test substance, characteristics of the sample, dosage, interventions, duration, primary results, and references. The data were then checked by reviewer 2 (GL). Discussion with the third party (AY) was performed if any discrepancies occurred between the two reviewers.

4.2.4 Data analysis

Characteristics of the included pharmacological studies of each herb and its possible mechanisms of action were descriptively summarised.

4.3 Methods for Phase IIb: Identification of targets and chemical compounds

4.3.1 Identification of anti-obesity protein targets

The possible anti-obesity targets were identified from two types of resources:

1) literature search from the 7 English databases listed in Table 4.2. Keywords used were 'overweight', 'obesity', 'appetite' and 'anti-obesity'.

2) an online database search through Herb Ingredients' Targets (HIT) database (Ye et al., 2011), Traditional Chinese Medicine Systems Pharmacology database (TCMSP) (Ru et al., 2014), the Protein Data Bank (PDB) (Berman et al., 2000) and DrugBank (Wishart et al., 2008; 2018). Keywords used were 'overweight' and 'obesity'.

4.3.2 Identification of anti-obesity agents

Drugs known to be used for weight management were searched using the online database Monthly Index of Medical Specialities (MIMS, 2019) for drugs available in Australia, and DrugBank (Wishart et al., 2018) for drugs available in US, Canada and the EU. Keywords used for search were overweight and obesity. The identified anti-obesity agents were used as control ligands in Phase III.

4.3.3 Identification of herbal chemical compounds

The chemical compounds of the herbs were identified through the following resources:

- the included studies of this research as described in Section 4.2;

- textbooks: *Chinese Herbal Medicine: Materia Medica* (Bensky et al., 2004) and *Chinese Medical Herbology and Pharmacology* (Chen & Chen, 2004);
- an official compendium of drugs: *The Pharmacopoeia of the People's Republic of China* (PPRC) (Chinese Pharmacopoeia Commission, 2015);
- an Encyclopaedia: *Encyclopaedia of Traditional Chinese Medicines: Molecular Structures, Pharmacological Activities, Natural Sources and Applications* (Zhou et al., 2012) and
- a database of systems pharmacology for drug discovery from herbal medicines: *Traditional Chinese Medicine Systems Pharmacology Database* (TCMSP) (Ru et al., 2014).

Information including chemical formula, molecular weight, and compound identifier of each the herbal compounds was extracted to an Excel file from an open chemistry database PubChem (Kim et al., 2021). 3D structure of each compound in SDF (Spatial Data File) format was downloaded from PubChem in preparation for the docking process in Phase III.

4.4 Methods for Phase III: Computational analysis

Computational molecular modelling, docking and analysing approaches were used in this phase to understand the anti-obesiy pathways of the individual herbs of RCM-104, evaluate the synergistic effects of the individual herbs of RCM-104, identifiy the active herbal compounds of RCM-104 which could have potential therapeutic effects on weight management and understand the interactions of the identified compounds with the relevant anti-obesity targets. The process of this phase is illustrated in Figure 4.4 and the findings are presented in Chapters 8 and 9.

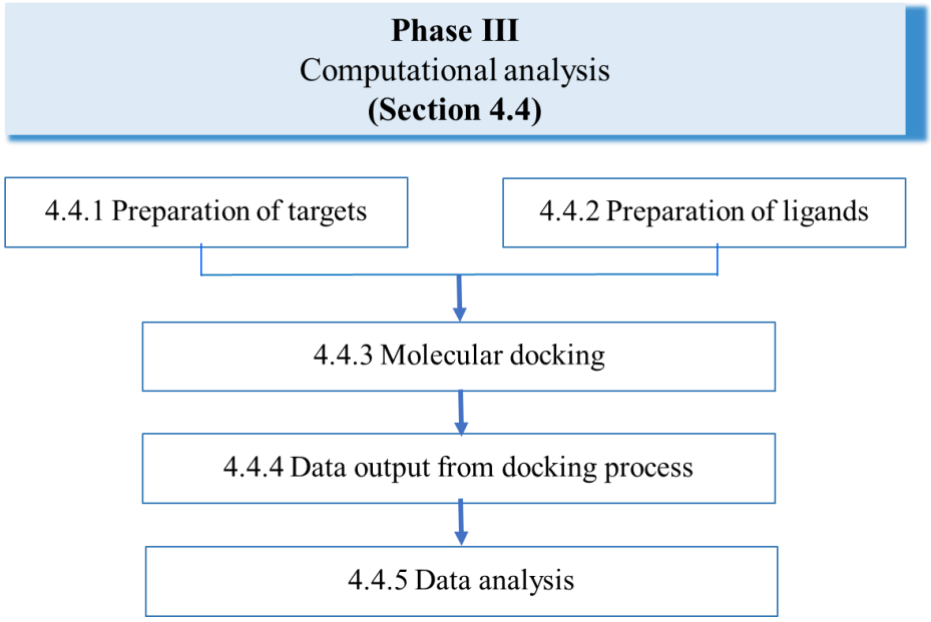


Figure 4.4: Methods for computational analysis

4.4.1 Preparation of protein targets

After the anti-obesity protein targets were identified in Phase IIb, their protein structures were chosen using the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) for computational analysis. The identified receptors were generally in complex form with either agonist or antagonist ligands or some other small ligands. The computer software Visual Molecular Dynamics (VMD) (Universtiy of Illnois at Urbana-champaign, 2021) was used to prepare the protein targets by removing ligands, waters and other unwanted components from the protein. If there were multiple chains in the structure, then the appropriate chain/s was/were selected for molecular docking. The protein files created from VMD, in PDB format, were loaded into the docking Graphical User Interface (GUI) frontend Python Prescription Virtual Screening Tool (PyRx) version 0.8 (the Scripps Research Institute, La Jolla, CA, USA) (Dallakyan, 2020) and were then converted to 'Protein Data Bank, Partial Charge (Q), & Atom Type (T)' (pdbqt) format in preparation for docking.

4.4.2 Preparation of ligands

The chemical structures of the identified herbal compound and anti-obesity drugs/agents identified in Phase IIb were downloaded from the PubChem database (National Centre for Biotechnology Information, National Library of Medicine, Bethesda, MD, USA) (NIH, 2021) as Spatial Data File (SDF) files. The SDF files were translated to PDB format with the online translator 'the simplified molecular input line entry system' (SMILES) (*Online SMILES Translator and Structure File Generator* (National Cancer Institute, 2019). The PDB files were then converted to pdbqt format using GUI and used as ligands for docking.

4.4.3 Molecular docking

Molecular docking methods typically make use of an energy-based scoring function in order to identify the most favourable energetic ligand conformation when we are bound to the target (Thomsen & Christensen, 2006).

Molecular docking of this project was performed using AutoDock Vina version 1.1.2 (The Scripps Research Institute, La Jolla, CA, USA) (Trott & Olson, 2017). GUI frontend PyRx version 0.8 (the Scripps Research Institute, La Jolla, CA, USA) (Dallakyan, 2020) was used to generate docking parameter input files. Protonation states for titratable sidechains of the protein were based on those assigned using OpenBabel (OpenEye Scientific Software, Santa Fe, NM, USA) at pH 7. Gasteiger charges were applied to protein and ligands. Docking boxes were set using the 'maximise' option in PyRx around the protein receptor in order to enable 'blind' docking in which the entire protein surface and accessible interior pockets were made available for the potential binding of ligands.

All dockings were performed with the default exhaustiveness value of 8. The dockings were semi-rigid, with full torsional flexibility allowed for the ligands, while the protein receptor

structures were kept fixed. AutoDock Vina calculations were performed using the Intel Xeon Sandy Bridge 2.6 GHz Broadwell nodes of the 'Raijin' high-performance computing cluster housed at the National Computational Infrastructure (NCI).

Two sets of output data, namely—score of binding affinity (BA) and output model file—were generated through the molecular docking process in this project.

4.4.4 Binding affinity analysis

Binding affinity (BA) indicates the strength of the interaction or the binding between a chemical compound (ligand) and its target (Thafar et al., 2019). The score of BA, prediction reflects the strength of binding between ligand and protein interaction (Abel et al., 2018), with a greater negative numerical value indicating a firmer binding. The BA score outputs from molecular docking process were exported into an Excel file for analysis. The data were then separated into 4 different spreadsheets: one for each of the herbs in RCM-104 plus one for the controls. In each of the spreadsheets, the protein structures were ranked according to their total score of predicted BA in order to identify the most prevalently bound targets. After the putative targets were identified for each herb, the BA analysis was carried out on the individual compounds of the identified target structures. The aims of the BA analysis were to predict the anti-obesity pathways of the individual herbs of RCM-104 and to identify the roles of different herbal compounds.

4.4.5 Network analysis

Cystoscope (Version 3.8.2.), an open-source software platform for visualising complex networks (Shannon et al., 2003) was used to create the pharmacological networks in this project.

A graphic network with all the anti-obesity targets in this project and the herbal compounds with BA scores lower than a cut-off value (this value was to be determined after the completion

of BA analysis), was created for each of the individual herbs of RCM-104. The BA cut-off value, affecting the complexity of the network (total number of nodes and edges), was determined after the completion of the BA analysis.

Based on the information provided by the network of individual herbs, a few anti-obesity targets were selected for further study. A pharmacological network detailing the interactions between formula RCM 104, its herbs and chemical compounds, and the selected targets was established.

4.4.6 Ligand-protein interaction analysis

The output data from the docking process also consists of a pdpqt file for each pair of ligand-protein pair. This file provides information for the models, usually the 10 of models of top BA scores, on both the binding location and the orientation of the ligand of the specific binding mode (Norgan et al., 2011).

In order to understand the active binding sites and key residues of the selected targets and herbal compounds, software Maestro (Schrodinger, 2021) from Schrodinger was employed to display a visual representation of the 3-dimension (3D) structures of the ligand-target complex and to plot the 2-dimension (2D) ligand–residue diagrams. Known active binding sites and the key active binding site residues of the structures were obtained in the RCSB Protein Data Bank database as part of this binding site analysis. The structures of the selected herbal compounds were descriptively summarised and compared with the known ligands of the targets.

4.5 Discussions

This chapter has reported the specific methods used in each phase of this research project. The structure of the entire project is presented in Figure 4.5, illustrating the methodologies chosen

to address the objectives, procedures, expected results and the correlations among different phases.

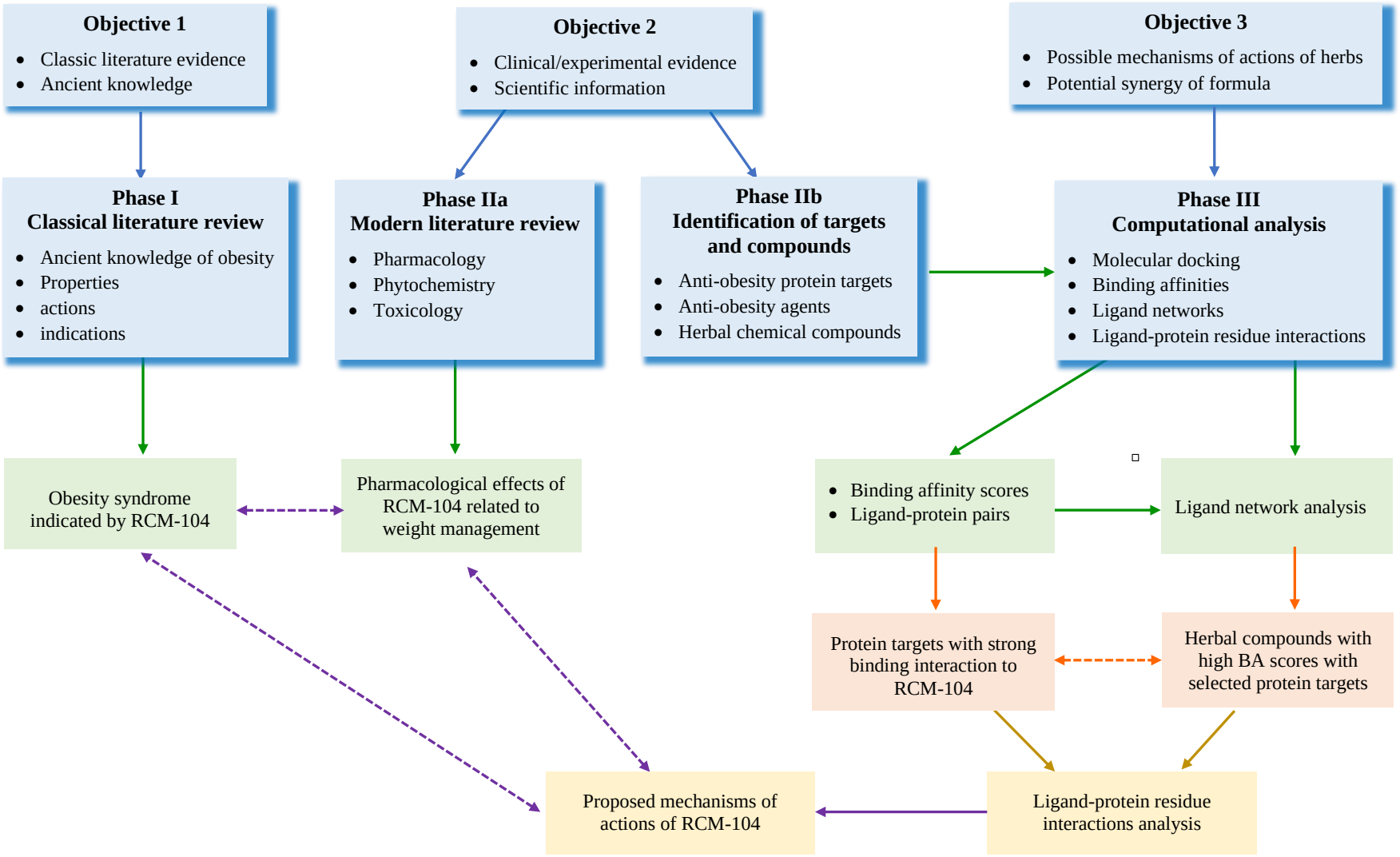


Figure 4.5: Schematic diagram of the general methodology of this project

The classical literature review in Phase 1 adopted a data-mining and text-mining approach to address Objective 1 of this research project—to acquire classical literature evidence and ancient knowledge.

The data-mining work in Phase I yielded information on the properties, actions and indications of the individual ingredients of formula RCM-104. *Encyclopaedia of Traditional Chinese Medicine CD-ROM* (China Association of Chinese Medicine, 2015), the most enormous electronic database with classical texts spanning many dynasties, enables access to the ocean of classical Chinese medical literature concerning the herbal components of RCM-104. This project also included a text-mining approach to access the traditional evidence from pre-modern CM literature by using the hardcopy of *the Complete Collection of Traditional Texts on Chinese Materia Medica* (ZGBCQS) (China Association For Culture Studies, 1999), the largest published full-text collection of traditional CM. Apart from providing information that is not available from electronic searching, it also served as a cross-referencing tool for verifying the information retrieved from the electronic data-mining search.

The information yielded in Phase I provided preconditions for deducing the actions of formula RCM-104 and valuable data for cross-reference with research results from later phases.

The modern literature review in Phase IIa addressed Objective 2 of this research project—to acquire clinical/experimental evidence and ancient and scientific information about the formula RCM-104. A data-mining approach was employed to perform literature search in 7 English and 3 Chinese online databases and to yield information on phytochemistry, pharmacology, and toxicology of the individual ingredients of formula RCM-104. The literature search of each herbal ingredient of formula RCM-104 was performed independently. Such methodology conduced to a transparent, comprehensive and structured approach to searching, selecting and synthesising the literature. The selection criteria were the same for all the three herbs, except

that only original experimental studies were included in search for JMZ and HH while only review papers were included in search for LCY (green tea). The variation in review method was because the phytochemistry, pharmacology, and toxicology of green tea and/or its major catechin EGCG had been reported extensively in review publications (Steinmann et al., 2013) and there would be no additional value to review the original experimental studies.

The information yielded in Phase IIa, especially the pharmacological effect of the individual ingredients of formula RCM-104 on weight-loss, provided valuable data for cross-reference with research results from later phases.

Also addressing Objective 2 of this research project, the modern literature review in Phase IIb focused on identifying the anti-obesity protein targets, anti-obesity agents and herbal chemical compounds of the individual ingredients of formula RCM-104, providing input data required for the molecular docking process. The literature search was carried out in 7 English electronic databases, and the information search was carried out in 5 online databases, 2 textbooks, 1 official compendium and 1 encyclopaedia.

Phase IIb played a crucial role in the research project because the docking output and the subsequent analyses in Phase III relied on the accuracy and completeness of the data identified in this phase.

The computational analysis in Phase III addressed Objective 3 of this research project—to find out the possible mechanisms of actions of the individual ingredients of formula RCM-104 and the potential synergy of formula RCM-104.

Molecular docking methods typically make use of an energy-based scoring function to identify the most favourable energetic ligand conformation when they are bound to the target. Molecular docking of this project was performed in AutoDock Vina between each of the

identified protein targets and ligands. Schematic 2D protein-ligand interaction diagrams presented in this project was useful for visualising the binding interactions between ligands and protein targets and provided important clues about their roles and functions.

At the end of Phase III, mechanisms of actions of RCM-104 may be proposed based on results of computational analysis and correlations among the results of phase I, IIa and III may be drawn. This information would also contribute to future experimental studies by enabling predicted residues to be mutated and tested for their impact on ligand binding using bioactivity assays.

Chapter 5 Results I – Review of classical literature

The classical literature review in Phase I adopted a data-mining and text-mining approach to acquire classical literature evidence and ancient knowledge. The review included a manual search in Zhong Guo Ben Cao Quan Shu (ZGBCQS, the Complete Collection of Traditional Texts on Chinese Materia Medica (China Association for Culture Studies, 1999) and an electronic database search in Zhong Hua Yi Dian (ZHYD, Encyclopaedia of Traditional Chinese Medicine CD-ROM) (China Association of Chinese Medicine, 2015).

The manual search and electronic database search were completed in October 2016 and September 2018 respectively. Details of the search results on Jue ming zi (JMZ, Cassiae Semen), Lu cha ye (LCY, green tea, unfermented Camellia Sinensis leaf) and Huai hua (HH, Flos Sophorae) are reported below. The material in this chapter has formed the basis of publication 2.

5.1 Jue ming zi (JMZ, Cassiae Semen)

A total of 2,498 records pertaining to JMZ were initially identified from ZHYD and ZGBCQS. Among them, 89 records were related to the properties, actions and indications of JMZ: 21 records on the properties, 39 on the actions and 29 on the indications. The search and selection procedures of the included texts from the classical CM literature are illustrated in Figure 5.1.

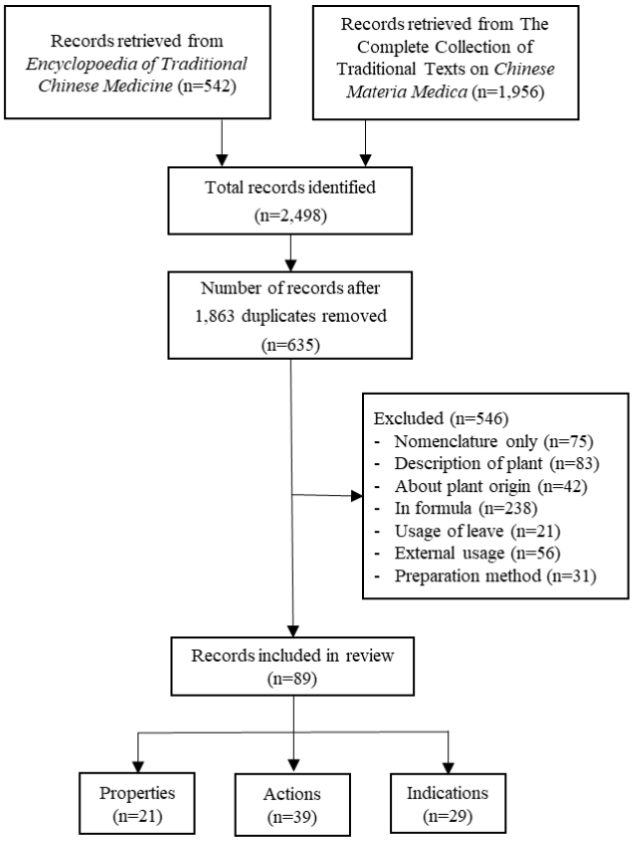


Figure 5.1: Selection process of classical literature for Jue ming zi

Details of properties, actions and indications of JMZ are shown in Table 5.1, 5.2 and 5.3 respectively.

Table 5.1: Books containing properties of Jue ming zi

No.	Classical book title	Book title in English	Author	Dynasty	Properties of Jue ming zi
1	神農本草經 *Shennong Ben Cao Jing*	Shennong's Classic of Materia Medica	佚名 Anonymous	漢朝 Han dynasty	Classified as 'upper class' herb.
2	名醫別錄 *Ming Yi Bie Lu*	The Supplementary Records of a Famous Physician	陶弘景 TAO, Hongjing	宋朝 Song dynasty	Taste is salty. Plain.
3	證類本草 *Zheng Lei Ben Cao*	Classified Materia Medica	唐慎微 TANG, Shenwei	宋朝 Song dynasty	Taste is salty. Bitter, plain. Temperature is slightly cool. Non-toxic.
4	本草蒙筌 *Ben Cao Meng Quan*	Herbal Medicine for Beginners	陳嘉謨 CHEN, Jiamo	明朝 Ming dynasty	Salty, bitter, sweet, slightly cold.

No.	Classical book title	Book title in English	Author	Dynasty	Properties of Jue ming zi
5	本草綱目 *Ben Cao Gang Mu*	Compendium of Materia Medica	李時珍 LI, Shizhen	明朝 Ming dynasty	Salty, neutral non-toxic.
6	藥性歌括四百味 *Yao Xing Ge Kuo Si Bai Wei*	Poems on the Properties of Drugs in 400 Prescriptions	龔廷賢 GONG, Tingxian	明朝 Ming dynasty	Sweet.
7	痘疹類編釋意全書 *Dou Zhen Lei Bian Shi Yi Quan Shu*	A Comprehensive Explanation of the Classified Works on Smallpox	翟良 ZHAI, Liang	明朝 Ming dynasty	Salty, sweet, neutral, cool.
8	古今醫統大全 *Gu Jin Yi Tong Da Quan*	A Classified Works Epitomised from Ancient and Modern Medical Books	徐春甫 XU, Chunfu	明朝 Ming dynasty	Salty, sweet, bitter, neutral Qi, slightly cool.
9	本草彙言 *Ben Cao Hui Yan*	Discourse on Herbal Medicine	倪朱謨 NI, Zhumo	明朝 Ming dynasty	Enters the Liver and the Kidney meridians.
10	醫宗必讀 *Yi Zong Bi Du*	Required Reading from the Masters of Medicine	李中梓 LI, Zhongzi	明朝 Ming dynasty	Salty, neutral, non-toxic.
11	類證普濟本事方釋義 *Lei Zheng Pu Ji Ben Shi Fang Shi Yi*	Formulae of Universal Benefit from My Practice: An Elucidation	葉天士 YE, Tianshi	清朝 Qing dynasty	Enters Foot Jue Yin meridian.
12	寶命真詮 *Bao Ming Zhen Quan*	A Reliable Interpretation of Precious Life Medicine	吳楚 WU, Chu	清朝 Qing dynasty	Salty, non-toxic, enter Pericardium meridian.
13	要藥分劑補正 *Yao Yao Fen Ji Bu Zheng*	A Revision and Update to ‘to ‘Categorised Essential Drugs’	劉鶚 LIU e	清朝 Qing dynasty	Salty, neutral, non-toxic.
14	顧松園醫鏡 *Gu Song Yuan Yi Jing*	Medical Reference Resources Compiled by Gu Songyuan	顧靖遠 GU, Jingyuan	清朝 Qing dynasty	Enters the Liver and the Kidney meridians.
15	本草從新 *Ben Cao Cong Xin*	The Completely Revised Materia Medica	吳儀洛 WU, Yiluo	清朝 Qing dynasty	Sweet, bitter, salty, neutral.
16	本草求真 *Ben Cao Qiu Zhen*	The Herbal Foundation for Dependability	黃宮繡 HUANG, Gongxiu	清朝 Qing dynasty	Enters the Liver meridian.

No.	Classical book title	Book title in English	Author	Dynasty	Properties of Jue ming zi
17	輔孝兩書 *Fu Xiao Liang Shu*	Two Books on Assisting Filial Piety	吳畹菴 WU, Wan'an	清朝 Qing dynasty	Salty, sweet, slightly cold, non-toxic. Enters the Liver meridian.
18	醫鈔類編 *Yi Chao Lei Bian*	Compendium of Medical Knowledge	翁藻 WENG, Zao	清朝 Qing dynasty	Salty, sweet, slightly cold, non-toxic. Enters the Liver meridian.
19	本草述鈎元 *Ben Cao Shu Gou Yuan*	Identifying the Basis of 'Herbal Medicine Explanation'	楊時泰 YANG, Shitai	清朝 Qing dynasty	Jue ming zi gets the Yin Qi of Water and Earth.
20	本草備要 *Ben Cao Bei Yao*	Essentials of Materia Medica	汪昂 WANG, Ang	清朝 Qing dynasty	Sweet, bitter, salty, plain, enters the Liver meridian.
21	漢藥良劣鑑別法 *Han Yao Liang Lie Jian Bie Fa*	Distinguishing the Benefits and Disadvantages of Chinese Drugs	一色直太郎 Isshki, Naotarō	大正 5 年 1916	Slightly cool, non-toxic

Table 5.2: Books containing actions of Jue ming zi

No.	Classic book title	Book title in English	Author	Dynasty	Actions of Jue ming zi
1	神農本草經 *Shennong Ben Cao Jing*	Shennong's Classic of Materia Medica	佚名 Anonymous	漢朝 Han dynasty	Tonifies the essences. In case of persistent use, reduces body weight and delays senility.
2	藥性賦 *Yao Xing Fu*	Poems on the Properties of Drugs	張元素, 李東垣 ZHUANG, Yuansu, LI, Dongyuan	宋朝 Song dynasty	Disperses the Liver heat and wind, benefits the Liver, brightens the eyes.
3	珍珠囊補遺藥性賦 *Zhen Zhu Nang Bu Yi Yao Xing*	The Pearl Bag with Rhapsodies on the Properties of Drugs	李杲 LI, Gao	宋朝 Song dynasty	Disperses Liver heat and wind, brightens the eye.
4	玉機微義 *Yu Ji Wei Yi*	Profound Truths of General Medicine	徐用誠 XU, Yongcheng	元朝 Yuan dynasty	Nourishes Yin and Yang.
5	醫學門徑 *Yi Xue Men Jing*	Elementary Medicine	佚名 Anonymous	明朝 Ming dynasty	Harmonises the Liver; benefits the eyes.

No.	Classic book title	Book title in English	Author	Dynasty	Actions of Jue ming zi
6	普濟方 *Pu Ji Fang*	Prescriptions for Universal Relief	朱橚 ZHU, Su	明朝 Ming dynasty	Removes toxic Liver heat, harmonises the Liver.
7	衛生易簡方 *Wei Sheng Yi Jian Fang*	Simple Prescriptions for Health	胡濙 HU, Ying	明朝 Ming dynasty	Nourishes the Liver; benefits the eyes.
8	蒼生司命 *Cang Sheng Si Ming*	For the Benefit of People's Lives	虞摶 YU, Tuan	明朝 Ming dynasty	Removes the Liver heat, reduces tears, relieves pain in eyes, stops bleeding from nose.
9	本草品彙精要 *Ben Cao Pin Hui Jing Yao*	The Collected Essentials of Herbal Species	劉文泰 LIU, Wentai	明朝 Ming dynasty	Tonifies the Jing, reduces body weight by nourishing the Liver and Kidney.
10	本草綱目 *Ben Cao Gang Mu*	Compendium of Materia Medica	李時珍 LI, Shizhen	明朝 Ming dynasty	Releases wind-heat in the Liver and Gallbladder, brightens the eyes.
11	藥性歌括四百味 *Yao Xing Ge Kuo Si Bai Wei*	Poems on the Properties of Drugs in 400 Prescriptions	龔廷賢 GONG, Tingxian	明朝 Ming dynasty	Removes the Liver heat, stops bleeding from nose, reduces excessive tears.
12	明醫指掌 *Ming Yi Zhi Zhang*	An Explicit Guide to Enlightened Physicians	皇甫中 HUANGFU, Zhong	明朝 Ming dynasty	Removes the Liver heat, stops nose bleeding, reduces tears, relieves pain in eyes.
13	醫學疑問 *Yi Xue Yi Wen*	Medical Queries	傅懋光 FU, Maoguang	明朝 Ming dynasty	Clears heat and tonifies Yin.
14	古今醫統大全 *Gu Jin Yi Tong Da Quan*	A Classified Works Epitomised from Ancient and Modern Medical Books	徐春甫 XU, Chunfu	明朝 Ming dynasty	Clears cataracts, brightens the eyes, stops tearing.
15	痘疹類編釋意 *Dou Zhen Lei Bian Shi Yi*	Explanation of the Classified Works on Smallpox	翟良 ZHAI, Liang	明朝 Ming dynasty	Clears the Liver heat.
16	本草彙言 *Ben Cao Hui Yan*	Discourse on Herbal Medicine	倪朱謨 NI, Zhumo	清朝 Qing dynasty	Removes wind, disperses heat, brightens the eyes.
17	醫宗說約 *Yi Zong Shuo Yue*	An abridged Version of the Works of the Medicine Masters	蔣示吉 JIANG, Shiji	清朝 Qing dynasty	Clears Liver heat, reduces tears, stops bleeding from nose.

No.	Classic book title	Book title in English	Author	Dynasty	Actions of Jue ming zi
18	馮氏錦囊秘錄 *Feng Shi Jin Nang Mi Lu*	The Secret Records of Master Feng's Brocade Bag	馮兆張 FENG, Zhao-zhang	清朝 Qing dynasty	Removes the Liver heat, harmonises the Liver Qi, relieves eye pain, brightens the eyes.
19	神農本草經百種錄 *Shen Nong Ben Cao Jing Bai Zhong Lu*	A Selection of a Hundred Types of Herbs from Shennong's Classic of Materia Medica	徐大椿 XU, Dachun	清朝 Qing dynasty	Treats eye diseases and pain in the eyes, tonifies the Jing, reduces body weight.
20	刪補名醫方論 *Shan Bu Ming Yi Fang Lun*	An Amended Version of Comments on Famous Case	吳謙 WU, Qian	清朝 Qing dynasty	Resolves blockages and stagnation.
21	本草詩箋 *Ben Cao Shi Jian*	Poems on Materia Medica	朱鑰 ZHU, Yao	清朝 Qing dynasty	Detoxifies snake poison.
22	秘傳眼科纂要 *Mi Chuan Yan Ke Zuan Yao*	Essential Ophthalmology Transmitted in Confidence.	黃巖 HUANG, Yan	清朝 Qing dynasty	Disperses the Liver wind heat.
23	本草從新 *Ben Cao Cong Xin*	The Completely Revised Materia Medica	吳儀洛 WU, Yiluo	清朝 Qing dynasty	Disperses the Liver heat and the wind, brightens the eye.
24	法古錄 *Fa Gu Lu*	The Learning from Previous Masters of Medicine	魯永斌 LU, Yongbin	清朝 Qing dynasty	Removes wind from the head, benefits the Kidney.
25	本草求真 下编 *Ben Cao Qiu Zhen Xia Bian*	The Herbal Foundation for Dependability: Volume 2	黃宮繡 HUANG, Gongxiu	清朝 Qing dynasty	Disperses heat and wind-heat from the Liver.
26	目科捷徑 *Mu Ke Jie Jing*	A Short Cut to Ophthalmology	劉松岩 LIU, Songyan	清朝 Qing dynasty	Treats the Liver heat and eye diseases.
27	類經證治本草 *Lei Jing Zheng Zhi Ben Cao*	Classified Herbal Treatments for Various Diseases	吳鋼 WU, Gang	清朝 Qing dynasty	Removes the Liver heat, benefits the Kidney.
28	內外十三科驗方五千種 *Nei Wai Shi San Ke Yan Fang Wu Qian Zhong*	The 5,000 Empirical Prescriptions for the 13 Categories of General and Surgical Medicine	黃統 HUANG, Tong	清朝 Qing dynasty	Clears the Liver heat.
29	經驗良方大全 *Jing Yan Liang Fang Da Quan*	A Complete Collection of Superior Empirical Prescriptions	黃伯垂 HUANG, Bochui	清朝 Qing dynasty	Clears the Liver heat.

No.	Classic book title	Book title in English	Author	Dynasty	Actions of Jue ming zi
30	本草正義 *Ben Cao Zheng Yi*	The Correct Meaning of Materia Medica	張山雷 ZHANG, Shanlei	清朝 Qing dynasty	Tonifies the Kidney Yin, improves physical strength.
31	醫鈔類編 *Yi Chao Lei Bian*	Compendium of Medical Knowledge	翁藻 WENG, Zao	清朝 Qing dynasty	Clears wind and heat.
32	眼科全書 *Yan Ke Quan Shu*	A Comprehensive Book on Ophthalmology	佚名 Anonymous	清朝 Qing dynasty	Benefits the Kidney and Liver, clears heat from the Liver and Gallbladder.
33	病病集 *Bing Bing Ji*	A Commentary on Disease	佚名 Anonymous	清朝 Qing dynasty	Tonifies Kidney Yin.
34	藥性 *Yao Xing*	Drug Properties	佚名 Anonymous	清朝 Qing dynasty	Clears the Liver heat, reduces tears, stops nose bleeding.
35	簡明藥性 *Jian Ming Yao Xing*	A Concise Book on Drug Properties	佚名 Anonymous	清朝 Qing dynasty	Disperses the Liver heat.
36	本草類考 *Ben Cao Lei Kao*	Types of Herbs	佚名 Anonymous	清朝 Qing dynasty	Treats the Liver heat.
37	眼科秘本 *Yan Ke Mi Ben*	Undisclosed Edition of Ophthalmology	佚名 Anonymous	清朝 Qing dynasty	Sedates the Liver, clears the Liver wind-heat.
38	本草備要 *Ben Cao Bei Yao*	Essentials of Materia Medica	汪昂 WANG, Ang	清朝 Qing dynasty	Clears wind and heat, cures all eye diseases, tonifies the Kidney Jing.
39	本草撮要 *Ben Cao Cuo Yao*	A Synopsis of Materia Medica	陳其瑞 CHEN, Qirui	清朝 Qing dynasty	Specialised in clearing wind and heat, treats all eye diseases.

Table 5.3: Books containing indications of Jue ming zi

No.	Classic book title	Book title in English	Author	Dynasty	Indications of Jue ming zi
1	神農本草經 *Shen Nong Ben Cao Jing*	Shennong's Classic of Materia Medica	佚名 Anonymous	漢朝 Han dynasty	Evil Qi, hot skin, itchy skin, greenish lips
2	本草經集注 *Ben Cao Jing Ji Zhu*	Variorum of the Classic of Materia Medica	陶弘景 TAO, Hongjing	南朝齊梁 Nan dynasty Qi Liang	Greenish lips
3	傳信適用方 *Chuan Xin Shi Yong Fang*	Transmission of Applicable Formulae	吳彥夔 WU, Yankui	宋朝 Song dynasty	Chronic blindness
4	珍珠囊補遺藥性賦 *Zhen Zhu Nang Bu Yi Yao Xing Fu*	Pearl handbook with Supplement on Medicine properties	李杲 LI, Gao	宋朝 Yuan dynasty	Running nose
5	普濟方 *Pu Ji Fang*	Prescriptions for Universal Relief	朱橚 CHU, Su	明朝 Ming dynasty	Nosebleed, poison boils (skin abscess), different types of rashes
6	奇效良方 *Qi Xiao Liang fang*	Fine Formulae of Wonderful Efficacy	董宿 DONG, Su	明朝 Ming dynasty	Tai Yang headache
7	本草綱目 *Ben Cao Gang Mu*	Compendium of Materia Medica	李時珍 LI shizhen	明朝 Ming dynasty	Chronic blindness, redness and swollen of eyes, skin diseases, headache
8	古今醫統大全 *Gu Jin Yi Tong Da Quan*	A Classified Works Epitomised from Ancient and Modern Medical Books	徐春甫 XU Chunfu	明朝 Ming dynasty	Eye diseases
9	醫學入門 *Yi Xue Ru Men*	The Elementary Course for Medicine	李梴 LI, Cha	明朝 Ming dynasty	Cataracts
10	藥性歌括四百味 *Yao Xing Ge Kuo Si Bai Wei*	Poems on the Properties of Drugs in 400 Prescriptions	龔廷賢 GONG, Tingxian	明朝 Ming dynasty	Nosebleed, eye pain, dry eyes
11	藥症忌宜 *Yao Zheng Ji Yi*	Incompatibility and Suitability of Medicine and Diseases	陳澈 CHEN, Che	明朝 Ming dynasty	Gallbladder deficiency
12	醫宗必讀 *Yi Zong Bi Du*	Required Reading from the Masters of Medicine	李中梓 LI, Zhongzi	明清 Ming dynesry	Eye diseases

No.	Classic book title	Book title in English	Author	Dynasty	Indications of Jue ming zi
13	喻選古方試驗 Yu Xuan Gu Fang Shi Yan	Yu's Selection and Clinical Trials of Ancient Prescriptions	喻昌 YU, Chang	明清 Ming Qing	Chronic blindness
14	痘疹類編釋意全書 *Dou Zhen Lei Bian Shi Yi Quan Shu*	A Comprehensive Explanation of the Classified Works on Smallpox	翟良 ZHAI, Liang	明清 Ming Qing	Red eyes, pain in eyes, inflammation in eyes
15	本草彙言 *Ben Cao Hui Yan*	Discourse on Herbal Medicine	倪朱謨 NI, Zhumo	明清 Ming Qing	Headache, Liver deficiency, burry eyesight
16	眼科全書 *Yan Ke Quan Shu*	A Comprehensive Book on Ophthalmology	佚名 Anonymous	清朝 Qing dynasty	Eye diseases
17	神農本草經百種錄 *Shen Nong ben Cao Jing Bai Zhong Lu*	A Selection of a Hundred Types of Herbs from Shennong's Classic of Materia Medica	徐大椿 XU, Dachun	清朝 Qing dynasty	Night blindness, pain in eyes
18	經驗丹方匯編 *Jing Yan Dan Fang Hui Bian*	A Collect of Prescriptions Approved by Clinical Trials	錢峻 QIAN, Jun	清朝 Qing dynasty	Burry eyes
19	本草從新 *Ben Cao Cong Xin*	The Completely Revised Materia Medica	吳儀洛 WU, Yiluo	清朝 Qing dynasty	Night blindness, cataracts
20	瘍醫大全 *Yang Yi Da Quan*	A Complete Collection of Surgical Medicine	顧世澄 GU, Shicheng	清朝 Qing dynasty	Bleeding gum
21	法古錄 *Fa Gu Lu*	The Learning from Previous Masters of Medicine	魯永斌 LU, Yongbin	清朝 Qing dynasty	Eye diseases
22	類經證治本草 *Lei Jing Zheng Zhi Ben Cao*	Classified Herbal Treatments for Various Diseases	吳鋼 WU, Gang	清朝 Qing dynasty	Eye diseases
23	經驗良方全集 *Jing Yan Liang Fang Quan Ji*	Collected Works of Superior Empirical Prescriptions	姚俊 YAO, Jun	清朝 Qing dynasty	Skin diseases

No.	Classic book title	Book title in English	Author	Dynasty	Indications of Jue ming zi
24	外治壽世方 *Wai Zhi Shou Shi Fang*	Prescriptions to Surgical Diseases	鄒存淦 ZOU, Cungan	清朝 Qing dynasty	Wind at head
25	本草正義 *Ben Cao Zheng Yi*	The Correct Meaning of Materia Medica	張山雷 ZHANG, Shanlei	清朝 Qing dynasty	Red eyes, pain in eyes, excessive tears
26	回生集 *Hui Sheng Ji*	Life Saving Prescriptions	陳樂天 CHEN, Letian	清朝 Qing dynasty	Eye diseases
27	春腳集 *Chun Jiao Ji*	Spring's Feet─ Prescriptions that Restore Health	孟文瑞 MENG Wenrui	清朝 Qing dynasty	Eye problem caused by chicken pox
28	藥性賦 *Yao Xing Fu*	Poems on the Properties of Drugs	林闈階 LIN Weijie	清朝 Qing dynasty	Liver Heat, nosebleed, pain in eyes
29	本草撮要	A Synopsis of Materia Medica	陳其瑞 CHEN, Qirui	清朝 Qing dynasty	Eye diseases, head wind.

JMZ was first documented in the oldest classical herbal medical book in China, titled: *Shen Nong Ben Cao Jing* (SNBCJ, Shennong's Classic of Materia Medica, 200–250 B.C., Han dynasty) and was categorised as 'top grade drug' due to its rejuvenating effect and uplifting properties. *Ming Yi Bie Lu* (Supplementary Records of Famous Physicians, TAO Hongjing, 452–536, Song dynasty) and *Lei Zheng Ben Cao* (Classified Materia Medica, TANG Shenwei, 1083, Song Dynasty) were the first two books to provide information on the properties of JMZ. These properties were: slightly cool in temperature, plain, salty and bitter in taste and non-toxic. *Ben Cao Hui Yan* (Discourse on Herbal Medicine, NI Zhumo, 1624, Ming dynasty) first indicated that JMZ was associated with the Liver and the Kidney meridians.

SNBCJ was also the first classical text mentioning the actions of JMZ, which were to tonify the essence and lighten the body weight. LU Wentai explained in *Ben Cao Pin Hui Jing Yao* (The Collected Essentials of Herbal Species, 1505, Ming dynasty) that the weight management

effect of JMZ was due to its actions in nourishing the Liver and clearing Liver heat. *Ben Cao Gang Mu* (BCGM, Compendium of Materia Medica, LI Shizhen, 1578, Ming dynasty) mentioned that the actions of JMZ were to remove the Liver wind and to disperse the Liver heat. Additionally, there were another three classical texts, *Yi Xue Men Jing* (Elementary Medicine, Anonymous, Ming dynasty), *Wei Sheng Yi Jian Fang* (Simple Prescriptions for Health, HU Ying, 1368–1644, Ming dynasty) and *Feng Shi Jin Nang Mi Lu* (Secret Records of Master Feng's Brocade Bag, FENG Shaozhang, 1702, Qing dynasty), which reported on the beneficial actions of the herb on the Liver such as cooling, purging, pacifying and nourishing the Liver.

In terms of the indications, SNBCJ, *Pu Ji Fang* (Prescriptions for Universal Relief, ZHU Su, 1390, Ming dynasty) and BCGM recorded that JMZ could be used for a number of conditions, including itchy skin, rashes, poison boils, snake bite, different types of eye diseases, bleeding nose and gums, and headache. The herb was indicated for syndromes related to Liver such as Liver deficiency, Liver heat toxin, Liver fire and Liver toxin.

In summary, from the traditional CM perspective, JMZ may assist in maintaining healthy body weight by purging the Liver, improving the Liver functions and nourishing the essences.

5.2 Lu cha ye (LCY, unfermented Camellia Sinensis leaf)

A total of 82 records pertaining to Lu cha ye (LCY, Camellia Sinensis leaf) were initially identified from ZHYD and ZGBCQS. Among them, 24 records are related to the properties, actions and indications: 8 records on the properties, 9 on the actions and 7 on the indications. The search and selection procedures of the included texts from the classical CM literature are illustrated in Figure 5.2.

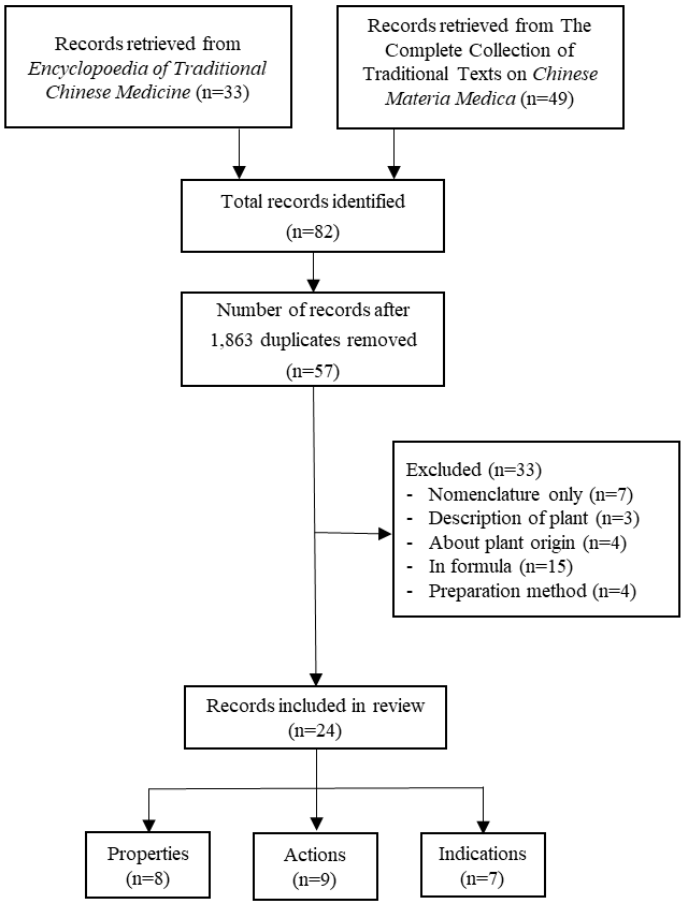


Figure 5.2: Selection process of classical literature for Lu cha ye

Details of the properties, actions and indications of LCY are shown in Table 5.4, 5.5 and 5.6 respectively.

Table 5.4: Books containing properties of Lu cha ye

No.	Classic book title	Book title in English	Author	Dynasty	Properties of Lu cha ye
1	神農本草經 *Shen Nong Ben Cao Jing*	Shennong's Classic of Materia Medica	佚名 Anonymous	漢朝 Han dynasty	Bitter taste, cold, classified as 'upper class' herb.
2	本草綱目 *Ben Cao Gang Mu*	Compendium of Materia Medica	李時珍 Li, Shizhen	明朝 Ming dynasty	Cold.
3	醫學統旨 *Yi Xue Tong Zhi*	Comprehensive Directives for Medical Studies	葉文齡 YE, Wenling	明朝 Ming dynasty	Slightly cold, sweat-bitter taste, non-toxic. Enters both the pericardium and the Liver meridians.

No.	Classic book title	Book title in English	Author	Dynasty	Properties of Lu cha ye
4	壽世青編 *Shou Shi Qing Bian*	Articles on Health Maintenance	李中梓 LI, Zhongzi	明朝 Ming dynasty	Bitter taste, refreshing.
5	類經證治本草 *Lei Jing Zheng Zhi Ben Cao*	Classified Herbal Treatments for Various Diseases	吳鋼 WU, Gang	清朝 Qing dynasty	Bitter taste, cold.
6	簡明藥性 *Jian Ming Yao Xing*	A Concise Book on Drug Properties	佚名 Anonymous	清朝 Qing dynasty	Bitter taste, cold.
7	病診必讀 *Bing Zhen Bi Du*	Required Readings on Disease Diagnosis	佚名 Anonymous	清朝 Qing dynasty	Bitter taste. Enters the Lung and Heart meridians.
8	醫鈔類編 *Yi Chao Lei Bian*	Compendium of Medical Knowledge	翁藻 WENG, Zao	清朝 Qing dynasty	Bitter taste, cold.

Table 5.5: Books containing actions of Lu cha ye

No.	Classic book title	Book title in English	Author	Dynasty	Actions of Lu cha ye
1	神農本草經 *Shen Nong Ben Cao Jing*	Shennong's Classic of Materia Medica	佚名 Anonymous	漢朝 Han dynasty	Calms the mind, enhances vital energy, increases alertness, reduces sleep time, reduces body weight, slows down ageing.
2	本草綱目 *Ben Cao Gang Mu*	Compendium of Materia Medica	李時珍 LI, Shizhen	明朝 Ming dynasty	Reduces pathogenic fire, purges the Gallbladder, reduces damp-heat when being decocted with other herbs, decreases internal heat, relieves the toxins in both food and wine, refreshes the mind. Being not drowsy.
3	痰火點雪 *Tan Huo Dian Xue*	Solution for Phlegm-fire	龔居中 GONG, Juzhong	明朝 Ming dynasty	Reduces pathogenic fire.

No.	Classic book title	Book title in English	Author	Dynasty	Actions of Lu cha ye
4	醫學統旨 *Yi Xue Tong Zhi*	Comprehensive Directives for Medical Studies	葉文齡 YE, Wenling	明朝 Ming dynasty	Treats phlegm heat and polydipsia, lowers abnormally arising Qi, assists digestion, clears dandruff, increases urination, allows people to require less sleeping time. In the case of over-eating, tea enables loss of weight and body fat.
6	壽世青編 *Shou Shi Qing Bian*	Articles on Health Maintenance	李中梓 LI, Zhongzi	明朝 Ming dynasty	Relieves poison from the nature, and clears heat caused by the five pungent spices.
7	類經證治本草 *Lei Jing Zheng Zhi Ben Cao*	Classified Herbal Treatments for Various Diseases	吳鋼 WU, Gang	清朝 Qing dynasty	Improves mood, promotes urination, improves digestion, resolves phlegm-heat, clears the head and eyes, removes toxicity from alcohol, greasy food and roasted food, eliminates fat and cools the Stomach.
8	病診必讀 *Bing Zhen Bi Du*	Required Readings on Disease Diagnosis	佚名 Anonymous	清朝 Qing dynasty	Resolves phlegm, heat and thirst, clears the heart.
9	醫鈔類編 *Yi Chao Lei Bian*	Compendium of Medical Knowledge	翁藻 WENG, Zao	清朝 Qing dynasty	Resolves issues caused by excess food accumulated in digestive system.

Table 5.6: Books containing indications of Lu cha ye

No.	Classic book title	Book title in English	Author	Dynasty	Indications of Lu cha ye
1	神農本草經 *Shen Nong Ben Cao Jing*	*Shennong's Classic of Materia Medica*	佚名 Anonymous	漢朝 Han dynasty	Evil Qi in internal organs, poor appetite, numbness of stomach.
2	本草綱目 *Ben Cao Gang Mu*	*Compendium of Materia Medica*	李時珍 LI, Shizhen	明朝 Ming dynasty	Excessive fire of the Heart, Lung, Spleen and Stomach.
3	類經證治本草 *Lei jing zheng zhi ben cao*	*Classified Herbal Treatments for Various Diseases*	吳鋼 WU, Gang	清朝 Qing dynasty	Dysentery characterised by blood and white mucous in stools.
4	醫學統旨 *Yi Xue Tong Zhi*	*Comprehensive Directives for Medical Studies*	葉文齡 YE, Wenling	明朝 Ming dynasty	Lethargic, excessive thirst, muddle-headed stroke patients, excessive sleep.
5	病診必讀 *Bing Zhen Bi Du*	*Required Reading on Disease Diagnosis*	佚名 Anonymous	清朝 Qing dynasty	Acute headache, flaccid carbuncle.
6	醫鈔類編 *Yi Chao Lei Bian*	*Compendium of Medical Knowledge*	翁藻 WENG, Zao	清朝 Qing dynasty	Indigestion, foggy head caused by heat, lethargy and drunkenness.
7	本草備要 *Ben Cao Bei Yao*	Essentials of Materia Medica	汪昂 WANG, Ang	清朝 Qing dynasty	Greasiness of food, inflammations and toxins, adipose.

LCY was first documented in the oldest classical herbal medical book in China titled: *Shen Nong Ben Cao Jing* (SNBCJ, Shennong's Classic of Materia Medica, 200–250 B.C.E., Han dynasty). The plant itself was named as 'tea tree' and the leaf was named as 'tea leaf' in SNBCJ. The plant is an evergreen bush which survives in extreme cold weather. The classical SNBCJ states that the plant is cold in temperature and bitter in taste. The leaves are normally harvested during March and are dried in shaded areas in preparation for consumption. CY is prescribed when evil Qi (xié qì) invades the Stomach causing indigestion and bloating. CY is able to soothe the nerves, enhance vital energy, enhance alertness, reduce sleeping hours, assist with weight-loss and slow down the ageing process.

According to *Ben Cao Gan Mu* (BCGM, *Compendium of Materia Medica*, Li Shizhen, 1596, Ming dynasty), LCY is cold in nature, and it can be used to reduce pathogenic fire in the body and purge the Gallbladder. When being decocted with other herbs, it is able to reduce damp-heat.

In summary, from the CM perspective, LCY may assist in maintaining a healthy body weight by burning the fat, purging the Gallbladder and reducing the damp-heat and pathogenic fire.

5.3 Huai hua (HH, Sophorae Flos)

A total of 968 records for the herb Huai hua (HH) were initially identified from ZHYD and ZGBCQS. Among them, 85 records were related to the properties, actions and indications including 24 records on the properties, 19 on the actions and 30 on the indications. The search and selection procedures of the included texts from the classical CM literature are illustrated in Figure 5.3.

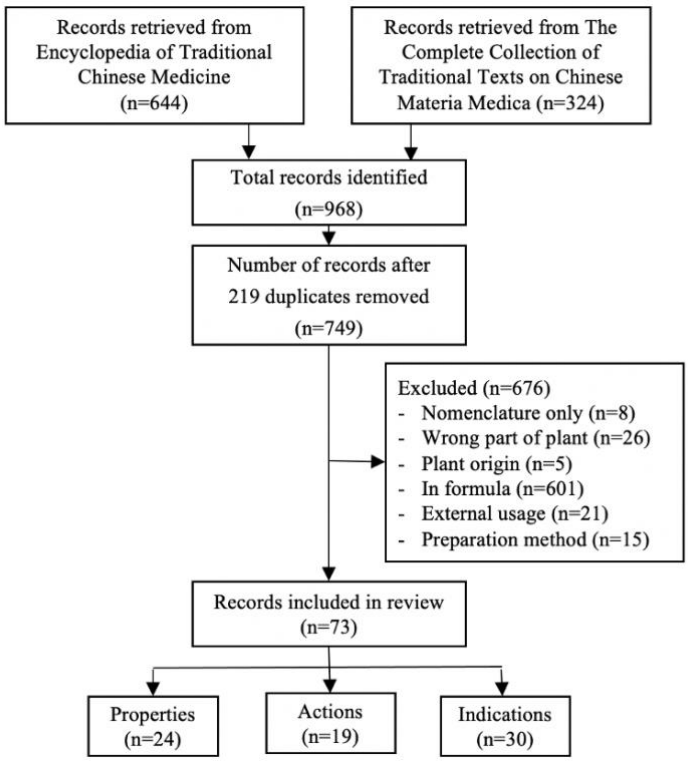


Figure 5.3: Selection process of classical literature for Huai hua

Details of the properties, actions and indications of HH are shown in Table 5.7, 5.8 and 5.9 respectively.

Table 5.7: Books containing properties of Huai hua

No.	Classic book title	Book title in English	Author	Dynasty	Properties of Huai hua
1	湯液本草 *Tang Ye Ben Cao*	Materia Medica for Decoctions	王好古 WANG, Haogu	元朝 Yuan dynasty	Bitter taste, non-toxic.
2	增廣和劑局方藥性總論 *Zeng Guang He Ji Ju Fang Yao Xing Zong Lun*	An Expanded Overview on Drug Properties of the Pharmacy Bureau Prescriptions	佚名 Anonymous	元朝 Yuan dynasty	Bitter taste, plain, non-toxic.
3	滇南本草 *Dian Nan Ben Cao*	The Materia Medica of Southern Yunnan	蘭茂 LAN, Mao	明朝 Ming dynasty	Associated with the Large Intestine meridian.
4	本草綱目 *Ben Cao Gang Mu*	Compendium of Materia Medica	李時珍 LI, Shizhen	明朝 Ming dynasty	Bitter taste, yellow in colour, cool. Medicine for Yang Ming meridian and Jue Yin blood level.
5	本草約言 *Ben Cao Yue Yan*	Concise Materia Medica	薛己 XUE, Ji	明朝 Ming dynasty	Bitter taste, plain and cold, non-toxic, Yin in nature.
6	普濟方 *Pu Ji Fang*	Prescriptions for Universal Relief	朱橚 ZHU, Su	明朝 Ming dynasty	Bitter taste, purely Yin.
7	蒼生司命 *Cang Sheng Si Ming*	For the Good of People's Lives	虞摶 YU, Tuan	明朝 Ming dynasty	Bitter taste.
8	醫學統旨 *Yi Xue Tong Zhi*	Comprehensive Directives for Medical Studies	葉文齡 YE, Wenling	明朝 Ming dynasty	Cold, bitter taste, non-toxic.
9	藥性通考 *Yao Xing Tong Kao*	General Studies on Drug Properties	太醫院 Imperial Hospital	清朝 Qing dynasty	Bitter and salty taste, cold and non-toxic. Enters the Large Intestine meridian. Anti-sialagogue.

No.	Classic book title	Book title in English	Author	Dynasty	Properties of Huai hua
10	要藥分劑 *Yao Yao Fen Ji*	Categorised Essential Drugs	沈金鰲 SHEN, Jin'ao	清朝 Qing dynasty	Cools the blood.
11	本草約編 *Ben Cao Yue Bian*	Herbal Series	王如鑒 WANG, Rujian	清朝 Qing dynasty	Thick and bitter taste, effective for blood level, purely Yin.
12	本草詩箋 *Ben Cao Shi Jian*	Poems on Materia Medica	朱鑰 ZHU, Yao	清朝 Qing dynasty	Bitter and cool. Specialised in treating blood level. Enters the Liver, the Pericardium, the Stomach, and the Large Intestine meridians.
13	要藥分劑補正 *Yao Yao Fen Ji Bu Zheng*	A Revision and Update to 'to 'Categorised Essential Drugs'	劉鶚 LIU, E	清朝 Qing dynasty	Bitter taste, plain, non-toxic.
14	寶命真詮 *Bao Ming Zhen Quan*	A Reliable Interpretation of Precious Life Medicine	吳楚 WU, Chu	清朝 Qing dynasty	Bitter taste, sour, cold, non-toxic. Enters the Liver and the Large Intestine meridians.
15	醫原 *Yi Yuan*	Fundamental Medical Solutions	石壽堂 SHI, Shoutang	清朝 Qing dynasty	Cool and dry.
16	醫學切要 *Yi Xue Qie Yao*	Medical Essentials	王錫鑫 WANG Xixin	清朝 Qing dynasty	Cold, bitter. Enters the Heart meridian.
17	類經證治本草 *Lei Jing Zheng Zhi Ben Cao*	Classified Herbal Treatments for Various Diseases	吳鋼 WU, Gang	清朝 Qing dynasty	Bitter and cool. Enters the Liver and Large Intestine blood level.
18	簡明藥性 *Jian Ming Yao Xing*	A Concise Book on Drug Properties	佚名 Anonymous	清朝 Qing dynasty	Bitter and cold.
19	醫會元要 *Yi Hui Yuan Yao*	Mastering Medical Bases	蔡貽績 CAI, Yiji	清朝 Qing dynasty	Cold, bitter. Enters the Heart meridian.
20	本草備要 *Ben Cao Bei Yao*	Essentials of Materia Medica	汪昂 WANG, Ang	清朝 Qing dynasty	Bitter and cool. Enters the Liver and Large Intestine blood level.

No.	Classic book title	Book title in English	Author	Dynasty	Properties of Huai hua
21	本草撮要 *Ben Cao Cuo Yao*	A Synopsis of Materia Medica	陳其瑞 CHEN, Qirui	清朝 Qing dynasty	Bitter and cool. Enter the hand and foot Yang Ming meridian, and foot Yue Yin meridian.
22	本草擇要綱目 *Ben Cao Ze Yao Gang Mu*	Selected Compendium of Materia Medica	蔣介繁 JIANG, Jiefan	清朝 Qing dynasty	Bitter taste, plain, non-toxic, yellow colour. Used for Yang Ming or Jue Yin blood level.
23	本草分經 *Ben Cao Fen Jing*	Materia Medica Classified by Meridian Tropism	姚瀾 YAO, Lan	清朝 Qing dynasty	Bitter and cool. Clears heat. Cool the blood.
24	藥性切用 *Yao Xing Qie Yong*	Practical Handbook on Drug Properties	徐大椿 XU, Dachun	清朝 Qing dynasty	Spirited in nature. Functions well in blood cooling and wind clearance.

Table 5.8: Books containing actions of Huai hua

No.	Classic book title	Book title in English	Author	Dynasty	Actions of Huai hua
1	珍珠囊補遺藥性賦 *Zhen Zhu Nang Bu Yi Yao Xing Fu*	The Pearl Bag with Rhapsodies on the Properties of Drugs	李杲 LI, Gao	宋朝 Song dynasty	Treats internal wind in intestines.
2	藥鑒 *Yao Jian*	Medicine Book	杜文燮 DU, Wenxie	明朝 Ming dynasty	Stops intestinal bleeding caused by internal heat.
3	本草約言 *Ben Cao Yue Yan*	Concise Materia Medica	薛己 XUE, Ji	明朝 Ming dynasty	Normalises reversed Qi flow, cools Large Intestine heat.
4	蒼生司命 *Cang Sheng Si Ming*	For the Good of People's Lives	虞摶 YU, Tuan	明朝 Ming dynasty	Cures anal fistula, intestinal wind, Large Intestine heat and dysentery.

No.	Classic book title	Book title in English	Author	Dynasty	Actions of Huai hua
5	醫學統旨 *Yi Xue Tong Zhi*	Comprehensive Directives for Medical Studies	葉文齡 YE, Wenling	明朝 Ming dynasty	Cools the heat of the Large Intestine and the skin wind-heat.
6	醫學門徑 *Yi Xue Men Jing*	Elementary Medicine	佚名 Anonymous	明朝 Ming dynasty	Stops hematochezia, clears toxin of large intestine heat. Promotes the flow of Qi and the blood.
7	本草約編 *Ben Cao Yue Bian*	Herbal Series	王如鑒 WANG, Rujian	清朝 Qing dynasty	Clears the Liver fire, moistens the skin.
8	醫談傳真 *Yi Tan Chuan Zhen*	True Knowledge of Medicine	陳定泰 CHEN, Dingtai	清朝 Qing dynasty	Clears the intestine heat, stops bleeding.
	類經證治本草 *Lei Jing Zheng Zhi Ben Cao*	Classified Herbal Treatments for Various Diseases	吳鋼 WU, Gang	清朝 Qing dynasty	Cools the blood, cures evil Qi of the five internal organs, stops uncontrolled salivation, treats excessive tearing, head and chest irritancy caused by wind heat, vertigo and staggering caused by wind.
10	得配本草 *De Pei Ben Cao*	Herbal Combinations	嚴西亭、施澹寧、洪輯庵 YAN, Xiting; SHI, Daning, HONG, Ji'an	清朝 Qing dynasty	Clears Large Intestine fire.
11	靈驗良方彙編 *Ling Yan Liang Fang Hui Bian*	A Collections of Empirical Prescriptions	田間來是庵 Tianjianlaishi'an	清朝 Qing dynasty	Cools the blood.
12	本草從新 *Ben Cao Cong Xin*	The Completely Revised Materia Medica	吳儀洛 WU, Yiluo	清朝 Qing dynasty	Clears heat, cools the blood.
13	本草求真 *Ben Cao Qiu Zhen*	The Herbal Foundation for Dependability	黃宮繡 HUANG, Gongxiu	清朝 Qing dynasty	Cools the Liver blood, clears the heat of the Large Intestine, Stomach, Liver and blood.

No.	Classic book title	Book title in English	Author	Dynasty	Actions of Huai hua
14	本草撮要 *Ben Cao Cuo Yao*	A Synopsis of Materia Medica	陳其瑞 CHEN, Qirui	清朝 Qing dynasty	Cools and detoxifies the blood, clears the wind and the phlegm, dredges the meridians, promotes blood circulation, cures hematochezia by Yang wind.
15	本草分經 *Ben Cao Fen Jing*	Materia Medica Classified by Meridian Tropism	姚瀾 YAO, Lan	清朝 Qing dynasty	Clears heat and cools the blood.
16	藥性切用 *Yao Xing Qie Yong*	Practical Handbook on Drug Properties	徐大椿 XU, Dachun	清朝 Qing dynasty	Spirited in nature. Functions well in blood cooling and wind clearance. It is a dedicated medicine for wind-heat redness, dysentery and hematochezia.
17	醫學切要 *Yi Xue Qie Yao*	Medical Essentials	王錫鑫 WANG, Xixin	清朝 Qing dynasty	Clears internal wind of intestine.
19	寶命真詮 *Bao Ming Zhen Quan*	A Reliable Interpretation of Precious Life Medicine	吳楚 WU, Chu	清朝 Qing dynasty	Improves eyesight, clears intestine, removes heat.
20	增訂通俗傷寒論 *Zeng Ding Tong Su Shang Han Lun*	An Expanded and Straightaway Treatise on Cold Damage Diseases	何廉臣 HE Lianchen	民國 Republic of China	Clears away heat located at nutrient tier, cools the blood, harmonises the meridians.

Table 5.9: Books containing indications of Huai hua

No	Classic book title	Book title in English	Author	Dynasty	Indications of Huai hua
1	孫真人海上方 *Sun Zhen Ren Hai Shang fang*	Sage Sun's Miracle Formulae	孫思邈 SUN Simiao	唐朝 Tang dynasty	Diarrhoea, anal prolapse.
2	證類本草 *Zheng Lei Ben Cao*	Classified Materia Medica	唐慎微 TANG, Shenwei	宋朝 Song dynasty	Excessive menstrual bleeding, flatulence, bleeding hemorrhoids.

No	Classic book title	Book title in English	Author	Dynasty	Indications of Huai hua
3	本草衍義 *Ben Cao Yan Yi*	Extension of the pharmacopoeia	寇宗奭 KOU, Zongshi	宋朝 Song dynasty	Flatulence, bleeding hemorrhoids.
4	仁齋直指方論 *Ren Zhai Zhi Zhi Fang Lun*	Renzhai's Comprehensive Prescriptions	楊士瀛 YANG, Shiying	宋朝 Song dynasty	Tongue bleeding, flatulence.
5	是齋百一選方 *Shi Zhai Bai Yi Xuan Fang*	Selected Formulae from the Praiseworthy Studio	王璆 WANG, qiu	宋朝 Song dynasty	Loss of voice, vomiting blood.
6	藥性賦 *Yao Xing Fu*	Poems on the Properties of Drugs	張元素、李東垣 ZHANG, Yuansu;	宋朝 Song dynasty	Bloody diarrhoea, flatulence, hemorrhoids.
7	本草約言 *Ben Cao Yue Yan*	Concise Materia Medica	薛己 XUE, Ji	明朝 Ming dynasty	Bleeding caused by intestinal wind, hematochezia, dysentery, gastric cavity pain and skin wind.
8	增廣和劑局方藥性總論 *Zeng Guang He Ji Ju Fang Yao Xing Zong Lun*	An Expanded Overview on Drug Properties of the Pharmacy Bureau Prescriptions	佚名 Anonymous	元朝 Yuan dynasty	Internal and external hemorrhoids, stomach pain, acute conjunctivitis, intestinal heat, wind and worms, skin disorder caused by wind, hematochezia and dysentery.
9	本草品彙精要 *Ben Cao Pin Hui Jing Yao*	The Collected Essentials of Herbal Species	劉文泰 LIU, Wentai	明朝 Ming dynasty	Internal and external hemorrhoids, stomach pain, acute conjunctivitis, worms in abdomen organ, skin wind, intestine wind, hematochezia and dysentery with hyperthermia therapy.
10	醫燈續焰 *Yi Deng Xu Yan*	Perpetuating the Medical Accomplishment	王紹隆 WANG, Shaolong	明朝 Ming dynasty	Tongue bleeding, tongue swollen.
11	急救良方 *Ji Jiu Liang Fang*	Remedies for emergencies	張時徹 ZHANG, Shiche	明朝 Ming dynasty	Aphonia, blood vomiting or stroke.

No	Classic book title	Book title in English	Author	Dynasty	Indications of Huai hua
12	衛生易簡方 *Wei Sheng Yi Jian Fang*	Simple Prescriptions for Health	胡濙 HU, Ying	明朝 Ming dynasty	Loss of voice, excessive menstrual bleeding, children diarrhoea and anal prolapse.
13	普濟方 *Pu Ji Fang*	Prescriptions for Universal Relief	朱橚 ZHU, Su	明朝 Ming dynasty	Tongue bleeding, skin ulcer, anus prolapse after diarrhoea. viscera worms.
14	魯府禁方 *Lu Fu Jin Fang*	Lu Family's Rare Prescriptions	龔廷賢 GONG, Tingxian	明朝 Ming dynasty	Tongue bleeding.
15	藥性歌括四百味 *Yao Xing Ge Kuo Si Bai Wei*	Poems on the Properties of Drugs in 400 Prescriptions	龔廷賢 GONG, Tingxian	明朝 Ming dynasty	Roundworm, hemorrhoids, flatulence.
16	醫便 *Yi Bian*	Handy Medicine	王三才 WANG, sancai	明朝 Ming dynasty	Tongue bleeding.
17	醫學統旨 *Yi Xue Tong Zhi*	Comprehensive Directives for Medical Studies	葉文齡 YE, Wenling	明朝 Ming dynasty	Internal and external hemorrhoids, hematochezia, spouting bleeding from anus, bloody dysentery, intestine wind, stomach pain, acute conjunctivitis, worms in abdomen organ.
18	本草便讀 *Ben Cao Ben Du*	Handy Materia Medica	張秉成 ZHANG, Bingcheng	清朝 Qing dynasty	Intestine wind, anal fistula, ulcer, skin wind and dampness of skin.
19	寶命真詮 *Bao Ming Zhen Quan*	A Reliable Interpretation of Precious Life Medicine	吳楚 WU, Chu	清朝 Qing dynasty	Hematochezia, blood dysentery, internal and external hemorrhoids.
20	醫學切要 *Yi Xue Qie Yao*	Medical Essentials	王錫鑫 WANG, Xixin	清朝 Qing dynasty	Hematochezia, anal fistula.
21	內外十三科驗方五千種 *Nei Wai Shi San Ke Yan Fang Wu Qian Zhong*	The 5,000 Empirical Prescriptions for the13 Categories of General and Surgical Medicine	黃統 HUANG, Tong	清朝 Qing dynasty	Anal fistula, intestinal wind, large intestine dysentery of heat type.

No	Classic book title	Book title in English	Author	Dynasty	Indications of Huai hua
22	鮿溪秘傳簡驗方 *Fu Xi Mi Chuan Jian Yan Fang*	Fu Xi's Esoteric Experienced Formulae	陸錦燧 LU Jinsui	清朝 Qing dynasty	Hematochezia, excessive menstrual bleeding.
23	靈驗良方彙編 *Ling Yan Liang Fang Hui bian*	A Collections of Empirical Prescriptions	田間來是庵 Tianjianlaishi'an	清朝 Qing dynasty	Hemorrhoids and intestinal wind disease.
24	大方脈 *Da Fang Mai*	Internal Medicine	鄭玉壇 ZHENG, Yutan	清朝 Qing dynasty	One-sided swelling and pain in the testis.
25	本草備要 *Ben Cao Bei Yao*	Essentials of Materia Medica	汪昂 WANG, Ang	清朝 Qing dynasty	Acute conjunctivitis caused by wind heat, dysentery, internal and external hemorrhoids, intestinal wind, vomiting blood, tongue bleeding.
26	本草從新 *Ben Cao Cong Xin*	The Completely Revised Materia Medica	吳儀洛 WU, Yiluo	清朝 Qing dynasty	Acute conjunctivitis caused by wind heat, dysentery, internal and external hemorrhoids, intestine wind, blood vomiting, hematochezia.
27	藥論 *Yao Lun*	A Discourse on Drugs	沈文彬 SHEN, Wenbin	清朝 Qing dynasty	Hematochezia, blood dysentery, hemorrhoids, internal and external hemorrhoids.
28	類經證治本草 *Lei Jing Zheng Zhi Ben Cao*	Classified Herbal Treatments for Various Diseases	吳鋼 WU, Gang	清朝 Qing dynasty	heat-toxicity, blurred vision, dizziness, dry mouth, bitter tongue, palpitation, hot sensation in the back, numbness in limbs, feeling a flushing sensation on the back, worms.
29	本草崇原 *Ben Cao Cong Yuan*	Traditional Value in Materia Medica	張志聰 ZHANG zhicong	清朝 Qing dynasty	Five kinds of kinds of haemorrhoids, heart pain, acute conjunctivitis, worms in internal organs, skin wind and heat, intestine wind, bloodletting, red-white dysentery.

No	Classic book title	Book title in English	Author	Dynasty	Indications of Huai hua
30	顧松園醫鏡 *Gu Song Yuan Yi Jing*	Gu's Medical Guide	顧靖遠 GU Jingyuan	清朝 Qing dynasty	Blood in stool, bloody diarrhea, five kinds of haemorrhoids, acute conjunctivitis

HH was first documented in the book SNBCJ and is described as having a bitter taste and cool nature. More information about HH was found in the *Classified Materia Medica* (*Zheng Lei Ben Cao*, TANG Shenwei, 1083). It emphasies that HH is harvested in the early stage of flowering. *Materia Medica for Decoctions* (*Tang Ye Ben Cao*, WANG Haogu, 1306) stated that HH has a bitter taste and is not poisonous.

HH was initially broadly classified as a herbal medicine for the Yang Ming and Jue Yin meridians in the *Compendium of Materia Medica* (*Ben Cao Gang Mu*, LI Shizhen, 1596). Later on in the Qing dynasty, four classical books, namely *Analysis of Medicine* (*Yao Yao Fen Ji*, SHEN Jinao, 1773), *Essentials of Materia Medica* (*Ben Cao Bei Yao*, WANG Ang, 1664), *A Synopsis of Materia Medica* (*Ben Cao Cuo Yao*, CHEN Qi-rui, Qing dynasty) and *Herbal Series* (*Ben Cao Yue Bian* [BCYB], Wang Ru-jian, Qing dynasty), identified HH as entering the Large Intestine (hand Yang Ming) and Liver (foot Jue Ying) meridians. According to the *Essentials of Materia Medica*, HH enters the blood level and cools the blood. In summary, HH is a bitter and cooling herb with descending function, entering the Large Intestine and Liver meridians and blood level.

Eight classical books record that the purposes of using of HH were in order to cool the Large Intestine, moisten the skin, clear the Liver fire, disperse wind-heat, dredge the meridians and collaterals, improve blood circulation, cool the blood and stop bleeding.

The indications of HH are thoroughly discussed in the classical texts. SUN Simiao mentioned in his book, *Sage Sun's Miracle Formulae* (*Sun Zhen Ren Hai Shang Fang*, Tang dynasty), that HH powder mixed with congee could treat diarrhoea in children. *Compendium of Materia Medica* (*Ben Cao Gang Mu*, LI Shizhen, 1596) recorded that HH could be used for such conditions as dysentery, coughing up blood, hematuria, bleeding hemorrhoids, stomachache, dysfunctional uterine bleeding and leukorrhea. *The Collected Essentials of Herbal Species* (*Ben Cao Pin Hui Jing Yao*, LIU Wentai, 1505) claimed that HH could treat heart pain and red eyes and kill parasites in the stomach. In addition, *Types of Herbs* (*Ben Cao Lei Kao*, Anonymous, Qing dynasty) indicated that HH was effective for the treatment of hematemesis, aphonia, dizziness, pruritus, purpura, and mange caused by wind-heat. Moreover, *Prescriptions for Universal Relief* (*Pu Ji Fang*, ZHU Su, 1390) mentioned that if HH were grounded into a powder and then applied externally, it would stop the bleeding of the tongue.

In summary, there are altogether 30 classical texts which discuss the indications of HH including hemorrhoids, hemoptysis, hematemesis, hematuria, dysfunctional uterine bleeding, leukorrhea, bleeding gums, bleeding tongue, dysentery, diarrhoea in children, parasites in the stomach, heart pain, red eyes, aphonia, dizziness and skin disorders caused by wind-heat.

According to the *Pharmacopoeia of the People's Republic of China* (Chinese Pharmacopoeia Commission, 2015), the daily dosage of HH is between 5g and 10 g.

5.4 Discussion

Phase I adopted a data-mining and text-mining approach to acquire classical literature evidence and ancient knowledge. From the electronic database *Encyclopaedia of Traditional Chinese Medicine CD-ROM* and the hardcopy publication *the Complete Collection of Traditional Texts*

on Chinese Materia Medica (ZGBCQS), a total of 186 records were identified and examined. These records yielded information on the properties, actions and indications of JMZ, LCY and HH, the individual ingredients of formula RCM-104.

JMZ was categorised as 'top grade drug' due to its rejuvenating effect and uplifting properties, which include being slightly cool, plain, salty, bitter, non-toxic and associated with the Liver and the Kidney meridians. The chief actions are nourishing the Liver and clearing Liver heat, tonifying the essence and lightening the body weight. JMZ is indicated for syndromes related to Liver such as Liver deficiency, Liver heat toxin, Liver fire and Liver toxin.

LCY is cold, bitter, non-toxic and associated with the Liver Heart meridians. It is able to soothe the nerves, enhance vital energy, enhance alertness, reduce sleeping hours, assist with weight-loss and slow down the ageing process. LCY is prescribed when evil Qi invades the Stomach causing indigestion and bloating.

HH is a bitter and cooling herb with descending function, entering the Large Intestine and Liver meridians and blood level. The chief actions of the herb include cooling the Large Intestine, clearing the Liver fire, disperse wind-heat and cooling the blood. HH can be used for such conditions as dysentery, coughing up blood, internal and external haemorrhoids, etc.

From the results generated in this phase, it can be derived that RCM-104 is appropriate for obesity syndromes that exhibit heat, fire and/or damp heat signs and symptoms relating to the Stomach-Large Intestine and/or the Liver-Gallbladder. Therefore RCM-104 is suitable for obesity patients with Stomach heat with Spleen deficiency pattern whereas patients with cold signs (such as those with Spleen and Kidney Yang Qi vacuity) may find the formula less effective.

In CM, retention of the phlegm is the type of obesity most frequently observed. In case of stagnation of the Liver Qi, it impairs the smooth flow of Qi, which gives rise to fluid retention

and results in phlegm accumulation and eventually obesity. JMZ may assist in maintaining a healthy body weight due to its actions in nourishing the Liver and clearing Liver heat.

CM considers that pathogenic factors of dampness cause phlegm accumulation and in turn fat tissue. LCY may assist in maintaining a healthy body weight by eliminating the fat, purging the Gallbladder and reducing the damp-heat and pathogenic fire.

In CM, phlegm stagnation and the eventual obesity may be due to heat in the Large Intestine and the Liver, as well as blood stasis caused by Qi flow stagnation. HH may assist in weight loss by cooling the Large Intestine, clearing the Liver fire, disperse wind-heat and cooling the blood.

At the collective level, the findings from classical literature review also tend to support the weight loss effect of RCM-104. According to CM theory, overeating can cause one of the obesity syndromes, namely Stomach heat and Spleen deficiency. Classical texts reveal that all the three herbs of RCM-104 are cool in nature; JMZ enters the Large Intestine meridian and HH enters the Stomach meridian. Therefore RCM-104 can help to prevent overeating by reducing the Stomach heat and prevent overeating.

Chapter 6 Results IIa – Reviews of modern literature

The modern literature review in Phase IIa adopted a data-mining approach to acquire clinical/experimental evidence and scientific information. Literature search was carried out in 7 English and 3 Chinese online databases, as listed in Table 4.2. to collect the data of the phytochemistry, pharmacology, and toxicology of individual ingredients of formula RCM-104. The search of each herbal ingredient of formula RCM-104 was performed independently.

The review of modern literature was completed on 30 April 2020. The pharmacological effects and potential applications on individual herbs in formula RCM-104 are presented in this chapter. The material in this chapter has formed the basis of publication 2.

6.1 Jue ming zi

A total of 2,019 papers were identified according to the search strategies provided in 4.2.1. Among them, 44 of those meeting the inclusion criteria were included for analysis. The 44 studies comprise 5 randomised controlled trials (RCT), 7 *in vivo* studies, 14 *in vitro* studies, 2 *in silico* studies and 16 studies of mixed types. The selection process of this review is illustrated in Figure 6.1.

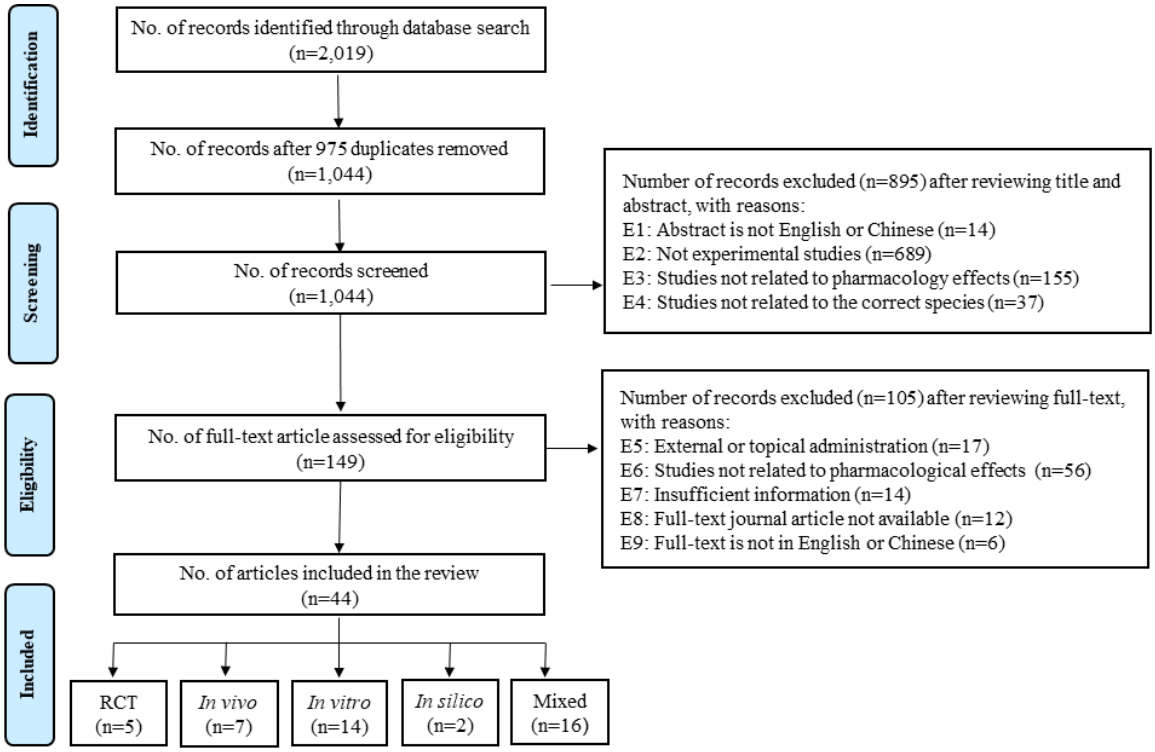


Figure 6.1: Selection process of modern literature review on Jue ming zi

Note: RCT: Randomised controlled trial.

A wide range of potential pharmacological effects were indicated for JMZ in terms of it being either a single herb, contained within CHM formula consisting of JMZ, or a chemical compound of JMZ. For clinical trials, the most commonly used dosage of JMZ in CHM decoction is 15 g per day. In animal experiments, multiple dosages ranging from 5 to 100 mg/kg/day were studied and the most common method was oral administration. The characteristics and primary findings of the included studies are summarised in Table 6.1.

Table 6.1: Characteristics of included studies of Jue ming zi

Included studies	Study type	Tested substances	Samples	Interventions	Duration	Primary results
1. Weight-loss activities						
Lenon et al., 2012	RCT	Granules of RCM-104, a CHM composing of JMZ (40%), camellia sinensis (40%) and sophora japonica (20%)	117 obese subjects aged between 18 and 60 years with a BMI ≥ 30 kg/m	Oral administration: RCM-104 or placebo capsules; 4 capsules per time, three times per day.	12 weeks	The weight, BMI and BF in RCM-104 group were reduced by 1.5 kg, 0.6 kg/m^2 and 0.9% and those in the placebo group were increased by 0.5 kg, 0.2 kg/m^2 and 0.1% respectively. There were significant differences in BW and BMI ($P < 0.05$) between the two groups. RCM-104 improved the quality of life in obese individuals.
Zhou et al., 2014	RCT	Decoction of Xin Ju Xiao Gao Fang (XJXGF), a CHM formulation comprising JMZ, rhubarb, coptis and citrus aurantium	18–60 years old, had a BMI >28 kg/m2 and < 40 kg/m2, waist circumference >85 cm (male) or >80 cm (female)	Oral administration: Treatment: 170 mL of XJXGF, twice a day. Control: 170 mL of 10% XJXGF, twice daily.	24 weeks	After 24-week treatment, among participants in the XJXGF formula group and low-dose XJXGF group, the mean +/- SE changes in the body weight were -3.58+/-0:48 and -1.91+/0.38 kg, respectively (p < 0:01). The changes in the IR-index of two groups were -2.65 +/-1:04 and -1.58+/-1.3, respectively (p < 0:05).
Au et al., 2003	*In vivo*	Chemical compound of JMZ: neotoralactone (NT). Note: NT is a derivative of toralactone.	20 female rats fed with a high nutrient diet for 35 days before the experiment.	All rats were continually fed with a high-nutrient diet. 50 mg/kg/day of NT was added for the treatment group.	30 days for experiment	The treated rats displayed an average of 10%-35% decrease in body weight gain compared with those of the untreated rats.
	In vitro	Chemical compound of JMZ: neotoralactone (NT).	HepG2 cells	30 mg/L of NT was added to the culture medium of confluent HepG2 cells, and then incubated for 24 hours. Cells without treatment were used as the control.	N/A	NT regulated APOC3 which has the function of inhibiting lipoprotein lipase and hepatic lipase and decreased the uptake of lymph chylomicrons by hepatic cells. This is considered to be a possible cause of the body weight reduction effect of NT.

Included studies	Study type	Tested substances	Samples	Interventions	Duration	Primary results
Zhuang et al., 2016	*In vivo*	Chemical compound of JMZ: obtusifolin	Three-month-old male Sprague-Dawley rats weighing 220 ±20 g	Oral application: 5 or 10 mg/kg of obtusifolin or 0.4 mg/kg of atorvastatin	4 weeks feeding period	20 mg/kg of obtusifolin significantly reversed the changes induced by hyperlipidemia in body weight, total cholesterol, triglyceride, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol.
Zhang et al., 2017	*in vivo*	Extracts of CHM formula consisting of JMZ named JM CHM and its ingredients	White adipose tissue (WAT) of rats	The explants of WAT treated with JMZ or JM CHM extracts or normal saline	N/A	JM CHM and JMZ stimulated lipolysis and reduced the size of adipocytes, possibly via the phosphorylation of HSL in cultured rat WAT.
Luo, S. et al., 2019	*In vitro*	Water extracts of CHM formula RCM-107 and its 8 individual ingredients including JMZ	Lipase from porcine pancreas (type VI-S L0382-100KU) and 4-methylumbelliferyl oleate (4-MUO 75164-25 mg)	Fluorometric based enzymatic assays, high-performance thin-layer chromatography (HPTLC) profiling	N/A	RCM-107 presented potent pancreatic lipase inhibitory activities with an IC_{50} value of 7.17 +/-0.69 μg/mL (mean +/-SD). JMZ displayed an average inhibition level of 80 % whereas orlistat (lipase inhibitor) showed a 73% inhibition of lipase.
	In silico	Selected chemical compounds of RCM-107 ingredients	N/A	Molecular docking study with protein target pancreatic lipase (1ETH)	N/A	A greater negative numerical value binding affinity indicates a firmer predicted binding in the ligand-target complex. No chemical compound of SC was selected in this projectstudy.
Yuen, Young, et al., 2020	*In silico*	50 chemical compounds of JMZ	N/A	Molecular docking study of two serotonin receptors 5-HT2C, 6BQG (an agonist-bound active conformation) and 6BQH (an antagonist-bound inactive conformation)	N/A	JMZ compounds, obtusifoliol and cassiaside B2, may be responsible for exerting anti-obesity effects via appetite suppression by 5-HT2C receptor activation. The binding affinity of obtusifoliol and cassiaside B2 with 6BQG are -10.5 and -9.9 kcal/mol respectively.

Included studies	Study type	Tested substances	Samples	Interventions	Duration	Primary results
Luo et al., 2020a	*In vitro*	Powder of CHM formula, RCM-107 and its ingredients. RCM-107 consists of JMZ, Camellia sinensis, Poria, Nelumbinis folium, Alismatis rhizome, Sophorae flos, Gardeniae fructus and Plantaginis semen	Human NCI-H716 cells ((intestinal enteroendocrine L-cells)	Cells were treated with herbal samples and positive control EGCG.	2 hours	Glucagon-like peptide-1 (GLP-1) has been linked with appetite suppression and weight-loss. JMZ (1.2662ng/mL) led to a statistically significant increase of GLP-1 secretion ($p<0.0001$). RCM-107 showed increases GLP-1 release but was not statistically significant ($p>0.5$).
	In silico	Chemical compounds of RCM-107 ingredients	N/A	Molecular docking study with 5NX2 (agonist-bound active conformation of GLP-1)	N/A	The binding affinity of stigmasterol, a chemical compound of JMZ, with 5NX2 is -10.9 kcal/mol, which is the strongest among the studied compounds.
Luo et al., 2020b	*In vitro*	Water extracts of CHM formula RCM-107 and its 8 individual ingredients including JMZ	Fluorescence porcine pancreatic alpha-amylase (PPA) inhibition assay	25 microliters of each individual herbal extract at the final concentration of 300 μg/ mL, the RCM-107 formula extraction (10–800μg/mL) and 25 μL of the PPA solution (final concentration 12mU/mL) were used in the study.	N/A	Alpha-amylase inhibitors have been used as an off-label agent to assist weight-loss. JMZ displayed a PPA inhibition rate of 17% and were statistically significant ($P < 0.05$).
	In silico	Chemical compounds of RCM-107 ingredients	N/A	Molecular docking study with IOSE (Porcine pancreatic alpha-amylase complexed with acarbose)	N/A	The binding affinity of compounds of JMZ stigmasterol, campesterol and cassiaside with IOSE are -9.8, -9.5 and -9.2 kcal/mol respectively
2. Hypolipidemic activities						
He et al., 2005	Clinical trial	Decoction of CHM formula composed of purslane 40g, JMZ 15g, parched hawthorn fruit 15g, kudzuvine root 15g, red peony root 12g, Szechwan lovage rhizome 12g	120 patients diagnosed as primary hyperlipemia	Oral administration: 3 x 20g per day	6 weeks	At 3 and 6 weeks, the level of total cholesterol and LDL-C was significantly lower in treatment group than the control group ($P<0.01$).; the level of HDL-C was significantly higher in the treatment group than in the control group ($P<0.05$ to 0.01).

Included studies	Study type	Tested substances	Samples	Interventions	Duration	Primary results
Wang et al., 2005	Clinical trial	Decoction of CHM formula composed of JMZ 20g, Rhizoma Alismatis 20g, lotus leave 10g, Radix Puerariae 15g, salvia miltiorrhiza 15g, urcuma longa L 12g, Ramulus Taxilli 15g and hawthorn fruit 15g	120 patients with dyslipidaemia. All patients had not used any drugs for lipid regulation 2 weeks before the experiment.	Oral administration: A: 1 dose/day of herbal docoction B: 10mg/day of pravastatin sodium C: 1 dose/day of herbal docoction + 10mg/day of pravastatin sodium	8 weeks	There was no significant difference in effective rates in comparison between CHM group and western drug group (P>0.05) but significant difference presented in comparison of integrative with CHM and western drug groups (P<0.05). The comparing parameters TG and TC and HDL-C.
Li and Gou, 2004	*In vivo*	Protein extract and chemical compound anthraquinone glycoside of JMZ	80 male and female SD rats weighing from 200 to 400g	Abdominal cavity injection	15 days	Both protein and anthraquinone glycoside of JMZ reduced plasma levels of total TC, TG and LDL-C
Li et al., 2007	*In vivo*	Ethanolic extract of JMZ	80 male mice	Intragastric administration	1 week	Reducing plasma levels of total TC, TG and LDL-C and apoB in treatment group were lower than those in the control group (P<0.05)
Li et al., 2008	*In vivo*	Chemical compound of JMZ: anthraquinones	45 male SD rats	Oral administration: 10mg/kg or 80 mg/kg once a day	20 days	Inhibition of cholesterol synthesis of anthraquinones may be one of the underlying mechanisms involved in decreasing blood lipid.
Chen et al., 2011 *	*In vivo*	Water extract of CHM formula, Jiang-Zhi-Ning (JZN), composed JMZ, Fleeceflower Root, Fructus Crataegi and Folium Nelumbinis	90 male Wistar rats	Oral administration: 10.5, 3.5 or 1.17 g/kg/day	6 weeks	JZN reduced TC level ($p < 0.01$), TG level ($p < 0.05$, $p < 0.01$), LDL-C level ($p < 0.05$, $p < 0.01$), AI ($p < 0.05$, $p < 0.01$) and CRI ($p < 0.01$).
	In vitro	Extract of CHM formula JZN	Human liver cell line Bel-7402	Culture liquid with $2 \times 10{-}4$, $2 \times 10{-}3$ or $2 \times 10{-}2$ mg/ml extract of JZN	N/A	The results showed JZN have significant effects in lowering lipids of rats when comparing with the control (atorvastatin)

Included studies	Study type	Tested substances	Samples	Interventions	Duration	Primary results
3. Antidiabetic activities						
Tian et al., 2018	*In vivo*	Powder of CHM formula WSZYF composed of JMZ, Radix Polygoni Multiflori Preparata, Mori fructus and Mori folium	36 Goto- Kakizaki (GK) rats	Oral administration: 300, 600 or 1200 mg/kg/day of WSZYF powder	8 weeks	Treatment of WSZYF lowered FBG, insulin concentration and IR index indicating that it could restore glucose metabolism disorders and improve the insulin sensitivity.
	In vitro	Powder of CHM formula WSZYF	MIN6 cells	Hematoxylin-eosin staining	N/A	WSZYF could improve IR by inhibiting pancreatic β cell apoptosis in Type 2 diabetes mellitus
Kang et al., 2012	*In vitro*	Methanol extract of JMZ and its chemical compounds	Alpha-glucosidase inhibition assay	Mass spectroscopic techniques for identifying JMZ compounds/ biological assay tests for investigating alpha-glucosidase inhibitory activity	N/A	3 JMZ compounds, chrysoobtusin, 8-O-methylchrysophanol and physcion were identified to have inhibiting alpha-glucosidase activities
Jung et al., 2017	*In vitro*	JMZ compounds: 16 anthraquinones; 2 naphthopyrone glycosides; 1 naphthalene glycoside	HepG2 cell line/ Alpha-glucosidase inhibition assay/ PTP1B inhibition assay/ glucose uptake assay	Insulin-resistant HepG2 cell model and glucose uptake/ Column chromatography	N/A	These findings suggest that alaternin and emodin could regulate the insulin sensitivity, modulating glucose transport.
	In silico	19 selected JMZ compounds	N/A	Molecular docking simulation in PTP1B inhibition Using Autodock 4.2	N/A	All 19 selected JMZ compounds, including anthraquinones, naphtopyrone, and naphthalene glycosides, were shown to be potent α-glucosidase and PTP1B inhibitors.
Zhou et al., 2019	*In silico*	Chemical compounds of CHM formula XKYS composing of JMZ, Coptidis rhizoma, Liriopes radix and bitter melon	N/A	Screening main components from the four herb extracts and construction of PPI Networks.	N/A	JMZ compounds cassiaside, rubrofusarin 6-O-β-D- gentiobioside, glucoaurantio-obtusin, cassiaside C and curantio- obtusin exerted antidiabetic effects.

Included studies	Study type	Tested substances	Samples	Interventions	Duration	Primary results
4. Inhibitory activities						
Kim et al., 2007	*In vivo*	Ethanolic extract of JMZ	Male ICR mice (25 – 30 g)	12.5, 25, 50, or 100 mg/kg was orally administrated 1 hour before passive avoidance/ Y-maze/ Morris water maze task	2 weeks	The study demonstrated that JMZ had the ability to ameliorate memory impairments due to a dysfunctional central cholinergic nervous system and hypoperfusion-induced memory deterioration.
	In vitro	Ethanolic extract of JMZ	AChE activity assay	Colorimetric method	N/A	JMZ may play key roles in the stimulation of the central cholinergic nervous system and also JMZ potently inhibits AChE.
Lin et al., 2017	*In vivo*	Chemical compound of JMZ: chrysophanol	Male C57BL/6 mice (25–30 g body weight)	50 mg/kg of chrysophanol was orally administered daily using a feeding needle	7 days	chrysophanol prevented the functional and morphological features of MNU-induced retinal degeneration.
	In vitro	Chemical compound of JMZ: chrysophanol	The mouse BV-2 microglia cell line	Scotopic ERG analysis/ SD-OCT imaging/ Immunofluorescence/ Western blot analysis/ Gelatin zymography analysis	N/A	The retina-protective effects provided by chrysophanol might be mediated by the inhibition of apoptosis, proliferative gliosis, microglia activation, and MMP -9 induction.
Huang et al., 2012	*In vitro*	Water-soluble polysaccharides of JMZ	Alpha-amylase/ haemoglobin/ lipase/ bile acid mixture/ cholesterol-micellar solutions	Chemically analyses performed in triplicate.	N/A	JMZ had significant inhibitory effects on the activities of alpha-amylase and pancreatic lipase, while they rendered an increase in protease activity (up to approximately 7-fold).
Jung et al., 2016	*In vitro*	Methanolic extract of JMZ	Cholinesterase enzyme assays of AChE, BChE and BACE1	FRET assay kits/ Spectrophotometer method	N/A	JMZ compounds inhibited α-amylase and pancreatic lipase. In particular, alaternin, physcion, and emodin exhibited potent AChE inhibitory activity, with IC_{50} values of 6.29 +/- 0.65, 8.25 +/- 0.13, and 9.17 +/- 0.41 μg/mL, compared with the positive control berberine with an IC_{50} value of 0.70 +/- 0.29.

Included studies	Study type	Tested substances	Samples	Interventions	Duration	Primary results
	In silico	Major constituents of JMZ	n/a	Molecular docking study of the inhibitory activity of alaternin and emodin against BACE1	N/A	The binding energies for alaternin and emodin were –6.62 kcal/mol and -6.89 kcal/mol respectively.
Luo, H.Y. et al., 2019 *	*In vitro*	Petroleum ether fraction/chemical compounds of JMZ	4-Nitrophenyl α-D-glucopyranoside (PNPG) as substrate.	Chromatographic separation/ inhibitory effects against α-glucosidase of JMZ compounds were determined with 4-Nitrophenyl α-D-glucopyranoside substrate	N/A	Most of the isolated JMZ compounds had an inhibitory effect on α-glucosidase. The IC_{50} values of the 4 top compounds were 50.60 ± 1.10, 22.57 ± 0.07, 60.09 ± 1.40, and 80.01 ± 2.66 μg/mL, respectively.
Pang et al., 2019	*In vitro*	Ethanolic extract of JMZ	HEK293 cell lines	Fluorescence spectroscopy	N/A	A new anthraquinone analogue, obtusifolin-2-O-β-D-(6'-O-α,β-unsaturated butyryl)-glucopyranoside, was isolated from JMZ. It exhibited a strongly specific inhibitory effect on OAT1 at 100 μM.
Yu et al., 2019	*In vitro*	Major anthraquinone constituents of JMZ	Thrombin fluorescent substrate Z-GGRAMC acetate	Enzyme inhibition assays/ Inhibition kinetic analyses	N/A	Four JMZ anthraquinones (obtusifolin, obtusin, aurantio-obtusin and chryso-obtusin) demonstrated good potency for the inhibition on human thrombin, with IC_{50} values ranging from 9.08 μM to 27.88 μM respectively.
	In silico	Major anthraquinone constituents of JMZ	N/A	Molecular docking simulations were performed using Discovery Studio.	N/A	Two anthraquinones (obtusifolin and aurantio-obtusin) created key interactions with human thrombin via forming a hydrogen bonding.

Included studies	Study type	Tested substances	Samples	Interventions	Duration	Primary results
5. Hepatoprotection activities						
Chen et al., 2006	RCT	Decoction of CHM formula composed of JMZ 15g, Indigo Naturalis 10g, Alumen 3g, Fructus Cratagi 15g, Radix Bupleuri 10g, Radix Curcumae 10g, Radix Salviae Miltiorrhizae 12g, Herba Lycopi 12g, talc 12g and Radix Glycyrrhizae 2g	62 patients with non-alcoholic steatohepatitis of Phlegm Blood Stasis syndrome typesteatohepatitis	Oral administration: Treatment: 1 dose of CHM twice per day Control: UAT 150mg 3 times per day	12 weeks	Levels of ALT, AST, HOMA-IR and t-PA and main symptoms were improved in treatment group ($P<0.05$ or $P<0.01$). The effects of CHM were better than that of UAT.
Luo et al., 2011	*In vivo*	Anthraquinone of JMZ	120 SD rats	Intragastric administration: 40% ethanol twice a day to establish alcoholic fatty liver 0.1, 0.2 or 0.4 g/kg of JMZ anthraquinones twice a day	3 months	Anthraquinone of JMZ could remarkably decrease the content of ALT, ASDT, TC, TG and increase the content of superoxide dismutase (SOD) in the serum.
	In vitro	Anthraquinone of JMZ	Liver tissues of rats	RT-PCR test/ immunohistochemical staining	N/A	Anthraquinone of JMZ could remarkably increase the expression of PPARG mRNA in the liver of the experimental fatty liver ($P<0.01$).
Xie et al., 2012	*In vivo*	Ethanolic extract of JMZ	50 male Kun-Ming mice (weighing 18-22g)	Gavage feeding: 0.5, 1.0, or 2.0 g/kg body weight	12 days	JMZ showed a potent protective effect against CCl4 -induced liver injury. JMZ pre-treatment significantly inhibited the increase of the serum aminotransferase activities, attenuated oxidative stress-induced mitochondrial dysfunction
	In vitro	Ethanolic extract of JMZ	Blood and liver tissues of mice	Commercial assay kits	N/A	
Seo et al., 2017	*In vitro*	Ethanolic extract of JMZ	Human hepatic HepG2 cells	Hepatoprotection/ Luciferase/ Real-time polymerase chain reaction (PCR) assays	N/A	JMZ had hepatoprotective effects against oxidative stress-induced cell damage and it induced Nrf2 activation

Included studies	Study type	Tested substances	Samples	Interventions	Duration	Primary results
Ali et al., 2018	*In vitro*	JMZ methanol extract/ active constituents	Human hepatic HepG2 cells	HPLC analysis/ cytoprotective assay/ Measurement of the level of intracellular ROS/ Measurement of glutathione	N/A	JMZ protected HepG2 cells against t-BHP-induced hepatotoxicity. The possible mechanism is that alaternin, aloe emodin, and cassiaside potently scavenge ROS in t-BHP-induced HepG2 cells.
(Paudel et al., 2018)	*In vitro*	JMZ anthraquinone and naphthopyrone glycosides	Human hepatic HepG2 cells	Cytoprotective assay/ Determination of intracellular ROS levels/ Pro-oxidant assay/ Measurement of glutathione	N/A	Pre-treatment with the JMZ glycosides increased Nrf2-mediated HO-1 expression. The protective effects of JMZ against t- BHP-induced oxidative damage in HepG2 cells were due to the prevention of ROS generation.
6. Neuroprotective activities						
Kim et al., 2009	*In vivo*	Ethanolic extract of JMZ	Male ICR mice (25–30 g) Sample size=8	10 or 50 mg/kg/day	7 days	Immunohistochemical and western blot studies showed that levels of inducible iNOS and COX-2 in the hippocampal region were attenuated by the JMZ extract.
	In vitro	Ethanolic extract of JMZ	Cells of mice at hippocampal region of brains	Immunohistochemistry/ Cresyl violet staining/ Western blot analysis	N/A	The neuroprotective effects of JMZ extract are due to its anti-inflammatory effects and to its upregulation of BDNF expression and CREB phosphorylation.
Ju et al., 2010	*In vivo*	Ethanolic extract of JMZ	Male C57BL/6 mice Sample size=8	Oral administration: 50 mg/kg/day	15 days	JMZ extract attenuated the cell damage and inhibited the overproduction of reactive oxygen species, glutathione depletion, mitochondrial membrane depolarization and caspase-3 activation. JMZ has neuroprotective effects in Parkinson's disease models.
	In vitro	Ethanolic extract of JMZ	Brains from mice with induced brain damage	Fluorescence microplate reader	N/A	

Included studies	Study type	Tested substances	Samples	Interventions	Duration	Primary results
Drever et al., 2008	*In vitro*	Ethanolic fraction of JMZ (range: 0.1–10μg/ml)	Hippocampal cultures prepared from 3 to 4-day-old C57Bl/6 mice with brain injury	Calcium dysregulation and cell death models/ Fura-2 fluorescence imaging	N/A	JMZ treatment attenuated secondary Ca2+ dysregulation induced by NMDA (700 μM), while a pre-application of CS also reduced NMDA-induced cell death. Furthermore, JMZ was neuroprotective against the mitochondrial toxin 3-NP (1 mM).
7. Anti- inflammatory activities						
Chen et al., 2017	*In vivo*	Powder from crude decoction of JMZ	Male Sprague–Dawley rats (160–180 g)	Single dose of 10g/kg of JMZ powder 3 hours after LPS administration	3 hours	SC markedly reduced pulmonary interleukin (IL)-6, tumor necrosis factor (TNF)-α, and 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels. JMZ treatment significantly increased EETs and HO-1 activities and protects rats with induced ALI.
	In vitro	Powder from crude decoction of JMZ	Lung tissues from rats with acute lung injury (ALI)/ RAW264.7 cells	Pulmonary histological analysis/ Enzyme-Linked Immunosorbent Assay (ELISA) kits	N/A	
Hou et al., 2018	*In vitro*	JMZ compound: Aurantio-obtusin	RAW264.7 cells	Real time PCR/ western blot assay/ laser scanning microscopy	N/A	Aurantio-obtusin was shown to prevent inflammation through an underlying mechanism involved the activation of NF-kB in LPS-stimulated RAW264.7 cells.
Kwon et al., 2018	*In vivo*	JMZ compound: Aurantio-obtusin	Male ICR Mice (18–22 g) Sample size=7	Oral administration: 10 or 100 mg/kg of aurantio-obtusin	N/A	Aurantio-obtusin significantly and strongly inhibited total cell recruitment in the BALF. It also reduced inflammatory responses, especially in the 100 mg/kg-treated group.
	In vitro	JMZ compound: Aurantio-obtusin	A549 human lung epithelial cells/ MH-S cells, a mouse alveolar macrophage cell line	Western blot analysis / ELISA kits	N/A	Aurantio-obtusin considerably inhibited NO possibly by interrupting MAPK and NF-κB activation and proinflammatory cytokine production from the lung-related cells.

Included studies	Study type	Tested substances	Samples	Interventions	Duration	Primary results
8. Antioxidant activities						
Lee et al., 2008	*In vitro*	25 types of herbs commonly used in Chinese medicinal culinary diets	Lyophilized herbal powders extracted with methanol containing 5% acetic acid.	Measurement of radical-scavenging activities, ascorbic acid content and tocopherol content.	N/A	The highest antioxidant activity was found in chrysanthemum, followed by hawthorn, licorice root, hibiscus and JMZ.
Liu et al., 2014	*In vitro*	Water-soluble polysaccharide of JMZ	DPPH/ Diethylaminoethyl-celluose (DEAE-cellulose)	Fourier Transform Infrared Spectroscopy (FTIR) Analysis	N/A	The results of scavenging activity showed that JMZ was a better inhibitor against hydroxyl and superoxide radicals than vitamin C, except on DPPH.
Chen et al., 2011 *	*In vivo*	Water extract of CHM formula, Jiang-Zhi-Ning (JZN) consisting of JMZ	90 male Wistar rats	Oral administration: 10.5, 3.5 or 1.17 g/kg/day	6 weeks	Compared with control group, JNZ has caused a significant change in NO level, ET-1 level, MDA level, SOD activity and T-AOC activity ($p < 0.01$).
	In vitro	Extract of CHM formula JZN consisting of JMZ	Human liver cell line Bel-7402	Culture liquid with $2 \times 10{-}4$, $2 \times 10{-}3$ or $2 \times 10{-}2$ mg/ml extract of JZN	N/A	The results showed the formula JZN has significant effects on antioxidant activities of tested cells when compared with the control (atorvastatin)
Luo, H.Y. et al., 2019 *	*In vitro*	Petroleum ether fraction/chemical compounds of JMZ	4-Nitrophenyl α-D-glucopyranoside (PNPG) as substrate.	DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) assay	N/A	Among these compounds, rubrofusarin (IC_{50} 3.03 ± 0.31 μg/mL) showed stronger free radical scavenging capacity than ascorbic acid.
9. Other pharmacological activities						
Jang and Yang, 2018	*In vivo*	Ethanolic extract JMZ, Foeniculum Vulgare M (FV). and a mixture of JMZ and FV	60 Sprague-Dawley rats	Oral gavage: JMZ or FV group: 300 mg/kg/day of JMZ or FV extract alone Mixture group: 100, 300 or 500 mg/kg/day of JMZ and FV mixture	4 weeks	These results demonstrated that JMZ and FV, especially in combined treatment of JMZ and FV, improved loperamide-induced constipation in rats through the enhancement of faecal parameters.

Included studies	Study type	Tested substances	Samples	Interventions	Duration	Primary results
	In vitro	N/A	Tissue of transverse colon of rats in study	Histological analysis of the transverse colon/ RT-PCR/ Western blot analysis	N/A	JMZ and FV mixture treatment had the laxative effect by recovering stool-parameters, colonic morphology, and activation of mAchRs and their downstream signalling pathway in constipation.
Sung et al., 2004	*In vitro*	Methanolic extract and fractions JMZ anthraquinones	Different strains of bacteria	Growth responses by spectrophotometric and impregnated paper disk methods	N/A	1,2-Dihydroxyanthraquinone, isolated from CS strongly inhibited the growth of C. perfringens and E. coli and exhibited strong growth- promoting activity to B. bifidum.
Kim et al., 2011	*In vivo*	Aqueous extract of JMZ	15 Female BALB/c mice (six weeks old)	Oral administration: 1g/kg/day of JMZ extract or 150mg/kg/day of sulfasalazine	7 days	JMZ significantly suppressed the levels of interleukin (IL)-6 and expression of cyclooxygenase-2 in DSS-treated colon tissues.
Yang et al., 2019	*In vivo*	Aqueous extract of JMZ	8–12 weeks old male and female SD rats (180–200 g) Sample size=8	Oral administration: 4.73, 15.75 or 47.30 g/kg/day	28 days	Aqueous extract of JMZ could cause hepatotoxicity after 28-day repeated oral administration in rats. The possible hepatotoxicity mechanisms involved in the disorder of glycerophospholipid and glycerolipid metabolism.

Note: *: study for multiple-pharmacological effects; AChE: acetylcholinesterase; AI: Atherogenic Index; ALT: alanine aminotransferase; APOC3: apolipoprotein C-III; AST: aspartate aminotransferase; BACE1: beta-site amyloid precursor protein cleaving enzyme 1; BALF: bronchoalveolar lavage fluid; BChE: butyrylcholinesterase; CCL: carbon tetrachloride; COX-2:cyclooxygenase-2; CRI: Coronary Risk Index; DDS: dextran sulfate sodium; EETs: epoxyeicosatrienoic acids; ERG: electroretinography; ET-1:endothelin-1 level; FBG: fasting blood glucose; FRET: Fluorescence resonance energy transfer; HDL-C: high-density lipoprotein cholesterol; HepG2: human hepatocarcinoma; HO-1: heme oxygenase-1; HOMA-IR: homeostatic model assessment of insulin resistance; HSL: Hormone-sensitive lipase; IR: insulin resistance; LPS: lipopolysaccharide; MAPK: mitogen-activated protein kinase; MDA: malondialdehyde; MMP: matrix metalloproteinase; N/A: not applicable; NF-kB: nuclear factor kappaB; NO: nitric oxide level; NRF2: nuclear factor erythroid-2-related factor 2; OAT1:organic anion transporters 1; PPARG: Peroxisome proliferator- activated receptor gamma; PPI: protein-protein interaction; PTP1B: protein-tyrosine phosphatase; ROS: reactive oxygen species; RT-PCR: Real-time reverse transcription–polymerase chain reaction; SD: standard deviation; SD-OCT: Spectral-Domain Optical Coherence Tomography; SE: standard error; SOD: superoxide dismutase; t-BHP: tert-butylhydroperoxide; T-AOC: total antioxidant capacity; TC: total cholesterol; TG: triglyceride; t-PA: tissue plasminogen activator; UAT: ursodeoxycholic acid tablet; WSZYF: *Wushenziye Fang* (Formula of five herbs that nourish the Liver); XKYS: Xiao Ke Yin Shui (Wasting and thirsting disorder).

Details of the potential pharmacological activities of JMZ are reported in 6.1.1–6.1.9.

6.1.1 Weight-loss activities

Out of the 44 studies, nine of them investigated the weight-loss effect of JMZ. A RCT (Lenon et al., 2012) with 117 participants evaluated the efficacy and safety of a CHM formula as one of the three ingredients in the management of simple obesity. The results showed statistically significant differences in bodyweight and BMI between the treatment and placebo groups after 12 weeks of treatment. A 24-week RCT (Zhou et al., 2014) with 140 obese subjects demonstrated that the administration of a decoction of CHM formula comprising JMZ resulted in body weight-loss, along with reductions in BMI and waist circumference.

An *in vivo* and *in vitro* study (Au et al., 2003) showed that the JMZ compound neotoraclactone (a derivative of toralactone) reduced the body weight of rats fed with a high nutrient diet by alteration of lipid metabolism primarily taking place in the liver. Another *in vivo* study (Zhuang et al., 2016) showed that oral treatment with 20 mg/kg of the JMZ compound obtusifolin reduced the body weight of hyperlipidemic rats. Antioxidation activity accounted for the lipid-reducing effect of obtusifolin. An *in vivo* study (Y. Zhang et al., 2017) showed that a CHM composed of JMZ had strong anti-obesity effects on rats. It also showed that the CHM extracts reduced the size of adipocytes in the white adipose tissue of the cultured rats. Four *in silico* studies revealed different pathways of weight-loss with JMZ: 1) reducing lipid absorption via the inhibition of pancreatic lipase (S. Luo et al., 2019b); 2) suppressing appetite via 5-hydroxytryptamine receptor 2C (5-HT2C) receptor activation (Yuen et al., 2020); 3) influencing the satiety signal via GLP-1 (Glucagon-like peptide-1) receptor activation (Luo et al., 2020a) and 4) reducing carbohydrate absorption via suppressing the activity of porcine pancreatic alpha-amylase (S. Luo et al., 2020b).

In this review, nine active chemical compounds of JMZ are predicted or identified to have weight reduction effects including:

1) toralactone (Au et al., 2003);
2) obtusifolin (Au et al., 2003; Zhuang et al., 2016),
3) obtusifoliol (Yuen et al., 2020),
4) friedelin (Yuen et al., 2020),
5) cassiaside B2 (S. Luo et al., 2020b; Yuen et al., 2020),
6) cassiaside C (Yuen et al., 2020),
7) rubrofusarin gentiobioside (Yuen et al., 2020),
8) stigmasterol (S. Luo et al., 2020a, 2020b; Yuen et al., 2020) and
9) campesterol (S. Luo et al., 2020b).

6.1.2 Hypolipidemic activities

Two RCTs (He et al., 2005; Wang et al., 2005) indicated that JMZ had hypolipidemic effects. The RCT (He et al., 2005) involving 120 patients with primary hyperlipidaemia found that the CHM formula consisting of JMZ and purslane could decrease the level of blood lipids and reduce blood hyperviscosity. Wang et al (2005) compared the outcomes of treatment with a CHM formula consisting of JMZ to treatment with pravastatin sodium on 120 patients with dyslipidaemia. It was found that the CHM formula was more effective for reducing the triglyceride (TG) and total cholesterol (TC) together with fewer adverse events and side effects.

Four *in vivo* studies (Chen et al., 2011; Li et al., 2008; Li et al., 2007; Li & Gou, 2004), involving 295 mice in total, indicated that mice treated with JMZ extract or anthraquinones of JMZ had reduced the plasma levels of TC, TG and LDL-C (low-density lipoprotein-cholesterol). Two of these studies (Chen et al., 2011; Li et al., 2008) showed that anthraquinones of JMZ increased the serum HDL-C level of the mice.

6.1.3 Antidiabetic activities

Four studies (Jung et al., 2017; Kang et al., 2012; Tian et al., 2018; Zhou, Wang, et al., 2019) have demonstrated the antidiabetic effects of JMZ. In an *in vivo* and *in vitro* study (Tian et al., 2018), 36 Goto-Kakizaki rats were fed with a high glucose and fat diet for 4 weeks in order to induce diabetes. They were then divided into six groups (n=6 for each group). The treatment groups were fed with different dosages of a CHM formula consisting of JMZ and the control groups were given with an equivalent volume of normal saline for eight weeks. The results indicated that the treatment using CHM in high dosage reduced glucose metabolism disorders, improved insulin sensitivity and reduced TG and free fatty acids levels in serum. There was no effect noted for either the low dosage groups or the control groups.

An *in vitro* and *in silico* study (Jung et al., 2017) found that alaternin and emodin of JMZ improved insulin sensitivity by increasing insulin-stimulated glucose uptake in HepG2 cells and therefore suggested that these constituents could regulate the insulin sensitivity *in vitro* and thus modulate glucose transport. Another study (Kang et al., 2012) found that amongst six anthraquinone compounds of JMZ, three of them had higher alpha-glucosidase inhibitory effects than the control, acarbose. A network pharmacology analysis (Zhou, Wang, et al., 2019) found that a CHM formula consisting of JMZ exhibited an antidiabetic effect mainly via reducing insulin resistance.

Eight active chemical compounds of JMZ are predicted/identified to have antidiabetic effects, including:

1) chryso-obtusin (Kang et al., 2012),
2) 8-O methylchrysophanol (Kang et al., 2012),
3) physcion (Kang et al., 2012; H.-Y. Luo et al., 2019),
4) alaternin (Jung et al., 2017),

5) emodin (Jung et al., 2017),
6) chrysophanol (H.-Y. Luo et al., 2019),
7) rubrofusarin (H.-Y. Luo et al., 2019) and
8) toralactone (H.-Y. Luo et al., 2019)

6.1.4 Inhibitory activities

An *in vitro* experiment (Huang et al., 2012) revealed that a JMZ aqueous extract had inhibitory effects on the activities of both alpha-amylase and pancreatic lipase and that it reduced the amount of cholesterol available for absorption. The inhibitory activities of JMZ on alpha-glucosidase have been demonstrated in two *in vitro* studies (Kang et al., 2012; H.-Y. Luo et al., 2019). Other studies revealed that JMZ has potential inhibitory effects for different disorders, such as: inhibiting acetylcholinesterase (AChE), butyrylcholinesterase (BChE) and beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) activities for Alzheimer's disease (Jung et al., 2016); acetylcholinesterase for attenuation of memory impairment (Kim et al., 2007); organic anion transporters for treatment of hyperuricemia (Pang et al., 2019); lipopolysaccharide lipopolysaccharide (LPS)-induced (explained in Table 6.1, not in the text) inducible nitric oxide synthase (iNOS). and cyclooxygenase-2 (COX-2) expression for retinal degeneration (Lin et al., 2017); and human thrombin (Yu et al., 2019).

6.1.5 Hepatoprotective activities

Hepatoprotection was investigated in six contemporary studies, including: one RCT (Chen et al., 2006); two animal studies (Luo et al., 2011; Xie et al., 2012); and three *in vitro* studies (Ali et al., 2018; Paudel et al., 2018; Seo et al., 2017).

The 12-week RCT involved 62 patients with non-alcoholic steatohepatitis, with the treatment group (n=34) taking CHM containing JMZ as one of the ingredients and the control group

(n=28) taking ursodeoxycholic acid tablets (UAT). The results demonstrated that there was a significant difference in the liver function index, insulin resistance, levels of tissue plasminogen activator and plasminogen activator inhibitor-1 between the treatment group and the control group. The study concluded that the CHM was more effective than UAT for improving liver function and fibrinolytic status (Chen et al., 2006).

Xie et al (2012) demonstrated in an *in vivo* study that JMZ extract possessed protective effects against carbon tetrachloride-induced liver injury in mice. JMZ extract treatment significantly inhibited elevated serum aminotransferase activities, attenuated oxidative stress-induced mitochondrial dysfunction, and decreased pathological changes. JMZ extract boosted the activities of antioxidant enzymes which could account for its hepatoprotective activity (Xie et al., 2012). Another animal study, with 112 male mice, revealed that JMZ treatment on mice with hepatic fatty liver decreased the content of Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), TC, TG and malondialdehyde (MDA). This study indicated that JMZ exerted the effect of regulating lipid metabolism disorder and ameliorating hepatic functions (Luo et al., 2011).

JMZ mediates hepatoprotection through different pathways (Ali et al., 2018; Paudel et al., 2018; Seo et al., 2017), mainly related to anthraquinone and naphthopyrone glycosides. The active chemical compounds of JMZ identified to have hepatoprotective effects are:

1) toralactone-9-O-β-D-gentiobioside (Seo et al., 2017),
2) alaternin (Ali et al., 2018),
3) aloe emodin (Ali et al., 2018),
4) cassiaside A (Ali et al., 2018),
5) 1- desmethylaurantio-obtusin 2-O-b-D-glucopyranoside (Paudel et al., 2018),
6) rubrofusarin 6-O-b-D-apiofuranosyl-(1→6)-O-b- D-glucopyranoside (Paudel et al., 2018) and

7) rubrofusarin 6-O-b-gentiobioside (Paudel et al., 2018)

6.1.6 Neuroprotective activities

The neuroprotective activities of JMZ were investigated in three studies, including two *in vivo* and *in vitro* studies (Kim et al., 2009; Ju et al., 2010) and one *in vitro* study (Drever et al., 2008).

The *in vitro* study conducted by Drever et al. (2008) found that treatment of hippocampal neuronal cell cultures with JMZ attenuated cell death and secondary Ca^{2+} dysregulation, whilst having no significant effect on cell death induced by incubation with naturally secreted amyloid beta peptide. The results of this study are relevant to a potential therapeutic use of JMZ in the treatment of neurodegenerative disorders by regulating and maintaining cellular homeostasis and apoptosis.

Two studies on the brain cells of mice found that JMZ has effects on attenuating inflammatory responses (Kim et al., 2009), upregulation of brain-derived neurotrophic factor (BDNF) expression and cyclic AMP-response element binding protein (CREB) phosphorylation (Kim et al., 2009) and protecting dopaminergic neurons against the toxicities involved in Parkinson's disease (Ju et al., 2010).

6.1.7 Anti-inflammatory activities

Two *in vivo* and *in vitro* studies (Chen et al., 2017; Kwon et al., 2018) found that JMZ reduced pulmonary oedema and inflammation in mice with lipopolysaccharide (LPS)-induced acute lung injury. Kwon et al. (2018) isolated eight major anthraquinone derivatives and found that aurantio-obtusin had a significant down-regulating action on inducible nitric oxide synthase expression. An *in vitro* study (Hou et al., 2018) on anti-inflammatory properties found that the

anti-inflammatory mechanism of aurantio obtusin was related to inhibition of the activation of the nuclear factor kappa B (NF-κB) pathway.

6.1.8 Antioxidant activities

Two *in vitro* studies found that JMZ has an antioxidative effect (Y.-C. Lee et al., 2008; Liu et al., 2014). Y.-C. Lee et al. (2008) analysed the antioxidant activity of JMZ by measuring its radical-scavenging activities and total phenolics, ascorbic acid and tocopherol contents and concluded that JMZ had a wide range of antioxidant activity. Another experiment (Liu et al., 2014) compared the scavenging capacities of JMZ and vitamin C. The results showed that the extract from JMZ was a better inhibitor against the formation of hydroxyl and superoxide radicals than Vitamin C. The antioxidant effects of JMZ are mainly due to the presence of anthraquinones and naphthopyrones (Paudel et al., 2018).

6.1.9 Other pharmacological activities

A four-week *in vivo* study (Jang & Yang, 2018) with 60 male Sprague-Dawley rats demonstrated that JMZ improved loperamide-induced constipation in rats through the enhancement of faecal parameters (including stool numbers and weights). It was suggested that JMZ treatment has a laxative effect as determined by recovering stool-parameters, colonic morphology, and activation of muscarinic acetylcholine receptors (mAChRs) and their downstream signalling pathway in constipation.

Two other studies (Kim et al., 2011; Sung et al., 2004) are related to activities of JMZ on the digestive system. In the study on human intestinal bacteria (Sung et al., 2004), a chemical compound, 1,2-Dihydroxyanthraquinone, isolated from JMZ, strongly inhibited the growth of *C. perfringens* and *E. coli* and exhibited strong growth-promoting activity to *B. bifidum*. The

results indicated that JMZ had growth-inhibiting and growth-promoting effects towards specific bacteria from the human intestines.

The *in vivo* and *in vitro* study conducted by Kim at al. (2011) with 20 mice demonstrated that treatment with JMZ could significantly reduce the clinical signs and the levels of inflammatory mediators in a colitis model caused by DSS (dextran sulfate sodium) treatment.

An *in vivo* and *in vitro* study (Yang et al., 2019) explored the potential hepatotoxicity mechanisms and the hepatotoxic components of JMZ. It was found that an aqueous extract of JMZ in high dosages could cause hepatotoxicity after a 28-day period of repeated oral administration in rats.

6.2 Lu cha ye

Historically, the medicinal use of LCY dates back 4700 years to China (Cooper, 2012). Biologically, LCY acts as antioxidant, anti-inflammatory and antiproliferative substance, which is potentially significant to the prevention and treatment of various forms of diseases (Singhal et al., 2017). LCY also contains four main catechins; they are: epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC), and epigallocatechin gallate (EGCG). Of these catechins, EGCG and EGC are found in the highest amounts in LCY and have been the subject of most of the studies (Westerterp-Plantenga, 2010).

A total of 8,439 papers were identified according to search strategies and 49 of those meeting the inclusion criteria were included for analysis. This included 33 review articles of single pharmacological effect and 16 review articles of multiple pharmacological effects. The selection process of this review is illustrated in Figure 6.2.

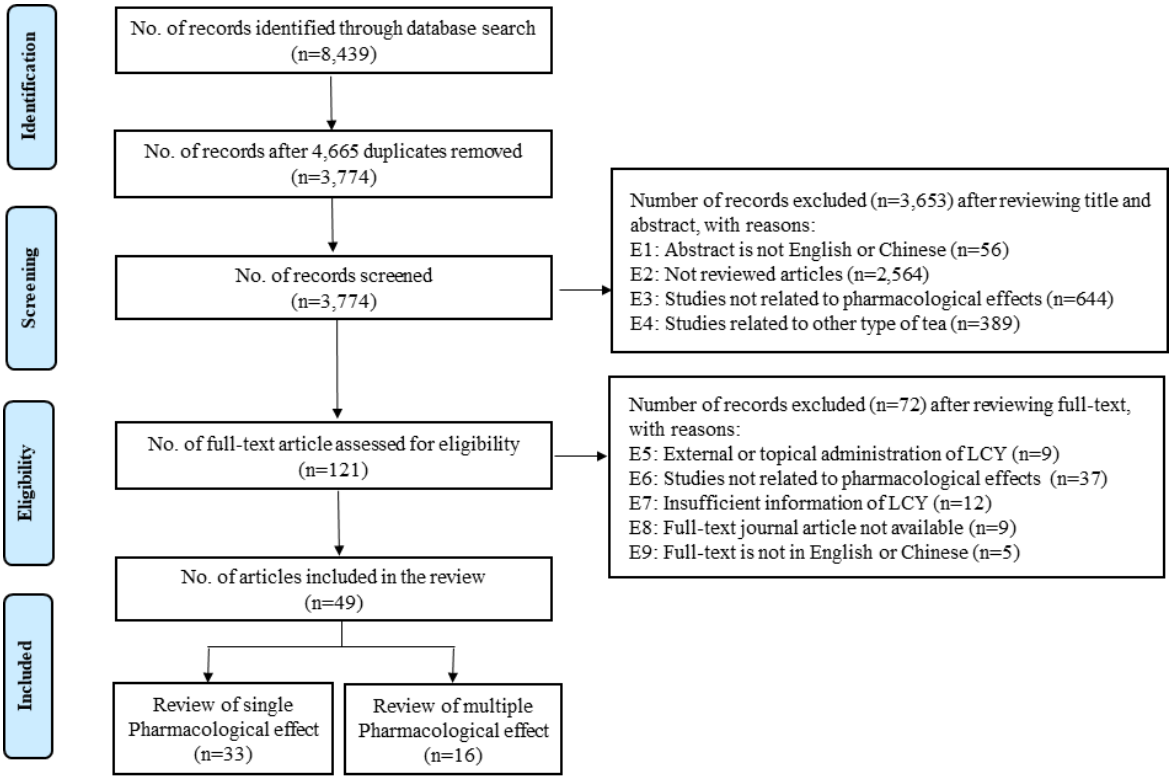


Figure 6.2: Selection process of modern literature review on Lu cha ye

The outcomes of the modern literature review on LCY are summarised in two separated tables: Table 6.2 for potential single pharmacological effects and Table 6.3 for potential multiple pharmacological effects. The effects studied include anticancer, weight-loss, antimicrobial, neuroprotective, cardiovascular protective, antidiabetic, anti-inflammatory, antioxidant and other effects.

Table 6.2: Summary of potential pharmacological effects of Lu Cha Ye – single activity

Included studies	Article title	Study type	Findings
1. Anticancer activities (n =11)			
Lee et al., 2006	Protective effects of green tea against prostate cancer.	epidemiological, *in vivo*, and *in vitro*	LCY is demonstrated as a practical preventive and therapeutic agent for prostate cancer in both *in vivo* and *in vitro* studies, without any side or adverse effects. Further evidence emerging from epidemiological studies is envisaged.
Liu et al., 2008	Green tea (Camellia sinensis) and cancer prevention: a systematic review of randomised trials and epidemiological studies.	epidemiological and clinical	More than half of the studies (58%) suggest that long-term consumption of LCY may reduce the risk of certain types of cancer, such as esophageal, stomach, pancreatic, liver and colorectal cancer. Some epidemiological studies demonstrated protective effects of LCY consumption on gastrointestinal, breast, lung and prostate cancer. However, the beneficial effects are not consistent across all studies.
Boehm et al., 2009	Green tea (Camellia sinensis) for the prevention of cancer.	epidemiological and clinical	Findings from epidemiological studies are inconsistent and therefore provide limited evidence for the benefit of LCY consumption on risk of cancers. Some RCTs and case-control studies have provided the evidence of beneficial effect of LCY at some cancer sites but there are limitations on their methodologies, such as small sample sizes. Also, the results of cohort studies are inconsistent.
Trudel et al., 2012	Green tea for ovarian cancer prevention and treatment: a systematic review of the in vitro, in vivo and epidemiological studies.	epidemiological, *in vivo*, and *in vitro*	Overall, *in vivo*/ *in vitro* studies assess the use of LCY and mostly of EGCG in EOC treatment, showing promising properties such as the capacity to decrease the expression and/or activity of a large spectrum of cancer-related proteins. Other LCYCs such as ECG are also thought to be effective against EOC. Epidemiological studies show that LCY intake increases disease-free survival of women diagnosed with EOC and decreases the occurrence of EOC.
Henning et al., 2013	Epigenetic effects of green tea polyphenols in cancer.	*in vivo* and *in vitro*	LCY products have the potential to alter epigenetic processes through DNA methylation, histone modification and miRNA regulation. *In vitro* cell culture studies provide clear evidence that extended LCY treatment can change DNA methylation and reactivate gene expression.
Li et al., 2014	Green tea compounds in breast cancer prevention and treatment.	epidemiological and *in vivo*	In this review, recent studies on tea polyphenols and their applications in the prevention and treatment of breast cancer are highlighted and mechanisms of action of LCY components in breast cancer are discussed.

Included studies	Article title	Study type	Findings
Rafieian-Kopaei & Movahedi, 2017	Breast cancer chemopreventive and chemotherapeutic effects of Camellia Sinensis (green tea): An updated review.	*in vivo* and *in vitro*	The result of this study suggests that the catechin available in LCY has properties which may prevent and treat breast cancer. It is also shown to inhibit proliferation of breast cancer cells and to block carcinogenesis. It is found that increased LCY consumption may lower the risk of breast cancer. LCY intake is shown to reduce the risk of breast cancer incidence.
Rashidi et al., 2017	Green tea and its anti-angiogenesis effects.	*in vivo* and *in vitro*	The finding of the review shows that GTCs especially EGCG inhibit angiogenesis through different mechanisms such as the use of miRNAs, suppression of cell proliferation, induction of apoptosis, inhibition the expression of angiogenic factors, suppression the phosphorylation of receptors and inhibition of binding of VEGF to its receptor.
Le et al., 2018	Effects of the green tea polyphenol EGCG on glioma: A critical evaluation of the literature.	epidemiological, *in vivo*, and *in vitro*	Although limited, there is evidence of the inhibitory effects of EGCG on glioma from different types of studies and experimental settings. The most promising potential of EGCG is as an adjuvant to conventional anti-glioma therapies but caution is needed.
Miyata et al., 2019	Anti-cancer effects of green tea polyphenols against prostate cancer.	clinical, *in vivo* and *in vitro*	Current knowledge regarding the anticancer effects of GTE in the prevention and treatment of prostate cancer is presented. Focus is on the molecular mechanisms of action, such as influencing tumour growth, apoptosis, androgen receptor signalling, cell cycle, and various malignant behaviours.
Cheng et al., 2020	A review on anti-cancer effect of green tea catechins.	*in vivo* and *in vitro*	In this review, evidence of the cancer chemo-preventive and chemotherapeutic effects of LCY and its major catechins are summarised and current research investigating their effects on cancer development and possible mechanisms behind are illustrated.
2. Weight-loss activities (n = 9)			
Wolfram et al., 2006	Anti-obesity effects of green tea: from bedside to bench.	clinical, *in vivo* and *in vitro*	The anti-obesity effects of LCY, its catechins, and EGCG are demonstrated in both *in vitro* and *in vivo* models of obesity. Studies report decreased body weight and fat mass. Three human studies assess the mode of action of LCY and GTCs and demonstrate increased fat oxidation which could contribute to the fat loss observed in response to these compounds.

Included studies	Article title	Study type	Findings
Hursel et al., 2009	The effects of green tea on weight-loss and weight maintenance: a meta-analysis.	clinical	This review concludes that GTCs or EGCG has a small positive effect on weight-loss and weight management.
Westerterp-Plantenga, 2010	Green tea catechins, caffeine and body-weight regulation.	clinical	Positive effects of LCY on body-weight management are shown. The action of LCY is predicted to be inhibition of catechol O-methyl-transferase and phosphodiesterase. It improves weight maintenance through thermogenesis, fat oxidation, regulation of lipolysis and sparing fat-free mass.
Rains et al., 2011	Anti-obesity effects of green tea catechins: a mechanistic review.	clinical	This review indicates that the relationship between LCY and thermogenesis is unclear, and future work should seek to clarification. Other possible mechanisms, including increased fat oxidation, decreased appetite, and disrupted nutrient absorption may play roles in the anti-obesity effects of LCY.
Thavanesan, 2011	The putative effects of green tea on body fat: an evaluation of the evidence and a review of the potential mechanisms.	clinical, *in vivo* and *in vitro*	This review concludes that it is reasonable to suggest that in fact, LCY does seem to enable and aid the global reduction of fat—be it through increased energy expenditure or decreased absorption.
Huang et al., 2014	The anti-obesity effects of green tea in human intervention and basic molecular studies.	clinical, *in vivo* and *in vitro*	Human and animal studies provide evidence to support that LCY and its catechins may be beneficial for the prevention or treatment of obesity. The weight loss pathways include reducing food intake, interrupting lipid emulsification and absorption, suppressing adipogenesis and lipid synthesis, increasing body thermogenesis and increasing fecal lipid excretion.
Suzuki et al., 2016b	Beneficial effects of tea and the green tea catechin EGCG on obesity.	epidemiological, clinical, *in vivo*, *in vitro*, and *in silico*	This review indicates that one of the mechanisms of the anti-obesity effect of LCY catechins is enhanced cellular production of reactive oxygen species, which is mediated through the pro-oxidant action of EGCG, leading to the activation of adenosine monophosphate-activated protein kinase, which suppresses gene and protein expression of enzymes and transcription factors involved in adipogenesis and lipogenesis, and stimulates those involved in lipolysis.
Türközü & Tek, 2017	A minireview of effects of green tea on energy expenditure.	clinical	It is reported that LCY causes an increase in thermogenesis and substrate with fat oxidation by affecting on the sympathetic nervous system. The two main components associated with energy expenditure, caffeine and catechin content have a separate impact on energy mechanism.

Included studies	Article title	Study type	Findings
Lin et al., 2020	The effect of green tea supplementation on obesity: A systematic review and dose–response meta-analysis of randomised controlled trials.	clinical	This review indicates that LCY supplementation is likely to be associated with a decrease in BW and BMI in obese patients.
3. Antimicrobial activities (n = 4)			
Reygaert, 2014	The antimicrobial possibilities of green tea.	*in vivo* and *in vitro*	This review suggests that LCY can be an effective antimicrobial agent, especially against multidrug-resistant strains and in particular, MRSA and ESBL producing organisms although there are certain issues that need to be addressed concerning these results.
Noormandi & Dabaghzadeh, 2015	Effects of green tea on Escherichia coli as a uropathogen.	*in vitro*	In this review, antimicrobial and synergistic effects of LCY for treatment of UTIs are evaluated. Different studies report the antimicrobial effect of LCY against E. coli which is the most important cause of 80–90% of all UTIs.
Reygaert, 2014	Green tea catechins: Their use in treating and preventing infectious diseases.	*in vitro*	Studies using human and mammalian cells lines show that LCY binding significantly decrease bacterial ability to bind to host cells. LCY can also damage the cell membrane resulting in loss of function to transmembrane transporter proteins.
Wang et al., 2021	Antiviral effects of green tea EGCG and its potential application against COVID-19.	*in vitro* and *in silico*	In this review, the antiviral effects of EGCG on DNA, RNA, coronaviruses and other viruses are summarised and discussed. Although the anti-inflammatory effects of EGCG on COVID-19 are shown by molecular docking experiments, it needs to be confirmed *in vivo*.
4. Neuroprotective activities (n = 3)			
Kakuda, 2002	Neuroprotective effects of the green tea components theanine and catechins.	*in vivo* and *in vitro*	This review suggests that one of the mechanisms of LCY theanine responsible for its neuroprotective effect is associated with glutamate receptors and transporters.
Pervin et al., 2018	Beneficial effects of green tea catechins on neurodegenerative diseases.	epidemiological, clinical, *in vivo*, *in vitro* and *in silico*	These findings suggest that GTCs have the potential to be used in the prevention and treatment of neurodegenerative diseases and should be useful for the development of new drugs.

Included studies	Article title	Study type	Findings
Farkhondeh et al., 2020	Green tea catechins inhibit microglial activation which prevents the development of neurological disorders.	*in vivo* and *in vitro*	This review indicates that LCY catechins are promising therapeutic agents in inhibiting inflammatory and apoptotic mediators in microglia and subsequently neuroprotective effects in neurodegeneration diseases.
5. Cardiovascular protective activities (n = 2)			
Wolfram, 2007	Effects of green tea and EGCG on cardiovascular and metabolic health.	epidemiological, clinical, *in vivo* and *in vitro*	Several intervention studies demonstrate that daily consumption of 200–300 mg EGCG exert cardiovascular protective effects. These studies are consistent with the epidemiological evidence that the consumption of 5–6 or more cups of LCY per day protects cardiovascular and metabolic health. However, the results of the intervention studies are equivocal.
Islam, 2012	Cardiovascular effects of green tea catechins: progress and promise.	clinical, *in vivo* and *in vitro*	The evaluation of cardioprotective effects of LCY and tea catechins in humans is difficult because of other confounding factors. Animal and cell line studies with isolated LCY flavonoids and catechins show promising cardioprotective effects and mechanistic insights on their effects. However, extrapolation of the results of animal or cell culture studies to human clinical situations is uncertain mainly because of the concentrations of LCY catechins used in animal or in vitro studies are far higher than the plasma concentrations achievable in human after LCY consumption.
6. Antidiabetic activities (n = 2)			
Wang et al., 2014	Effects of green tea or green tea extract on insulin sensitivity and glycaemic control in populations at risk of type 2 diabetes mellitus: a systematic review and meta-analysis of randomised controlled trials.	clinical	Compared to placebo, the consumption of LCY or GTE does not significantly decrease the level of fasting plasma glucose, fasting serum insulin, OGTT–2 h glucose, haemoglobin A1C and HOMA-IR in populations at risk of Type 2 diabetes mellitus.
Xu et al., 2020	Effects of green tea consumption on glycaemic control: a systematic review and meta-analysis of randomised controlled trials.	clinical	LCY intake has a favourable effect on fasting blood glucose concentration but does not significantly affect fasting blood insulin or HbA1C.
7. Other pharmacological activities (n = 2)			
H.-T. Huang et al., 2020	Osteoprotective roles of green tea catechins.	epidemiological, clinical, *in vivo* and *in vitro*	GTE is shown to have bone health-promoting effects in the studies reviewed in this paper. Improvement in muscle function may also contribute to bone fracture reduction.

Included studies	Article title	Study type	Findings
Maleki et al., 2021	A comprehensive insight into effects of green tea extract in polycystic ovary syndrome: a systematic review.	clinical, *in vivo*	Current evidence indicates that LCY extract supplementation has potential beneficial effects on PCOS. Animal studies support the impact of LCY extract in improving ovarian function and histology. However, conclusions about the effect of LCY extract on inflammation are contradictory.

Note*:* BMI: Body mass index; BW: Body weight; COVID-19: Coronavirus disease of 2019; DNA: Deoxyribonucleic acid; E. coli: Escherichia coli; ECG: Epicatechin gallate; EGCG: Epigallocatechin gallate; EOC: epithelial ovarian cancer; ESBL: extended-spectrum beta- lactamase; GTC: Green tea catechin; GTE: Green tea extract; HbA1C: Haemoglobin A1c; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; LCY: Lu cha ye (Green tea, Camellia Sinensis leaf); miRNA: Micro-ribonucleic acid; MRSA: Methicillin-resistant Staphylococcus aureus; OGTT–2 h: Oral glucose tolerance testing–2 hours; PCOS: Polycystic ovary syndrome; RCTs: Randomised controlled trials; RNA: Ribonucleic acid; UTIs: Urine track infections; VEGF: Vascular endothelial growth factor.

Table 6.3: Summary of potential pharmacological effects of Lu Cha Ye – multiple activities

Included study (n=16)	Article title	Study type	Areas of investigation
Katiyar, 2003	Skin photoprotection by green tea: antioxidant and immunomodulatory effects.	*in vivo*, *in vitro*	Pharmacological effects: anti-inflammatory, antioxidant and immunomodulatory effects; prevention of photo-carcinogenesis and DNA photodamage
Crespy & Williamson, 2004b	A review of the health effects of green tea catechins in *in vivo* animal models.	*in vivo*	Health conditions: liver cancer, lung cancer, mammary cancer and nephropathy Health parameters: drug-metabolising enzymes and antioxidant markers
Cooper et al., 2005	Medicinal benefits of green tea: Part I. Review of noncancer health benefits.	clinical, *in vivo*, *in vitro*	Pharmacological effects: weight-loss, cardioprotective, anti-cariogenic and antiviral effects Health conditions: arthritis, osteoporosis
Ikeda, 2008	Multifunctional effects of green tea catechins on prevention of the metabolic syndrome.	clinical, *in vivo*, *in vitro*	Pharmacological effects: anti-obesity and suppression of postprandial hyperglycaemia Health parameters: cholesterol level and lipid metabolism
Clement, 2009	Can green tea do that? A literature review of the clinical evidence.	epidemiological, clinical	Pharmacological effects: anticancer effect, productive effect on cardiovascular and cerebrovascular protective system, cholesterol lowering effect and reduction on LDL oxidation
Thielecke & Boschmann, 2009	The potential role of green tea catechins in the prevention of the metabolic syndrome–a review	clinical, *in vivo*, *in vitro*	Health parameters: body weight and body fat, glucose homeostasis and cardiovascular health
Sae-tan et al., 2011	Weight control and prevention of metabolic syndrome by green tea.	*in vivo*	Health parameters: Body weight, adipose tissue weight, plasma glucose, plasma insulin, insulin sensitivity and glucose tolerance HOMA-IR, blood pressure and cholesterol
Mak, 2012	Potential role of green tea catechins in various disease therapies: progress and promise.	clinical, *in vivo*, *in vitro*	Pharmacological effects: weight-loss, cardioprotective, antioxidant, neuroprotective, anti-inflammatory and anticancer. Health conditions: cardiovascular diseases, cancer, cigarette smoke-induced lung injury

Included study (n=16)	Article title	Study type	Areas of investigation
Onakpoya et al., 2014	The effect of green tea on blood pressure and lipid profile: a systematic review and meta-analysis of randomised controlled trials.	clinical	Health parameters: blood pressure and lipid profile
Oz, 2017	Chronic inflammatory diseases and green tea polyphenols.	clinical, *in vivo*, *in vitro*	Health conditions: Inflammatory bowel disease, GI malignancy/prevention, Hepatic complications, Neurodegenerative Disorders,
Chu et al., 2017	Green tea extracts EGCG for different treatments.	*in vivo* and *in vitro*	Pharmacological effects: anticancer, antioxidant, anti-inflammatory, anti-collagenase, osteogenic and antifibrosis effects
Saeed et al., 2017	Green tea (Camellia sinensis) and l-theanine: Medicinal values and beneficial applications in humans—A comprehensive review	*in vivo*, *in vitro*	Pharmacological effects: weight-loss, antimicrobial, hypolipidemic, anticancer, antidiabetic, hepato-protective, anti-angiogenic, neuroprotective and collagen protective effects
Kanlaya & Thongboonkerd, 2019	Protective effects of EGCG from green tea in various kidney diseases.	*in vivo*, *in vitro*	Health conditions: acute kidney injury, cisplatin-induced nephrotoxicity, kidney stone disease, glomerulonephritis and lupus nephritis, renal cell carcinoma, diabetic nephropathy and renal fibrosis
Prasanth et al., 2019	A review of the role of green tea (Camellia sinensis) in antiphotoaging, stress resistance, neuroprotection, and autophagy	clinical and *in vivo*,	Pharmacological effects: antioxidant, Neuroprotective, anti-photoaging and autophagy effects
Kochman et al., 2020	Health benefits and chemical composition of matcha green tea: A review.	clinical, *in vivo*, *in vitro*	Pharmacological effects: anti-carcinogenic, anti-Inflammatory, cardioprotective, neuroprotective and antiviral effects
Chen et al., 2021	Therapeutic effects of green tea on endometriosis.	*in vivo*	Pharmacological effects: anti-inflammatory, antimitotic and anti-angiogenic effects

Note*:* DNA: Deoxyribonucleic Acid; GI: Gastrointestinal; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; LDL: Low-density lipoprotein

Details of the potential pharmacological activities of LCY are reported in 6.2.1–6.2.9.

6.2.1 Weight-loss activities

Recently, scientific evidence supporting the beneficial weight-loss effect of LCY, its catechins, and EGCG has been increasing and is demonstrated in epidemiological, clinical, *in vitro*, *in vivo*, and *in silico* studies (Huang et al., 2014; Lin et al., 2020; Rains et al., 2011; Suzuki et al., 2016; Wolfram et al., 2006). Currently, it is believed that LCY plays a role in fat loss by reducing food intake; interrupting lipid emulsification, reducing lipid absorption; suppressing adipogenesis, disrupting lipid synthesis, raising body thermogenesis and increasing energy expenditure through faecal lipid excretion (Huang et al., 2014; Lin et al., 2020; Thavanesan, 2011). Although the evaluation of available evidence supports a role of LCY in weight-loss, the extent of the effects obtained is still subjected to debate and requires more objective quantification in any future research (Thavanesan, 2011).

6.2.2 Anticancer activities

Anticancer is one of the most well-known pharmacological effects of LCY. Many *in vivo* studies have reported that LCY extract or EGCG protects against chemical carcinogens in various organs such as the intestines, lung, liver, prostate, and breast (Crespy & Williamson, 2004; Li et al., 2014; Miyata et al., 2019).

Angiogenesis is one of the important factors in the growth and development of tumours. EGCG as a main catechin of LCY inhibits angiogenesis through different mechanisms such as the use of miRNAs, suppression of cell proliferation, induction of apoptosis, inhibition the expression of angiogenic factors, suppression the phosphorylation of receptors, and inhibition of binding of VEGF (vascular endothelial growth factor) to its receptor (Rashidi et al., 2017). Animal

studies have found that EGCG inhibits proliferative activity in hematoma cells, regulates immune activity and protects against mammary cancer post-initiation in animal studies (Crespy & Williamson, 2004).

6.2.3 Antimicrobial activities

In the past two decades several studies have reported that LCY and EGCG have anti-infective properties (Steinmann et al., 2013). LCY has been illustrated as an effective antimicrobial agent, especially against multidrug- resistant strains, and in particular, Methicillin-resistant Staphylococcus aureus (MRSA) and extended-spectrum beta-lactamase (ESBL) producing organisms. However, there are certain issues that need to be addressed concerning these results (Reygaert, 2014). Studies using human and mammalian cells lines have shown that LCY binding has significantly decreased the bacterial ability to bind to host cells (Reygaert, 2018). The antiviral effects of EGCG on deoxyribonucleic acid (DNA), ribonucleic acid (RNA), coronaviruses and other viruses have been summarised and discussed. Reygaert (2018) has stated that although the anti-inflammatory effects of EGCG on cardiovascular disease have been disclosed by molecular docking experiments, it needs to be confirmed by *in vivo* studies.

6.2.4 Neuroprotective activities

Several epidemiological and human intervention studies have demonstrated beneficial effects of the consumption of LCY on neurodegenerative impairment, such as cognitive dysfunction and memory loss. In more specific brain disorders, studies have supported the beneficial effects of LCY on Parkinson's disease and Alzheimer's disease (Pervin et al., 2018). The mechanisms of the neuroprotective effects of LCY are proposed to be associated with microglia (Farkhondeh et al., 2020) and glutamate receptors and transporters (Kakuda, 2002).

6.2.5 Cardiovascular protective activities

Several human intervention studies have demonstrated that LCY and EGCG may contribute to the maintenance of cardiovascular health and to the treatment of the related diseases. It was shown that a daily consumption of 200–300 mg EGCG exerts cardiovascular protective effects. These studies are consistent with the epidemiological evidence that the consumption of 5–6 or more cups of LCY per day protects cardiovascular and metabolic health.

However, the results of the intervention studies are equivocal (Wolfram, 2007). Comprehensive studies have been performed on the cardioprotective effects of LCY and tea catechins in human as well as in both *in vitro* and *in vivo* models. But the extrapolation of the results of animal or cell culture studies to human clinical situations is uncertain mainly because of the concentrations of LCY catechins used in animal or *in vitro* studies are far higher than the plasma concentrations achievable in humans after LCY consumption (Islam, 2012).

6.2.6 Antidiabetic activities

A meta-analysis study found that the LCY extract did not significantly decrease the level of fasting plasma glucose, fasting serum insulin, OGTT–2 h glucose, haemoglobin A1c (HbA1c) or HOMA-IR in populations at risk of Type 2 diabetes mellitus (Wang et al., 2014). The result of another systematic review and meta-analysis of RCTs on the effects of LCY consumption has shown that LCY intake has a favourable effect on fasting blood glucose concentration, which significantly lowers fasting blood glucose level by 1.44mg/dL. with no obvious heterogeneity. However, LCY intake does not significantly affect fasting blood insulin or HbA1c (Xu et al., 2020).

6.2.7 Anti-inflammatory activities

Inflammatory response is an integral part of many diseases. It may lead to an increase in the production of reactive oxygen species (ROS), which can damage the cell structures and cause long-term disruption in the functioning of the body as a whole. The main effect of anti-inflammatory and antioxidant substances is to inhibit the signalling in the inflammatory process by scavenging ROS (Chu et al., 2017). The anti-inflammatory bioactivities of LCY have been well-studied (Hodges et al., 2020; Kochman et al., 2020; Mak, 2012; Oz, 2017). EGCG has been shown to possess anti-inflammatory properties in both *in vivo* and *in vitro* studies (Chen et al., 2021; Trekli et al., 2004).

6.2.8 Anti-oxidative activities

In vivo studies have shown that administration of LCY extract and polyphenols elevated the serum antioxidative activity in rats (Skrzydlewska et al., 2002; Yokozawa et al., 2002). The effectiveness of LCY catechins as radical scavengers is in the order of ECG > EGCG > EGC > EC > catechin (Gopal et al., 2016).

6.2.9 Other pharmacological activities

LCY extract has been shown to have health-promoting effects on bones and the improvement in muscle function may also contribute to bone fracture reduction (H.-T. Huang et al., 2020).

In addition, current evidence indicates that GT extract supplementation has potential beneficial effects on polycystic ovary syndrome which is characterised by ovarian tissue inflammation. Animal studies support the impact of LCY extract in improving ovarian function and histology. However, conclusions about the effect of LCY extract on inflammation were contradictory. (Maleki et al., 2021).

6.3 Huai hua

A total of 2,113 papers were identified according to the search strategies employed and 35 of those meeting the inclusion criteria were included for analysis, including 11 *in vivo* studies, 21 *in vitro* studies, and 3 combinations of *in vivo* and *in vitro* studies. The selection process of this review is illustrated in Figure 6.3.

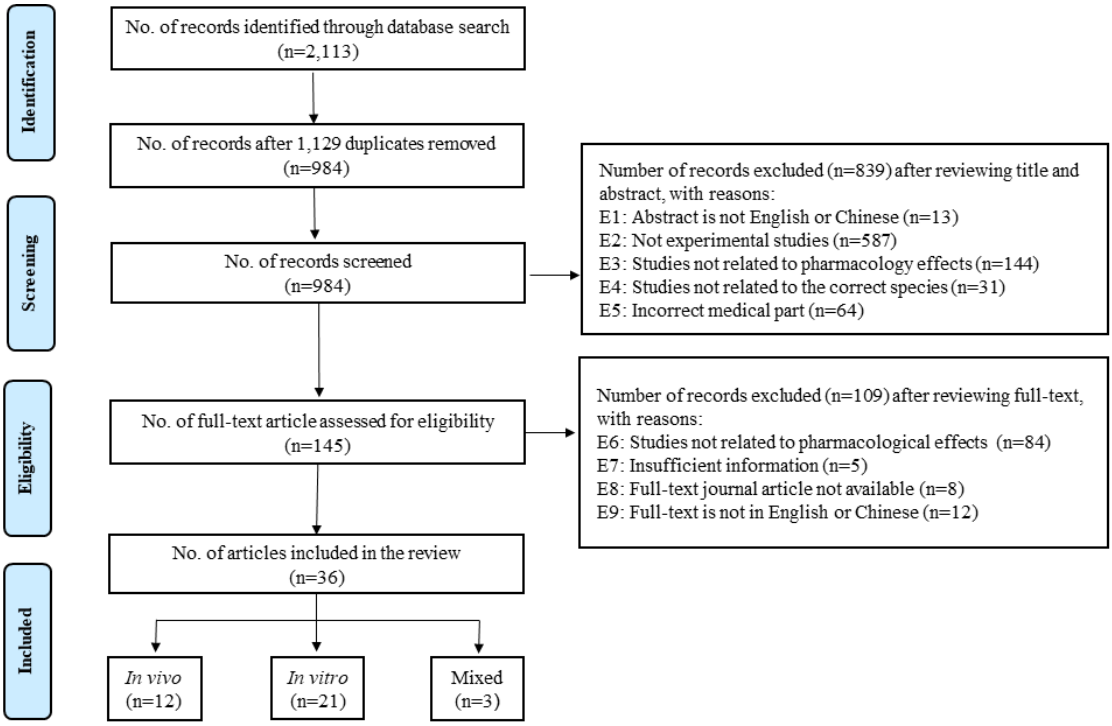


Figure 6.3: Selection process of modern literature review on Huai hua

A wide range of pharmacological activities of HH have been identified which include antioxidant (n=9), anticancer (n=6), antidiabetic (n=4), anti-infective (n=4), inhibitory (n=4), anti-inflammatory (n=2), haemostatic (n=2) and others (n=4), where n is the number of studies. Characteristics and primary findings of the included studies are summarised in Table 6.4.

Table 6.4: Potential pharmacological activities of Huai hua

Included studies	Type of study	Tested substance	Model or sample	Active concentration	Administration (*In vivo*)
1. Antioxidant activities (n=9)					
R. Huang et al., 2020	*In vivo* and *in vitro*	CHM formula consisting of HH	Male KM mice (*in vivo*) Mice serum (*in vitro*)	5, 10, and 15g/kg (CHM/bw)	Oral
Yang et al., 2002	*In vivo*	Aqueous solution of HH	Female ICR mice	200 and 300 mg/kg	Intragastric
Zhang et al., 2007b	*In vivo*	Aqueous solution of HH	ICR mice	0.1 g/mL, 250 mL/kg per day	Gastric gavage
(Liu, Bai, Li, Fu, Chen, et al., 2019	*In vivo*	CHM formula consisting of HH	Male C57BL/6 mice	1.2 g/kg (clinical equivalent dose)	Oral
Lu et al., 2003	*In vitro*	Aqueous extract of HH	PC12 cells of mice	1, 10, 200, 500 and 1000 μg/mL	N/A
Hou et al., 2015	*In vitro*	Ethanolic extract of HH	Livers from male Wistar rats	N/A	N/A
J. R. Wang et al., 2019	*In vitro*	Methanolic extract of HH	Antioxidant activity assays	200, 400, 600, 800, and 1000 μg/mL	N/A
Tan et al., 2020	*In vitro*	Ethanolic/ aqueous solution of HH	Covalent triazine framework with luminol	50 mg HH powder in 20 mL of 70% (V/V) ethanol/water solution	N/A
Tan et al., 2020	*In vitro*	Ethanolic of HH	Antioxidant activity assays	200, 400, 600, 800, and 1000 μg/mL	N/A
2. Anticancer activities (n=6)					
Li et al., 2017	*In vivo*	Ethanolic extract CHM formula consisting of HH	Mice bearing B16F10 melanomas	0.6, 1.2 and 2.4 g/kg	Intragastric
Shi et al., 2017	*In vivo* and *in vitro*	Ethanolic extract CHM formula consisting of HH	B16F10 mice (*in vivo*) Human A375 melanoma cells (*in vitro*)	50, 100, 200, 300, 400, 600, 800 and 1000 μg/mL	Intragastric
Zhang et al., 2012	*In vitro*	Aqueous extract of HH	MCF-7 Breast Cancer Cell Line	0.5, 1.0, 2.0, 5.0, 10.0 and 20.0 mmol/L	N/A

Included studies	Type of study	Tested substance	Model or sample	Active concentration	Administration (*In vivo*)
Chen et al., 2019	*In vitro*	Ethanolic extract of HH	Human nasopharyngeal carcinoma CNE1 cells	2.0, 4.0, 8.0, 12.0, 16.0 and 20.0 g/mL	N/A
Yang et al., 2011	*In vitro*	Ethanolic extract of HH	Human nasopharyngeal carcinoma CNE2 cells	20, 40, 60 and 80 μmol/L	N/A
Kim et al., 2017	*In vitro*	Ethanolic extract of HH	Cells of mice with osteoclast	N/A	N/A
3. Antidiabetic activities (n=4)					
W. Zhang et al., 2017	*In vivo*	Ethanolic extract of HH	Female SPF mice	25, 25 and 100 μg/g	Gastric gavage
Hou et al., 2014	*In vitro*	Methanolic extract of HH	UPLC–MS/MS technique	0.2, 1 and 10 μmol/L	N/A
Ha et al., 2010	*In vitro*	Compounds isolated from HH	Mouse 3T3-L1 cell line	N/A	N/A
Chen et al., 2010	*In vitro*	Methanolic extract of HH	Analytical HPLC	N/A	N/A
4. Antimicrobial activities (n=4)					
Yao et al., 2011	*In vitro*	Essence oil from HH	Selected strains of bacteria	50 g of HH was purged with nitrogen to ~1 mL	N/A
Chen et al., 2008	*In vitro*	Essential oil from HH	Different types of bacteria: *escherichia coli*, staphylococcus aureus, salmonella typhi, shigella dysentery and aspergillus niger	50g dried HH in 1mL distilled essential oil	N/A
Zhang & Zheng, 2006	*In vitro*	Compound K3 purified from HH	MTT assay	N/A	N/A
Mou et al., 2021	*In vitro*	Alkali solution and acid precipitation of the buds of and rutin from HH	Chromatography	N/A	N/A
5. Inhibitory activities (n=4)					
Le et al., 2017	*In vitro*	Ethanolic, ethylacetate and dichloromethane extracts of HH	Urease, an enzyme that catalyses the hydrolysis of urea	1.5, 2.0, 2.5 g/L	N/A
Lo et al., 2009	*In vitro*	Ethanolic extract of HH	Human epidermal melanocytes	N/A	N/A
Yang et al., 2015	*In vitro*	Methanolic extract of HH	Streptococcus mutans	N/A	N/A

Included studies	Type of study	Tested substance	Model or sample	Active concentration	Administration (*In vivo*)
Jiang et al., 2019	*In vitro*	Methanol extract of HH	BSA-MGO assay	N/A	N/A
6. Anti-inflammatory activities (n=2)					
Man et al., 2008	*In vivo*	Herbal extract of HH	Female hairless mice and CD-1 male mice	60 µl of 1% herbal extract	Topical
Zhang & Shi, 2018	*In vivo*	Ethanolic extract of HH	Male and female mice	0.1, 0.2 and 0.4 g/kg	Intragastric
7. Haemostatic activities (n=2)					
Li et al., 2004	*In vivo*	Powder of raw dried HH	Chinese mice (19–21 g) and Wistar rats (180–200 g)	10.0 and 20.0 g/kg for mice 7.2 and 14.4 for rats	Gastric gavage
Zhao et al., 2010	*In vivo*	Aqueous solution of HH	SD mice	4 g/mL, 0.2 mL/kg	Oral
8. Other activities (n=3)					
Immunoregulatory activity (He et al., 2016)	*In vivo*	Ethanolic extract of HH	Chinese mice	0.5, 1.0 and 1.5 mL/day	Intragastric
Protective activity (Nie, 2013)	*In vivo*	Aqueous solution of HH	Male KM mice	15 and 60 mg/kg	Intragastric
Ameliorative activity (Liu et al., 2020)	*In vivo* and *in vitro*	CHM formula consisting of HH	Male Sprague-Dawley rats (*in vivo*) HPLC (*in vitro*)	1 g/mL	Oral
Anti-allergic activity (J. H. Lee et al., 2008)	*In vitro*	Ethanolic extract of HH	Mast cells from male ICR mice	10, 30 and 100 µg/mL	N/A

Note: B16F10: a murine melanoma cell line from a C57BL/6J mouse; BSA-MGO: bovine serum albumin-methylglyoxal; C57BL/6: C57 black 6 – a common inbred strain of mouse used in laboratory; CD-1 male mice: albino outbred strain of male mice model that have frequently been used in toxicology and pharmacological research; CHM: Chinese herbal medicine; CNE: nasopharyngeal carcinoma; SPF: specific pathogen free; HH: Huai hua; HPLC: High-performance liquid chromatography; ICR: Institute of Cancer Research; KM mouse: an inbred strain of mouse from a Chinese province, Kunming; MTT assay 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide assay; N/A: not applicable; PC12 cell: a cell line derived from a pheochromocytoma of the rat adrenal medulla; SD mice: a spontaneous mutation of the house mice; UPLC–MS/MS: Ultraperformance liquid chromatography-tandem mass spectrometry; V/V: volume/volume

Details of the potential pharmacological activities of HH are reported in 6.3.1–6.3.8

6.3.1 Antioxidant activities

An *in vivo* and *in vitro* study (R. Huang et al., 2020) indicated that HH has synergistic effects on improving the antioxidant capacity of a CHM formula, *Yu Ping Feng San*, in the body on the basis of free radical scavenging capacity. The results of three *in vivo* studies (Liu, Bai, Li, Fu, Chen, et al., 2019; Yang et al., 2002; Zhang et al., 2007) performed on the serum of ICR mice showed that HH can enhance the antioxidative capacity of the mice. An *in vitro* study found that HH protected the induced oxidative damage of microsomes and nerve cells in mice (Lu et al., 2003).

An *in vitro* study investigated the anti-lipid peroxidation activities and the inhibitory capacities of Advanced glycation end products formation for 17 common Chinese herbal extracts such as HH, baical skullcap root, ginkgo biloba, and licorice root. The results demonstrated that HH, among all the herbal extracts in the study, had the strongest inhibitory activities against oxidative stress (Hou et al., 2015). The antioxidant activities of HH are mainly contributed by its flavonoid compounds: rutin, narcissin, quercetin and isorhamnetin while the quantification of these compounds varied with the maturity stages of the flowers (J. R. Wang et al., 2019).

6.3.2 Anticancer activities

A CHM formula, namely Sophorae lonicerae extract (SLE), comprising HH and another herb *Lonicerae Japonicae Flos*, is traditionally used for treating melanoma, the most aggressive form of skin cancer (Li et al., 2017). SLE alters the compositions of the immune cells and molecules of the signal transducer and activator of the transcription 3 (STAT3) pathway in the melanoma microenvironment (Liu, Bai, Li, Fu, Guo, et al., 2019). A study involving both *in vivo* and *in vitro* experiments demonstrated that SLE restrained tumour growth and STAT3 activation in a B16F10 allograft model and exhibited higher cytotoxicity in melanoma cells

than in normal skin cells (Li et al., 2017). An *in vitro* study indicated that quercetins extracted from HH, at concentrations of 5.0 and 10.0 mmol/L, inhibited the growth of human breast cancer cells, Michigan Cancer Foundation-7 (MCF-7), significantly ($p < 0.05$) (Zhang et al., 2012). The rate of apoptosis of MCF-7 cells treated with quercetin aqueous extract at concentrations of 10.0 mmol/L for 1 day, 2 days and 3 days were 9.2 ± 1.5%, 30.0 ± 11.8% and 60.8 ± 10.6%, respectively. Rutin is one of the main constitutions of HH (Chinembiri et al., 2014; Nobili et al., 2009). Quercetin de-glycosylated from an ethanolic extract of HH rutin possesses an inhibitory effect on the proliferation of human nasopharyngeal carcinoma cells CNE1, with the half maximal inhibitory concentration (IC_{50}) at 29.95 μmol/L after 48 hours (Chen et al., 2019).

The results of an *in vitro* study with human nasopharyngeal carcinoma epithelioid cell line CNE 2 demonstrated that the proliferation and apoptosis effects of quercetin are dose- and time-dependent. During an *in vitro* experiment on CNE 2 cells, it was observed that after treatment with quercetin extract at a concentration of 80 μmol/L, the activities of CNE 2 were significantly inhibited ($p < 0.01$) after 48 hours (Yang et al., 2011). An *in vitro* study on mouse-derived bone marrow macrophages found that the HH extract significantly decreased osteoclast differentiation in a dose-dependent manner. The inhibitory effect was elicited through a reduction of the nuclear factor of activated T cells expression during the differentiation of osteoclasts, which are the cells responsible for bone destruction and are associated with inflammation-related bone diseases (Kim et al., 2017).

6.3.3 Antidiabetic activities

In an *in vivo* study, after three weeks' intragastric administration of HH extract at the daily dose of 100 μg/g, the level of blood glucose in Type 2 diabetic mice was reduced and the glucose tolerance in oral glucose tolerance test was improved. Using the antidiabetic drug

rosiglitazone as control, an ethanolic extract of HH significantly reduced fasting blood sugar level ($p < 0.05$) at 30 and 60 minutes (W. Zhang et al., 2017). The results of three *in vitro* studies indicated that certain flavonoid compounds from the HH flower can inhibit aldose reductase activity and AGEs formation (Hou et al., 2014) and improve glucose uptake (Chen et al., 2010; Ha et al., 2010).

6.3.4 Antimicrobial activities

Two *in vitro* studies (Chen et al., 2008; Yao et al., 2011) investigated the antimicrobial activities of HH and the result indicated that the essential oil of HH has an antibacterial effect on 13 out of 16 strains of bacteria, with the highest potency on *Escherichia coli* and *Staphylococcus aureus*. In an *in vitro* study, Zhang and Zheng (2006) found that a compound K3 with chemical formula $C_{11}H_8O_2$, purified from HH was found to have anti-human immunodeficiency virus activities.

6.3.5 Inhibitory activities

Ethanolic, ethylacetate and dichloromethane extracts from HH were revealed to have urease inhibitory activities, with IC_{50} of 2.63, 1.90, 0.53 g/L, respectively. These findings provided a reasonable explanation for the stomach protection and restoration functions of HH (Le et al., 2017). An *in vitro* study conducted by Lo et al. (2009) found a new compound, *N*-feruloyl-*N*′-cis-feruloyl-putrescine, together with four flavonoids and three putrescine derivatives, which were obtained after an assay-guided isolation of HH. This new compound exhibited high potent cellular tyrosinase inhibition in human epidermal melanocytes. In another *in vitro* study, a new maltol derivative along with three known maltol derivatives and flavonol glycosides were isolated from HH. Based on the results of combined spectroscopic methods, the structure of the new compound was determined to be maltol-3-*O*-(4'-*O*-*cis*-*p*-coumaroyl-6'-*O*-(3-hydroxy-3-methylglutaroyl))-*β*-glucopyranoside. These compounds strongly inhibited the action of

sortase A from *Streptococcus mutans* (Yang et al., 2015). Advanced glycation end products (AGEs) are a diverse group of highly oxidant compounds with pathogenic significance in diabetes (Uribarri et al., 2010). An *in vitro* study was performed to investigate the effects of rutin and methylglyoxal reaction (1:1, 1:3, 3:1) for 6 days on the formation of AGEs. The results showed that the inhibition activity of rutin on AGEs production was most obvious when the reaction ratio was 1:3, and the most inhibition was within 24 hours and it stabilised after three days (Jiang et al., 2019).

6.3.6 Anti-inflammatory activities

An *in vivo* study showed that the topical application of a CHM composed of HH on the skin of hairless mice could reduce cutaneous inflammation (Man et al., 2008). The anti-inflammatory and analgesic effects of total flavonoids in HH were investigated in an *in vivo* study on 50 mice treated with three different dosages (0.10, 0.20 and 0.40 g/kg·d) of HH extract, aspirin (0.25 g/kg·d) and saline. The degree of auricle oedema induced by xylene in mice in the aspirin group, middle and high HH dosage groups was lower than that in the saline group ($p < 0.05$). The severity of torsional body reactions in the aspirin group and the high HH dosage group was less than that in the saline group ($p < 0.05$). The hot-plate pain threshold in the aspirin group and the middle and high dosage groups were higher than those in the saline group ($p < 0.01$) (Zhang & Shi, 2018).

6.3.7 Haemostatic activities

An *in vivo* study with Wister rats and Kunming mice found that HH in crude, parched and carbonised forms, and its extracts rutin, quercetin and tannin, have haemostatic effects. All the samples lowered the capillary permeability, bleeding time and coagulation time in mice and also decreased the plasma prothrombin time in rats. Additionally, rutin had the effect of raising the platelet count (Li et al., 2004). Another *in vivo* study using bleeding time and recalcification

time as specificity indicators for hematischesis function revealed that carbonised HH could increase the haemostatic effect (Zhao et al., 2010).

6.3.8 Other pharmacological activities

Other pharmacological activities of HH identified in this study were immunoregulatory (Chen et al., 2016), protective activities on mice with anxiety (Nie, 2013), ameliorative activities on rats with colitis (Liu et al., 2020) and anti-allergic activities on mice (J. H. Lee et al., 2008).

In summary, HH and its bioactive compounds have demonstrated various potentials to against cancers, gastrointestinal diseases, microbial diseases, Type 2 diabetes, oxidation, haemorrhagic disorder and inflammations in *in vivo* and *in vitro* experiments.

6.4 Discussions

The modern literature review in Phase IIa included literature searches done in 7 English and 3 Chinese online databases to yield information on phytochemistry, pharmacology, and toxicology of the individual ingredients of formula RCM-104. In this review, a total of 129 articles were included to investigate the characteristics of JMZ, LCY and HH.

This Chapter has reported the results from the review. Each of the three herbs possesses multiple pharmacological activities. The discussion here is focused on their contributions to weight loss.

The results of the search found JMZ and nine of its active chemical compounds are predicted or identified to have weight reduction effects. The major pathway is reducing food intake by suppressing appetite and increasing satiety via influencing the signals for 5-hydroxytryptamine receptor 2C (5-HT2C) and GLP-1 (Glucagon-like peptide-1) receptor activation.

The findings positively support the weight-loss effect of LCY. The beneficial weight-loss effect of LCY, its catechins, and EGCG is demonstrated in epidemiological, clinical, *in vitro*, *in vivo*, and *in silico* studies.

Although the included articles do not focus on the weight-loss effect of HH, HH and its bioactive compounds have demonstrated various potentials to against major obesity-related health risks such as diabetes.

At the collective level, one of the pathways of weight loss for RCM-104 is the effects on lipid metabolism. JMZ contributes to reducing lipid absorption via the inhibition of pancreatic lipase. LCY plays the role by reducing food intake; interrupting lipid emulsification, reducing lipid absorption; suppressing adipogenesis, disrupting lipid synthesis, raising body thermogenesis and increasing energy expenditure through fecal lipid excretion. Moreover, the antioxidation activity of all these three herbs accounted for the lipid-reducing effect of RCM-104.

It may provide more cures on the actions of RCM-104 when we compare the results generated in this Phase IIa with those generated in Phase I. A significant common finding is that RCM-104 can help to prevent overeating. As discussed in 5.4, from Chinese medicine perspective, overeating can cause the obesity syndrome of ‘Stomach heat and Spleen deficiency’; RCM-104 can help to prevent overeating by reducing the Stomach heat.

In summary, the findings from both classical and modern reviews show that RCM-104 may contribute to weight loss through the similar pathways.

Chapter 7 Results IIb – Identification of protein targets and chemical compounds

In the modern literature review of Phase IIb, literature search was carried out in 7 English electronic databases, and the information search was carried out in 5 online databases, 2 textbooks, 1 official compendium and 1 encyclopaedia, as listed in Section 4.3.

This chapter presents the identified the anti-obesity protein targets, anti-obesity agents and herbal chemical compounds of the individual ingredients of formula RCM-104, providing input data required for the molecular docking process in Phase III.

7.1 Anti-obesity protein targets

Thirty-eight anti-obesity targets were identified with the methodology described in Section 4.3.1. A complete list of anti-obesity targets that were used for modular docking in this project is shown in Table 7.1. An eight-digit code is assigned to each protein structure, with the identifier (ID) in the first three digits, the PDB code in 4th–7th digits and chain label in the last digit.

Table 7.1: Characteristics of anti-obesity targets

Anti-obesity targets		
ID	**Target code**	**Target name**
p01	p011lpaB	Pancreatic lipase
p02	p021lpbB	Pancreatic lipase
p03	p031n8sA	Pancreatic lipase
p04	p041hlgA	Gastric lipase
p05	p051hlgB	Gastric lipase
p06	p066e7kA	Lipoprotein lipase
p07	p076e7kB	Lipoprotein lipase
p08	p086oazA	Lipoprotein lipase
p09	p094x9yA	Pancreatic amylase
p10	p104gqqA	Pancreatic amylase

Anti-obesity targets		
ID	**Target code**	**Target name**
p11	p114z49A	Fatty acid synthase
p12	p124z49B	Fatty acid synthase
p13	p136nnaA	Fatty acid synthase
p14	p146nnaB	Fatty acid synthase
p15	p156g79S	Serotonin receptor 5-HT1B
p16	p164iraA	Serotonin receptor 5-HT1B
p17	p175v54A	Serotonin receptor 5-HT1B
p18	p186bqgA	Serotonin receptor 5-HT2C
p19	p196bqhA	Serotonin receptor 5-HT2C
p20	p206dzzA	Serotonin transporter
p21	p216dgoA	PPARG
p22	p226dgoB	PPARG
p23	p233e00D	PPARG
p24	p245zmdA	FTO
p25	p253h8oA	FTO
p26	p263h8rA	FTO
p27	p273h8xA	FTO
p28	p283v6oA	Leptin receptor
p29	p293v6oB	Leptin receptor
p30	p306e2pC	Leptin receptor
p31	p316e2pD	Leptin receptor
p32	p325nx2A	GLP1 receptor
p33	p336b3jR	GLP1 receptor
p34	p345vexA	GLP1 receptor
p35	p355vexB	GLP1 receptor
p36	p365i6xSM	Sodium-dependent serotonin transporter
p37	p374xp4SM	Sodium-dependent dopamine transporter
p38	p384xptSM	Sodium-dependent norepinephrine transporter

Note: 5-HT1B: 5-hydroxytryptamine receptor 1B; 5-HT2C: 5-hydroxytryptamine receptor 2C; FTO: Fat mass and obesity-associated protein; GLP1: Glucagon-like peptide-1; PPARG: Peroxisome proliferator-activated receptor gamma

7.1.1 Lipase

Lipase is an enzyme that breaks down triglycerides into free fatty acids and glycerol by catalysing the hydrolysis of the ester bonds in triglycerides. Pancreatic lipase is found within the small intestine and is involved in degrading dietary triglycerides. Lipoprotein lipase is

found in the vascular endothelial cells and is responsible for degrading triglycerides that circulate from chylomicrons and very low-density lipoproteins (Pirahanchi & Sharma, 2022). Gastric lipase is generated by the gastric cells found in the mucosal lining of the stomach. They are responsible for the digestion of extra lipid (Tomasik et al., 2013).

7.1.2 Pancreatic amylase

Amylase is a digestive enzyme predominantly secreted by the pancreas and salivary glands. Its main function is to hydrolyse the glycosidic bonds in starch molecules, converting complex carbohydrates to simple sugars (Akinfemiwa & Muniraj, 2021).

7.1.3 Fatty acid synthase

Fatty acid synthase is a class of multifunctional enzyme protein that catalyses fatty acid synthesis (Wakil, 1989).

7.1.4 Serotonin receptors

Serotonin receptors are a group of G protein-coupled receptor and ligand-gated ion channels found in the central and peripheral nervous systems (Frazer & Hensler, 1999). They influence numerous biological and neurological processes including anxiety, aggression, cognition, learning, memory, mood, nausea, appetite, sleep and thermoregulation (D. Nichols & C. Nichols, 2008).

7.1.5 Peroxisome proliferator activated receptor gamma

Peroxisome proliferator activated receptor gamma (PPARG) is the protein encoded by PPARG gene is PPAR-gamma and is a regulator of adipocyte differentiation (National Center for Biotechnology Information, 2022c).

7.1.6 Fat mass and obesity-associated protein

Fat mass and obesity-associated protein (FTO) is an enzyme in humans encoded by the FTO gene located on chromosome 16. The exact physiological function of FTO gene is not known but studies in humans and mice indicate a role in nervous and cardiovascular systems. FTO has a strong association with BMI, obesity risk, and type 2 diabetes (National Center for Biotechnology Information, 2022d).

7.1.7 Leptin receptor

Leptin receptor is a protein functions as a receptor for the fat cell-specific hormone leptin. Adipocytes express leptin receptors and increase their rates of lipolysis in response to autocrine stimulation. Leptin acts directly on pancreatic beta cells and inhibits insulin synthesis and secretion. (Holt et al., 2022).

7.1.8 Glucagon-like peptide-1 receptor

Glucagon-like peptide-1 (GLP1) receptor is a receptor protein found on beta cells of the pancreas and on neurons of the brain. GLP1 receptor agonists are a class of medications utilised in the treatment of type 2 diabetes and obesity (Collins & Costello, 2022).

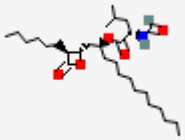
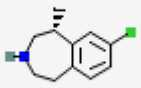
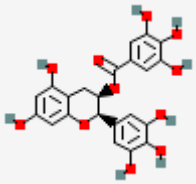
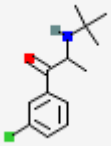
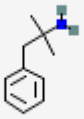
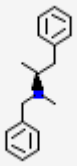
7.1.9 Neurotransmitter transporters

Neurotransmitter transporters are a class of membrane transport proteins that span the cellular membranes of neurons. Their primary function is to carry neurotransmitters across these membranes and to direct their further transport to specific intracellular locations. Members of this family include the membrane carriers for dopamine, serotonin, norepinephrine, and γ-aminobutyric acid (ScienceDirect, 2021).

7.2 Anti-obesity agents

Seven anti-obesity agents were selected as controls for the current project using the methodology described in Section 4.3.2. Characteristics and details of anti-obesity drugs are shown in Table 7.2 and Table 7.3 respectively.

Table 7.2: Characteristics of anti-obesity agents

Chemical compounds of anti-obesity agents					
ID	**Compound name**	**Description**	**Molecular formula / PubChem CID**	**Molecular weight (g/mol)**	**Chemical structure**
d1	orlistat	Gastrointestinal lipases (GI) inhibitor	$C_{29}H_{53}NO_5$ 3034010	495.7	
d2	liraglutide	Glucagon-like peptide-1 (GLP-1) analogue	$C_{172}H_{265}N_{43}O_{51}$ 16134956	3751	
d3	lorcaserin	Appetite suppressant	$C_{11}H_{14}CIN$ 11658860	195.69	
d4	epigallocatechin gallate	Energy expenditure stimulant	$C_{22}H_{18}O_{11}$ 65064	458.4	
d5	bupropion	Norepinephrine and dopamine reuptake inhibitor	$C_{13}H_{18}CINO$ 444	239.74	
d6	phentermine	Sympathomimetic anorectic agent	$C_{10}H_{15}N$ 4771	149.23	
d7	benzphetamine	Sympathomimetic anorectic agent	$C_{17}H_{21}N$ 5311017	239.35	

Note: Details of the anti-obesity agents were extracted from the online database Drugbank 5.0 (Wishart et al., 2018) and reported in Table 7.3. Colour coding of the atoms in chemical structures: Red = Oxygen, Blue = Nitrogen, Cyan = Polar Hydrogen, Green = Chlorine

Table 7.3: Details of anti-obesity agents

Drug name/ Description	Indication	Mechanism of action
Orlistat A reversible inhibitor of gastrointestinal lipases indicated for weight-loss and weight maintenance.	Indicated for obesity management including weight-loss and weight maintenance when used in combination with calorie reduction in overweight and obese adults.	Orlistat helps with weight reduction and maintenance by lowering the absorption of dietary fats via the inhibition of lipase enzymes. It acts in the gastrointestinal (GI) tract via covalent binding to the serine residues located on the active site of both gastric and pancreatic lipase. When orlistat is taken with food containing fat, it partially inhibits the hydrolysis of triglycerides. This decreases absorption of mono-glyceride, diglycerides and free fatty acids, thus contributing to weight maintenance and weight-loss.
Liraglutide An agonist of the GLP-1 receptor used in the management of Type 2 diabetes mellitus and prevention of cardiovascular complications associated with diabetes.	Indicated as an adjunct to diet and exercise for chronic weight management in adult patients who are obese (BMI ≥ 30 kg/m2), or who are overweight (BMI ≥ 27 kg/m2) and have at least one weight-related comorbidity. It is also indicated for chronic weight management in paediatric patients ≥ 12 years old who weigh ≥ 60 kg and who have an initial BMI.	The prolonged action of liraglutide is achieved by attaching a fatty acid molecule at position 26 of the GLP-1 molecule thus enabling it to bind reversibly to albumin within the subcutaneous tissue and bloodstream and then be released slowly over time. Binding with albumin results in slower degradation and reduced elimination of liraglutide from the circulation by the kidneys compared with GLP-12,3.

Drug name/ Description	Indication	Mechanism of action
Lorcaserin An agonist of serotonin receptor, 5HT2CR. It produces a dose-dependent weight-loss effect by promoting satiety and decreasing food consumption.	Lorcaserin is used in conjunction with physical activity and calorific restriction for weight-loss in obese patients with a body mass index (BMI) of 30 and above, and in overweight patients with weight-related comorbidities.	Although the exact mechanism is unknown, it is believed to involve the selective activation of 5-HT2C receptors in the anorexigenic pro-opiomelanocortin neurons in the arcuate nucleus of the hypothalamus. This results in decreased food intake and satiety by promoting the release of alpha-melanocortin stimulating hormone, which acts on melanocortin-4 receptors.
Epigallocatechin gallate (EGCG) Has been investigated for the treatment of hypertension and diabetes.	Not available in Drugbank database. Although minimal information of EGCG is found in the Drugbank database, the pharmacological effects, pharmacodynamics and mechanism of action of EGCG have been extensively investigated in both clinical trials and animal studies. The results of these clinical trials and studies have indicated that ECCG lowers dose-dependently plasma cholesterol levels and increases faecal excretion of total lipids and cholesterol (Hursel et al., 2009; Raederstorff et al., 2003; Wolfram et al., 2006).	
Bupropion A norepinephrine and dopamine reuptake inhibitor used in the treatment of major depressive disorder,	It is indicated for the treatment of major depressive disorder, seasonal affective disorder, and as an aid to smoking cessation. When used in combination with naltrexone (marketed as Contrave®), bupropion is indicated as an adjunct to a reduced-calorie diet and	Bupropion is a norepinephrine/dopamine-reuptake inhibitor that exerts its pharmacological effects by weakly inhibiting the enzymes involved in the uptake of the neurotransmitters, norepinephrine and dopamine from the synaptic cleft, thus prolonging their duration of action within the neuronal synapse

Drug name/ Description	Indication	Mechanism of action
seasonal affective disorder, and as an aid to smoking cessation.	increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m2 or greater (obese) or 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, Type 2 diabetes mellitus, or dyslipidemia).	and the downstream effects of these neurotransmitters. More specifically, bupropion binds to the norepinephrine transporter and the dopamine transporter. Due to these stimulant effects and selective activity at dopamine and norepinephrine receptors, bupropion has been identified as having an abuse potential.
Phentermine A sympathomimetic anorectic agent used as a short-term adjunct therapy that is included in a regimen of weight reduction in cases of exogenous obesity.	It is indicated, alone or in combination with topiramate, as a short-term adjunct, (not for more than a few weeks), in a regimen of weight reduction based on exercise, behavioural modifications and calorific restriction in the management of exogenous obesity for patients with an initial BMI greater than 30 kg/m2 or greater than 27 kg/m2 in the presence of other risk factors such as controller hypertension, diabetes or hyperlipidaemia.	Phentermine is an indirect-acting sympathomimetic agent that acts by releasing noradrenaline from the presynaptic vesicles in the lateral hypothalamus. This increase in noradrenaline concentration in the synaptic cleft results in the stimulation of beta2-adrenergic receptors. Phentermine is classified as an indirect sympathomimetic agent due to the increase in the level of norepinephrine, dopamine and its indirect effect towards serotonin. Some reports have indicated that phentermine inhibits the neuropeptide Y which is a principal signalling pathway for the induction of hunger. The combined effect on serotonin and neuropeptide produces a continuous flight-or-fight response in the body which reduces the hunger signal as this state is on the immediate need for energy. It is reported that phentermine's main mechanism of action is the generation of appetite suppression, perhaps due to the increase in leptin. However, it is thought that

Drug name/ Description	Indication	Mechanism of action
		other mechanisms could be involved. Some reports have indicated that the weight-loss effect is mainly due to the increase in resting energy expenditure.
Benzphetamine A sympathomimetic used to manage exogenous obesity in the short term.	Benzphetamine is an anorectic agent indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction.	Benzphetamine is a sympathomimetic amine with pharmacological activity similar to the prototype drugs of this class used in obesity, the amphetamines. The actions of this compound include central nervous system stimulation and elevation of blood pressure. The mechanism of action of benzphetamine is not fully understood. However, it may be similar to that of amphetamines. Amphetamines stimulate noepinephrine and dopamine release in nerve endings in the lateral hypothalamic feeding centre thereby decreasing appetite. This release is mediated by the binding of benzphetamine to centrally located adrenergic receptors.

7.3 Herbal chemical compounds

The herbal compounds of each herb in formula RCM-104 were identified with the methodology described in Section 4.3.3.

7.3.1 Jue ming zi

A total number of 50 chemical compounds of JMZ were identified. Table 7.3 shows the characteristics of the 50 compounds in descending order of molecular weight.

Table 7.4: Characteristics of chemical compounds of Jue ming zi

Chemical Compounds of Jue ming zi					
ID	**Compound code**	**Compound name**	**Molecular formula**	**Molecular weight (g/mol)**	**PubChem CID**
jm01	ljm001CID1110	succinic acid	$C_4H_6O_4$	118.088	1110
jm02	ljm002CID101405	2,5-dimethoxybenzoquinone	$C_8H_8O_4$	168.148	101405
jm03	ljm003CID5281343	5,7-dihydroxychromone	$C_9H_6O_4$	178.15	5281343
jm04	ljm004CID54162047	(2s,4s)-4-hydroxyarginine	$C_6H_{14}N_4O_3$	190.24	54162047
jm05	ljm005CID122841	aspidinol	$C_{12}H_{16}O4$	224.28	122841
jm06	ljm006CID87014	2-hydroxymethylanthraquinone	$C_{15}H_{10}O_3$	238.242	87014
jm07	ljm007CID6688	quinizarin	$C_{14}H_8O_4$	240.22	6688
jm08	ljm008CID68111	chrysophanol-9-anthrone	$C_{15}H_{12}O_3$	240.258	68111
jm09	ljm009CID6029	uridine	$C_9H_{12}N_2O_6$	244.203	6029
jm10	ljm010CID5321977	torachrysone	$C_{14}H_{14}O_4$	246.262	5321977
jm11	ljm011CID10208	chrysophanol	$C_{15}H_{10}O_4$	254.241	10208
jm12	ljm012CID72537	rubrofusarin	$C_{15}H_{12}O_5$	254.241	72537
jm13	ljm013CID5281607	chrysin	$C_{15}H_{10}O_4$	254.25	5281607
jm14	ljm014CID135453893	nor-rubrofusarin	$C_{14}H_{10}O_5$	258.228	135453893
jm15	ljm015CID3220	emodin	$C_{15}H_{10}O_5$	270.24	3220
jm16	ljm016CID10207	aloe-emodin	$C_{15}H_{10}O_5$	270.24	10207
jm17	ljm017CID157661	isotoralactone	$C_{15}H_{12}O_5$	272.256	157661
jm18	ljm018CID5321980	toralactone	$C_{15}H_{12}O_5$	272.27	5321980
jm19	ljm019CID10168	rhein	C15H8O6	284.223	10168
jm20	ljm020CID10639	physcion	$C_{16}H_{12}O_5$	284.267	10639
jm21	ljm021CID160717	questin	$C_{16}H_{12}O_5$	284.267	160717

Chemical Compounds of Jue ming zi					
ID	**Compound code**	**Compound name**	**Molecular formula**	**Molecular weight (g/mol)**	**PubChem CID**
jm22	ljm022CID3083575	obtusifolin	$C_{16}H_{12}O_5$	284.267	3083575
jm23	ljm023CID5280863	kaempferol	$C_{15}H_{10}O_6$	286.239	5280863
jm24	ljm024CID10446798	torosachrysone	$C_{16}H_{16}O_5$	288.299	10446798
jm25	ljm025CID5280343	quercetin	$C_{15}H_{10}O_7$	302.238	5280343
jm26	ljm026CID627638	cassialactone	$C_{16}H_{16}O_6$	304.298	627638
jm27	ljm027CID155011	aurantio-obtusin	$C_{17}H_{14}O_7$	330.292	155011
jm28	ljm028CID155380	obtusin	$C_{18}H_{16}O_7$	344.319	155380
jm29	ljm029CID155381	chrysoobtusin	$C_{19}H_{18}O_7$	358.346	155381
jm30	ljm030CID164146	cassiaside A	$C_{20}H_{20}O_9$	404.4	164146
jm31	ljm031CID5280794	stigmasterol	$C_{29}H_{48}O$	412.702	5280794
jm32	ljm032CID222284	beta-sitosterol	$C_{29}H_{50}O$	414.718	222284
jm33	ljm033CID5318717	juglanin	$C_{20}H_{18}O_{10}$	418.354	5318717
jm34	ljm034CID65252	obtusifoliol	$C_{30}H_{50}O$	426.729	65252
jm35	ljm035CID91472	friedelin	$C_{30}H_{50}O$	426.729	91472
jm36	ljm036CID99649	emodin-8-glucoside	$C_{21}H_{20}O_{10}$	432.381	99649
jm37	ljm037CID3035617	rubrofusarin-6-glucoside	$C_{21}H_{22}O_{10}$	434.397	3035617
jm38	ljm038CID68972	triacontan-1-ol	$C_{30}H_{62}O$	438.825	68972
jm39	ljm039CID442761	gluco-obtusifolin	$C_{22}H_{22}O_{10}$	446.408	442761
jm40	ljm040CID64971	betulinic acid	$C_{30}H_{48}O_3$	456.711	64971
jm41	ljm041CID442725	gluco-aurantio-obtusin	$C_{23}H_{24}O_{12}$	492.433	442725
jm42	ljm042CID439336	galactomannan	$C_{18}H_{32}O_{16}$	504.438	439336
jm43	ljm043CID442730	gluco-chrysoobtusin	$C_{25}H_{28}O_{12}$	520.486	442730
jm44	ljm044CID131752379	cassiaside B 2017	$C_{26}H_{30}O_{14}$	566.512	131752379
jm45	ljm045CID101617058	cassiaside C 2019	$C_{26}H_{30}O_{14}$	566.512	101617058
jm46	ljm046CID503733	rubrofusarin gentiobioside	$C_{27}H_{32}O_{15}$	596.538	503733
jm47	ljm047CID100813	physcion-beta-D-gentiobioside	$C_{28}H_{32}O_{15}$	608.549	100813
jm48	ljm048CID10557731	cassiaside B2 2006	$C_{39}H_{52}O_{25}$	920.8	10557731
jm49	ljm049CID85185010	cassiaside B2 2014	$C_{39}H_{52}O_{25}$	920.8	85185010
jm50	ljm050CID10350826	cassiaside C2	$C_{39}H_{52}O_{25}$	920.8	10350826

7.3.2 Lu cha ye

A total number of 64 chemical compounds of LCY were identified. Table 7.4 presents the characteristics of the 64 compounds in descending order of molecular weight.

Table 7.5: Characteristics of chemical compounds of Lu cha ye

Chemical Compounds of Lu cha ye					
ID	**Compound code**	**Compound name**	**Molecular formula**	**Molecular weight (g/mol)**	**PubChem CID**
lc01	lcy001CID13854	pyrrole-2-aldehyde	$C_5H_5N_O$	95.1	13854
lc02	lcy002CID7361	furfuryl alcohol	$C_5H_6O_2$	98.1	7361
lc03	lcy003CID12508287	heptenol	$C_7H_{14}O$	114.19	12508287
lc04	lcy004CID5318017	trans-2-hepten-1-ol	$C_7H_{14}O$	114.19	5318017
lc05	lcy005CID5364517	cis-3-hepten-1-ol	$C_7H_{14}O$	114.19	5364517
lc06	lcy006CID71349956	hept-1-en-1-ol	$C_7H_{14}O$	114.19	71349956
lc07	lcy007CID5367536	(z)-hept-4-en-1-ol	$C_7H_{14}O$	114.19	5367536
lc08	lcy008CID543123	hept-6-en-1-ol	$C_7H_{14}O$	114.19	543123
lc09	lcy009CID23264402	bicyclo[2.2.1]heptenol	$C_7H_{14}O$	114.19	23264402
lc10	lcy010CID798	1H-indole	C_8H_7N	117.15	798
lc11	lcy011CID6998	salicylaldehyde	$C_7H_6O_2$	122.12	6998
lc12	lcy012CID7409	methyl phenyl carbinol	$C_8H_10_O$	122.16	7409
lc13	lcy013CID181575	3,5-octadiene-2-one	$C_8H_{12}O$	124.18	181575
lc14	lcy014CID7708	benzyl formate	$C_8H_8O_2$	136.15	7708
lc15	lcy015CID17000	2,2,6-trimethyl cyclohexanone	$C_9H_{16}O$	140.22	17000
lc16	lcy016CID7711	phenyl ethyl formate	$C_9H_{10}O_2$	150.17	7711
lc17	lcy017CID1188	xanthine	$C_5H_4N_4O_2$	152.11	1188
lc18	lcy018CID638011	geranial	$C_{10}H_{16}O$	152.23	638011
lc19	lcy019CID5366264	3,7-dimethyl-1,5,7-octatrien-3-ol	$C_{10}H_{16}O$	152.23	5366264
lc20	lcy020CID17100	α-terpineol	$C_{10}H_{18}O$	154.25	17100
lc21	lcy021CID101115	2,6,6-trimethyl-2-hydroxycyclohexanone	$C_9H_16_O2$	156.22	101115
lc22	lcy022CID1549018	jasmone	$C_{11}H_{16}O$	164.24	1549018
lc23	lcy023CID80220	1-methylxanthine	$C_6H_6N_4O_2$	166.14	80220
lc24	lcy024CID439378	l-theanine	$C_7H_{14}N_2O_3$	174.2	439378
lc25	lcy025CID5429	theobromine	$C_7H_8N_4O_2$	180.16	5429
lc26	lcy026CID2153	theophylline	$C_7H_8N_4O_2$	180.16	2153

Chemical Compounds of Lu cha ye					
ID	**Compound code**	**Compound name**	**Molecular formula**	**Molecular weight (g/mol)**	**PubChem CID**
lc27	lcy027CID5319748	methyl 4-oxononanoate	$C_{10}H_{18}O_3$	186.25	5319748
lc28	lcy028CID2519	caffeine	$C_8H_{10}N_4O_2$	194.19	2519
lc29	lcy029CID11019926	sodium theobromine	$C_7H_7N_4NaO_2$	202.15	11019926
lc30	lcy030CID5352456	2-hexenyl benzoate	$C_{13}H_{16}O_2$	204.26	5352456
lc31	lcy031CID6430825	3-keto-β-ionone (3-hydroxy-7,8-didehydro-.beta.-ionone)	$C_{13}H_{18}O_2$	206.28	6430825
lc32	lcy032CID5321925	theaspirone	$C_{13}H_{20}O_2$	208.3	5321925
lc33	lcy033CID73160	catechin	$C_{15}H_{14}O_6$	290.27	73160
lc34	lcy034CID72276	epicatechin	$C_{15}H_{14}O_6$	290.27	72276
lc35	lcy035CID6050	tributyrin	$C_{15}H_{26}O_6$	302.36	6050
lc36	lcy036CID72277	epigallocatechin	$C_{15}H_{14}O_7$	306.27	72277
lc37	lcy037CID65084	gallocatechin	$C_{15}H_{14}O_7$	306.27	65084
lc38	lcy038CID1794427	chlorogenic acid	$C_{16}H_{18}O_9$	354.31	1794427
lc39	lcy039CID5326970	22,23-dihydroergosterol	$C_{28}H_{46}O$	398.7	5326970
lc40	lcy040CID13889661	5,6-dihydroergosterol	$C_{28}H_{46}O$	398.7	13889661
lc41	lcy041CID65064	(-)-epigallocatechin gallate	$C_{22}H_{18}O_{11}$	458.4	65064
lc42	lcy042CID107905	epicatechin gallate	$C_{22}H_{18}O_{10}$	442.4	107905
lc43	lcy043CID65056	epicatechin 3-gallate	$C_{22}H_{18}O_{10}$	442.4	65056
lc44	lcy044CID44256700	idaein	$C_{21}H_{21}O_{11}+$	449.4	44256700
lc45	lcy045CID199472	gallocatechin gallate	$C_{22}H_{18}O_{11}$	458.4	199472
lc46	lcy046CID5280804	isoquercitrin	$C_{21}H_{20}O_{12}$	464.4	5280804
lc47	lcy047CID531649	empetrin (delphinidin 3-galactoside)	$C_{21}H_{21}ClO_{12}$	500.8	531649
lc48	lcy048CID5280489	beta-carotene	$C_{40}H_{56}$	536.9	5280489
lc49	lcy049CID135438671	isotheaflavin	$C_{29}H_{24}O_{12}$	564.5	135438671
lc50	lcy050CID5487342	camellinanin B	$C_{27}H_{30}O_{14}$	578.5	5487342
lc51	lcy051CID15922818	delphinidin 3-O-beta-D-(6-O-(E)-p-coumaryl) galactopyranoside	$C_{30}H_{27}O_{14}+$	611.5	15922818
lc52	lcy052CID5487343	camellianin A	$C_{29}H_{32}O_{15}$	620.6	5487343
lc53	lcy053CID442543	theasinensin A	$C_{44}H_{34}O_{22}$	914.7	442543
lc54	lcy054CID14520989	oolonghomobisflavan A - Wu Long Cha	$C_{45}H_{36}O_{22}$	928.8	14520989
lc55	lcy055CID10843814	desacyl-theasaponin E	$C_{52}H_{82}O_{25}$	1107.2	10843814
lc56	lcy056CID11953922	theasaponin	$C_{59}H_{92}O_{27}$	1233.3	11953922
lc57	lco04egcg	EGCG = d04	$C_{22}H_{18}O_{11}$	928.8	65064
lc58	ljm025CID5280343	quercetin = jm25	$C_{15}H_{10}O_7$	884.7	5280343
lc59	ljm023CID5280863	kaempferol = jm023	$C_{15}H_{10}O_6$	732.6	5280863

Chemical Compounds of Lu cha ye					
ID	**Compound code**	**Compound name**	**Molecular formula**	**Molecular weight (g/mol)**	**PubChem CID**
lc63	lcy063CID135403798	theaflavin	$C_{29}H_{24}O_{12}$	564.5	135403798
lc64	lcy064CID71307578	theaflavin-3'-O-gallate	$C_{36}H_{32}O_{15}$	704.6	71307578

7.3.3 Huai hua

A total number of 29 chemical compounds of HH were identified. The characteristics of all 29 compounds are summarised in Table 7.5, presented in descending order of molecular weight.

Table 7.6: Characteristics of chemical compounds of Huai hua

Chemical Compounds of HH					
ID	**Compound code**	**Compound name**	**Molecular formula**	**molecular weight (g/mol)**	**PubChem CID**
hh01	lhh001CID3893	lauric acid	$C_{12}H_{24}O_2$	200.32	3893
hh02	lhh002CID11005	myristic acid	$C_{14}H_{28}O_2$	228.37	11005
hh03	lhh003CID985	palmitic acid	$C_{16}H_{32}O_2$	256.42	985
hh04	lhh004CID5280961	genistein	$C_{15}H_{10}O_5$	270.24	5280961
hh05	lhh005CID5280863	kaempferol	$C_{15}H_{10}O_6$	286.24	5280863
hh06	lhh006CID10467	arachidic acid	$C_{20}H_{40}O_2$	312.5	10467
hh07	lhh007CID5280681	quercetin-3-methyl ether	$C_{16}H_{12}O_7$	316.26	5280681
hh08	lhh008CID5281654	isorhamnetin	$C_{16}H_{12}O_7$	316.26	5281654
hh09	lhh009CID92797	sophorose	$C_{12}H_{22}O_{11}$	342.3	92797
hh10	lhh010CID146515	N-[6-(acridin-9-ylamino)hexyl]benzamide	$C_{26}H_{27}N_{3O}$	397.5	146515
hh11	lhh011CID222284	beta-sitosterol	$C_{29}H_{50}O$	414.7	222284
hh12	lhh012CID5321398	sophoricoside	$C_{21}H_{20}O_{10}$	432.4	5321398
hh13	lhh013CID72326	betulin	$C_{30}H_{50}O_2$	442.7	72326
hh14	lhh014CID9846221	sophoradiol	$C_{30}H_{50}O_2$	442.7	9846221
hh15	lhh015CID11968944	sophorabioside	$C_{27}H_{30}O_{14}$	578.5	11968944
hh16	lhh016CID5318767	kaempferol-3-rutinoside	$C_{27}H_{30}O_{15}$	594.5	5318767
hh17	lhh017CID5280805	rutin 2005	$C_{27}H_{30}O_{16}$	610.5	5280805
hh18	lhh018CID5282155	kaempferol 3-O-sophoroside 2005	$C_{27}H_{30}O_{16}$	610.5	5282155
hh19	lhh019CID6728944	rutoside (rutin) 2006	$C_{27}H_{30}O_{16}$	610.5	6728944

Chemical Compounds of HH					
ID	**Compound code**	**Compound name**	**Molecular formula**	**molecular weight (g/mol)**	**PubChem CID**
hh20	lhh020CID46936193	quercetin-3-O-rutinose	$C_{27}H_{30}O_{16}$	610.5	46936193
hh21	lhh021CID17751019	isorhamnetin-3-rutinoside	$C_{28}H_{32}O_{16}$	624.5	17751019
hh22	lhh022CID102004842	kaempferol 3-O-sophoroside 2015	$C_{33}H_{40}O_{20}$	756.7	102004842
hh23	lhh023CID14103656	azukisaponin I	$C_{42}H_{68}O_{13}$	781	14103656
hh24	lhh024CID102120183	kaikasaponin I	$C_{42}H_{68}O_{13}$	781	102120183
hh25	lhh025CID13326387	azukisaponin II	$C_{42}H_{68}O_{14}$	797	13326387
hh26	lhh026CID21607811	soyasaponin III	$C_{42}H_{68}O_{14}$	797	21607811
hh27	lhh027CID188384	kaikasaponin III 2005	$C_{48}H_{78}O_{17}$	927.1	188384
hh28	lhh028CID101538997	kaikasaponin II 2015	$C_{48}H_{78}O_{17}$	927.1	101538997
hh29	lhh029CID122097	soyasaponin I	$C_{48}H_{78}O_{18}$	943.1	122097

7.4 Discussion

In the modern literature review of Phase IIb, literature search and information search were carried out in resources detailed in Section 4.3. Information about the identified anti-obesity protein targets, anti-obesity agents and the herbal compounds of formula RCM-104's three ingredients has been reported in this chapter.

There were 38 anti-obesity protein targets identified and listed in Table 7.1. Descriptive summary of different types of targets were presented.

7 anti-obesity agents were selected as controls for the current project. The characteristics of these agents were studied and sorted out.

50 JMZ compounds, 64 LCY compounds and 29 HH compounds were identified, making a total of 143 herbal compounds. With the 7 anti-obesity agents counted in, there were 150 chemical compounds identified in this phase. Information on the chemical formula, molecular

weight and compound identifier of each identified herbal compounds were drawn from the chemistry database PubChem.

The data yielded in Phase IIb serves as the input data for Phase III. However, only 147 compounds were used in the molecular docking because EGCG in LCY was used as a control ligand and two of them co-exist in the different herbs. The accuracy and completeness of the data identified in this phase is crucial for the docking output and the subsequent analyses in the following phase.

Chapter 8 Results III – Molecular docking computational analysis: binding affinities and ligand networks

This chapter firstly describes the characteristics of the docking results, and then reports the docking results of the anti-obesity agents and the docking results of the herbal compounds. The ligand-protein network of three herbs in RCM-104 based on predicted binding affinities is also presented in this chapter.

The following were incorporated in the docking process: 150 ligands (50 from JMZ, 64 from LCY, 29 from HH and 7 from anti-obesity drugs) and 38 protein targets. However, only 147 compounds were used in the molecular docking because EGCG in LCY was used as a control ligand and two of them co-exist in the different herbs. A total of 5586 raw output data of BA score generated from the molecular docking process are included in the Appendix C. Ligand-protein pairs predicted to have strong binding interactions (BA score < -10 kcal/mol) were selected to study in detail.

Each output model file, generated from the molecular docking process in pdbqt format, contains 10 predicted binding locations and poses by default. Each ligand-target pair consists of multiple 3D models of the same ligand in different positions and orientations: model 1 possesses the lowest BA value and model 2 possesses the second lowest BA value and so on.

8.1 Docking results of anti-obesity agents

The molecular binding interaction between 7 anti-obesity agents and 38 protein targets were calculated, generating 266 results of BA scores, in kcal/mol, as shown in Table 8.1.

Table 8.1: Binding affinity scores of anti-obesity agents with obesity targets

Protein target	Anti-obesity agents							Total
	d1	d2	d3	d4	d5	d6	d7	
p01	-5.8	-5.9	-6.7	-7	-6.9	-6.3	-8	-46.6
p02	-6.7	-5.6	-7	-7	-6.9	-5.9	-8.2	-47.3
p03	-4.9	-6.3	-6.3	-6.2	-5.5	-5	-5	-39.2
p04	-4.5	-4.5	-6.4	-6.4	-5.9	-6.1	-7	-40.8
p05	-6	-5.7	-6.8	-6.8	-6.1	-6.5	-7	-44.9
p06	-5.8	-5.2	-6.7	-6.7	-6.7	-5.3	-7.3	-43.7
p07	-5.2	-5	-6.5	-6.2	-6.5	-5.3	-6.8	-41.5
p08	-4.9	-4.6	-5.8	-6	-6.5	-5.3	-6.7	-39.8
p09	-6	-5.7	-6.2	-6.1	-5.9	-5.6	-6	-41.5
p10	-6.4	-6.5	-6.3	-7	-6.6	-5.6	-6.7	-45.1
p11	-5.4	-5.5	-5.6	-5.6	-5.6	-4.8	-5	-37.5
p12	-4.5	-6.4	-6.4	-6.4	-5.4	-5	-5.6	-39.7
p13	-6.4	-6.7	-6.3	-6.8	-6	-5.8	-7.9	-45.9
p14	-6.6	-5.4	-7.4	-7.4	-6.3	-5.9	-7.4	-46.4
p15	-5.4	-5.9	-6.6	-7	-6.9	-6	-7.5	-45.3
p16	-7	-5.7	-6.9	-7.2	-6.8	-6.2	-7.1	-46.9
p17	-5.7	-6.2	-6	-6	-5.9	-6.5	-8.1	-44.4
p18	-7.4	-5.3	-7.5	-6.9	-7.2	-6	-6.3	-46.6
p19	-7.3	-4.6	-7.6	-7	-7.4	-6.6	-8.3	-48.8
p20	-5	-5.8	-7.8	-7.3	-5.5	-6.8	-8	-46.2
p21	-4.9	-4.9	-6.4	-7.1	-6.4	-5.6	-7.5	-42.8
p22	-6.3	-6.7	-6.5	-6.7	-6.3	-5.6	-6.5	-44.6
p23	-6.8	-7.4	-6.5	-6.5	-6.1	-5.2	-5.8	-44.3
p24	-6.3	-6.3	-5.6	-5.5	-5.6	-5.2	-6.8	-41.3
p25	-6.2	-5.1	-5.8	-6.4	-6	-5.2	-6.7	-41.4
p26	-6.3	-5.9	-6.1	-5.9	-6.5	-5.5	-6.1	-42.3
p27	-6.1	-5	-6.2	-6.6	-6.2	-5.4	-6.6	-42.1
p28	-4.7	-4.8	-5.1	-5	-4.7	-4.3	-5	-33.6
p29	-5	-5.2	-5.4	-5.4	-5.2	-4.9	-6.3	-37.4
p30	-3.4	-3.4	-4.3	-4.3	-4	-3.8	-4	-27.2
p31	-4.2	-3.5	-4.5	-4.5	-4.5	-4	-5.3	-30.5
p32	-7.2	-5.8	-6.5	-6.8	-7	-6.2	-6.8	-46.3
p33	-5.2	-6.4	-6.1	-5.9	-6.1	-5.3	-5.7	-40.7
p34	-5.9	-5.3	-6.2	-6.3	-6.4	-5.4	-5.7	-41.2
p35	-5.9	-4.8	-6.5	-6.1	-6.1	-5.6	-5.9	-40.9
p36	-7.1	-7.3	-7.1	-6.6	-7	-6.2	-7.3	-48.6
p37	-6.9	-4.7	-7.3	-6.4	-7.8	-6.6	-8	-47.7
p38	-5.4	-5.7	-6.4	-6.4	-5.9	-5.2	-6	-41

Note**:** d1: Orlistat; d2: Liraglutide; d3: Lorcaserin; d4: Epigallocatechin gallate; d5: Bupropion; d6: Phentermine; d7: Benzphetamine; p01 to p38: protein targets.

8.2 Docking results of herbal compounds

8.2.1 Binding affinity scores of Jue ming zi compounds

The molecular binding interaction between 50 JMZ chemical compounds and 38 protein targets were calculated, generating 1,900 results of BA scores. Table 8.2 lists the protein targets and the average BA score with the 50 compounds in ascending order (most negative value at top). The ligand-protein pairs that predicted to have strong binding interaction (BA score < -10 kcal/mol) are summarised in Table 8.3.

Table 8.2: Average binding affinity scores of Ju ming zi compounds

Target ID	Target name	Ave. BA score (kcal/mole)
p164iraA	Serotonin receptor 5-HT1B	-9.1
p365i6xSM	Sodium-dependent serotonin transporter	-9.1
p021lpbB	Pancreatic lipase	-8.9
p196bqhA	Serotonin receptor 5-HT2C	-8.8
p011lpaB	Pancreatic lipase	-8.7
p325nx2A	GLP1 receptor	-8.6
p374xp4SM	Sodium-dependent dopamine transporter	-8.6
p104gqqA	Pancreatic amylase	-8.5
p186bqgA	Serotonin receptor 5-HT2C	-8.4
p146nnaB	Fatty acid synthase	-8.3
p233e00D	PPARG	-8.2
p156g79S	Serotonin receptor 5-HT1B	-8.1
p263h8rA	FTO	-8.1
p206dzzA	Serotonin transporter	-8.1
p253h8oA	FTO	-8.0
p175v54A	Serotonin receptor 5-HT1B	-8.0
p273h8xA	FTO	-8.0
p094x9yA	Pancreatic amylase	-8.0
p051hlgB	Gastric triacylglycerol lipase	-7.9
p066e7kA	Lipoprotein lipase	-7.9
p226dgoB	PPARG	-7.8
p216dgoA	PPARG	-7.8
p076e7kB	Lipoprotein lipase	-7.8
p245zmdA	FTO	-7.7

Target ID	Target name	Ave. BA score (kcal/mole)
p136nnaA	Fatty acid synthase	-7.7
p041hlgA	Gastric triacylglycerol lipase	-7.7
p345vexA	GLP1 receptor	-7.7
p355vexB	GLP1 receptor	-7.6
p384xptSM	Sodium-dependent noradrenaline transporter	-7.5
p086oazA	Lipoprotein lipase	-7.5
p031n8sA	Pancreatic lipase	-7.4
p336b3jR	GLP1 receptor	-7.4
p114z49A	Fatty acid synthase	-7.2
p124z49B	Fatty acid synthase	-7.0
p293v6oB	Leptin receptor	-6.7
p283v6oA	Leptin receptor	-6.5
p306e2pC	Leptin receptor	-5.2
p316e2pD	Leptin receptor	-5.2

Note: 5-HT1B: 5-hydroxytryptamine receptor 1B; 5-HT2C: 5-hydroxytryptamine receptor 2C; FTO: Fat mass and obesity-associated protein; GLP1: Glucagon-like peptide-1; PPARG: Peroxisome proliferator-activated receptor gamma.

Table 8.3: Protein targets with strong binding interaction to Ju ming zi compounds

Receptor	Ligand ID	BA score (kcal/mole)
p365i6xSM	ljm045	-11.8
p196bqhA	ljm035	-11.7
p164iraA	ljm034	-11.3
p164iraA	ljm031	-11.1
p164iraA	ljm045	-11.1
p365i6xSM	ljm047	-11.1
p216dgoA	ljm047	-11
p164iraA	ljm047	-10.9
p325nx2A	ljm031	-10.9
p164iraA	ljm041	-10.8
p365i6xSM	ljm034	-10.8
p374xp4SM	ljm050	-10.8
p186bqgA	ljm031	-10.7
p365i6xSM	ljm031	-10.7
p365i6xSM	ljm046	-10.7
p021lpbB	ljm036	-10.6
p196bqhA	ljm031	-10.6
p146nnaB	ljm049	-10.5
p164iraA	ljm036	-10.5
p164iraA	ljm039	-10.5

Receptor	Ligand ID	BA score (kcal/mole)
p186bqgA	ljm034	-10.5
p196bqhA	ljm045	-10.5
p325nx2A	ljm035	-10.5
p325nx2A	ljm045	-10.5
p365i6xSM	ljm039	-10.5
p021lpbB	ljm047	-10.4
p365i6xSM	ljm036	-10.4
p365i6xSM	ljm050	-10.4
p104gqqA	ljm034	-10.3
p186bqgA	ljm035	-10.3
p196bqhA	ljm032	-10.3
p206dzzA	ljm034	-10.3
p325nx2A	ljm032	-10.3
p365i6xSM	ljm032	-10.3
p374xp4SM	ljm031	-10.3
p374xp4SM	ljm034	-10.3
p011lpaB	ljm013	-10.2
p011lpaB	ljm019	-10.2
p164iraA	ljm032	-10.2
p186bqgA	ljm045	-10.2
p374xp4SM	ljm048	-10.2
p374xp4SM	ljm049	-10.2
p011lpaB	ljm011	-10.1
p021lpbB	ljm013	-10.1
p146nnaB	ljm045	-10.1
p156g79S	ljm036	-10.1
p156g79S	ljm045	-10.1
p164iraA	ljm040	-10.1
p186bqgA	ljm046	-10.1

8.2.2 Ligand-protein network of Jue ming zi compounds

Figure 8.1 illustrates the network, in ‘profuse force directed layout’, links up the identified compounds and proteins for the ligand-protein pairs with BA score less than -10 kcal/mol. Theblue and yellow nodes in the network represent the chemical compounds and the protein targets respectively. There are 31 nodes in total featuring 18 compounds and 13 proteins.

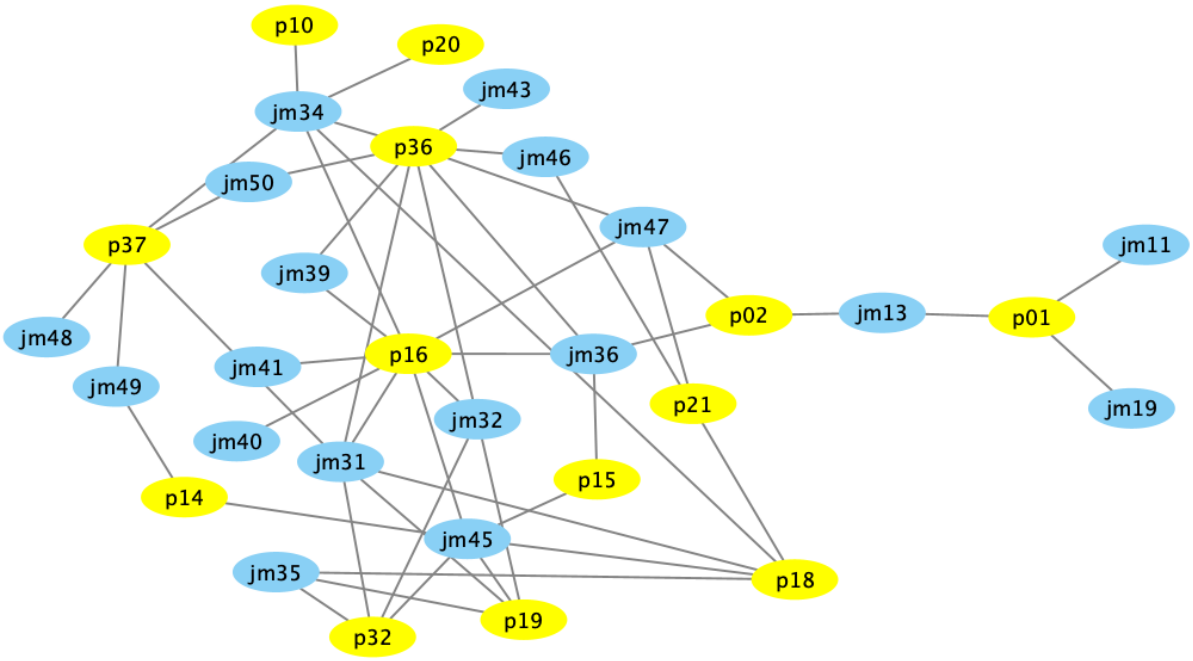


Figure 8.1: Ligand-protein network of Jue ming zi compounds

Note: p: protein target; jm: Jue ming zi compound

Figure 8.2 shows the network with another layout named ‘attribute circle layout’. The protein nodes with the top three number of degrees are highlighted in yellow and circled with green lines. The compound nodes connected with these protein nodes are highlighted in yellow.

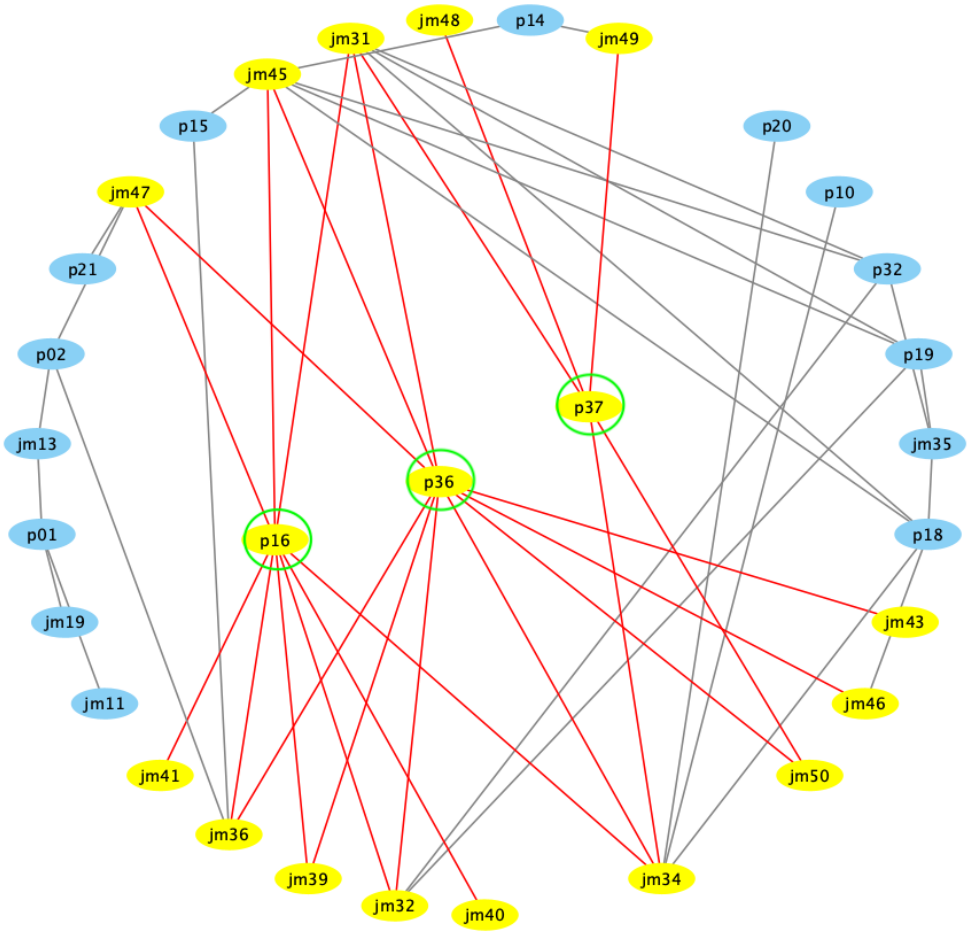


Figure 8.2: Jue ming zi compounds strongly interacted with p36, p16 or p17

Note: p: protein target; jm: Jue ming zi compound

The number of degrees of the protein nodes in the network indicates the number of herbal compounds BA score < -10 kcal/ mol, when interacting with that protein. The nodes with the top 3 number of degrees are listed as follows:

- Number of degrees of p36 = 10
- Number of degrees of p16 = 9
- Number of degrees of p17 = 5

8.2.3 Binding affinity scores of Lu cha ye compounds

The molecular binding interaction between 64 LCY chemical compounds and 38 protein targets were calculated, generating 2,432 results of BA scores. Table 8.4 lists the protein targets

and the average BA score with the 64 compounds in ascending order (most negative value at top). The ligand-protein pairs that predicted to have strong binding interaction (BA score < -10 kcal/mol) are summerised in Table 8.5.

Table 8.4: Average binding affinity scores of Lu cha ye compounds

Target ID	Target name	Ave. of BA score (kcal/mol)
p365i6xSM	Sodium-dependent serotonin transporter	-7.3
p196bqhA	Serotonin receptor 5-HT2C	-7.3
p374xp4SM	Sodium-dependent dopamine transporter	-7.2
p164iraA	Serotonin receptor 5-HT1B	-7.1
p146nnaB	Fatty acid synthase	-7.1
p206dzzA	Serotonin transporter	-7.0
p175v54A	Serotonin receptor 5-HT1B	-7.0
p021lpbB	Pancreatic lipase	-7.0
p104gqqA	Pancreatic amylase	-7.0
p011lpaB	Pancreatic lipase	-7.0
p325nx2A	GLP1 receptor	-6.9
p186bqgA	Serotonin receptor 5-HT2C	-6.9
p051hlgB	Gastric triacylglycerol lipase	-6.9
p156g79S	Serotonin receptor 5-HT1B	-6.9
p263h8rA	FTO	-6.8
p094x9yA	Pancreatic amylase	-6.8
p233e00D	PPARG	-6.7
p136nnaA	Fatty acid synthase	-6.7
p253h8oA	FTO	-6.7
p041hlgA	Gastric triacylglycerol lipase	-6.7
p273h8xA	FTO	-6.7
p355vexB	GLP1 receptor	-6.6
p226dgoB	PPARG	-6.6
p345vexA	GLP1 receptor	-6.5
p384xptSM	Sodium-dependent noradrenaline transporter	-6.5
p076e7kB	Lipoprotein lipase	-6.4
p066e7kA	Lipoprotein lipase	-6.4
p336b3jR	GLP1 receptor	-6.3
p031n8sA	Pancreatic lipase	-6.3
p216dgoA	PPARG	-6.3
p245zmdA	FTO	-6.3
p086oazA	Lipoprotein lipase	-6.2

Target ID	Target name	Ave. of BA score (kcal/mol)
p124z49B	Fatty acid synthase	-6.0
p114z49A	Fatty acid synthase	-5.8
p293v6oB	Leptin receptor	-5.6
p283v6oA	Leptin receptor	-5.4
p306e2pC	Leptin receptor	-4.4
p316e2pD	Leptin receptor	-4.4

Note: 5-HT1B: 5-hydroxytryptamine receptor 1B; 5-HT2C: 5-hydroxytryptamine receptor 2C; FTO: Fat mass and obesity-associated protein; GLP1: Glucagon-like peptide-1; PPARG: Peroxisome proliferator-activated receptor gamma.

Table 8.5: Protein targets with strong binding interaction to Lu cha ye compounds

Receptor	Ligand ID	BA score (kcal/mol)
p164iraA	lcy049	-11.4
p164iraA	lcy051	-11.3
p175v54A	lcy040	-11.3
p094x9yA	lcy049	-11
p156g79S	lcy045	-11
p164iraA	lcy040	-11
p196bqhA	lcy051	-11
p206dzzA	lcy040	-11
p206dzzA	lcy050	-11
p164iraA	lcy039	-10.9
p196bqhA	lcy040	-10.9
p365i6xSM	lcy043	-10.9
p196bqhA	lcy052	-10.8
p365i6xSM	lcy044	-10.8
p365i6xSM	lcy052	-10.8
p156g79S	lcy043	-10.7
p175v54A	lcy045	-10.7
p186bqgA	lcy039	-10.7
p196bqhA	lcy050	-10.7
p146nnaB	lcy051	-10.6
p206dzzA	lcy039	-10.6
p325nx2A	lcy040	-10.6
p325nx2A	lcy048	-10.6
p365i6xSM	lcy050	-10.6
p196bqhA	lcy039	-10.5
p253h8oA	lcy049	-10.5
p325nx2A	lcy053	-10.5
p263h8rA	lcy049	-10.4
p273h8xA	lcy049	-10.4

Receptor	Ligand ID	BA score (kcal/mol)
p011lpaB	lcy054	-10.3
p164iraA	lcy050	-10.3
p365i6xSM	lcy045	-10.3
p365i6xSM	lcy051	-10.3
p374xp4SM	lcy040	-10.3
p384xptSM	lcy053	-10.3
p011lpaB	lcy048	-10.2
p021lpbB	lcy040	-10.2
p104gqqA	lcy048	-10.2
p104gqqA	lcy052	-10.2
p146nnaB	lcy040	-10.2
p164iraA	lcy042	-10.2
p164iraA	lcy043	-10.2
p186bqgA	lcy040	-10.2
p226dgoB	lcy048	-10.2
p325nx2A	lcy039	-10.2
p325nx2A	lcy049	-10.2
p374xp4SM	lcy039	-10.2
p374xp4SM	lcy050	-10.2
p156g79S	lcy041	-10.1
p175v54A	lcy043	-10.1
p196bqhA	lcy041	-10.1
p325nx2A	lcy055	-10.1
p336b3jR	lcy054	-10.1
p365i6xSM	lcy048	-10.1

8.2.4 Ligand-protein network of Lu cha ye compounds

Figure 8.3 illustrates the network, in ‘profuse force directed layout’, links up the identified compounds and proteins for the ligand-protein pairs with BA score less than -10 kcal/mol. The blue and yellow nodes in the network represent the chemical compounds and the protein targets respectively. There are 35 nodes in total featuring 15 compounds and 20 proteins.

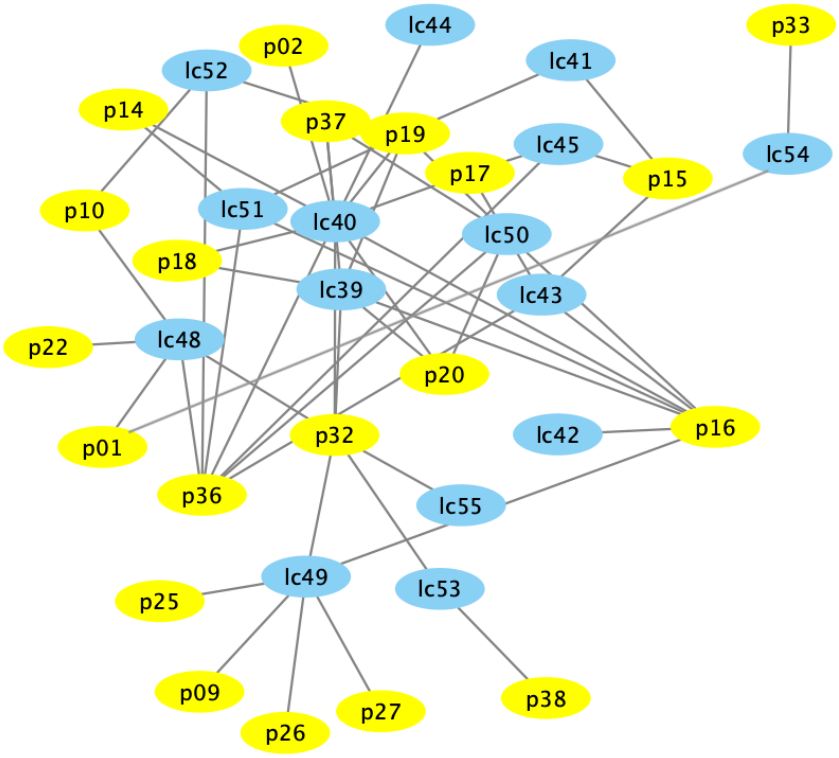


Figure 8.3: Ligand-protein network of Lu cha ye compounds

Note: p: protein target; lc: Lu cha ye compound.

Figure 8.4 shows the network with another layout named ‘attribute circle layout’. The protein nodes with the top three number of degrees are highlighted in yellow and circled with green lines. The compound nodes connected with these protein nodes are highlighted in yellow.

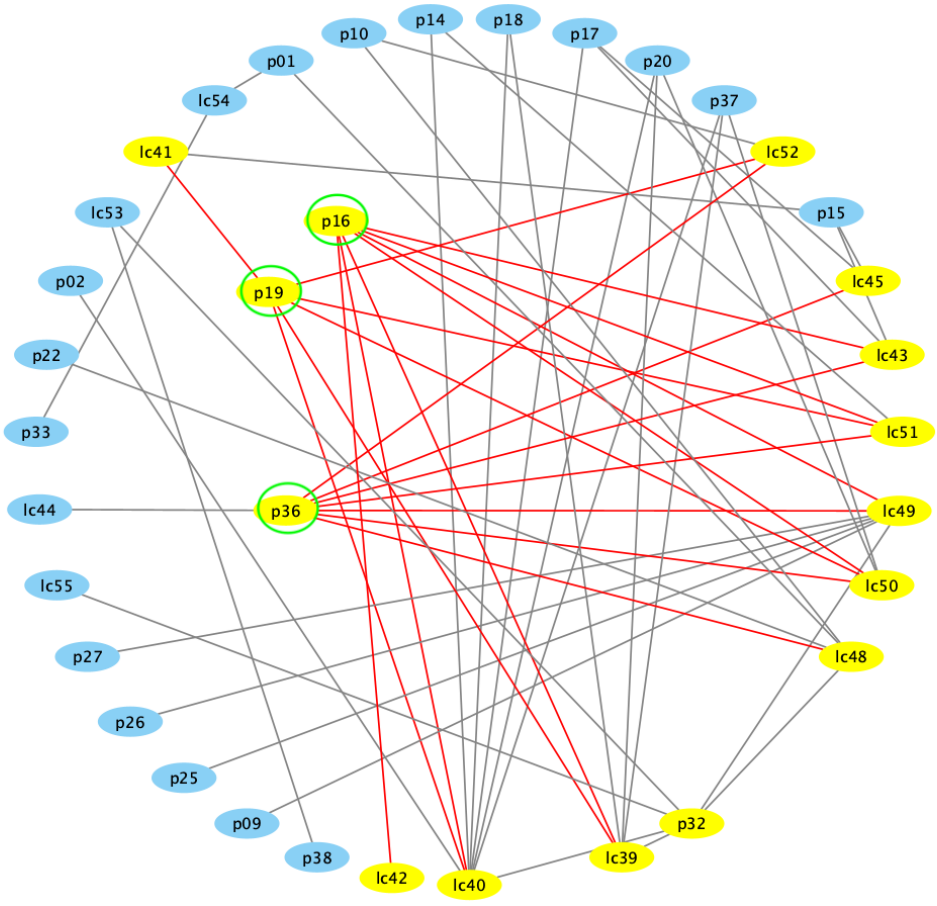


Figure 8.4: Lu cha ye compounds strongly interacted with p36, p16 or p19

Note: p: protein target; lc: Lu cha ye compound.

The number of degrees of the protein nodes in the network indicates the number of herbal compounds BA score < -10 kcal/ mol, when interacting with that protein. The nodes with the top 3 number of degrees are listed as follows:

- Number of degrees of p36 = 7
- Number of degrees of p16 = 7
- Number of degrees of p19 = 6

8.2.5 Binding affinity scores of Huai hua compounds

The molecular binding interaction between 29 HH chemical compounds and 38 protein targets were calculated, generating 1,102 results of BA scores. Table 8.6 lists the protein targets and

the average BA score with the 29 compounds in ascending order (most negative value at top). The ligand-protein pairs that predicted to have strong binding interaction (BA score < -10 kcal/mol) are summerised in Table 8.7.

Table 8.6: Average of binding affinity scores of Huai hua compounds

Target ID	Target name	Ave. of BA Score (Kcal/mol)
p374xp4SM	Sodium-dependent dopamine transporter	-8.9
p325nx2A	GLP1 receptor	-8.8
p104gqqA	Pancreatic amylase	-8.7
p164iraA	Serotonin receptor 5-HT1B	-8.7
p196bqhA	Serotonin receptor 5-HT2C	-8.5
p186bqgA	Serotonin receptor 5-HT2C	-8.5
p021lpbB	Pancreatic lipase	-8.5
p011lpaB	Pancreatic lipase	-8.4
p175v54A	Serotonin receptor 5-HT1B	-8.4
p206dzzA	Serotonin transporter	-8.4
p365i6xSM	Sodium-dependent serotonin transporter	-8.4
p146nnaB	Fatty acid synthase	-8.3
p136nnaA	Fatty acid synthase	-8.3
p094x9yA	Pancreatic amylase	-8.2
p233e00D	PPARG	-8.1
p051hlgB	Gastric triacylglycerol lipase	-7.9
p336b3jR	GLP1 receptor	-7.9
p253h8oA	FTO	-7.8
p156g79S	Serotonin receptor 5-HT1B	-7.8
p226dgoB	PPARG	-7.8
p273h8xA	FTO	-7.8
p076e7kB	Lipoprotein lipase	-7.8
p263h8rA	FTO	-7.7
p041hlgA	Gastric triacylglycerol lipase	-7.7
p384xptSM	Sodium-dependent noradrenaline transporter	-7.7
p066e7kA	Lipoprotein lipase	-7.7
p355vexB	GLP1 receptor	-7.7
p345vexA	GLP1 receptor	-7.6
p031n8sA	Pancreatic lipase	-7.6
p245zmdA	FTO	-7.5
p086oazA	Lipoprotein lipase	-7.5
p216dgoA	PPARG	-7.3

Target ID	Target name	Ave. of BA Score (Kcal/mol)
p114z49A	Fatty acid synthase	-7.1
p124z49B	Fatty acid synthase	-6.9
p293v6oB	Leptin receptor	-6.8
p283v6oA	Leptin receptor	-6.7
p306e2pC	Leptin receptor	-5.3
p316e2pD	Leptin receptor	-5.2

Note: 5-HT1B: 5-hydroxytryptamine receptor 1B; 5-HT2C: 5-hydroxytryptamine receptor 2C; FTO: Fat mass and obesity-associated protein; GLP1: Glucagon-like peptide-1; PPARG: Peroxisome proliferator-activated receptor gamma.

Table 8.7: Protein targets with strong binding interaction to Huai hua compounds

Receptor	Ligand ID	BA score (Kcal/mol)
p325nx2A	lhh028	-11.5
p164iraA	lhh015	-11.2
p325nx2A	lhh024	-11.1
p374xp4SM	lhh028	-11.1
p325nx2A	lhh027	-11
p104gqqA	lhh016	-10.9
p325nx2A	lhh029	-10.9
p374xp4SM	lhh024	-10.9
p021lpbB	lhh028	-10.7
p051hlgB	lhh028	-10.7
p175v54A	lhh027	-10.7
p365i6xSM	lhh010	-10.7
p365i6xSM	lhh020	-10.7
p374xp4SM	lhh014	-10.7
p164iraA	lhh011	-10.6
p186bqgA	lhh011	-10.5
p186bqgA	lhh016	-10.5
p196bqhA	lhh010	-10.5
p196bqhA	lhh021	-10.5
p206dzzA	lhh010	-10.5
p374xp4SM	lhh029	-10.5
p041hlgA	lhh028	-10.4
p104gqqA	lhh023	-10.4
p164iraA	lhh019	-10.4
p196bqhA	lhh016	-10.4
p094x9yA	lhh024	-10.3
p164iraA	lhh020	-10.3
p196bqhA	lhh011	-10.3
p325nx2A	lhh011	-10.3
p374xp4SM	lhh025	-10.3

Receptor	Ligand ID	BA score (Kcal/mol)
p374xp4SM	lhh026	-10.3
p021lpbB	lhh029	-10.2
p104gqqA	lhh013	-10.2
p186bqgA	lhh025	-10.2
p196bqhA	lhh024	-10.2
p374xp4SM	lhh022	-10.2
p051hlgB	lhh029	-10.1
p164iraA	lhh012	-10.1
p164iraA	lhh016	-10.1
p186bqgA	lhh026	-10.1
p196bqhA	lhh014	-10.1
p374xp4SM	lhh023	-10.1

8.2.6 Ligand-protein network of Huai hua compounds

Figure 8.5 illustrates the network, in 'profuse force directed layout', links up the identified compounds and proteins for the ligand-protein pairs with BA score less than -10 kcal/mol. The blue and yellow nodes in the network represent the chemical compounds and the protein targets respectively. There are 31 nodes in total featuring 18 compounds and 13 proteins.

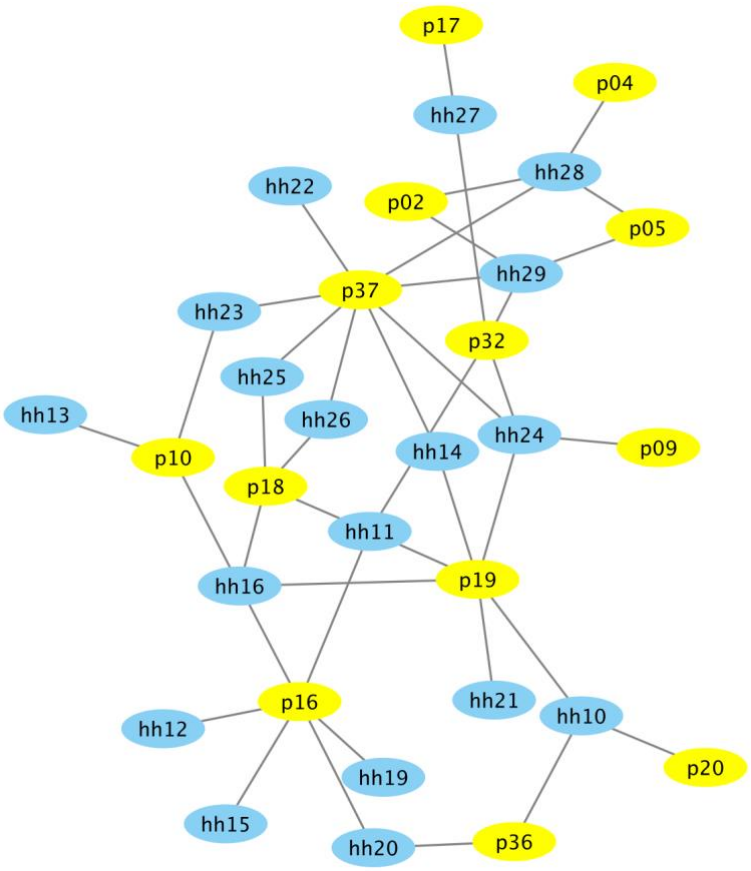


Figure 8.5: Ligand-protein network of Huai hua compounds

Note: p: protein target; hh: Huai Hua compound

Figure 8.6 shows the network with another layout named ‘attribute circle layout’. The protein nodes with the top three number of degrees are highlighted in yellow and circled with green lines. The compound nodes connected with these protein nodes are highlighted in yellow.

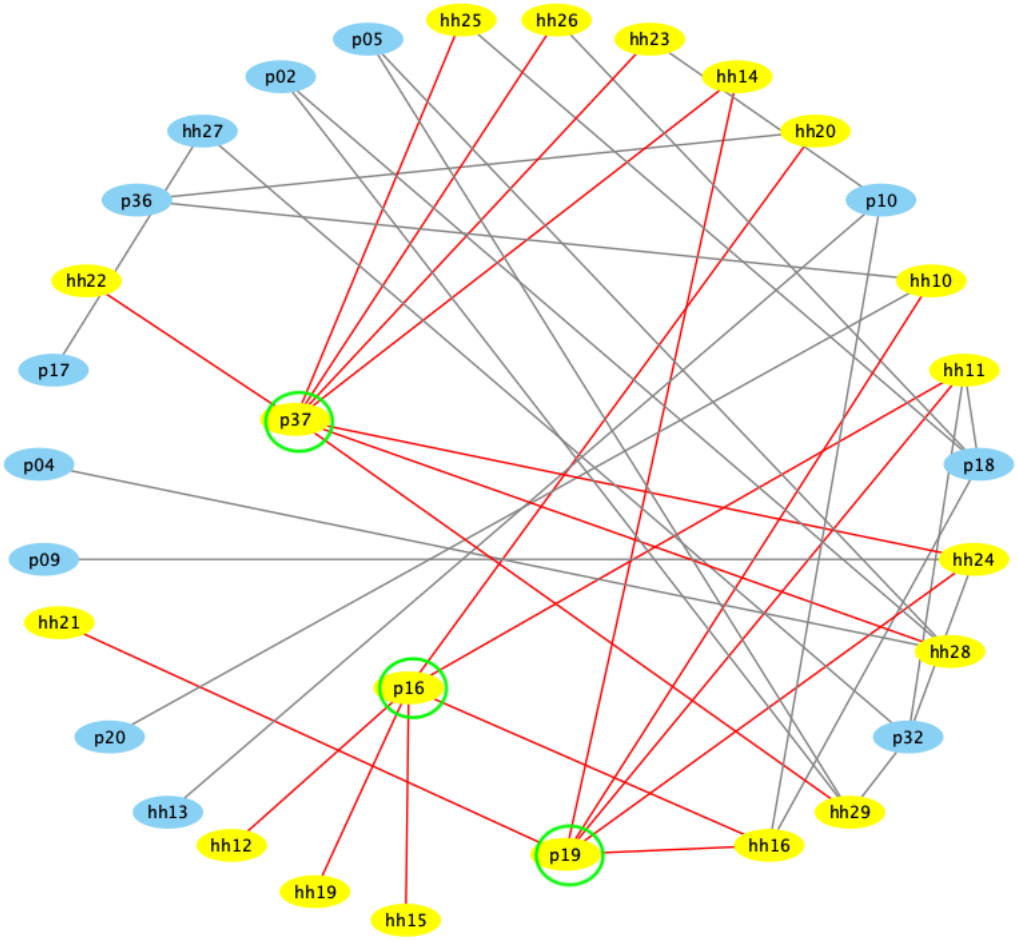


Figure 8.6: Huai hua compounds strongly interacted with p37, p19 or p16

Note: p: protein target; hh: Huai Hua compound

The number of degrees of the protein nodes in the network indicates the number of herbal compounds BA score < -10 kcal/ mol, when interacting with that protein. The nodes with the top 3 number of degrees are listed as follows:

- Number of degrees of p37 = 8
- Number of degrees of p19 = 6
- Number of degrees of p16 = 6

8.3 Discussion

To recapitulate, this chapter presents the docking results of each protein target to each of the control ligand and the herbal compound.

Through the network analysis of chemical compounds of the individual herbs, it has identified that:

- proteins p36, p16 and p17 were highly targeted by JMZ
- proteins p36, p19 and p16 were highly targeted by LCY
- proteins p37, p19 and p16 were highly targeted by HH

The protein target structures of p16, p19, p36 and p37 are serotonin receptor 5-HT1B, serotonin receptor 5-HT2C, serotonin transporter and dopamine transporter respectively. Specific discussion regarding the physiological roles of these receptors in appetite satiety will be discussed in the following Chapter. They are most likely to be highly targeted by compounds in the formula RCM-104 and therefore the following chapter will focus on the detailed analysis of the molecular docking results of these proteins.

These proteins are involved in mood, addiction, appetite and other reward pathways in the brain. It is proposed that the herbal compounds primarily target these pathways and may have some functional or structural similarity to neurotransmitters. The following chapter will examine specific ligand-receptor interactions.

Chapter 9 Results III – Molecular docking analysis: Ligand-protein residue interactions and potential synergistic mechanisms

In biomedicine, two or more drugs of similar effects are often prescribed in combination in order to obtain synergistic effects. A synergistic interaction may reduce adverse reactions as it allows the use of lower doses of constituents in the combination (Tallarida, 2011). This section attempts to establish the potential synergistic effect of the three herbs contained in RCM-104 by analysing the molecular docking results.

9.1 Analysis of neurotransmitter receptors and transporters

9.1.1 Selection of protein targets

While the graphical networks in the previous chapter provide information of individual herbs, Figure 9.1 presents the network for all ligand-protein pairs with BA score < -10 kcal/mol of the herbal formula RCM-104. In this network, yellow nodes represent protein targets and green nodes represent herbal compounds. The number of degrees for p16, p19, p36 and p37 are 22, 17, 19 and 16 respectively. They represent the top 4 favorable protein targets for the herbal compounds of the formula and therefore were selected for the synergistic analysis.

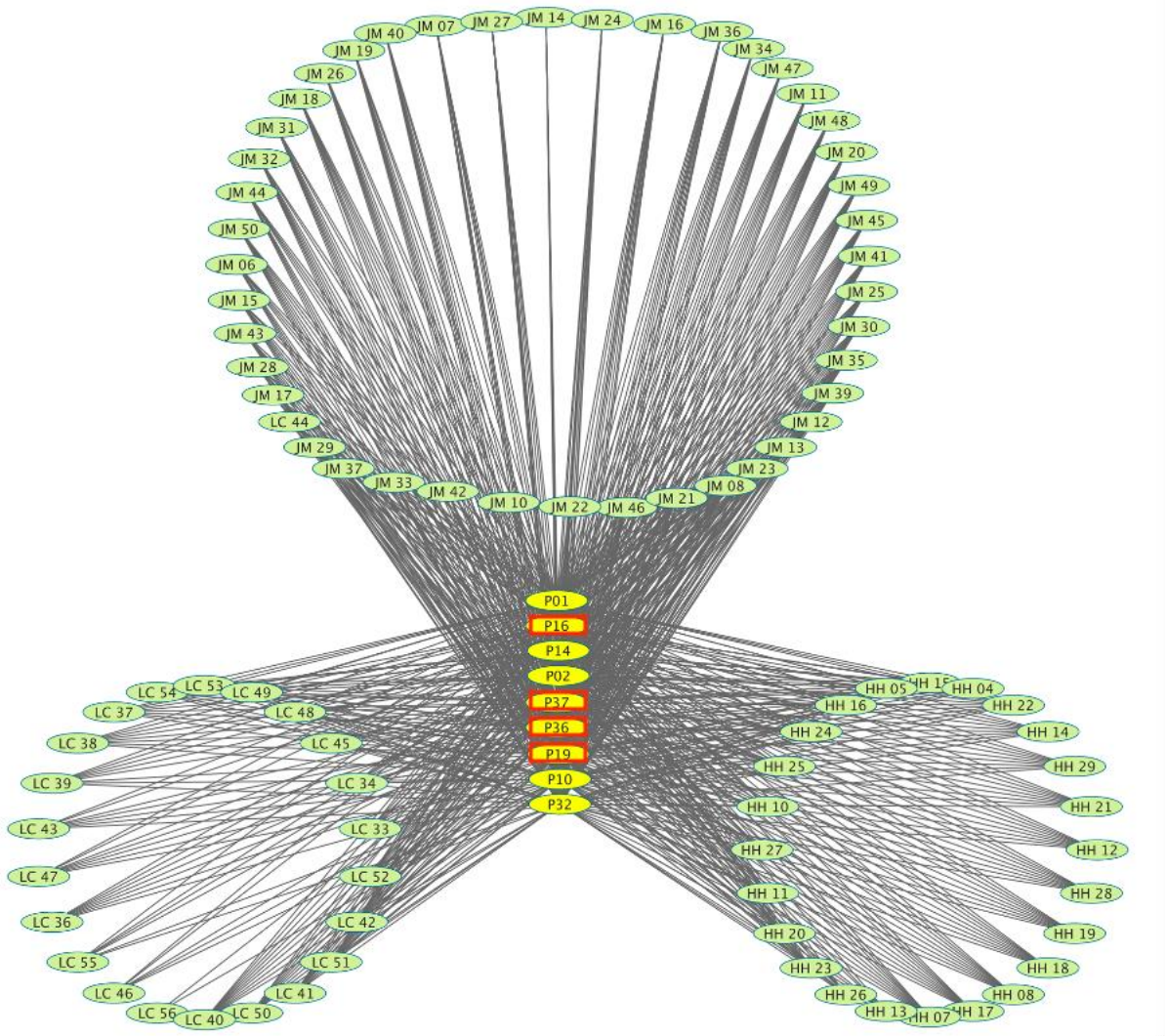


Figure 9.1: Network of formula RCM-104 compounds to anti-obesity agents

Note: P: protein; JM: Jue ming zi compound; LC: Lu cha ye compound; HH: Huai hua compound

Figure 9.2 to 9.6 illustrate the 3D models of the targets generated from the application Maestro (Schrodinger, 2021).

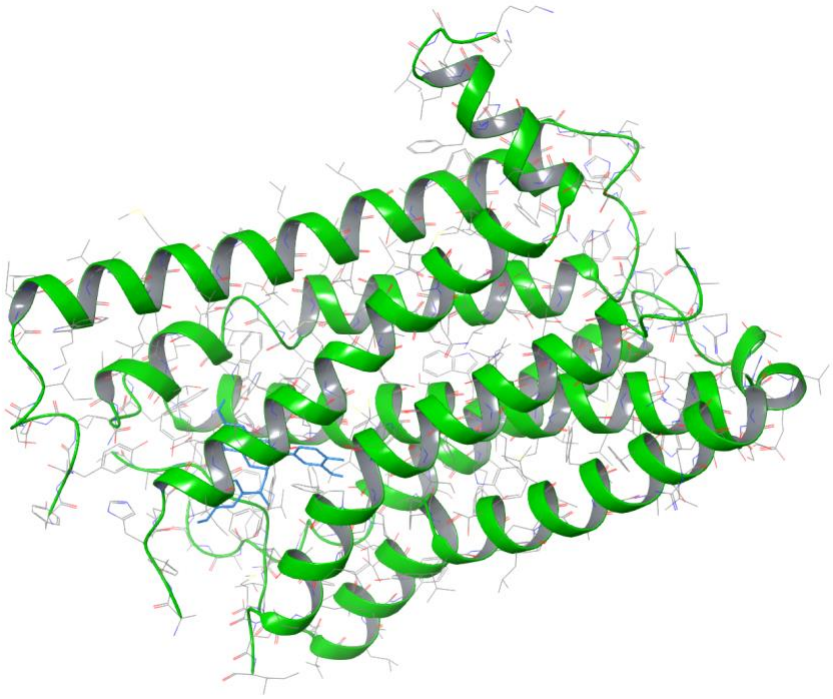


Figure 9.2: p16 - Serotonin receptor 5-HT1B (PDB model of chain A 4IRA)

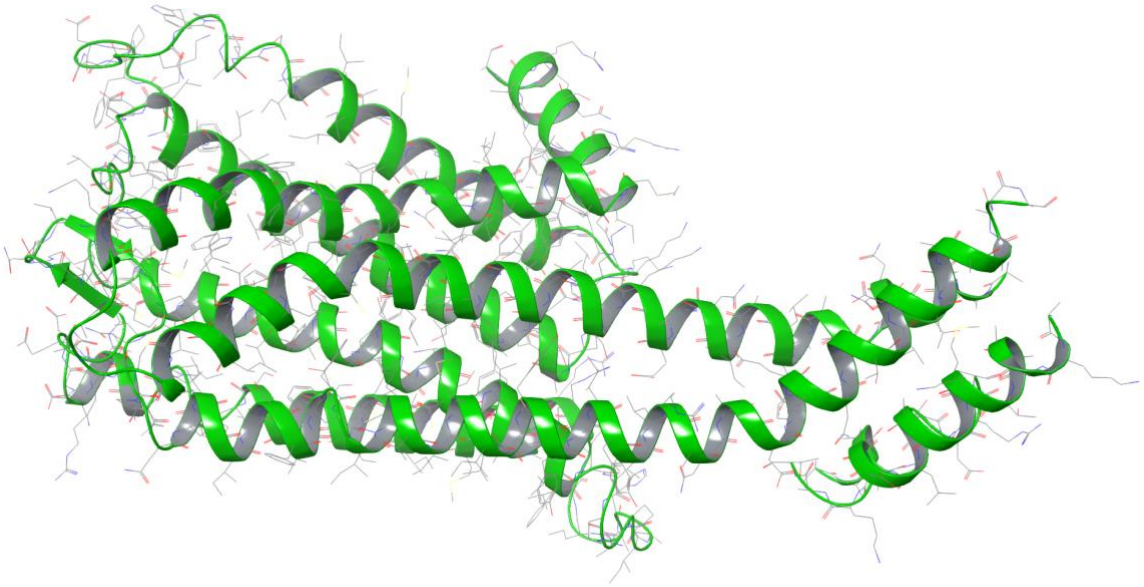


Figure 9.3: p19 - Serotonin receptor 5-HT2C (PDB model of chain A 6BQH)

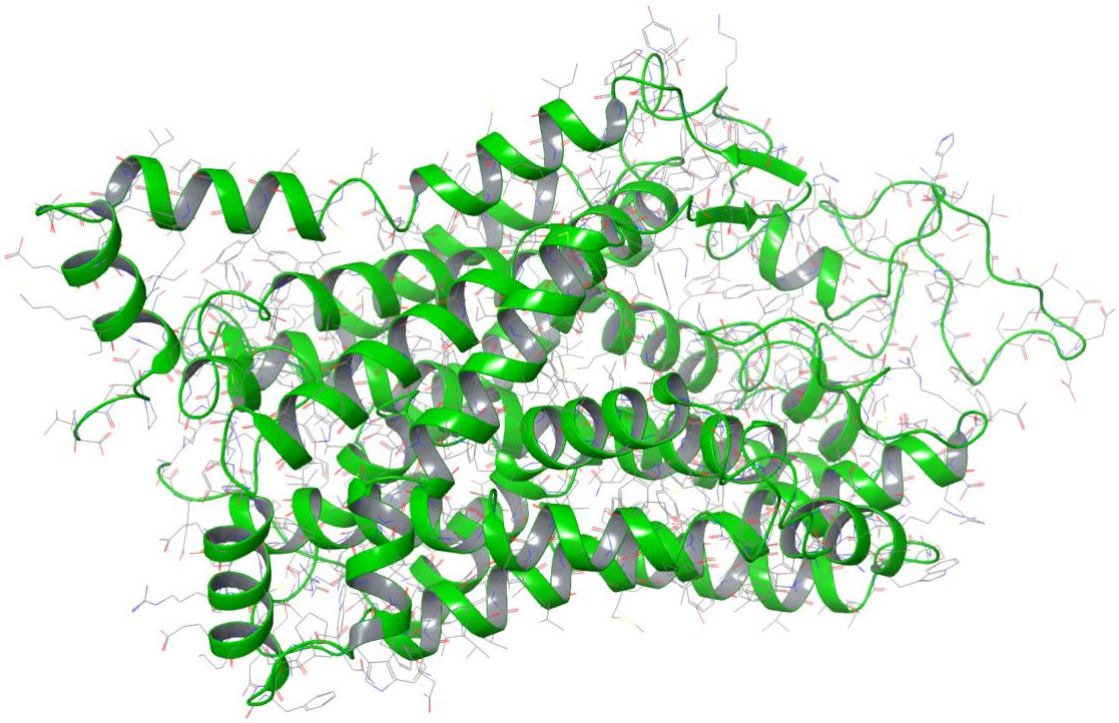


Figure 9.4: p36 - serotonin transporter (SMILE model of 516X)

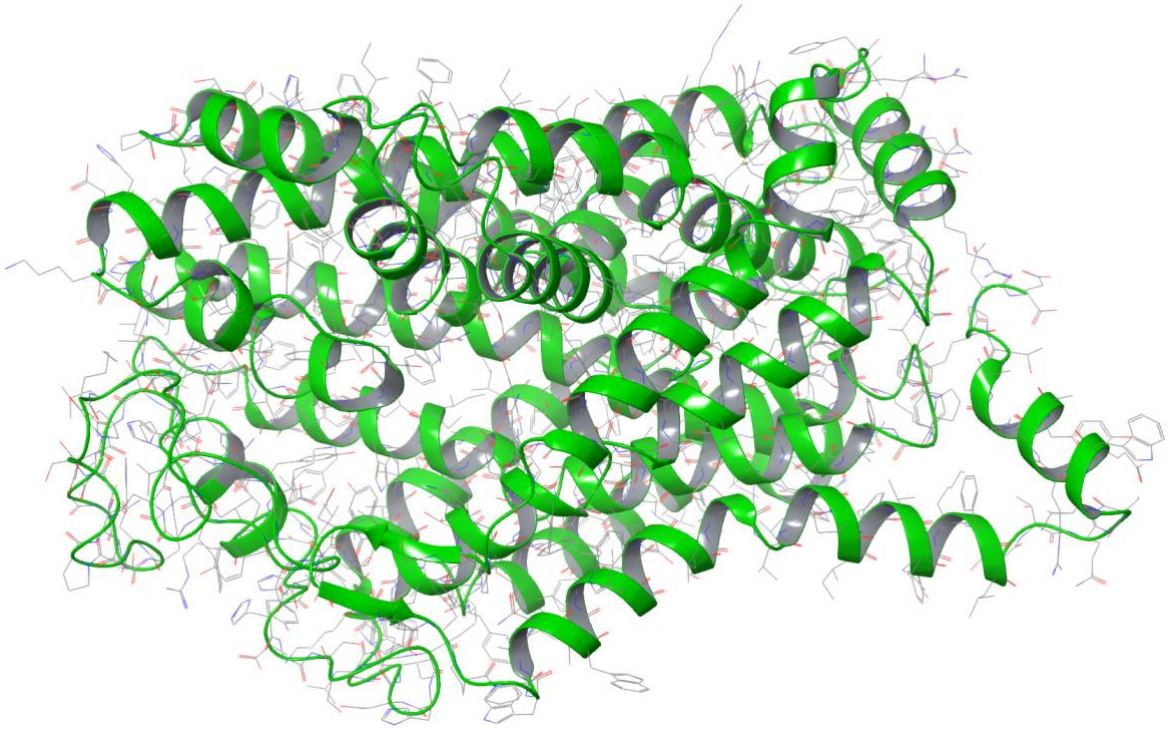


Figure 9.5: p37 - dopamine transporter (SMILE model of 4XP4)

9.1.2 Selected control ligands

Table 9.1 shows the predicted BA (kcal/ mol) of each of the anti-obesity agents with the selected anti-obesity targets. Each column of the table was conditionally formatted in a colour scale, with the red representing the lowest energy value and the green representing the highest energy value. The value of 'Average of BA' in the last column of the Table was calculated by adding the BA value of the ligands on the same row and dividing the sum by the number of the binding protein targets.

Table 9.1: Predicted binding affinities of anti-obesity agents to selected protein targets

	p16	p19	p36	p37	Average of BA
d1	-7	-7.3	-7.1	-6.9	-7.1
d2	-5.7	-4.6	-7.3	-4.7	-5.6
d3	-6.9	-7.6	-7.1	-7.3	-7.2
d4	-7.2	-7	-6.6	-6.4	-6.8
d5	-6.8	-7.4	-7	-7.8	-7.3
d6	-6.2	-6.6	-6.2	-6.6	-6.4
d7	-7.1	-8.3	-7.3	-8	-7.7

Two anti-obesity agents—d3 (lorcaserin) and d7 (benzphetamine)—were selected as the control ligands for synergistic analysis. The reason for this is that d3 is a selective serotonin agonist and d7 has the lowest value of 'Sum of BA' among all the control ligands of this project. The 3D models of d3 and d7, downloaded from online database PubChem (National Center for Biotechnology Information, 2022a; 2022b), are shown in Figures 9.6 and Figure 9.7 respectively.

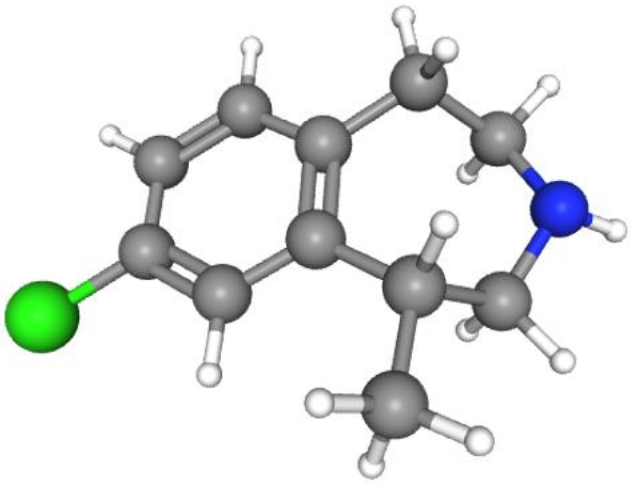


Figure 9.6: 3D model of selected control ligand - d3, lorcaserin

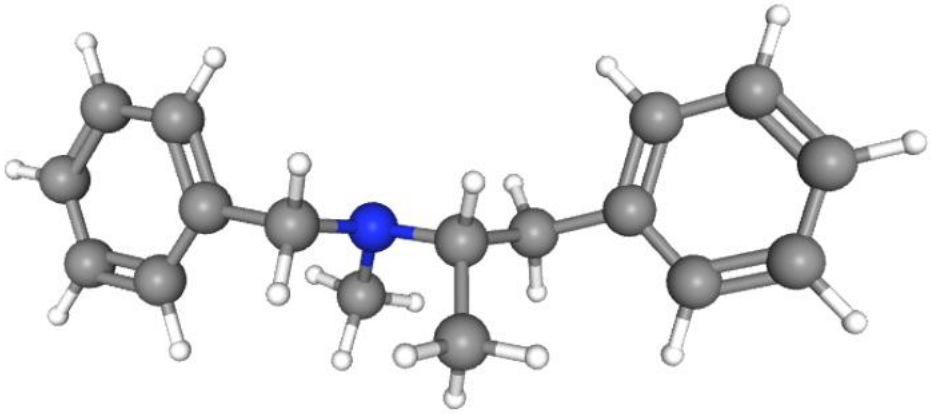


Figure 9.7: 3D model of selected control ligand - d7, benzphetamine

9.1.3 Selected herbal compounds

Figure 9.8 shows the network of the selected proteins with their herbal compounds of high BA value (BA score < -10 kcal/mol). The nodes of the protein targets are highlighted in yellow and circled with green lines. The nodes of herbal compounds are coloured blue. It was observed that some of the herbal compound nodes are connected to a single protein node, while the others are connected to multiple protein nodes. The compounds belonging to the same herb, with a

high BA value to multiple protein targets, are most likely to act synergistically by targeting multiple proteins. These herbal compounds were grouped together in a magenta colourd ellipse as shown in the network. Compounds with known pharmacology activities, and the most abundant compound in each herb (see Appendix D for information from herbal supplier of the formula RCM-104) were selected for synergistic analysis. Although jm11 was not predicted to have high BA value to the selected protein, it was included for synergistic analysis because it is the most abundant compound of JMZ. The BA values of JMZ to the selected proteins p16, p19, p36 and p37 are -8.8, -9.5, -9.2, -8.9 kcal/mol respectively. Table 9.2 shows details of the selected herb compounds.

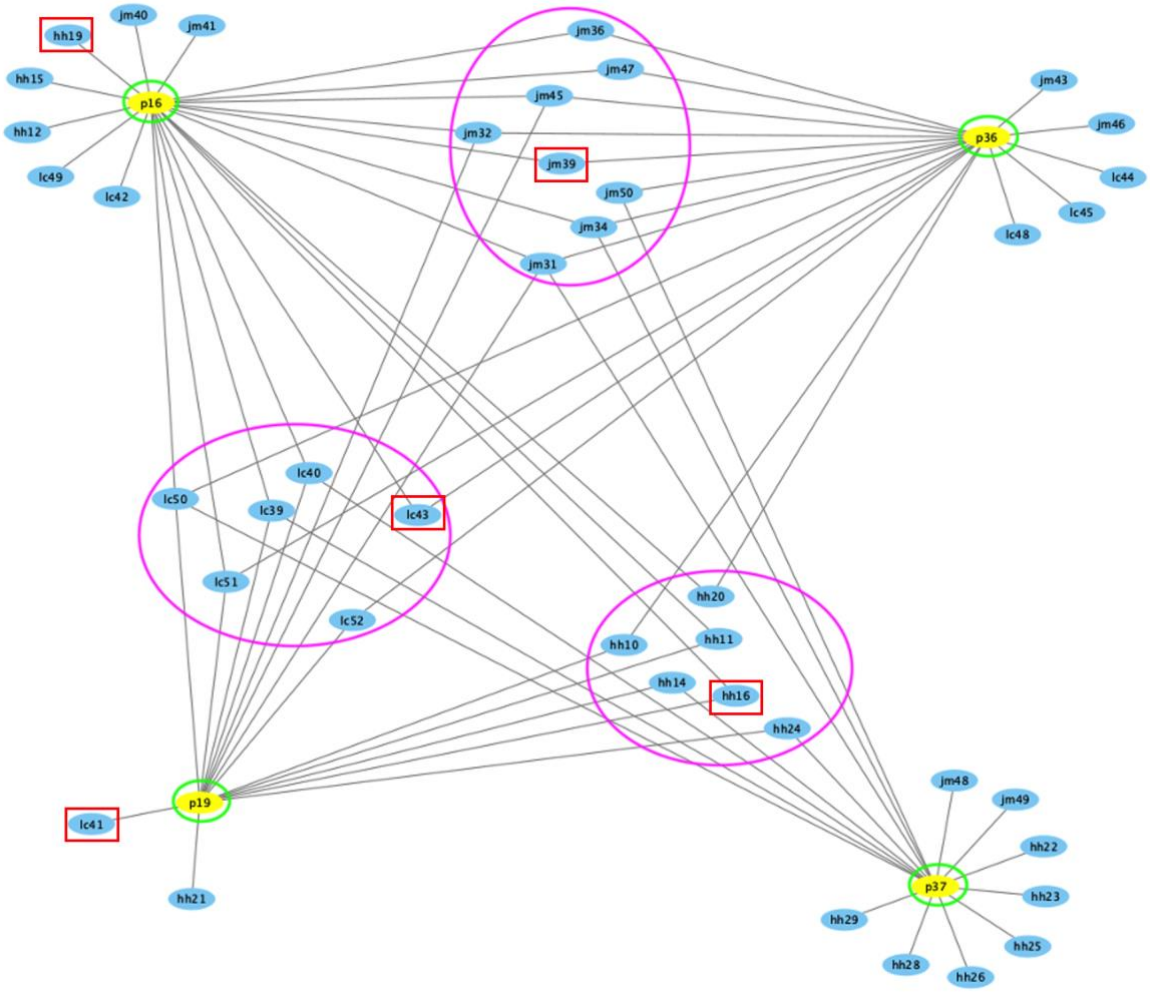
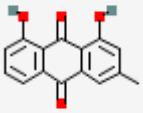
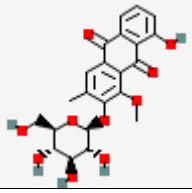
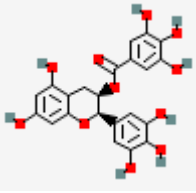
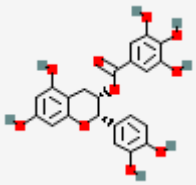
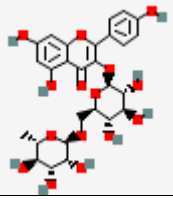
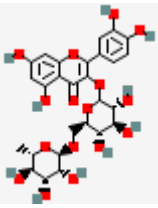


Figure 9.8: Network of selected proteins with their high binding affinity herbal compounds

Note: P = protein; jm = JMZ compound; lc = LCY compound; hh = HH compound

Table 9.2: Selected herbal compounds for synergistic analysis

ID	Compound name/ Herbal source	Chemical formula/ PubChem ID	Chemical Structure	Major known pharmacological activities (references)
jm11*	Chrysophanol JMZ	$C_{15}H_{10}O_4$ 10208		Neuroprotective, anticancer, antimicrobial, anti-inflammatory (Su et al., 2020; Xie et al., 2019)
jm39	Gluco-obtusifolin JMZ	$C_{22}H_{22}O_{10}$ 442761		Neuroprotective, antidiabetic, platelet anti-aggregatory, anti-inflammatory (Ali et al., 2021; Kim et al., 2009)
lc41*	Epigallocatechin gallate (EGCG) LC	$C_{22}H_{18}O_{11}$ 65064		anti-obesity, neuroprotective, antiproliferative, anti-angiogenic, inhibition of tumorigenesis, antimicrobial (Astell et al., 2013; Chakrawarti et al., 2016; Singh et al., 2011)
lc43	Epicatechin gallate (ECG) LC	$C_{22}H_{18}O_{10}$ 65056		anti-obesity, antioxidant, antimicrobial (Astell et al., 2013; Perumal et al., 2017)
hh16	kaempferol-3-rutinoside HH	$C_{27}H_{30}O_{15}$ 5318767		Hepatic protective (Abdullah & Ismail, 2018)
hh19*	rutoside (rutin) HH	$C_{27}H_{30}O_{16}$ 6728944		Neuroprotective, retinoprotective, cardioprotective, hepatoprotective, nephroprotective, protective effect on blood vasculature, anticonvulsive (Demir et al., 2019; Ganeshpurkar & Saluja, 2017)

Note: *Most abundant compound of the herb (information from herbal supplier - see Appendix D). Colour coding of the atoms in chemical structures: Red = Oxygen, Blue = Nitrogen, Cyan = Polar Hydrogen, Green = Chlorine

9.1.4 Binding site analysis

For binding site analysis, a project file was created in the application Maestro for each of the selected protein target. The structures of the protein target and the most favorable predicted pose of each of the selected ligands were first imported into Maestro. Then the 3D models of the protein and all ligands were loaded on to the screen for a visual assessment. The purpose of doing this was to identify the predicted binding sites where the ligands are located.

In order to further analyse the binding sites, 2D interaction diagrams of the protein-ligand pairs were calculated. The common residues of the protein were identified from the 2D interaction drawings and recorded in Table 9.3 to 9.6.

In these Tables, a 'x' marks the existence of a contact between the residue (rows) and the ligand (columns), should any atom of the residue and ligand lie within 4 Angstroms from the others. The right-most column sums up all the interactions for each residue and provides the total number of ligands that make contact with each respective residue.

9.1.4.1 Protein target p16 - serotonin receptor 5-HT1B

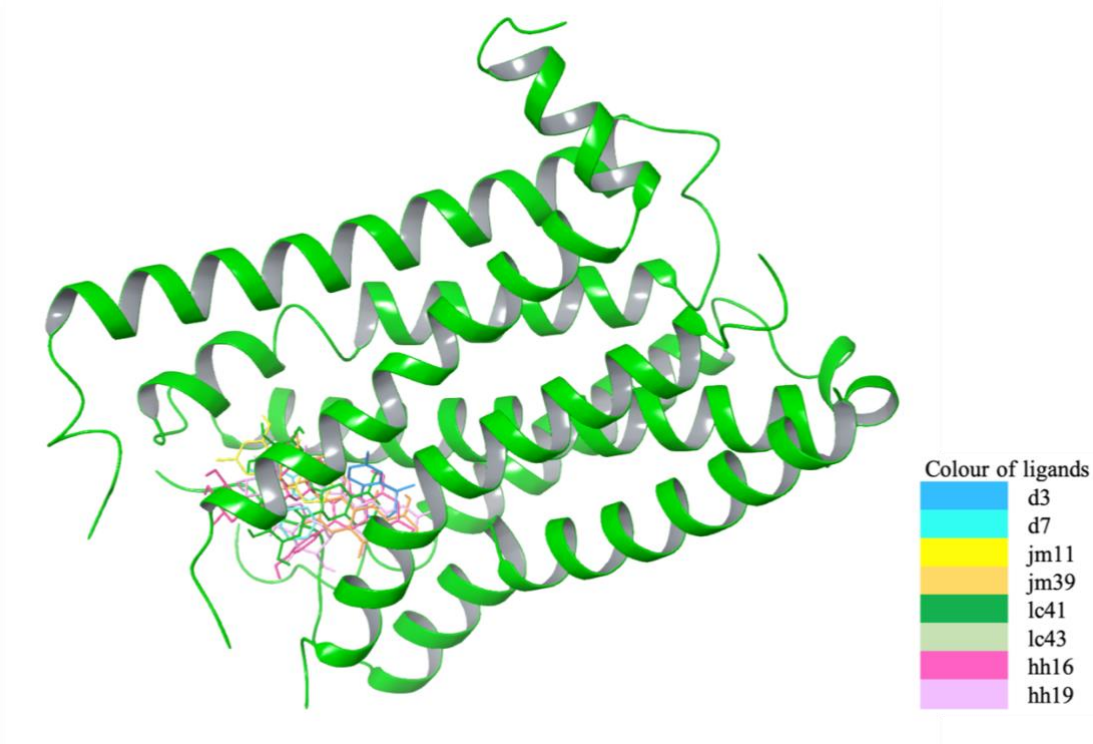


Figure 9.9: Binding site of protein target p16

Table 9.3: Common residues of p16 with selected ligands

Protein	p16 - Serotonin receptor 5-HT1B (PDB Model of Chain A 4IRA)								
Residues	**d3**	**d7**	**jm11**	**jm39**	**lc41**	**lc43**	**hh16**	**hh19**	**Count**
TYR109		x	x		x	x	x	x	6
TRP125		x	x	x	x	x	x	x	7
LEU126		x		x	x		x	x	5
ASP129	x	x	x	x	x	x	x	x	8
ILE130	x			x	x	x	x	x	6
CYS133	x								1
CYS199		x				x			2
VAL200		x	x			x	x	x	5
VAL201	x	x		x			x	x	5

Protein	p16 - Serotonin receptor 5-HT1B (PDB Model of Chain A 4IRA)								
Residues	**d3**	**d7**	**jm11**	**jm39**	**lc41**	**lc43**	**hh16**	**hh19**	**Count**
TRP327	x					x		x	3
PHE330	x	x	x	x		x	x	x	7
PHE331	x	x		x		x	x	x	6
ASP352		x	x	x	x	x	x	x	7
THR355		x	x	x	x	x	x	x	7
TYR359	x		x	x	x	x	x	x	7
THR365	x								1
Total	**9**	**11**	**8**	**10**	**8**	**12**	**12**	**13**	

9.1.4.2 Protein target p19 - serotonin receptor 5-HT2C

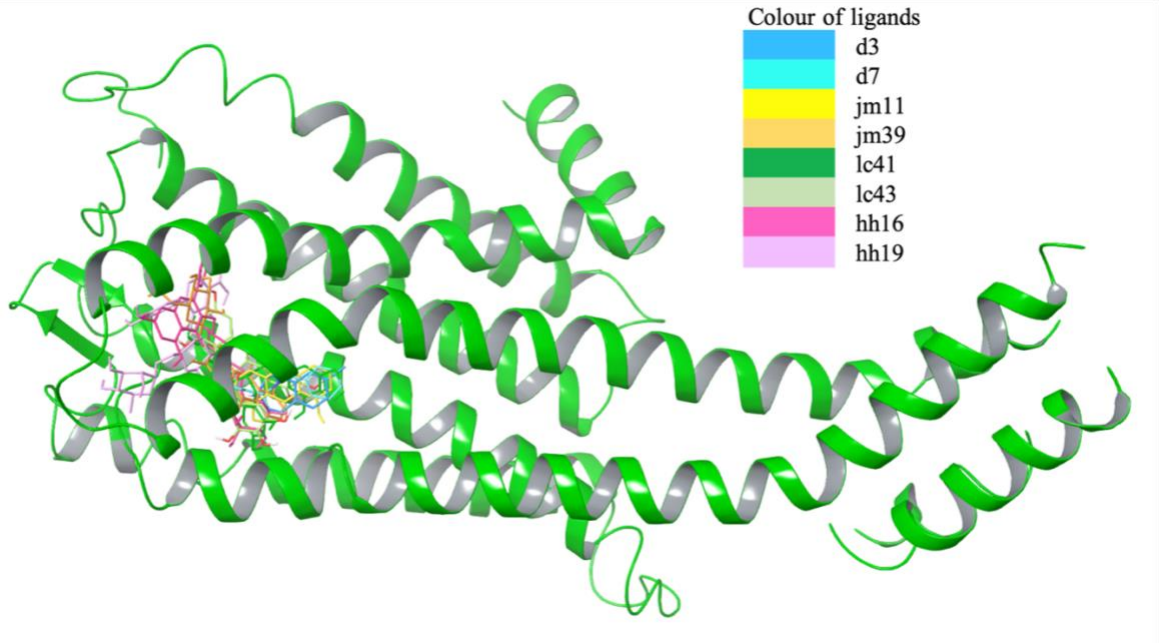


Figure 9.10: Binding site of protein target p19

Table 9.4: Common residues of p19 with selected ligands

Protein	p19 - Serotonin receptor 5-HT2C (PDB model of Chain A 6BQH)								
Residues	**d3**	**d7**	**jm11**	**jm39**	**lc41**	**lc43**	**hh16**	**hh19**	**Count**
ASP134	x	x		x	x	x	x		6
VAL135	x	x	x	x	x	x	x		7
SER138	x	x	x	x	x	x			6
THR139		x	x		x	x			4
ILE142	x	x	x		x				4
LEU209		x	x		x	x	x	x	6
VAL215		x		x		x	x	x	5
ALA222	x	x	x	x	x	x	x		7
PHE223	x	x	x		x	x			5
PHE320	x								1
TRP324	x	x	x		x	x			5

Protein	p19 - Serotonin receptor 5-HT2C (PDB model of Chain A 6BQH)								
Residues	**d3**	**d7**	**jm11**	**jm39**	**lc41**	**lc43**	**hh16**	**hh19**	**Count**
PHE327	x	x	x	x	x	x	x	x	8
PHE328	x	x	x	x	x	x	x		7
ASN331		x		x		x	x		4
Total	**10**	**13**	**10**	**8**	**11**	**12**	**8**	**3**	

9.1.4.3 Protein target p36 - sodium-dependent serotonin transporter

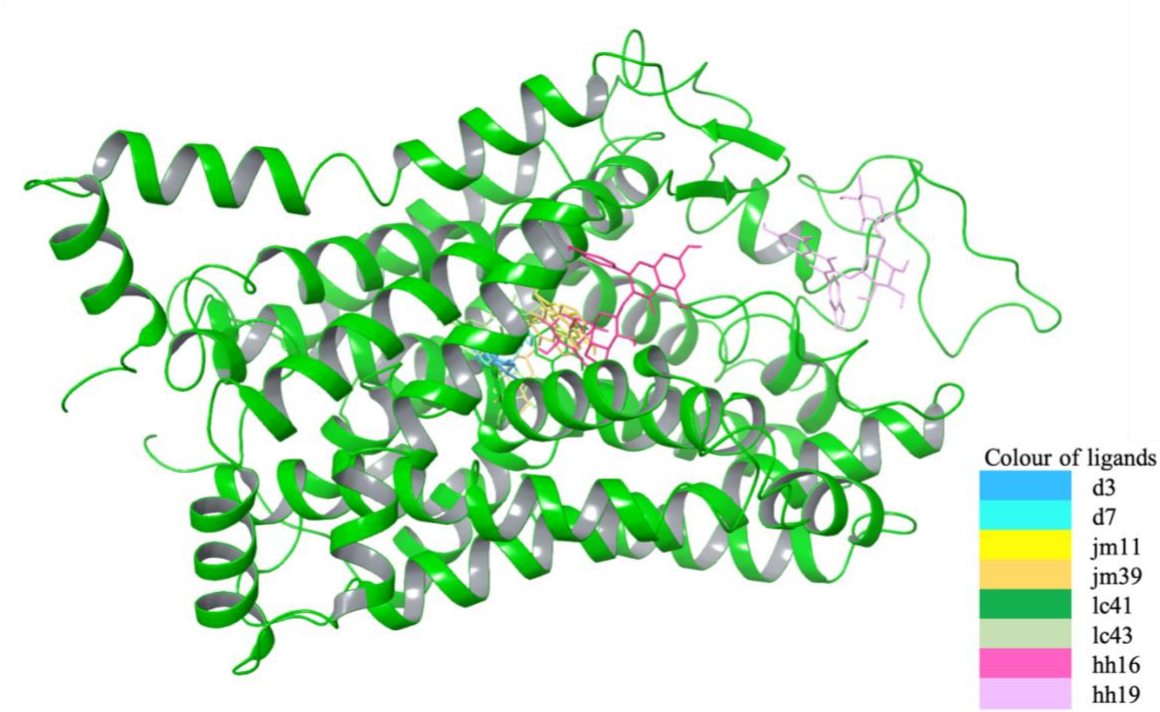


Figure 9.11: Binding site of protein target of p36

Table 9.5: Common residues of p36 with selected ligands

Protein	p36 - Serotonin transporter (SMILE Model of 516X)								
Residues	**d3**	**d7**	**jm11**	**jm39**	**lc41**	**lc43**	**hh16**	**hh19**	**Count**
TYR95	x	x		x	x	x			5
ASP98	x	x	x	x	x	x			6
ILE172	x	x		x	x	x			5
TYR175	x	x	x	x	x	x	x		7
TYR176	x	x	x	x	x	x	x		7
PHE335	x	x	x	x	x	x	x		7
GLY338	x	x			x	x	x		5
PHE341	x	x			x	x			4
SER438	x	x		x	x	x			5
THR439	x				x	x			3
GLY442	x				x	x			3
THR497		x	x	x		x	x		5
VAL501		x							1
Total	**11**	**11**	**5**	**8**	**11**	**12**	**5**	**0**	

Table 9.4 indicates that herbal compound hh19 does not interact with any residues common with drugs d3 and d7. This can be verified by viewing the active binding site and poses of the ligand structures as shown in Figure 9.12.

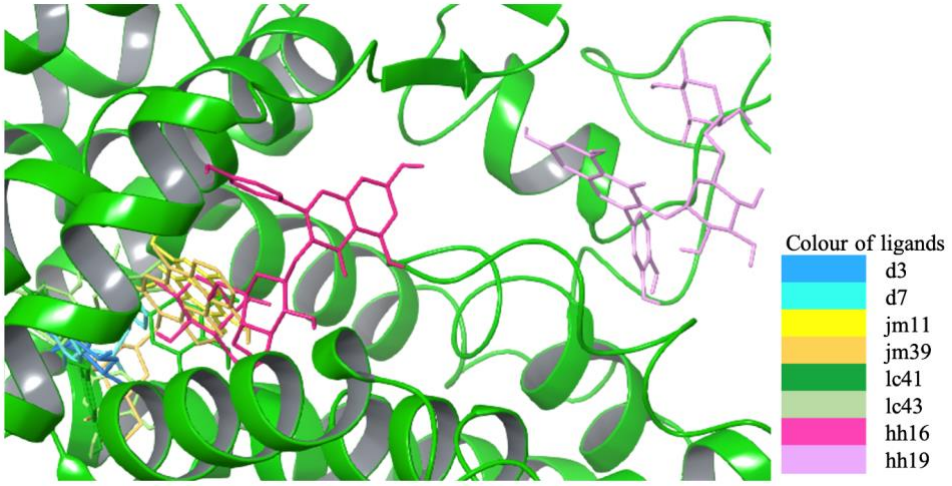


Figure 9.12: Most favourable pose for selected ligands while interacting with p36

9.1.4.4 Protein target p37 - sodium-dependent dopamine transporter

Figure 9.13: Binding site of protein target of p37

Table 9.6: Common residues of p37 with selected ligands

Protein	p37 - Dopamine transporter (SMILE Model of 4XP4)								
Residues	**d3**	**d7**	**jm11**	**jm39**	**lc41**	**lc43**	**hh16**	**hh19**	**Count**
PHE72	x	x	x	x	x	x		x	7
ALA73	x				x	x		x	4
ASP75	x	x	x	x	x			x	6
ALA77	x	x	x	x	x	x		x	7
VAL148	x	x	x	x				x	5
TYR151		x	x	x	x	x		x	6
TYR152		x	x	x	x	x		x	6
PHE317	x	x	x	x	x	x	x		7
SER318	x		x		x	x		x	5
GLY320	x					x		x	3
PHE323	x	x	x	x	x	x		x	7
SER419		x	x	x		x		x	5
GLY423		x							1
ALA477		x				x		x	3
Total	**9**	**11**	**10**	**9**	**9**	**11**	**1**	**12**	

9.2 Analysis of pancreatic lipase

Pancreatic lipase (PL) is a single-chain glycoprotein comprising 449 amino acids belonging to the serine esterase family (Winkler et al.,1990). It can be inhibited by classical serine reagents such as diisopropyl fluoride or E600 (Egloff et al., 1995). As shown in Tables 8.2, 8.4 and 8.6, PL is one of the protein targets having the top (most negative) average BA score with the compounds of each individual herb of formula RCM-104. Therefore, it is hypothesised that RCM-104 may potentially interact strongly with PL.

9.2.1 Selection of protein target

Three different structures of human PL were available in the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) (Protein Data Bank, 2020), including 1N8S (van Tilbeurgh et al., 1992), 1LPA (van Tilbeurgh et al., 1993) and 1LPB (Egloff et al., 1995), and they were all included as protein target in this research project. According to the docking results, 1LPB has the most negative BA score amongst the three PL. Also, it was considered the most suitable for further study as it is the only structure that bound by an inhibitor.

9.2.2 Selection of control ligand

Orlistat, $C_{29}H_{53}NO_5$, was selected as a positive control for this further study as it is a known effective PL inhibitor (Luo et al., 2019; Rodgers et al., 2012). It acts by binding to the active site of the gastric and pancreatic lipases in the lumen of both the stomach and the small intestine thus deactivating the enzyme. As a result, the inactivated enzyme is unable to hydrolyse dietary fat from triglycerides into absorbable free fatty acids and monoglycerides (Monthly Index of Medical Specialties, 2020). Orlistat was approved by the Food and Drug Administration of the United States (FDA) for obesity management including weight loss and weight maintenance when used in conjunction with a reduced calorie diet (The Food and Drug Administration, 2021).

9.2.3 Selection of herbal compounds

The compounds of highest content for each herb were selected for this further study. They were chrysophanol, EGCG and rutin for JMZ, LCY and HH respectively. The chemical compositions of the individual ingredients of herbal formula RCM-104 are shown in Appendix D.

The compounds with top binding affinity (BA) for each herb were selected for further study. They were emodin-8-glucoside, 5,6-dihydroergosterol and kaikasaponin II for JMZ, LCY and HH respectively.

The characteristics of the control and selected herbal ligands are shown in Table 9.7.

Table 9.7 Characteristics of control and selected herbal ligands

ID	Herbal source	Compound name	Chemical formula	Molecular weight (g/mol)	PubChem CID	Binding affinity (kcal/mol)
d1	n/a	Orlistat	$C_{29}H_{53}NO_5$	495.7	3034010	-6.7
jm11	*Cassiae semen*	Chrysophanol	$C_{15}H_{10}O_4$	254.24	10208	-10.1
jm36	*Cassiae semen*	Emodin-8-glucoside	$C_{21}H_{20}O_{10}$	432.4	99649	-10.6
lc41	*Camellia sinensis*	EGCG	$C_{22}H_{18}O_{11}$	458.4	65064	-8.6
lc40	*Camellia sinensis*	5,6-Dihydroergosterol	$C_{28}H_{46}O$	398.7	13889661	-10.2
hh17	*Flos Sophora*	Rutin	$C_{27}H_{30}O_{16}$	610.5	5280805	-8.3
hh28	*Flos Sophora*	Kaikasaponin II	$C_{48}H_{78}O_{17}$	927.1	101538997	-10.7

9.2.4 Binding site analysis p02 - pancreatic lipase

Figure 9.14 shows the binding sites and poses of selected herbal compounds and orlistat with 1LPB. Except for rutin (hh17), all the ligands were predicted to interact with 1LPB in the same binding site.

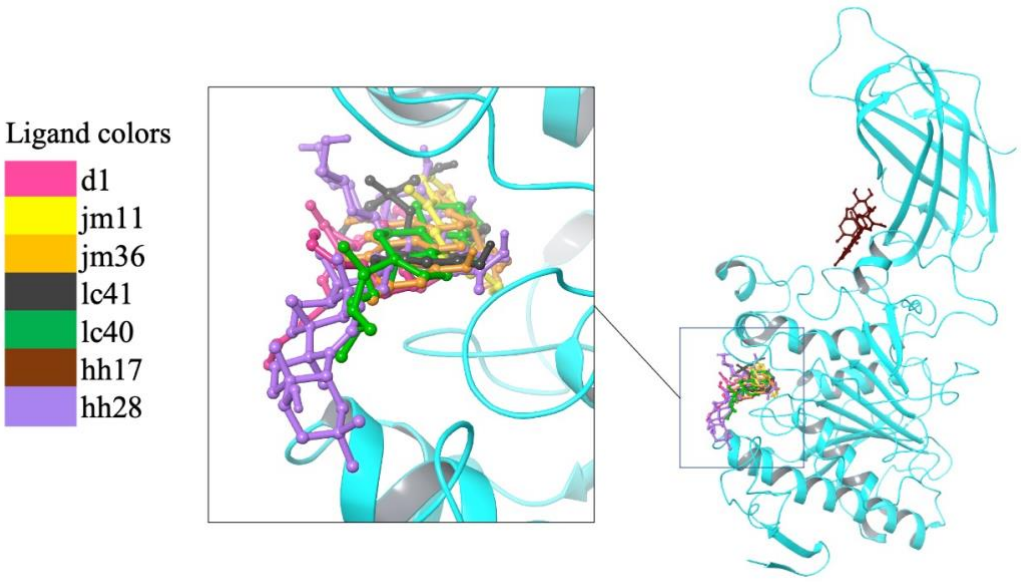


Figure 9.14 Binding sites and poses of all ligands with 1LPB

Table 9.8 shows the residues which form the most common contacts with orlistat and the selected herbal compounds: chrysophanol (jm11), emodin-8-glucoside (jm36), EGCG (lc41), 5,6-dihydroergosterol (lc40) and kaikasaponin II (hh28). Rutin (hh17) is excluded in Table 9.8 because it interacts with 1LPB Chain B in a different binding site from that of orlistat.

In Table 9.8, 'x' indicates the interaction between the residue (rows) and the ligand (columns) if any atom of the residue and ligand lies within 4 angstroms of each other. The column on the extreme right is an aggregate of all of the interactions for each residue and provides the total number of ligands making contact with the respective residue.

Table 9.8 Common ligand-binding residues of orlistat and selected herbal compounds

Residue	Ligands						Total
	d1	jm11	jm36	lc41	Lc40	hh28	
GLY76	x	x	x				**3**
PHE77	x	x	x	x	x	x	**6**
ILE78	x		x	x	x	x	**5**
ASP79	x	x	x	x	x	x	**6**
TYR114	x		x	x	x	x	**5**

Residue	Ligands						Total
	d1	jm11	jm36	lc41	Lc40	hh28	
HIS151	x	x	x				**3**
SER152	x	x	x	x	x	x	**6**
ALA178	x		x	x		x	**4**
PRO180	x		x	x	x	x	**5**
ILE209	x				x		**2**
LEU213	x					x	**2**
PHE215	x	x	x	x	x	x	**6**
TRP252	x						**1**
THR255	x						**1**
ARG256	x	x	x	x	x	x	6
ALA259		x		x			**2**
ALA260	x	x		x		x	**4**
HIS263	x	x	x	x	x	x	**6**
LEU264	x	x	x	x	x	x	**6**

Note: Rutin (hh17) is excluded in this table because it interacts with 1LPB Chain B in a different binding site to orlistat.

9.3 Discussion

9.3.1 Serotonergic system

Serotonin receptors, a type of G-protein-coupled receptors (GPCRs) existing in the nervous system and periphery of the body, are important for the regulation of brain functions (McCorvy & Roth, 2015). Dysregulation of the serotonergic system may imply psychiatric and neurological disorders. Research shows that serotonin has critically important functions in many human organ systems outside the central nervous system, including the regulation of energy balance and food intake and gastrointestinal functions (Berger et al., 2009). The dopaminergic system is involved in the motivational aspects of reward (Bhatia A, 2021). Decreased levels of dopamine hormone and dopamine receptors have been hypothesised to lead to increased motivation for palatable food (Pandit et al., 2011).

GPCRs show high binding affinity compared with other targets. This may be due to their deep and relatively large binding pockets which allow for a higher number of contacts (Kratochwil et al., 2011).

Published literature has identified residues Trp125, Asp129, Ile130, Val201, Phe330, Phe331 and Thr355 in the active site of serotonin 5-HT1B receptor (Baitha et al., 2019; Contreras et al., 2022; Yang et al., 2021). It was observed in our study that the herbal compounds jm39, lc43, hh16 and hh19 are predicted to interact strongly to all these identified residues.

According to published literature, the interaction of residue Asp134 with molecules is essential in enabling the agonist activity of serotonin 5-HT2C receptor (Ahmed et al., 2009; Veeramachaneni et al., 2019). Other residues that are predicted to commonly interact with the selected herbal compounds including Val135, Ser138, Ala222, Phe327 and Phe328, are considered as important residues involved in facilitating ligand binding activity for a range of small-molecule organic compounds (Zuo et al., 2007). It was observed in our study that all the selected herbal compounds, except jm11 and hh19, are predicted to interact strongly with these identified residues.

9.3.2 Pancreatic lipase

All the herbal ligands in Table 9.8 share general structural similarities. In particular, they are all composed of a hydrophobic polyaromatic ring section (resembling cholesterol) and a more hydrophilic section composed of multiple hydroxyl groups. They are, therefore, amphiphiles which are similar to many lipids. This is not unexpected given the lipase's function in strongly binding lipids and catalysing their reactions. Therefore, effective inhibitors are likely to be composed of partial polar and non-polar segments.

The polar sections bind to residues including Asp79, Ser152, Arg256, and His263. It is noted that Ser152, located in the larger N-terminal domain at the C-terminal edge of a doubly wound parallel β-sheet is the nucleophilic residue essential for catalysis (Winkler et al., 1990). His263, Asp176 and Ser152 together form a catalytic triad analogous to the serine proteases representing the lipolytic site (Birari & Bhutani, 2007) and could interact with the polar part of a bound lipid substrate (van Tilbeurgh et al., 1994).

The non-polar polyaromatic ringed groups of the present herbal ligands bind with a group of common residues which principally comprise Phe77, Asp79, Pro180 and Phe215. In PL, residues 76–84 form a mobile surface loop (β5- loop) which renders the catalytic serine accessible to substrate (van Tilbeurgh et al., 1994). Residues 213–217 form another loop with the same function as β5-loop (Lowe, 1997).

Thus, the predicted herbal compound inhibitors may act by both: 1) directly interacting with the catalytic side residues thus preventing their enzymatic function; and 2) binding with non-polar residues by preventing the interaction of the hydrophobic tails of endogenous lipids with the lipase binding site in the vicinity of the catalytic site.

Experimental studies have previously been performed on chrysophanol and have established that chrysophanol significantly inhibits cholesterol absorption and lowers the triglyceride level in zebra fish fed with a high-fat/cholesterol diet (Prateeksha et al., 2019). Whilst the cholesterol and triglyceride suppression effects of chrysophanol have been demonstrated, its molecular target remains unknown. The use of docking methodology has revealed the possibility that chrysophanol acts via direct inhibition of PL and provides a basis for directing future studies to fully elucidate the mechanisms of actions of chrysophanol. The result of an *in vivo* study has shown that the treatment with EGCG on obese mice may modulate lipid absorption, possibly

through PL inhibition (Grove et al., 2012). This current study has predicted via docking methodology that EGCG directly inhibits PL.

9.3.3 Proposed synergistic effects of formula RCM-104 based on molecular docking results

Numerous research studies have suggested that activation of 5-HT2C receptor and 5- HT1B receptor alone is beneficial in controlling food intake and also balancing the energy (Bickerdike et al., 1999; Jensen et al., 2010; Kennett & Curzon, 1988; Kennett et al., 1987). However, Maxwell et al. (2022) hypothesised that both the 2C and 1B 5HT receptors are necessary for the anorectic effects of leptin. On the other hand, Doslikova et al. (2013) report a significant reduction in food intake by combining 5-hydroxytryptamine receptor 2C (5-HT2CR) agonist with 5-hydroxytryptamine receptor 1B (5-HT1BR) agonist at concentrations that alone do not influence feeding (Doslikova et al., 2013).

In our studies, the herbal compounds lc43, hh16 and hh19 (from green tea and sophorae flos) are predicted to interact strongly with 5-HT1BR, while jm11, lc41and lc43 (from Cassiae Semen and green tea) are predicted to interact strongly with 5-HT2CR. Therefore, we hypothesise that there are synergistic effects of RCM-104 by combining these three herbs in the formula to target both 5-HT1BR and 5-HT2CR.

On the other hand, there is evidence supporting a critical role of 5-HT2C in mediating the interaction between serotonergic and dopaminergic systems (Jensen et al., 2010). Our study has shown that jm11, lc43 and hh19 are predicted to interact strongly with a dopamine transporter. The prediction of the interaction of these herbal compounds with dopamine transporter support the hypothesis that the formula RCM-104 may exert its anti-obesity effects by its action on both serotonergic and dopaminergic systems.

Apart from influencing the serotonergic and dopaminergic systems, RCM-104 is predicted to inhibit PL, thereby activating for its weight loss effect by mimicking the action of orlistat. Our study has shown that chrysophanol (jm11), emodin-8-glucoside (jm36), EGCG (lc41), 5,6-dihydroergosterol (lc40) and kaikasaponin II (hh28). are predicted to interact strongly with PL.

9.3.4 Strengths and limitations of molecular docking and analysis

The methods of molecular docking and analysis provide a scientific basis for the effectiveness of a given substance based on a molecular-level understanding of key ligand-protein interactions and help to reveal some of the mechanisms behind the therapeutic efficacy of CHM.

The strengths include rapid estimation of binding affinity (BA) to determine possible preferred targets of herbal compounds and accurate determination of binding poses. However, molecular docking is often limited by poor correlation between the predicted BA values and biological activity.

Some of the reasons for this poor performance in binding energy prediction are:

- Proteins are rigid, while ligands allow limited flexibility (can rotate, but no bond vibrations allowed).
- No solvent and ions can strongly affect ligand-receptor interactions.
- Incorrect poses can also be resulted due to lack of water molecules. For example, in the approach taken in this work, it was not possible to have ‘bridging waters.’
- Lipid bilayer is absent—some of the herbal compounds may interact with the membrane and, therefore, may require the presence of lipids in order to accurately model the manner in which they interact with the receptors.

The above limitations highlight the need for further work to ascertain the action of RCM-104 on the serotoninergic and dopaminergic proteins identified in this study. Nonetheless, this computational study forms the foundation for a molecular-level understanding of the anti-

obesity properties of RCM-104, paving the way for the rational optimisation of the formula based on knowledge of the bioactivities of formula molecular components on specific physiological pathways associated with satiety.

Chapter 10 General discussion and conclusion

The goal of this research project is to understand the clinical effects and mechanisms of actions of the Chinese herbal formula RCM-104 for weight management. The entire project is divided into 3 phases: Phase I classical literature review, Phase II modern literature review and Phase III computational analysis.

The objectives of phase I are to acquire classic literature evidence and ancient knowledge of the individual ingredients of formula RCM-104, through classic literature review with the method of data mining and text mining.

Phase II is modern literature review. The objectives of phase II are to acquire clinical/experimental evidence and ancient and scientific information about the formula RCM-104 as the input for phase III

Phase III is computational analysis. The objectives of phase III are to find out the possible mechanisms of actions of the three herbs and to propose potential synergy of formula RCM-104.

The key findings of this research project are descriptively summarised in this chapter. The strengths and limitations of the project are discussed and future directions for research are recommended. The final conclusion of the project is presented at the end of the chapter.

10.1 Key findings

This is the first research project that systematically investigates the mechanisms of actions of Chinese herbal formula RCM-104 for weight management.

In Phase I, the electronic search on CD-ROM database and manual search on hard copies of the ancient Chinese texts related to the three herbal ingredients of formula RCM-104, namely, Jue ming zi (JMZ, Cassiae semen), Lu cha ye (LCY, unfermented Camellia Sinensis leaf) and Huai hua (HH, Sophorae Flos) has provided information of the origin, historical evolution and details of the specific herbs including their properties, actions and indications. The findings show that JMZ may assist in maintaining a healthy body weight due to its actions in nourishing the Liver and clearing Liver heat. LCY may assist in maintaining a healthy body weight by eliminating the fat, purging the Gallbladder and reducing the damp-heat and pathogenic fire. HH may assist in weight loss by cooling the Large Intestine, clearing the Liver fire, disperse wind-heat and cooling the blood. In addition, RCM-104 can help to prevent overeating by reducing the heat from Stomach and Large Intestine, because all the three herbs of RCM-104 are cool in nature; JMZ enters the Large Intestine meridian and HH enters the Stomach meridian.

The modern literature review of Phase IIa on the phytochemistry, pharmacology and toxicity of the herbal ingredients of formula RCM-104 has demonstrated a profound influence of these herbs and their chemical compounds on various diseases and health conditions apart from overweight and obesity. The results of the search found that JMZ and nine of its active chemical compounds are identified to have weight reduction effects. It was found that JMZ compounds may exert anti-obesity effects via inhibiting amylases and lipases and suppress appetite by 5-HT2C receptor activation. LCY plays a role in weight loss by by reducing food intake; interrupting lipid emulsification, reducing lipid absorption; suppressing adipogenesis, disrupting lipid synthesis, raising body thermogenesis and increasing energy expenditure through faecal lipid excretion. HH and its bioactive compounds have demonstrated various potentials to against major obesity-related health risks such as diabetes. In summary, the main

pathways of weight loss effect of ECM-104 are reducing food intake through appetite suppression and reducing lipid absorption through inhibition of digestive enzymes.

One of the pathways of weight loss for RCM-104 is the effects on lipid metabolism. Both JMZ and LCY contributes to reducing lipid absorption. The antioxidation activity of all these three herbs accounted for the lipid-reducing effect of RCM-104.

In Phase IIb, through extensive search on multiple databases, seven anti-obesity drugs/agents were identified. Further, 38 anti-obesity protein target structures and a total of 147 herbal compounds of formula RCM-104 were identified for the molecular docking of the computational analysis phase of the project.

In Phase III, the binding mechanism predictions of all ligands to the protein targets identified in this project have been performed using computational molecular docking. The output of the docking process consisted of the predicted affinity scores of protein-target pairs and the top 10 most energetically favourable 3D models of each pair. Through analysing the docking results, it was established that each herb of formula RCM-104 contains chemical compounds which are effective in inhibiting pancreatic lipase and could suppress lipid absorption and thus achieve weight-loss.

The computational molecular docking and analysis contributes to the knowledge of mechanisms of actions of the individual herbs towards its specific targets. A pharmacological network detailing the interactions between the formula, herbs, chemical compounds and targets is being established, as shown in Figure 9.1. This visual presentation has provided further insights on the mechanisms of actions of formula RCM-104 towards its specific targets. Further analysis on the interaction of these targets and their selected herbal compounds discovered that a major Mechanism of action of formula RCM-104 is to supress appetite by influencing the serotonergic and dopaminergic systems. The effectiveness of the formula is predicted to be

increased by the synergistic effect of interacting with both 5HT1B receptor and 5HT2C receptor.

There were strong correlations among the results of different phases. Results from the classical literature review of Phase I suggested that RCM-104 may contribute to weight-loss by preventing overeating in the Chinese medicine perspective. Results from the modern literature review of Phase IIa confirmed the weight-loss effect of RCM-104 by reducing lipid in the Western medicine perspective. Results from the computational analysis of Phase III further echo the weight-loss effect of RCM-104 by, with the molecular docking results suggesting that the formula inhibits pancreatic lipase. Phase IIb played a crucial role in the research project because the docking output and the subsequent analyses in Phase III relied on the accuracy and completeness of the data identified in this phase.

10.2 Strengths

The strengths of the present research can be outlined in three parts.

Firstly, the comprehensive searches on classical literature allowed access to an unprecedented number of classical texts from numerous CM authors/practitioners spanning many dynasties, achieving a task of collecting classical knowledge on specific herbs from highly dispersed records across time and space. The comprehensive searches on modern literature allowed access to the work and results of many studies and experiments, collecting known and reliable modern information on specific herbs for pharmacological analysis. Information yielded in these two phases not only made possible in-depth understandings of the herbs, but also provided preconditions for deducing the actions of formula RCM-104.

Secondly, online investigation for a combination of classical and modern literature coupled with computational analysis provided a comprehensive, integrated method for non-

experimental research. With vigorous selection criteria and procedures, the adopted methodologies conduced to a transparent, comprehensive and structured approach to searching, selecting and synthesising the literature. It was also an efficient approach for screening active herbal chemical compounds for the input of molecular docking. The interdisciplinary nature of this research project not only filled some knowledge gaps in individual knowledge systems, such as the understandings of obesity, but also provided valuable data for cross-reference among research results generated from different disciplines. Despite its complexity, this research methodology is relatively easy to replicate for studying other Chinese herbal formula.

Thirdly, Computational analysis for drug discovery is a valuable approach to characterise the interrelated dynamic connections between *in vivo* processes and the effectiveness of drugs (Aminpour et al., 2019). It is suitable for explaining the interactions of multiple targets and chemical compounds rather than conventional experimental studies which are more focussed on a specific biological mechanism. For medicinal herbs, both reviews on classical and modern literature indicated their multiple functions which implied their multi-target intervention characters. In other words, a herb can be used to treat different diseases or to treat the same diseases through different pathways. Therefore, computational analysis could explain the multiple mechanisms of actions of medicinal herbs on multiple targets of the disease through a low-cost and high throughput approach. The strengths of molecular docking include rapid estimation of binding affinities to determine possible preferred targets of herbal compounds and actuate determination of binding poses. The analysis on docking results enables the hypothesis of the synergistic effects of the herbal formula RCM-104.

10.3 Limitations

The literature search involved in this project was limited solely to Chinese and English languages only. Therefore, the medical literature published in other languages was not

considered. For example, green tea, one of the three ingredients of formula RCM-104, is a very popular traditional beverage in Japanese and Korean culture. Thus, some insights and ancient knowledge may have been missed due to the language barrier.

Another limitation of this project is that molecular docking is often limited by poor correlation between the predicted BA values and biological activity. Some of the reasons for this poor performance in binding energy prediction are the rigidity of the proteins, ligand-receptor interactions which are affected by the absence of solvent and ions, the incorrect poses of ligands and absence of lipid bilayer.

10.4 Future directions

This research has provided an initial insight into one of the possible mechanisms of action of formular RCM-104 through molecular docking study, that is suppressing the appetite by influencing the serotonergic and dopaminergic systems. Further analysis of the docking results of the other protein targets identified in this research project, such as pancreatic lipase and glucagon like peptide 1 receptor (GLP1R) receptor may assist in discovering other potential pathways of RCM-104 on weight management. On the other hand, molecular dynamics simulation is recommended to analyse the physical movements of atoms and molecules for further understanding and confirmation of the mechanisms of action of the formula. Experimental validations for the molecular docking results are also recommended.

10.5 Conclusions

The findings from classical literature review revealed that RCM-104 is indicated for obese people with Stomach Heat syndrome and Liver Qi stagnation syndrome. The mechanisms of actions of formula RCM-104 from Chinese medicine perspective are prevention of overeating

by clearing the Stomach Heat and improvement of metabolic rate and energy flow by removing the Liver Qi stagnation.

The findings of modern literature review revealed that the major pathways of weight loss for formula RCM-104 from Western medicine perspective are appetite suppression, inhibiting pancreatic lipase and reducing lipid absorption.

The findings from computational analysis revealed that a major mechanism of action of formula RCM-104 is to suppress the appetite by influencing the serotonergic and dopaminergic systems. It was also established that each herb of formula RCM-104 contains chemical compounds which are effective in inhibiting pancreatic lipase.

In summary, the goal of this research project has been achieved by revealing the clinical effects and mechanisms of actions of formula RCM-104 for weight management.

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Appendices

Appendix A: List of Publications

List of Publications

Peer-reviewed journal articles

1. **Yuen, H.**, Lenon, G. B., Yang, A. W. H., & Hung, A. (2020). How does traditional knowledge of Cassiae Semen shed light on weight management? —A classical and modern literature review. *Journal of Ethnopharmacology*, 113572–113572. https://doi.org/10.1016/j.jep.2020.113572

2. **Yuen, H.**, Hung, A., Yang, A. W. H., & Lenon, G. B. (2020). Mechanisms of action of Cassiae Semen for weight management: A computational molecular docking study of serotonin receptor 5-HT2C. *International Journal of Molecular Sciences, 21*(4), 1326. https://doi.org/10.3390/ijms21041326

3. Luo, S., Lenon, G. B., Gill, H., **Yuen, H.**, Yang, A. W. H., Hung, A., & Nguyen, L. T. (2019). Do the natural chemical compounds interact with the same targets of current pharmacotherapy for weight management?—A review. *Current Drug Targets, 20*(4), 399–411. https://doi.org/10.2174/1389450119666180830125958

Conference proceedings

1. Yuen, H., (2021). Clinical effects and mechanisms of action of a Chinese herbal formula (RCM-104) for weight management: Literature reviews and computational analysis. *Australian Acupuncture and Chinese Medicine Association (AACMA) Webinar: Sharing from Chinese Medicine Researcher Part 1*. Queensland, Australia.

2. Yuen, H., Hung, A., Yang, A. W. H., & Lenon, G. B. (2021). Mechanisms of Action of Cassiae Semen for Weight Management: A Computational Molecular Docking Study of Serotonin Receptor 5-HT2C [Video presentation]. *2020 Annual Conference*. Australia and New Zealand Obesity Society (ANZOS). Fully virtually

3. Yuen, H. (2019). Mechanisms of action of Cassiae Semen for weight management: A computational molecular docking study of serotonin receptor 5-HT2C [Oral presentation]. *RMIT 2019 Traditional Chinese Medicine (TCM) Forum*. Victoria, Australia.

4. Yuen, H., Hung, A., Yang, A. W. H., & Lenon, G. B. (2018). Molecular docking study of Cassiae Semen compounds to identify amylase and lipase inhibitors for weight management [Poster presentation]. *2018 Annual Conference—Breakthrough Discoveries Program*. Australia and New Zealand Obesity Society (ANZOS) Melbourne Convention and Exhibition Centre, Australia.

Appendix B: Genre categories of Zhong Guo Ben Cao Quan Shu

中國本草全書

Zhong Guo Ben Cao Quan Shu

(The Complete Collection of Traditional Texts on Chinese Materia Medica)

Classic book title	Book title in English	Volume, page
神農本草經（馬繼興輯本） *Shen Nong Ben Cao Jing (Ma Ji Xing Ji Ben)*	Shennong's Classic of Materia Medica (compiled by MA, Jixing)	Vol. 2, P. 001
神農本經（盧複輯本） *Shen Nong Ben Jing (Lu Fu Ji Ben)*	Shennong's Materia Medica (compiled by LU, Fu)	Vol. 2, P. 147
本草經 *Ben Cao Jing*	Classic of Materia Medica	Vol. 2, P. 205
神農本草經（孫星衍、孫馮翼輯本） *Shen Nong Ben Cao Jing (Sun Xing Yan, Sun Feng Yi Ji Ben)*	Shennong's Classic of Materia Medica (compiled by SUN, Xinyan & SUN, Fengyi)	Vol. 2, P. 239
神農本草經（狩穀齋輯本） *Shen Nong Ben Cao Jing (Shou Yu Zhai Ji Ben)*	Shennong's Classic of Materia Medica (compiled by SHOU, Zhaiji)	Vol. 2, P. 413
神農本草經（森立之輯本） *Shen Nong Ben Cao Jing (Sen Li Zhi Ji Ben)*	Shennong's Classic of Materia Medica (compiled by SEN, Lizhi)	Vol. 2, P. 475
神農本草（王仁俊輯本） *Shen Nong Ben Cao (Wang Ren Jun Ji Ben)*	Shennong's Materia Medica (compiled by WANG, Renjun)	Vol. 2, P. 563
注釋神農本草經 *Zhu Shi Shen Nong Ben Cao Jing*	Annotated Shennong's Classic of Materia Medica	Vol. 3, P. 001
神農本經（姜國伊輯本） *Shen Nong Ben Jing (Jiang Guo Yi Ji Ben)*	Shennong's Classic of Materia Medica (compiled by JIANG, Gouyi)	Vol. 3, P. 341
神農本經校注 *Shen Nong Ben Jing Xiao Zhu*	Shennong's Classic of Materia Medica, Checked and Annotated	Vol. 3, P. 395
神農本草經（顧觀光輯本）	Shennong's Classic of Materia Medica (compiled by GU, Guanguang)	Vol. 4, P. 001

Classic book title	Book title in English	Volume, page
Shen Nong Ben Cao Jing (Gu Guan Guang Ji Ben)		
神農本草（王閣運輯本） *Shen Nong Ben Cao (Wang Kai Yun Ji Ben)*	Shennong's Materia Medica (compiled by WANG, Kaiyun)	Vol. 4, P. 063
神農本草經（黃奭輯本） *Shen Nong Ben Cao Jing (Huang Shi Ji Ben)*	Shennong's Classic of Materia Medica (compiled by HUANG, Shi)	Vol. 4, P. 143
神農古本草經 *Shen Nong Gu Ben Cao Jing*	Ancient Edition of Shennong's Classic of Materia Medica	Vol. 4, P. 345
藥錄 *Yao Lu*	Drug Records	Vol. 4, P. 409
吳氏本草 *Wu Shi Ben Cao*	Wu's Materia Medica	Vol. 4, P. 415
雷公炮炙論 *Lei Gong Pao Zhi Lun*	Master Lei's Discourse on Drug Processing	Vol. 4, P. 443
本草經集注（敦煌殘卷・甲本） *Ben Cao Jing Ji Zhu (Dun Huang Can Juan, Jia Ben)*	Variorum of the Classic of Materia Medica (Dunhuang Surviving Section, Edition A)	Vol. 4, P. 529
本草經集注（輯本） *Ben Cao Jing Ji Zhu (Ji Ben)*	Variorum of the Classic of Materia Medica (A compilation)	Vol. 5, P. 001
本草經集注（敦煌殘卷・乙本） *Ben Cao Jing Ji Zhu (Dun Huang Can Juan, Yi Ben)*	Variorum of the Classic of Materia Medica (Dunhuang Surviving Section, Edition B)	Vol. 5, P. 281
亡名氏本草序例 *Wang Ming Shi Ben Cao Xu Li*	Preface to Materia Medica by Anonymous Author	Vol. 5, P. 287
唐新修本草殘卷 *Tang Xin Xiu Ben Cao Can Juan*	Surviving Section of Newly Revised Materia Medica in Tang Dynasty	Vol. 5, P. 293
新修本草（傅雲龍本） *Xin Xiu Ben Cao (Fu Yun Long Ben)*	Newly Revised Materia Medica (FU, Yunlong Edition)	Vol. 5, P. 385
新修本草（敦煌殘卷・甲本） *Xin Xiu Ben Cao (Dun Huang Can Juan, Jia Ben)*	Newly Revised Materia Medica (Dunhuang Surviving Section, Edition A)	Vol. 6, P. 001

Classic book title	Book title in English	Volume, page
新修本草（敦煌殘卷・乙本） *Xin Xiu Ben Cao (Dun Huang Can Juan, Yi Ben)*	Newly Revised Materia Medica (Dunhuang Surviving Section, Edition B)	Vol. 6, P. 009
新修本草（敦煌殘卷・丙本） *Xin Xiu Ben Cao (Dun Huang Can Huan, Bing Ben)*	Newly Revised Materia Medica (Dunhuang Surviving Section, Edition C)	Vol. 6, P. 029
新修本草序例（敦煌殘卷・丁本） *Xin Xiu Ben Cao Xu Li (Dun Huang Can Juan, Ding Ben)*	Preface to Newly Revised Materia Medica (Dunhuang Surviving Section, Edition D)	Vol. 6, P. 035
新修本草（森立之影寫本） *Xin Xiu Ben Cao (Sen Li Zhi Ying Xie Ben)*	Newly Revised Materia Medica (SEN, Lizhi's Imitation Edition)	Vol. 6, P. 041
重輯新修本草 *Zhong Ji Xin Xiu Ben Cao*	Recompilation of Newly Revised Materia Medica compiled	Vol. 6, P. 229
食療本草 *Shi Liao Ben Cao*	Materia Medica for Dietary Therapy	Vol. 6, P. 483
石藥爾雅 *Shi Yao Er Ya*	Refined Book on Mineral Medicine	Vol. 6, P. 493
何首烏錄 *He Shou Wu Lu*	Book on Fallopia multiflora	Vol. 6, P. 515
食醫心鑒 *Shi Yi Xin Jian*	Insightful Reference for Dietary Therapy	Vol. 6, P. 521
藥譜 *Yao Pu*	Dispensatory	Vol. 6, P. 565
彰明附子記 *Zhang Ming Fu Zi Ji*	Book on Monkshood in Zhang Ming County	Vol. 6, P. 577
海藥本草 *Hai Yao Ben Cao*	Oversea Materia Medica	Vol. 7, P. 001
經史證類備急本草 *Jing Shi Zheng Lei Bei Ji Ben Cao*	Classified Materia Medica from Historical Classics for Emergency	Vol. 7, P. 041
經史證類大觀本草 *Jing Shi Zheng Lei Da Guan Ben Cao*	Classified Materia Medica from Historical Classics Complied during the Daguan period	Vol. 9, P. 285

Classic book title	Book title in English	Volume, page
重修政和經史證類備用本草 *Zhong Xiu Zheng Yi Ji Jing Shi Zheng Lei Bei Yong Ben Cao*	The Revised Zhenghe Classified Materia Medica from Historical Classics for Emergency	Vol. 11, P. 517
紹興校定經史證類備急本草（龍谷大學本） *Shao Xing Xiao Ding Jing Shi Zheng Lei Bei Ji Ben Cao (Long Gu Da Xue Ben)*	Classified Materia Medica from Historical Classics for Emergency Revised in the Shaohsing Period (RyuKoku University Edition)	Vol. 13, P. 477
紹興校定經史證類備急本草畫卷 *Shao Xing Xiao Ding Jing Shi Zheng Lei Bei Ji Ben Cao Hua Juan*	Scroll Painting of Classified Materia Medica from Historical Classics for Emergency Revised in the Shaohsing Period	Vol. 14, P. 505
紹興校定經史證類備急本草（神古克楨本 *Shao Xing Xiao Ding Jing Shi Zheng Lei Bei Ji Ben Cao (Shen Gu Ke Zhen Ben)*	Classified Materia Medica from Historical Classics for Emergency Revised in the Shaohsing Period (Kamiya Katsutei Edition)	Vol. 15, P. 381
本草衍義 *Ben Cao Yan Yi*	Extension of the Materia Medica	Vol. 16, P. 339
圖經本草藥性總論 *Tu Jing Ben Cao Yao Xing Zong Lun*	General Discourse on Illustrated Drug Properties of Materia Medica	Vol. 16, P. 471
圖經衍義本草 *Tu Jing Yan Yi Ben Cao*	Illustrated Materia Medica Extension	Vol. 17, P. 001
類編圖經集注衍義本草 *Lei Bian Tu Jing Ji Zhu Yan Yi Ben Cao*	Compendium of Illustrated Variorum of Materia Medica Extension	Vol. 19, P. 493
履巉岩本草 *Lu Chan Yan Ben Cao*	Materia Medica by LU Chanyan	Vol. 20, P. 001
本草圖譜（周祜、周禧彩色繪畫本） *Ben Cao Tu Pu (Zhou Hu, Zhou Xi Cai Se Hui Hua Ben)*	Atlas of Materia Medica (Colour Paintings by ZHOU, Hu & ZHOU, Xi)	Vol. 20, P. 431
寶慶本草折衷 *Bao Qing Ben Cao Zhe Zhong*	Compromised Materia Medica of Baoqing Reign	Vol. 21, P. 001
潔古珍珠囊 *Jie Gu Zhen Zhu Nang*	Jiegu's Edition of the Pearl Bag	Vol. 21, P. 517
藏府標本藥式 *Cang Fu Biao Ben Yao Shi*	Medical Treatments for the Tip and Root Diseases of Internal Organs	Vol. 21, P. 533

Classic book title	Book title in English	Volume, page
珍珠囊 *Zhen Zhu Nang*	The Pearl Bag	Vol. 22, P. 001
湯液本草 *Tang Ye Ben Cao*	Materia Medica for Decoctions	Vol. 22, P. 031
本草元命苞 *Ben Cao Yuan Ming Bao*	Bud of the Original Mandate on Materia Medica	Vol. 22, P. 223
本草衍義補遺 *Ben Cao Yan Yi Bu Yi*	Addendum to Extension of the Materia Medica	Vol. 22, P. 339
日用本草（嘉靖四年刻本） *Ri Yong Ben Cao (Jia Jing Si Nian Ke Ben)*	Materia Medica for Daily Use (Printed Edition of the 4th year of the Jiajing Period)	Vol. 22, P. 387
日用本草（萬曆四十八年刻本） *Ri Yong Ben Cao (Wan Li Si Shi Ba Nian Ke Ben)*	Materia Medica for Daily Use (Printed Edition of the 48th year of the Wanli Period)	Vol. 22, P. 475
飲膳正要 *Yin Shan Zheng Yao*	Orthodox Essentials of Dietetics	Vol. 23, P. 001
藥准 *Yao Zhun*	Bases of Drugs	Vol. 23, P. 171
救荒本草（明代刻本） *Jiu Huang Ben Cao (Ning Dai Ke Ben)*	Materia Medica for Famine Relief (Ming Dynasty Printed Edition)	Vol. 23, P. 295
救荒本草（朝鮮抄本） *Jiu Huang Ben Cao (Chao Xian Chao Ben)*	Materia Medica for Famine Relief (Choson Hand Copy Edition)	Vol. 24, P. 001
滇南草本（務本堂本） *Dian Nan Cao Ben (Wu Ben Tang Ben ）*	The Materia Medica of Southern Yunnan (Wubentang Edition)	Vol. 24, P. 079
滇南本草圖說 *Dian Nan Cao ben Tu Shuo*	The Materia Medica of Southern Yunnan with Illustrations	Vol. 24, P. 317
滇南本草（雲南叢書冊） *Dian Nan Ben Cao (Yun Nan Cong Shu Ce)*	The Materia Medica of Southern Yunnan (in Yunnang Book Series)	Vol. 24, P. 459
滇南本草（雲南刻本） *Dian Nan Ben Cao (Yun Nan Ke Ben)*	The Materia Medica of Southern Yunnan (Yunnan Printed Edition)	Vol. 25, P. 001

Classic book title	Book title in English	Volume, page
滇南本草（沐忠本） *Dian Nan Ben Cao (Mu Zhong Ben)*	The Materia Medica of Southern Yunnan (Mu Zhong Edition)	Vol. 25, P. 123
藥性賦 *Yao Xing Fu*	Poems on the Properties of Drugs	Vol. 25, P. 257
本草集要 *Ben Cao Ji Yao*	Collection of Essentials of Materia Medica	Vol. 25, P. 273
新編注釋藥性賦 *Xin Bian Zhu Shi Yao Xing Fu*	Poems on the Properties of Drugs, Revised and Annotated	Vol. 26, P. 001
本草約言 *Ben Cao Yue Yan*	A Summary of Materia Medica	Vol. 26, P. 161
食物本草（胡文煥精抄本） *Shi Wu Ben Cao (Hu Wen Huan Jing Chao Ben)*	Dietary Materia Medica (WU Wenhuan's Fine Hand Copy Edition)	Vol. 26, P. 451
食物本草（隆慶四年彩色抄繪本） *Shi Wu Ben Cao (Long Qing Si Nian Cai Se Chao Hui Ben)*	Dietary Materia Medica (Hand Copy and Colour Painting Edition of the 4th year of the Longqing Period)	Vol. 27, P. 001
本草品彙精要（羅馬本） *Ben Cao Pin Hui Jing Yao (Luo Ma Ben)*	The Collected Essentials of Herbal Species (Rome Edition)	Vol. 28, P. 001
本草綱目（金陵本） *Ben Cao Gang Mu(Jin Ling Ben ）*	Compendium of Materia Medica (Jinling Edition)	Vol. 38, P. 001
本草綱目（武林本） *Ben Cao Gang Mu (Wu Lin Ben)*	Compendium of Materia Medica (Wulin Edition)	Vol. 41, P. 341
本草綱目（味古齋本） *Ben Cao Gang Mu (Wei Gu Zhai Ben)*	Compendium of Materia Medica (Weiguzhai Edition)	Vol. 47, P. 153
神農本經會通 *Shen Nong Ben Jing Hui Tong*	Mutual Annotation of Shennong's Classic of Materia Medica	Vol. 53, P.001
鼎刻京板太醫院校正分類青囊藥性賦 *Ding Ke Jing Ban Tai Yi Yuan Xiao Zheng Fen Lei Qing Nang Yao Xing Fu*	Poems on the Classified Medical Drug Properties, Printed in the Capital City and Proofread by the Imperial Medical College	Vol. 54, P. 271
醫方藥性合編 *Yi Fang Yao Xing He Bian*	A Combined Collection on Medical Formulae and Drug Properties	Vol. 54, P. 357

Classic book title	Book title in English	Volume, page
食品集 *Shi Pin Ji*	Book on Food	Vol. 54, P. 471
食鑒本草 *Shi Jian Ben Cao*	A Standard Dietary Materia Medica	Vol. 55, P. 001
體仁彙編、十二經絡臟腑病情藥性 *Ti Ren Hui Bian, Shi Er Jing Luo Zang Fu Bing Qing Yao Xing*	A Collection on Humanity Practising, Patient Conditions and Drug Properties Concerning the Twelve Meridians and Organs	Vol. 55, P. 061
新刻藥證類明 *Xin Ke Yao Zheng Lei Ming*	Reprinted Edition of Comprehensible Classified Drugs and Diseases	Vol. 55, P. 131
太醫院補遺本草歌訣雷公炮製 *Tai Yi Yuan Bu Yi Ben Cao Ge Jue Lei Gong Pao Zhi*	Imperial Academy of Medicine's Addenda to Materia Medica Rhymes and the Drug Preparations of Master Lei	Vol. 55, P. 263
南產志 *Nan Chan Zhi*	A Chorography of the Southern Products	Vol. 55, P. 483
藥性粗評 *Yao Xing Cu Ping*	Rough Comments to Drug Properties	Vol. 56, P. 001
本草發明 *Ben Cao Fa Ming*	An Insightful Explanation to Materia Medica	Vol. 56, P. 361
本草蒙筌 *Ben Cao Meng Quan*	An Introduction to Materia Medica	Vol. 57, P. 001
茹草編 *Ru Cao Bian*	On Agriculture	Vol. 57, P. 307
本草便 *Ben Cao Bian*	Materia Medica Handbook	Vol. 57, P. 445
新刻太乙仙製本草藥性大全 *Xin Ke Tai Yi Xian Zhi Ben Cao Yao Xing Da Quan*	Reprinted Edition of the Transcendent Great One's Comprehensive Compendium of the Properties of Medicinal Herbs	Vol. 58, P. 001
飲饌服食譜 *Yin Zhuan Fu Shi Pu*	Food and Drink Manual	Vol. 58, P. 475
本草定衡 *Ben Cao Ding Heng*	Materia Medica Standards	Vol. 59, P. 001

Classic book title	Book title in English	Volume, page
萬病回春、藥性歌 *Wan Bing Hui Chun, Yao Xing Ge*	Rejuvenate of All Diseases, Poems on the Properties of Drugs	Vol. 59, P. 495
傷寒論條辨、本草鈔 *Shang Han Lun Tiao Bian, Ben Cao Chao*	Comparative Study on Treatise on Cold Damage Diseases, Copied from Materia Medica	Vol. 59, P. 515
本草選 *Ben Cao Xuan*	A Selected Collection of Materia Medica	Vol. 60, P. 001
藥鑒 *yao jian*	Insightful Book on Drugs	Vol. 61, P. 001
本草原始（李中立繪圖本） *Ben Cao Yuan Shi (Li Zhong Li Hui Tu Ben)*	Origins of the Materia Medica (Illustrated Edition by LI, Zhong li)	Vol. 61, P. 107
本草原始（永懷堂刻本） *Ben Cao Yuan Shi (Yong Huai Tang Ke Ben)*	Origins of the Materia Medica (Printed Edition by Yonghuaitang)	Vol. 62, P. 001
炮炙大法 *Pao Zhi Da Fa*	The Great Skills of Drug Processing	Vol. 62, P. 501
本草真詮 *Ben Cao Zhen Quan*	True Interpretation of Materia Medica	Vol. 63, P. 001
食物輯要 *Shi Wu Ji Yao*	Important Items of Food	Vol. 63, P. 231
芷園臆草題藥 *Zhi Yuan Yi Cao Ti Yao*	Zhiyuan’s Herbal Medicine Book	Vol. 63, P. 399
本草彙言 *Ben Cao Hui Yan*	A Collection of Articles on Materia Medica	Vol. 64, P. 001
醫學彙函 *Yi Xue Hui Han*	A Collection of Articles on Medical Study	Vol. 66, P. 001
上醫本草 *Shang Yi Ben Cao*	Materia Medica from Brilliant Doctors	Vol. 66, P. 201
珍珠囊指掌補遺藥性賦 *Zhen Zhu Nang Zhi Zhang Bu Yi Yao Xing Fu*	The Pearl Bag’s Explicit Guide to the Addended Poems of Properties of Drugs	Vol. 66, P. 431

Classic book title	Book title in English	Volume, page
食物本草 *Shi Wu Ben Cao*	Dietary Materia Medica	Vol. 67, P. 001
野菜博錄 *Ye Cai Bo Lu*	A Comprehensive Record of Wild Vegetables	Vol. 67, P. 161
景岳全書、本草正 *Jing Yue Quan Shu, Ben Cao Zheng*	The Complete Compendium of Jingyue, Unbiased Materia Medica	Vol. 67, P. 419
珍珠囊指掌補遺藥性賦 *Zhen Zhu Nang Zhi Zhang Bu Yi Yao Xing Fu*	The Pearl Bag's Explicit Guide to the Addended Poems of Properties of Drugs	Vol. 68, P. 001
鐫補雷公炮製藥性解 *Juan Bu Lei Gong Pao Zhi Yao Xing Jie*	Revised Exposition on the Properties of Drugs Prepared According to Lei's Methods	Vol. 68, P. 141
鐫補雷公炮製藥性解 *Juan Bu Lei Gong Pao Zhi Yao Xing Jie*	Revised Exposition on the Properties of Drugs Prepared According to Lei's Methods	Vol. 68, P. 293
養生要括 *Yang Sheng Yao Kuo*	A Summary of Health-nurturing Essentials	Vol. 68, P. 461
神農本草經疏 *Shen Nong Ben Cao Jing Shu*	Explanatory Notes on Shennong's Classic of Materia Medica	Vol. 69, P. 001
分部本草妙用 *Fen Bu Ben Cao Miao Yong*	The Magical Functions of Classified Materia Medica	Vol. 71, P. 175
醫宗必讀、本草徵要 *Yi Zong Bi Du, Ben Cao Zheng Yao*	Required Reading from the Masters of Medicine, Proof Essentials of Materia Medica	Vol. 71, P. 479
食物本草（姚可成輯本） *Shi Wu Ben Cao (Yao Ke Cheng Ji Ben)*	Dietary Materia Medica (Compiled by YAO, Kecheng)	Vol. 72, P. 001
明醫選要、藥性詩訣 *Ming Yi Xuan Yao, Yao Xing Shi Jue*	A Concise Selection of Brilliant Medical Articles, Mnemonic Rhymes on Drug Properties	Vol. 74, P. 075
山公醫旨食物類 *Shan Gong Yi Zhi Shi Wu Lei*	Master Shan's Medical Aspiration on Dietary	Vol. 74, P. 131
本草乘雅半偈 *Ben Cao Cheng Ya Ban Ji*	The Quadruple Refinement of Materia Medica, Half Content	Vol. 75, P. 001
藥鏡	Insightful Book on Drugs	Vol. 76, P. 097

Classic book title	Book title in English	Volume, page
Yao Jing		
藥品化義 *Yao Pin Hua Yi*	Understanding Drugs	Vol. 76, P. 231
新鍥藥性會元 *Xin Qie Yao Xing Hui Yuan*	Reprinted Collection of Drug Property Essentials	Vol. 76, P. 367
藥性全備食物本草 *Yao Xing Quan Bei Shi Wu Ben Cao*	Comprehensive Dietary Materia Medica on Drug Properties	Vol. 77, P. 001
軒岐救正論、藥性微蘊 *Xuan Qi Jiu Zheng Lun, Yao Xing Wei Yun*	A Discourse on Xuan's and Qi's Theories and Treatment of Chinese Medicine, The Profound Meaning of Drug Properties	Vol. 77, P. 165
新刊風科本草治風藥品 *Xin Kan Feng Ke Ben Cao Zhi Feng Yao Pin*	Wind-Dispersing Drugs in the Wind Category of Materia Medica, A New Edition	Vol. 77, P. 239
藥性要略大全 *Yao Xing Yao Lue Da Quan*	A Complete Handbook on Drug Property Essentials	Vol. 77, P. 295
本草纂要 *Ben Cao Zuan Yao*	Essentials of Materia Medica	Vol. 78, P. 001
仁壽堂藥鏡 *Ren Shou Tang Yao Jing*	Renshoutang's Insightful Book on Drugs	Vol. 78, P. 121
新刊校正李東垣官板藥性大全 *Xin Kan Xiao Zheng Li Dong Yuan Guan Ban Yao Xing Da Quan*	A Complete Handbook on Drug Properties, the Newly Published Official Edition Proofread by Lidongyuan	Vol. 78, P. 439
本草品彙精要（大塚本） *Ben Cao Pin Hui Jing Yao (Da Zhong Ben)*	The Collected Essentials of Herbal Species (Otsuka edition)	Vol. 79, P. 001
本草歌括（八卷本） *Ben Cao Ge Kuo (Ba Juan Ben)*	Materia Medica with Songs (Eight Volumes Edition)	Vol. 83, P. 209
本草歌括（二卷本） *Ben Vao Ge Kuo (Er Juan Ben)*	Materia Medica with Songs (Two Volumes Edition)	Vol. 83, P. 337
本草發揮 *Ben Cao Fa Hui*	An Exposition of Materia Medica	Vol. 83, P. 423
本草大成藥性賦 *Ben Cao Da Cheng Yao Xing Fu*	An Agglomeration of An Agglomeration of Poems on Herbal Drug Properties	Vol. 84, P. 001

Classic book title	Book title in English	Volume, page
本草綱目類纂必讀 *Ben Cao Gang Mu Lei Zuan Bi Du*	Required Readings from the Classified Compendium of Materia Medica	Vol. 84, P. 155
食憲鴻秘 *Shi Xian Hong Mi*	Secrets of the Governing Principles of Cuisine	Vol. 84, P. 417
本草匯 *Ben Cao Hui*	A Collection of Materia Medica	Vol. 85, P. 001
壽世秘典 *Shou Shi Mi Dian*	The Secret Book of Health Maintenance	Vol. 86, P. 369
本草彙箋 *Ben Cao Hui Jian*	Treasury of Letters on Materia Medica	Vol. 87, P. 001
經方衍義 *Jing Fang Yan Yi*	Extension of the Experienced Formulae	Vol. 87, P. 511
本草洞詮 *Ben Cao Dong Quan*	Insightful Interpretation of Materia Medica	Vol. 88, P. 001
本草述 *Ben Cao Shu*	Herbal Medicine Explanation	Vol. 89, P. 001
本草詳節 *Ben Cao Xiang Jie*	An Overview of Materia Medica	Vol. 92, P. 193
本草綱目必讀 *Ben Cao Gang Mu Bi Du*	Required Readings from the Compendium of Materia Medica	Vol. 93, P. 001
本草通玄 *Ben Cao Tong Xuan*	Explaining Abstruseness of Materia Medica	Vol. 95, P. 063
農經酌雅 *Nong Jing Zhuo Ya*	Knowledge Gained from Classics of Materia Medica	Vol. 95, P. 193
本草崇原 *Ben Cao Chong Yuan*	Traditional Values in Materia Medica	Vol. 95, P. 307
生草藥性備要 *Sheng Cao Yao Xing Bei Yao*	Essentials of Medical Characteristics of Raw Herbs	Vol. 95, P. 511
藥性纂要 *Yao Xing Zuan Yao*	Essentials of Drug Properties	Vol. 96, P. 001

Classic book title	Book title in English	Volume, page
藥品辨義 *Yao Yin Yian Yi*	Discerning the Functions of Medical Drugs	Vol. 96, P. 349
握靈本草 *Wo Ling Ben Cao*	Thorough Comprehension of the Materia Medica	Vol. 97, P. 001
本草必用 *Ben Cao Bi Yong*	Indispensable Applied Knowledge of Materia Medica	Vol. 97, P. 507
醫學啟蒙彙編 *Yi Xue Qi Meng Hui Bian*	A Collection on Enlightening Medical Literatures	Vol. 98, P. 001
食物本草會纂 *Shi Wu Ben Cao Hui Zuan*	A Collection on Dietary Materia Medica	Vol. 98, P. 081
頤生秘旨 *Yi Sheng Mi Zhi*	Secrets of Health-nurturing	Vol. 98, P. 533
山居本草 *Shan Ju Ben Cao*	Materia Medica for Rural Life	Vol. 99, P. 001
飲食須知 *yin shi xu zhi*	Information about Diet	Vol. 100, P.083
本草備要 *Ben Cao Bei Yao*	Essentials of Materia Medica	Vol. 100, P.201
食物須知 *Shi Wu Xu Zhi*	Information about Food	Vol. 100, P. 475
本經逢原 *Ben Jing Feng Yuan*	Encountering the Sources of the Classic of Materia Medica	Vol. 101, P. 001
藥理近考 *Yao Li Jin Kao*	Recent Research on Drug Theory	Vol. 101, P. 487
雜症痘疹藥性合參 *Za Zheng Dou Zhen Yao Xing He Can*	Integrated References for Medical Characteristics of Drugs Prescribed for Exanthema Variolosum in the Category of Miscellaneous Disease	Vol. 102, P. 001
得宜本草分類 *De Yi Ben Cao Fen Lei*	Classified Suitable Herbs	Vol. 102, P. 369
長沙藥解 *Chang Sha Yao Jie*	Changsha’s Explanation on Drugs	Vol. 102, P. 429

Classic book title	Book title in English	Volume, page
夕庵讀本草快編 *Xi An Du Ben Cao Kuai Bian*	Xian's Sharp Understanding on Materia Medica	Vol. 103, P. 001
絳雪園得宜本草 *Jiang Xue Yuan De Yi Ben Cao*	On Suitable Herbs by Jiangxueyuan	Vol. 103, P. 335
醫林纂要探源 *Yi Lin Zuan Yao Tan Yuan*	Exploring the Origins of Medical Essentials	Vol. 103, P. 365
本草萬方針線 *Ben Cao Wan Fang Zhen Xian*	Introducing Ten Thousand Herbal Formulae	Vol. 104, P. 001
本草經解要 *Ben Cao Jing Jie Yao*	Explaining the Essentials of Classic of Materia Medica	Vol. 104, P. 243
玉楸藥解 *Yu Qiu Yao Jie*	Drug Explanation by Yuqiu	Vol. 104, P. 475
藥性通考 *Yao Xing Tong Kao*	General Studies on Drug Properties	Vol.105, P. 001
要藥分劑 *Yao Yao Fen Ji*	Categorised Essential Drugs	Vol. 105, P. 353
本草約編（王如鑒著本） *Ben Cao Yue Bian (Wang Ru Jian Zhu Ben)*	Concise Herbal Series (Written by WANG, Rujian)	Vol. 106, P. 001
神農本草經百種錄 *Shen Nong Ben Cao Jing Bai Zhong Lu*	A Selection of a Hundred Types of Herbs from Shennong's Classic of Materia Medica	Vol. 107, P. 237
本草詩牋 *Ben Cao Shi Jian*	Poems on Materia Medica	Vol. 107, P. 289
要藥分劑補正 *Yao Yao Gen Ji Bu Zheng*	A Revision and Update to Categorised Essential Drugs	Vol. 108, P. 001
食物小錄 *Shi Wu Xiao Lu*	Brief Records of Food	Vol. 108, P. 427
本草從新 *Ben Cao Cong Xin*	The Completely Revised Materia Medica	Vol. 109, P. 001
人參考（刻本） *Ren Shen Kao (Ke Ben)*	Researches on Ginseng (Printed Edition)	Vol. 109, P. 317

Classic book title	Book title in English	Volume, page
人參考（抄本） *Ren Shen Kao (Chao Ben)*	Researches on Ginseng (Hand Copy Edition)	Vol. 109, P. 339
羅氏會約醫鏡 *Luo Shi Hui Yue Yi Jing*	Luo's Concise Medical References	Vol. 109, P. 361
醒園錄 *Xing Yuan Lu*	Articles by Xingyuan	Vol. 109, P. 509
法古錄 *Fa Gu Lu*	Learning from Previous Masters of Medicine	Vol. 110, P. 001
質問本草 *zhi Wen Ben Cao*	Interrogation on Herbs	Vol. 110, P. 339
脈藥聯珠藥性食物考 *Mai Yao Lian Zhu Yao Xing Shi Wu Kao*	Research on the Properties of Effective Drugs for Meridians in Diet Therapy	Vol. 111, P. 001
本草分經審治 *Ben Cao Fen Jing Shen Zhi*	Materia Medica Classified by Meridian Tropism, Reviewed and Rearranged	Vol. 112, P. 001
本草分經（姚瀾著本） *Ben Cao Fen Jing (Yao Lan Zhu Ben)*	Materia Medica Classified by Meridian Tropism (Written by YAO, Lan)	Vol. 112, P. 107
藥性簡要 *Yao Xing Jian Yao*	Concise Drug Properties	Vol. 112, P. 221
本草三家合注 *Ben Cao San Jia He Zhu*	Materia Medica Jointly Annotated by Three Masters	Vol. 112, P. 259
毛詩名物圖說 *Mao Shi Ming Wu Tu Shuo*	An Illustrated Commentary on the Classic Maoshi	Vol. 113, P. 001
本草輯要 *Ben Cao Ji Yao*	A Collection of Materia Medica Essentials	Vol. 113, P. 157
藥性歌（蔡恭著本） *Yao Xing Ge (Cai Gong Zhu Ben)*	Poems on the Properties of Drugs (Written by CAI, Gong)	Vol. 113, P. 457
補充藥性雷公炮製 *Bu Chong Yao Xing Lei Gong Pao Zhi*	Properties of Drugs Prepared According to Lei's Methods, Supplemented	Vol. 114, P. 001
本草述錄 *Ben Cao Shu Lu*	Book of Herbal Medicine Explanation	Vol. 114, P. 411

Classic book title	Book title in English	Volume, page
本草綱目拾遺 *Ben Cao Gang Mu Shi Yi*	Supplements to Compendium of Materia Medica	Vol. 115, P. 001
隨園食單 *Sui Yuan Shi Dan*	Recipes from the Garden of Contentment	Vol. 116, P. 247
人參譜（陸烜著本） *Ren Shen Pu (Lu Hui Zhu Ben)*	Book on Ginseng (Written by LU, Hui)	Vol. 116, P. 337
解毒編 *Jie Du Bian*	Book on Detoxification	Vol. 116, P. 399
本草經讀 *Ben Cao Jing Du*	Reading Notes on Materia Medica	Vol. 116, P. 459
本草經疏輯要 *Ben Cao Jing Shu Ji Yao*	Essentials of Explanatory Notes on Classic of Materia Medica	Vol. 117, P. 001
本草正義 *Ben Cao Zheng Yi*	The Correct Meaning of Materia Medica	Vol. 117, P. 461
修事指南 *Xiu Shi Zhi Nan*	A Guide to Drug Processing	Vol. 118, P.001
藥籠小品 *Yao Long Xiao Pin*	On Clinical Drugs	Vol. 118, P. 081
調疾飲食辯 *Diao Ji Yin Shi Bian*	Discussions on Treatment and Diet	Vol. 118, P. 133
本草纂要稿 *Ben Cao Zuan Yao Gao*	A Manuscript on the Essentials of Materia Medica	Vol. 119, P. 001
四言藥賦 *Si Yan Yao Fu*	Four Word Poems on Drugs	Vol. 119, P. 075
類經證治本草 *Lei Jing Zheng Zhi Ben Cao*	Classified Herbal Treatments for Various Diseases	Vol. 119, P. 159
簡易草藥草方圖說 *Jian Yi Cao Yao Cai Fang Tu Shuo*	Illustrated Concise Herbs and Herbal Prescriptions	Vol. 119, P. 445
藥達 *Yao Da*	Proficiency in Drugs	Vol. 119, P. 513

Classic book title	Book title in English	Volume, page
分經本草四種 *Fen Jing Ben Cao Si Zhong*	Four Editions of Materia Medica Classified by Meridian Tropism	Vol. 120, P. 001
本草隨錄征實 *Ben Cao Sui Lu Zheng Shi*	Verification of Facts in Extracts of Materia Medica	Vol. 120, P. 127
本草 *Ben Cao*	Materia Medica	Vol. 120, P. 293
壽世醫竅 *Shou Shi Yi Qiao*	Keys to Health-nurturing Medicine	Vol. 120, P. 433
本草述鉤元 *Ben Cao Shu Gou Yuan*	Exploring the Essentials of Herbal Medicine Explanation	Vol. 121, P. 001
藥性賦音釋 *Yao Xing Fu Yin Shi*	Pronunciation Notes for Poems on the Properties of Drugs	Vol. 122, P. 529
本經疏證 *Ben Jing Shu Zheng*	Notes and Verification on Classic of Materia Medica	Vol. 123, P. 001
本草飲食譜 *Ben Cao Yin Shi Pu*	Book on Dietary Materia Medica	Vol. 123, P. 523
本經續疏、本經序疏要 *Ben Jing Xu Shu, Ben Jing Xu Shu Yao*	Explanatory Notes on Classic of Materia Medica Replenishment, Explanatory Notes on Essentials of Preface to Classic of Materia Medica	Vol. 124, P. 001
濟荒必備 *Ji Huang Bi Bei*	Required Knowledge for Famine Relief	Vol. 124, P. 489
本草求真 *Ben Cao Qiu Zhen*	The Herbal Foundation for Dependability	Vol. 125, P. 001
藥性集要便讀 *Yao Xing Ji Yao Bian Du*	Handbook on the Essentials of Drug Properties	Vol. 126, P. 101
錦囊藥性賦 *Jin Nang Yao Xng Fu*	Tips for Poems on the Properties of Drugs	Vol. 126, P. 389
植物名實圖考 *Zhi Wu Ming Shi Tu Kao*	Researched and Illustrated Herbal Names and Facts	Vol. 127, P. 001
植物名實圖考長編 *Zhi Wu Ming Shi Tu Kao Zhang Bian*	Extension to Researched and Illustrated Herbal Names and Facts	Vol. 131, P. 001

Classic book title	Book title in English	Volume, page
務中藥性 *Wu Zhong Yao Xing*	Mastering the Essentials of Drug Properties	Vol. 135, P. 001
天寶本草 *Tian Bao Ben Cao*	Materia Medica Published in the Tianbao Period	Vol. 135, P. 535
神農本草經贊 *Shen Nong Ben Cao Jing Zan*	Praise Poems to Shennong's Classic of Materia Medica	Vol. 136, P. 001
藥性摘記 *Yao Xing Zhai Ji*	Extracts on Drug Properties	Vol. 136, P. 249
本草省常 *Ben Cao Sheng Chang*	Materia Medica for Daily Diet	Vol. 136, P. 337
隨息居飲食譜 *Sui Xi Ju Yin Shi Pu*	Suixiju’s Dietary Book	Vol. 136, P. 423
本草經考注 *Ben Cao Jing Kao Zhu*	Classic of Materia Medica, Researched and Annotated	Vol. 137, P. 001
本草再新 *Ben Cao Zai Xin*	Materia Medica Further Revised	Vol. 138, P. 409
本草彙編 *Ben Cao Hui Bian*	Collective Edition of Materia Medica	Vol. 139, P. 001
本草明覽 *Ben Cao Ming Lan*	Sharp Understanding on Materia Medica	Vol. 139, P. 089
藥性蒙求 *Yao Xing Meng Qiu*	Drug Properties for Beginners	Vol. 139, P. 181
本草彙纂 *Ben Cao Hui Zuan*	A Collection on Materia Medica	Vol. 139, P. 271
神農本草經指歸 *Shen Nong Ben Cao Jing Zhi Gui*	Intendment of Shennong's Classic of Materia Medica	Vol. 140, P. 001
藥性主治、分類主治 *Yao Xing Zhu Zhi, Fen Lei Zhu Zhi*	Main Curative Effects of Drug Properties, Main Curative Effects Classified	Vol. 141, P. 133
本經便讀 *Ben Jing Bian Du*	Classic of Materia Medica Made Easy	Vol. 141, P. 197

Classic book title	Book title in English	Volume, page
藥症忌宜 *Yao Zheng Ji Yi*	Incompatibility and Suitability of Medicine and Diseases	Vol. 141, P. 263
閩產錄異 *Min Chan Lu Yi*	Records on Strange Products from Fujian Province	Vol. 141, P. 339
本草綱目易知錄 *Ben Cao Gang Mu Yi Zhi Lu*	Easy access to the Compendium of Materia Medica	Vol. 142, P. 001
本草正論 *Ben Cao Zheng Lun*	Sound Reasonings of Materia Medica	Vol. 143, P. 151
稽古摘要 *Ji Gu Zhai Yao*	Summary of Ancient Literature Research	Vol. 143, P. 231
本草簡明圖說 *Nen Cao Jian Dan Ming Bai Tu Shuo*	Illustrated Concise Materia Medica	Vol. 143, P. 303
草木便方 *Cao Mu Bian Fang*	Easy Access to Herbal Prescriptions	Vol. 144, P. 001
藥要便蒙新編 *Yao Yao Bian Meng Xin Bian*	Newly Edited Drug Essentials for Beginners	Vol. 144, P. 145
本草害利 *Ben Cao Hai Li*	Pros and Cons of Various Herbs	Vol. 144, P. 267
本草衍句 *Ben Cao Yan Ju*	Supplements to Past Materia Medica Literatures	Vol. 144, P. 463
本草撮要 *Ben Cao Cuo Yao*	A Synopsis of Materia Medica	Vol. 145, P. 001
本草便讀 *Ben Cao Bian Du*	Easy Access to Materia Medica	Vol. 145, P. 125
何氏藥性賦 *He Shi Yao Xing Fu*	He’s Poems on the Properties of Drugs	Vol. 145, P. 315
本草思辨錄 *Ben Cao Si Bian Lu*	Judgment and Discretion on Materia Medica	Vol. 145, P. 329
蟲薈 *Chong Hui*	A Collection on Insects	Vol. 146, P. 001

Classic book title	Book title in English	Volume, page
本草問答 *Ben Cao Wen Da*	Questions and Answers about Materia Medica	Vol. 146, P. 365
本草韻語 *Ben Cao Yun Yu*	Poems on Materia Medica	Vol. 146, P. 417
藥性詩解 *Yao Xing Shi Jie*	An Explanation of Drug Property Poems	Vol. 147, P. 001
活人心法、藥性詩解 *Huo Ren Xin Fa, Yao Xing Shi Jie*	Good Ideas for Lifesaving, Explanations of Drug Property Poems	Vol. 147, P. 039
本草詩 *Ben Cao Shi*	Poems on Materia Medica	Vol. 147, P. 107
藥性粗評全注 *Yao Xing Cu Ping Quan Zhu*	A Complete Annotation on Rough Comments to Drug Properties	Vol. 147, P. 195
本草撮要類編 *Ben Cao Cuo Yao Lei Bian*	A Compendium of Materia Medica Synopsis	Vol. 147, P. 279
增訂偽藥條辨 *Zeng Ding Wei Yao Tiao Bian*	Comparative Study on Fake Medicine, a Revised and Enlarged Edition	Vol. 147, P. 487
每日食物卻病考 *Mei Ri Shi Wu Bi Mian Sheng Bing Kao*	Research on Daily Food for Disease Prevention	Vol. 148, P. 001
分類草藥性 *Fen Lei Cao Yao Xing*	Classified Herbal Drug Properties	Vol. 148, P. 043
本草（清抄本） *Ben Cao (Qing Chao Ben)*	Materia Medica (Hand Copy Edition in Qing Dynasty)	Vol. 148, P. 077
簡明藥性 *Jian Dan Ming Bai Yao Xing*	Concise Drug Properties	Vol. 148, P. 127
九龍蟲治病方 *Jiu Long Chong Zhi Bing Fang*	Prescriptions with Ulomoides Dermestoides for Disease Treatment	Vol. 148, P. 159
本草類考 *Ben Cao Lei Kao*	Research on Classified Materia Medica	Vol. 148, P. 181
本草分經（張節著本） *Ben Cao Fen Jing (Zhang Jie Zhu Ben)*	Materia Medica Classified by Meridian Tropism (Written by ZHANG, Jie)	Vol. 148, P. 317

Classic book title	Book title in English	Volume, page
藥性撮要歌訣 *Yao Xing Cuo Yao Ge Jue*	Summary on Drug Properties with Rhymes	Vol. 148, P. 349
藥性要略 *Yao Xing Yao Lue*	Drug Property Essentials	Vol. 148, P. 405
本草（清抄本） *Ben Cao (Qing Chao Ben)*	Materia Medica (Hand Copy Edition in Qing Dynasty)	Vol. 148, P. 443
本草知要 *Ben Cao Zhi Yao*	Knowing the Essentials of Materia Medica	Vol. 148, P. 527
本草釋名類聚 *Ben Cao Shi Ming Lei Ju*	Classified Herb Name Explanations	Vol. 149, P. 001
本草須知 *Ben Cao Xu Zhi*	Information about Materia Medica	Vol. 149, P. 279
本草分隊 *Ben Cao Fen Dui*	Herb Application Strategies	Vol. 149, P. 483
本草二十四品 *Ben Cao Er Shi Si Pin*	Twenty-four Chapters on Materia Medica	Vol. 150, P. 001
藥譜字類 *Yao Pu Zi Lei*	Classified Dispensatory Words	Vol. 150, P. 181
本草（程齡源著本） *Ben Cao (Cheng Ling Yuan Zhu Ben)*	Materia Medica (Written by CHENG, Linyuan)	Vol. 150, P. 285
備用藥物 *Bei Yong Yao Wu*	Reserved Drugs	Vol. 150, P. 373
藥性新編 *Yao Xing Xin Bian*	A Revised Edition of Drug Properties	Vol. 150, P. 397
四言藥性分類精要 *Si Yan Yao Xing Fen Lei Jing Yao*	Four Word Poems on Essentials of Classified Drug Properties	Vol. 150, P. 427
神農本草經抄今注 *Shen Nong Ben Cao Jing Chao Jin Zhu*	Newly annotated Shennong's Classic of Materia Medica Transcript	Vol. 151, P. 001
本草約編（清抄本） *Ben Cao Yue Bian (Qing Chao Ben)*	Concise Herbal Series (Hand Copy Edition in Qing Dynasty)	Vol. 151, P. 087

Classic book title	Book title in English	Volume, page
用藥法程 *Yong Yao Fa Cheng*	Principled Formulae of Drug Application	Vol. 151, P.151
藥性鈔 *Yao Xing Chao*	Transcript of Drug Properties	Vol. 151, P. 239
藥性探源 *Yao Xing Tan Yuan*	Exploring the Origins of Drug Properties	Vol. 151, P. 265
本草歌括詳注 *Ben Cao Ge Kuo Xiang Zhu*	Detailed Annotation of Materia Medica Rhymes	Vol. 151, P. 311
藥性驪珠 *Yao Xing Li Zhu*	The Invaluable Knowledge of Drug Properties	Vol. 151, P. 487
藥味別號錄 *Yao Wei Bie Hao Lu*	On Alias Name of Drugs	Vol. 152, P. 001
國藥出處 *Guo Yao Chu Chu*	Origins of Chinese Drugs	Vol. 152, P. 211
藥性韻語 *Yao Xing Yun Yu*	Rhymes on Drug Properties	Vol. 152, P. 283
草藥類纂新編 *Cao Yao Lei Zuan Xin Bian*	A New Edition of Classified Herbal Medicine	Vol. 152, P. 443
臟腑藥性論診脈訣 *Zang Fu Yao Xing Lun Zhen Mai Jue*	Discourse on Drug Properties and Pulse Taking Methods for Internal Organs	Vol. 152, P. 501
本草十三家注 *Ben Cao Shi San Jia Zhu*	Materia Medica Annotated by Thirteen Masters	Vol. 153, P. 001
辭典本草 *Ci Dian Ben Cao*	Materia Medica in Dictionary Form	Vol. 155, P. 225
食物治病新書 *Shi Wu Zhi Bing Xin Shu*	New Book on Dietary Therapy	Vol. 155, P. 487
藥名雜鈔 *Yao Ming Za Chao*	Drug Names from Various Sources	Vol. 155, P. 523
神農本草經注論 *Shen Nong Ben Cao Jing Zhu Lun*	A Discourse on Shennong's Classic of Materia Medica Annotation	Vol. 156, P. 001

Classic book title	Book title in English	Volume, page
黨參新研究 *Dang Shen Xin Yan Jiu*	New Researches on Codonopsis Radix	Vol. 156, P. 107
藥性精髓 *Yao Xing Jing Sui*	Essentials of Drug Property	Vol. 156, P. 129
國醫新藥物學 *Guo Yi Xin Yao Wu Xue*	New Pharmacology of Chinese Medicine	Vol. 156, P. 203
洋蟲 *Yang Chong*	On Ulomoides Dermestoides	Vol. 156, P. 539
本草疏證 *Ben Cao Shu Zheng*	Explanatory Notes and Researches on Materia Medica	Vol. 157, P. 001
雜類藥性書 *Za Lei Yao Xing Shu*	Book on Drug Properties of Miscellaneous Items	Vol. 157, P. 153
研藥指南 *Yan Yao Zhi Nan*	Herbal Drugs Handbook	Vol. 157, P. 197
本草求原 *Ben Cao Qiu Yuan*	Pursuing the Origins of Materia Medica	Vol. 158, P. 001
藥性選要 *Yao Xing Xuan Yao*	A Selection of Drug Property Essentials	Vol. 159, P. 051
藥名詩 *Yao Ming Shi*	Poems on Drug Names	Vol. 159, P. 179
中國新本草圖志 *Zhong Guo Xin Ben Cao Tu Zhi*	A New Illustrated Chorography of Herbs in China	Vol. 159, P. 233
藥物出產辨 *Yao Wu Chu Chan Bian*	Discerning Drug Origins	Vol. 159, P. 457
嶺南采藥錄 *Ling Nan Cai Yao Lu*	Records on Herb Gathering in Lingnan Region	Vol. 160, P. 001
中國實用藥物學 *Zhong Guo Shi Yong Yao Wu Xue*	Chinese Practical Pharmacology	Vol. 160, P. 099
藥物圖考 *Yao Wu Tu Kao*	Researched and Illustrated Herbal Drugs	Vol. 160, P. 147

Classic book title	Book title in English	Volume, page
分類飲片新參 *Fen Lei Yin Pian Xin Can*	New Reference for Classified Processed Drugs	Vol. 161, P. 001
國藥詮證 *Guo Yao Quan Zheng*	Explanations and Researches on Chinese Drugs	Vol. 161, P. 265

Sum of AFFINITY	Column Labels																																				
Row Labels	p011lpaB	p021lpbB	p031n8sA	p041hlgA	p051hlgB	p066e7kA	p076e7kB	p086oazA	p094x9yA	p104gqqA	p114s49A	p124z49B	p136nnaA	p146nnaB	p156g79S	p164iraA	p175v54A	p186bqgA	p196bqhA	p206dzA	p216dgoA	p226dgoB	p233e00D	p245zmdA	p253h8oA	p263h8rA	p273h8xA	p283v6oA	p293v6oB	p306e2pC	p316e2pD	p325nx2A	p336b3jR	p345vexA	p355vexB	p365i6xSM	p374xp4SM	p384xptSM	Grand Total
lco01orli.pdbqt	-5.8	-6.7	-4.9	-4.5	-6	-5.8	-5.2	-4.9	-6	-6.4	-5.4	-4.5	-6.4	-6.6	-5.4	-7	-5.7	-7.4	-7.3	-5	-4.9	-6.3	-6.8	-6.3	-6.2	-6.3	-6.1	-4.7	-5	-3.4	-4.2	-7.2	-5.2	-5.9	-5.9	-7.1	-6.9	-5.4	-220.7
lco02lira.pdbqt	-5.9	-5.6	-6.3	-4.5	-5.7	-5.2	-5	-4.6	-5.7	-6.5	-5.5	-6.4	-6.7	-5.4	-5.9	-5.7	-6.2	-5.3	-4.6	-5.8	-4.9	-6.7	-7.4	-6.3	-5.1	-5.9	-5	-4.8	-5.2	-3.4	-3.5	-5.8	-6.4	-5.3	-4.8	-7.3	-4.7	-5.7	-210.7
lco03lorc.pdbqt	-6.7	-7	-6.3	-6.4	-6.8	-6.7	-6.5	-5.8	-6.2	-6.3	-5.6	-6.4	-6.3	-7.4	-6.6	-6.9	-6	-7.5	-7.6	-7.8	-6.4	-6.5	-6.5	-5.6	-5.8	-6.1	-6.2	-5.1	-5.4	-4.3	-4.5	-6.5	-6.1	-6.2	-6.5	-7.1	-7.3	-6.4	-241.3
lco04egcg.pdbqt	-7	-7	-6.2	-6.4	-6.8	-6.7	-6.2	-6	-6.1	-7	-5.6	-6.4	-6.8	-7.4	-7	-7.2	-6	-6.9	-7	-7.3	-7.1	-6.7	-6.5	-5.5	-6.4	-5.9	-6.6	-5	-5.4	-4.3	-4.5	-6.8	-5.9	-6.3	-6.1	-6.6	-6.4	-6.4	-241.4
lco05bupr.pdbqt	-6.9	-6.9	-5.5	-5.9	-6.1	-6.7	-6.5	-6.5	-5.9	-6.6	-5.6	-5.4	-6	-6.3	-6.9	-6.8	-5.9	-7.2	-7.4	-5.5	-6.4	-6.3	-6.1	-5.6	-6	-6.5	-6.2	-4.7	-5.2	-4	-4.5	-7	-6.1	-6.4	-6.1	-7	-7.8	-5.9	-234.3
lco06hen.pdbqt	-6.3	-5.9	-5	-6.1	-6.5	-5.3	-5.3	-5.3	-5.6	-5.6	-4.8	-5	-5.8	-5.9	-6	-6.2	-6.5	-6	-6.6	-6.8	-5.6	-5.6	-5.2	-5.2	-5.2	-5.5	-5.4	-4.3	-4.9	-3.8	-4	-6.2	-5.3	-5.4	-5.6	-6.2	-6.6	-5.2	-211.7
lco07benz.pdbqt	-8	-8.2	-5	-7	-7	-7.3	-6.8	-6.7	-6	-6.7	-5	-5.6	-7.9	-7.4	-7.5	-7.1	-8.1	-6.3	-8.3	-8	-7.5	-6.5	-5.8	-6.8	-6.7	-6.1	-6.6	-5	-6.3	-4	-5.3	-6.8	-5.7	-5.7	-5.9	-7.3	-8	-6	-251.9
ljm001CID1110.pdbqt	-4.9	-4.7	-4.6	-5.3	-4.9	-4.9	-4.8	-4.5	-4.8	-5	-4	-4.2	-4.6	-4.8	-4.8	-4.6	-4.5	-4.7	-4.2	-4.2	-4.5	-4.3	-4.6	-5.1	-5	-5.2	-5	-3.9	-4.1	-3.1	-3.1	-4.1	-4.2	-4.9	-5.1	-4.6	-4.4	-4.6	-172.8
ljm002CID101405.pdbqt	-5.7	-5.4	-4.8	-5.9	-6	-5.3	-5.2	-5	-5	-5.7	-4.8	-5.3	-5.2	-5.6	-5.7	-5.4	-4.9	-4.9	-5.6	-5.4	-5.4	-5.3	-5	-5.2	-5.8	-5.5	-5.8	-4.7	-4.7	-3.4	-3.4	-5.4	-4.9	-5.3	-5.5	-5.9	-5.9	-5.3	-199.2
ljm003CID5281343.pdbqt	-7.3	-6.9	-6.4	-6.9	-7	-6.4	-6.2	-6.4	-6.4	-6.7	-5.6	-6.4	-6.5	-7.1	-6.9	-6.7	-6.1	-7	-7.1	-6.4	-6.4	-6.7	-6.1	-5.9	-6.9	-6.6	-6.9	-5	-5.3	-3.9	-4.1	-6.3	-5.6	-6.4	-6.5	-6.6	-6.3	-6.6	-240.5
ljm004CID5416204?.pdbqt	-6	-5.8	-5	-5	-6.1	-5.5	-5.4	-5.4	-5.7	-6.1	-4.9	-5	-5.5	-6	-5.4	-5.8	-5.6	-5.2	-5.2	-5.7	-5	-4.8	-5.2	-5.7	-6.3	-6.5	-6.4	-5	-4.6	-3.9	-3.8	-5.5	-4.7	-5.3	-5.4	-5.7	-5.9	-5.2	-205.2
ljm005CID122841.pdbqt	-6.7	-6.6	-5.7	-7.1	-7.3	-6.6	-6.4	-6	-5.7	-6.6	-5.4	-5.4	-6.3	-6.4	-6.3	-6.6	-6.8	-6.1	-6.9	-6.2	-6.6	-6.2	-5.9	-6.1	-6	-6.2	-6.2	-5	-5.5	-4.1	-4.2	-6.7	-5.5	-6.1	-6.2	-6.8	-6.8	-5.7	-232.9
ljm006CID87014.pdbqt	-9.3	-8.9	-7	-7.9	-8.1	-8.1	-8	-7.5	-8	-8.2	-7.5	-7.2	-7.3	-9.2	-8.5	-8.8	-8.2	-7.8	-9.3	-7.6	-8.6	-7.9	-7.8	-7.9	-8.4	-8.5	-8.4	-6.2	-6.7	-4.9	-5.5	-9.1	-7.5	-7.7	-7.6	-9	-8	-7.4	-299.5
ljm007CID66888.pdbqt	-9.2	-9.1	-7.7	-7.8	-8.5	-8.8	-8.5	-7.4	-7.7	-8.3	-7.3	-7.5	-7.2	-9.5	-8.6	-8.6	-8.5	-9.2	-8.8	-7.4	-8.4	-7.6	-7.9	-7.8	-8.2	-8.2	-8.2	-6.3	-6	-4.8	-5.2	-8.6	-7.4	-7.3	-7.1	-9	-7.8	-7.2	-298.6
ljm008CID68111.pdbqt	-9.9	-9.9	-7.4	-8.2	-8.2	-8.3	-8	-7.8	-7.8	-8.5	-7.6	-7.5	-7.7	-8.7	-9	-8.7	-8.9	-9.2	-9.8	-9	-8.6	-8	-8	-8	-8.4	-8.4	-8.4	-6.8	-6.4	-5.2	-5.8	-9	-7.1	-7.5	-7.5	-8.9	-8.5	-7.4	-308
ljm009CID66029.pdbqt	-7.3	-7.2	-6.2	-6.4	-6.6	-6.4	-6.7	-6.2	-6.5	-7.3	-5.9	-5.7	-7	-7.4	-6.8	-6.8	-5.9	-7	-7.1	-7	-5.8	-6.5	-7	-6.2	-6.5	-7	-6.5	-5.3	-5.8	-4.5	-4.2	-6.3	-5.7	-6.5	-6.5	-7.3	-7.2	-6.1	-244.3
ljm010CID5321977.pdbqt	-8.3	-8	-6.9	-6.7	-7.1	-7	-7.3	-6.9	-6.9	-7.6	-6	-6.5	-7	-8.1	-7.2	-7.9	-7.6	-7.5	-7.7	-7.6	-7.5	-7	-7.7	-7.2	-7.5	-8	-7.5	-5.7	-6.1	-4.9	-5.2	-7.8	-6.8	-6.7	-6.8	-7.6	-7.3	-6.4	-269.5
ljm011CID10208.pdbqt	-10.1	-9.9	-7.6	-8.5	-8.6	-8.4	-8.2	-7.9	-8	-8.7	-7.7	-7.9	-7.7	-9.4	-9.2	-8.8	-8.9	-9.1	-9.5	-9	-8.8	-8.1	-8.4	-8.3	-8.5	-8.6	-8.5	-6.8	-6.3	-5.2	-5.7	-9.1	-7.2	-7.7	-7.7	-9.2	-8.9	-7.5	-313.6
ljm012CID72537.pdbqt	-9.2	-9.1	-6.9	-7.2	-7.7	-7.5	-7.5	-6.7	-7.4	-8.3	-7.7	-6.7	-8.1	-8.7	-8.5	-8.7	-7.3	-8.4	-8.7	-7.7	-8.6	-7.9	-7.6	-7.3	-8.2	-8.2	-8.2	-6.5	-6.8	-5.2	-5.2	-8.4	-6.9	-7.3	-7.3	-8.7	-8.2	-7.1	-291.6
ljm013CID5281607.pdbqt	-10.2	-10.1	-7.3	-7.8	-7.8	-8.7	-8.9	-8.2	-8.1	-8.3	-7.2	-6.8	-8.1	-8.6	-9	-9	-8.8	-9	-9.2	-9.3	-9.1	-8.6	-8.3	-7.9	-7.8	-8	-8.4	-6.5	-7.2	-5.3	-5.4	-8.3	-7.7	-7.7	-7.7	-9.4	-9	-7.6	-310.3
ljm014CID135453893.pdbqt	-9	-9	-7.4	-7.6	-7.7	-7.9	-7.4	-7.2	-7.3	-8.2	-7.5	-6.9	-7.9	-8.5	-7.9	-8.9	-8.4	-8.6	-9.2	-8.8	-8.4	-7.7	-7.9	-7.6	-8.1	-8.2	-8.1	-6.3	-6.4	-5.2	-5.3	-8.3	-6.8	-7.6	-7.8	-8.8	-8	-7.2	-295
ljm015CID3220.pdbqt	-9.8	-9.6	-7.4	-8.1	-8.2	-8.5	-8.3	-7.7	-8.1	-8.7	-7.8	-6.9	-7.7	-7.5	-9.4	-9.2	-8.7	-8.9	-9.5	-8.7	-8.8	-8.2	-8.6	-8.1	-9	-9	-9	-6.6	-6.5	-5.1	-5.5	-9	-7.2	-7.7	-8	-9.6	-8.8	-7.6	-311
ljm016CID10207.pdbqt	-9.6	-9.4	-7.3	-8	-8.1	-8.2	-7.8	-7.3	-7.9	-8.7	-7.6	-7	-7.6	-9.2	-8.7	-9.1	-7.6	-9	-9.2	-7.6	-8.4	-7.9	-7.6	-8	-8.2	-8.3	-8.2	-6.5	-6.5	-5.4	-5.4	-8.6	-7.4	-7.3	-7.8	-9	-8.7	-7.4	-301.5
ljm017CID157661.pdbqt	-9.2	-9.5	-6.9	-7.8	-7.5	-8	-8	-7.3	-7.4	-8.4	-7.2	-7	-7.4	-8.6	-8.4	-9	-7.6	-7.2	-8.2	-7.3	-6.7	-7.7	-8.2	-7.9	-7.7	-7.6	-8.3	-6.2	-6.4	-5.5	-5.4	-8	-7.4	-7.1	-7.5	-8.7	-7.7	-7.1	-289
ljm018CID5321980.pdbqt	-9.9	-9.2	-6.9	-7.1	-7.4	-7.4	-7.2	-7.5	-7.5	-8	-7.7	-6.7	-7.1	-8.3	-8.5	-9.1	-7.2	-8.2	-9	-7.4	-8.4	-8	-8.2	-7.5	-8.4	-8.3	-8.4	-6.3	-6.6	-5.4	-5.4	-8.3	-7	-7.5	-7.1	-9	-8.2	-7	-292.3
ljm019CID10168.pdbqt	-10.2	-9.7	-7.5	-8.2	-8.3	-8.4	-8.3	-7.7	-8.3	-9.1	-8	-7.2	-7.7	-7.4	-9.1	-9.5	-8.5	-9.2	-9.3	-8.2	-7	-8.2	-8	-8.6	-8.5	-8.7	-8.5	-6.6	-6.8	-5.6	-5.5	-8.8	-7.6	-7.1	-7.6	-9.5	-9.1	-7.6	-309.1
ljm020CID10639.pdbqt	-10	-9.8	-7	-7.6	-7.8	-8.8	-8.3	-7.8	-7.8	-8.8	-7.7	-6.9	-7.8	-9.5	-8.6	-9.1	-8.7	-8.9	-9.4	-8.5	-8.9	-7.9	-8.2	-7.9	-8.6	-8.5	-8.6	-6.6	-6.3	-5.1	-5.5	-9	-7.3	-7.6	-7.9	-9.3	-8.9	-7.3	-308.2
ljm021CID160717.pdbqt	-9.5	-9.3	-7.6	-8	-8.2	-8.1	-7.7	-7.9	-7.8	-8.4	-7.7	-7.4	-7.2	-8.6	-7.1	-8.8	-9	-8.8	-8.4	-8.8	-8.9	-7.9	-8.6	-7.8	-8.6	-8.8	-8.6	-6.5	-6.5	-5.1	-5.3	-9	-7.3	-7.7	-7.3	-9.7	-8.5	-7.6	-304
ljm022CID3083575.pdbqt	-9.5	-9.2	-7.5	-6.9	-8.3	-7.9	-8	-7.3	-7.7	-8.6	-6.4	-7.7	-7.4	-9.6	-8.6	-8.9	-8.3	-8.6	-8.5	-8.8	-8.3	-8.1	-7.8	-8.2	-8.2	-8.2	-8.2	-6.1	-6.3	-5.1	-5.1	-8.9	-7.3	-7.4	-7.5	-9.7	-8.4	-7.5	-300
ljm023CID5280863.pdbqt	-9.4	-9.4	-7.6	-7.3	-7.4	-8.4	-8.4	-8	-8.3	-8.2	-6.7	-6.5	-8.4	-8.8	-9.1	-9.2	-8.7	-8.6	-8.3	-7.7	-8.9	-8	-8.7	-8	-8.2	-7.7	-8.2	-6.6	-7.5	-5.1	-5.3	-8.3	-6.9	-7.9	-7.7	-8.7	-9	-7.7	-302.8
ljm024CID10446798.pdbqt	-9.4	-9.5	-7.3	-7.2	-7.1	-7.3	-7.4	-7.2	-7.4	-8.3	-7	-6.6	-7.2	-8.8	-8	-8.8	-8.2	-8.5	-8.2	-9.2	-8.6	-8.4	-8.1	-7	-8.2	-8.2	-8.2	-6.3	-6.7	-5.1	-5.4	-8.2	-7.1	-7	-7.4	-9.2	-8.5	-7.2	-293.4
ljm025CID5280343.pdbqt	-9.5	-9.7	-7.6	-7.4	-7.9	-7.8	-8.2	-7.7	-8.6	-8.4	-6.8	-6.6	-8.7	-9	-9.1	-8.7	-8.7	-8.5	-8.7	-9.2	-8.8	-8.5	-8.1	-8.2	-7.6	-7.9	-7.6	-6.8	-7.6	-5.3	-5.3	-8.4	-7.6	-8.5	-7.9	-8.8	-9	-6.9	-305.6
ljm026CID627638.pdbqt	-8.4	-9.6	-7	-7.2	-7.8	-8.8	-8.8	-7.9	-7.6	-8.3	-6.5	-7	-7.5	-7.9	-8.1	-8.7	-7	-8.3	-8.2	-8.8	-6.9	-8	-8.4	-6.8	-7.8	-7.7	-7.8	-6.9	-6.6	-5.6	-5.4	-8.3	-7.5	-7.4	-7.5	-9.4	-8.5	-7.4	-293.3
ljm027CID155011.pdbqt	-8.9	-9	-6.9	-7.8	-7.9	-7.3	-7.6	-7	-7.9	-8.5	-7.2	-7.6	-7.1	-7.5	-8.2	-8.6	-8.2	-7.5	-8.3	-7	-8.9	-8.1	-8.3	-8.2	-8.2	-8.5	-8.2	-6.1	-6.3	-4.8	-4.8	-8.6	-7.1	-7.3	-7.3	-9.3	-8.5	-7.4	-291.9
ljm028CID155380.pdbqt	-8.9	-8.9	-6.7	-7.2	-7.3	-7.3	-7.3	-6.8	-7.3	-8.1	-6.4	-6.4	-7.3	-7.5	-8	-8.7	-8	-8.1	-8.3	-9.1	-6.5	-6.4	-7.6	-7.6	-7.7	-8	-7.7	-6	-6.1	-4.8	-4.7	-8.2	-7.1	-7.3	-7.2	-7.4	-8.2	-7.2	-279.3
ljm029CID155381.pdbqt	-8	-8.5	-6.4	-7.2	-7.2	-6.9	-7.3	-6.8	-7.8	-8.2	-7.1	-7	-7.1	-6.7	-6.1	-8.8	-6.9	-6.1	-8.3	-6.5	-6.6	-7.7	-7.5	-7.6	-7.4	-7.7	-7.6	-5.6	-5.8	-4.7	-4.5	-8.2	-6.8	-7	-6.6	-9.2	-8.1	-7.1	-270.6
ljm030CID164146.pdbqt	-8.1	-8.5	-7.6	-7.3	-7.5	-8.8	-8.3	-7.7	-8.7	-9.1	-6.8	-7.6	-7.8	-9.8	-7.6	-9.7	-8	-8.5	-9	-9.7	-9.1	-7.5	-8.5	-7.5	-8.6	-9	-8.6	-7.3	-6.8	-5.6	-5.3	-9.6	-7.8	-8.4	-7.4	-9.7	-8.5	-7.7	-309
ljm031CID5280794.pdbqt	-9.5	-9.7	-8.2	-7.6	-7.9	-8.3	-7.8	-8.5	-9.1	-9.4	-7.9	-7	-8.9	-8	-9.7	-11.1	-8.5	-10.7	-10.6	-8.1	-7.2	-9	-9.3	-7.4	-7.9	-7.9	-7.8	-6.9	-7.3	-5.4	-5.5	-10.9	-8.5	-7.6	-7.9	-10.7	-10.3	-8.6	-322.6
ljm032CID2222284.pdbqt	-9.2	-9.4	-7.9	-7.3	-8	-8.6	-7.6	-8.2	-8.3	-9.1	-7.3	-6.6	-8.4	-7.8	-9.3	-10.2	-7	-7.3	-10.3	-7.4	-6.7	-8.5	-8.8	-8.4	-7.7	-7.4	-7.7	-6.7	-7	-5.2	-5.3	-10.3	-7.7	-8.7	-8.1	-10.3	-9.9	-8.4	-308
ljm033CID5318717.pdbqt	-8.1	-8.9	-7.8	-7.7	-7.6	-7.9	-7.7	-7.2	-8	-9	-7.2	-6.9	-7.9	-7.7	-7.4	-9.5	-7.3	-6.7	-7.9	-7.7	-7.9	-7.5	-8.4	-7	-7.8	-8.1	-7.6	-6.2	-6.5	-5.1	-5	-8.4	-7.5	-7.6	-7.7	-9.4	-8	-7.3	-289.1
ljm034CID65252.pdbqt	-8.1	-9.9	-7.8	-7.5	-8	-8.4	-7.7	-7.4	-8.3	-10.3	-7.7	-7.1	-8.9	-8.7	-9.5	-11.3	-8	-10.5	-9.2	-10.3	-6.7	-8.9	-8.3	-6.9	-8	-7.7	-6.9	-7.1	-8.1	-5.6	-4.9	-9.4	-8	-8.5	-8.4	-10.8	-10.3	-9	-318.1
ljm035CID91472.pdbqt	-8.9	-10	-9	-8.5	-8.9	-9.9	-8.6	-8.8	-9.2	-8.7	-7.8	-8.7	-9.2	-9	-9	-9.5	-8.9	-10.3	-11.7	-9.1	-9.2	-8.9	-9.4	-7.8	-8.2	-8.3	-8.2	-8.1	-8	-6.9	-6.2	-10.5	-9.7	-8.5	-8.5	-8.7	-9.7	-9.8	-338.3
ljm036CID99649.pdbqt	-9.4	-10.6	-8.2	-8.2	-8.1	-9	-8.9	-8.7	-8.8	-9.3	-8.2	-7.5	-8.4	-8.9	-10.1	-10.5	-9.5	-9.5	-9.7	-8.2	-10	-7.8	-9.1	-8.7	-9	-9	-9.1	-7.2	-7.1	-5.9	-5.7	-9.6	-8.4	-7.8	-8.3	-10.4	-9.3	-8.3	-330.4
ljm037CID3035617.pdbqt	-8	-7.9	-7.6	-7.2	-7.4	-8.6	-7.6	-7.1	-8.3	-8.3	-8.5	-6.8	-7.6	-7.8	-8.9	-9.7	-8	-8.9	-9.5	-7.5	-6.8	-7.6	-8.7	-7.7	-8.6	-8.9	-8.6	-7.1	-6.7	-5.6	-5.2	-8.2	-7.5	-7.9	-8.1	-9.4	-8.6	-8.2	-300.6
ljm038CID68972.pdbqt	-5.4	-5.7	-4.8	-5	-5.6	-5.2	-4.2	-4.9	-5.2	-4.1	-5.2	-3.5	-4.8	-6.1	-6.4	-6.4	-4.7	-6.3	-6.2	-4.6	-3.9	-6.3	-5.4	-4.1	-4.9	-5	-4.2	-4	-3.8	-3.6	-3	-6	-4.6	-5.4	-4.8	-6	-5	-4.2	-188.5
ljm039CID442761.pdbqt	-8.5	-8.8	-7.7	-8	-8.4	-7.3	-7.7	-8	-8.4	-9.6	-7.2	-7.1	-8.1	-9.4	-7.1	-10.5	-7.6	-8.9	-9.1	-7.8	-8.5	-8	-8.4	-7.4	-8.7	-9.1	-8.7	-7.4	-6.5	-5.4	-4.9	-9.3	-7	-7.5	-7.2	-10.5	-8.5	-7.5	-305.7
ljm040CID64971.pdbqt	-8.7	-8.9	-8.4	-8	-8.1	-8.1	-7.9	-7.3	-8.9	-8.3	-8.4	-6.8	-8.4	-7.9	-8.1	-10.1	-8.8	-8	-9.3	-8.2	-7.1	-8.9	-9.4	-7.4	-7.4	-7.4	-7.4	-7.3	-7.5	-5.7	-5.5	-9.9	-8.2	-8	-7.5	-8.4	-9.3	-8.2	-307.1
ljm041CID442725.pdbqt	-8.7	-8.9	-8.4	-7.6	-7.7	-7.8	-7.6	-7.9	-9	-8.5	-8.4	-7.2	-7.6	-8.6	-6.8	-10.8	-7.8	-9	-9.4	-8.2	-7	-8.2	-8.9	-8	-8.1	-8	-8.1	-6.8	-6.4	-5.6	-5.3	-9.3	-7.5	-7.3	-7.7	-9.9	-9.3	-7.6	-304.9
ljm042CID439336.pdbqt	-6.8	-6.8	-7.3	-6.5	-6.5	-6.9	-7.4	-6.4	-7.7	-8.9	-7	-6.2	-7.5	-7.5	-7	-8	-7.1	-6.4	-7.5	-7.3	-5.6	-5.6	-7.5	-6.5	-7.1	-6.5	-7.1	-5.9	-6.3	-4.6	-4.5	-6.8	-7.3	-6.5	-7.5	-8.4	-8	-6.3	-260.7
ljm043CID442730..pdbqt	-8	-8.2	-7.4	-7.4	-7.5	-7.2	-7.7	-7.2	-8.1	-8.3	-6.6	-7	-7.5	-6.9	-6.9	-9.7	-7.6	-8.1	-8.5	-7.9	-6.8	-7.5	-8.3	-7.7	-7.7	-8.4	-7.7	-6.3	-7	-5.1	-4.9	-8.2	-7.2	-7.2	-7.3	-10.3	-8.7	-7	-287
ljm043CID442730.pdbqt	-8	-8.2	-7.4	-7.2	-7.5	-7.2	-7.8	-7.2	-8	-8.3	-6.6	-7	-7.2	-7.3	-6.9	-9.7	-7.8	-7.8	-8.5	-9.6	-6.3	-7.5	-8.3	-7.7	-7.7	-8.3	-7.7	-6.4	-7	-4.9	-5	-7.9	-7.6	-7.9	-7.1	-7	-8.3	-6.9	-284.7
ljm044CID131752379.pdbqt	-8.2	-8.1	-7.3	-7.4	-7.7	-7.8	-8.2	-7	-8.8	-8.6	-7.4	-7.1	-8	-8.5	-6.6	-9.7	-8.4	-9.5	-10	-8	-6.5	-8.9	-8.6	-7.6	-8.2	-8.7	-8.3	-6.4	-6.7	-5.1	-6.1	-9.1	-8.3	-7.3	-7.2	-8.5	-7.7	-7.7	-299.2
ljm045CID101617058.pdbqt	-8.9	-9.4	-8	-9.5	-9.6	-8.1	-7.9	-8.1	-9.6	-9.6	-7.9	-7.7	-8.1	-10.1	-10.1	-11.1	-8.6	-10.2	-10.5	-8.5	-9.6	-7.6	-10	-8.5	-8.5	-9.1	-8.5	-8.2	-7.7	-6.1	-5.2	-10.5	-8.5	-9.9	-9.1	-11.8	-9.6	-8.9	-338.8
ljm046CID503733.pdbqt	-8.3	-8.1	-7.9	-9.4	-9.6	-8.2	-7.7	-7.7	-8.4	-9	-7.6	-7.8	-7.8	-8.2	-8.8	-9.9	-9	-10.1	-9.9	-8.3	-9.8	-7.4	-9.6	-9	-8.3	-8.8	-8.3	-7.9	-7.4	-5.9	-5.6	-9.5	-8.2	-9.6	-9.8	-10.7	-9.6	-8.8	-325.9
ljm047CID100813.pdbqt	-8.3	-10.4	-8.9	-8.2	-8.8	-7.5	-7.9	-7.8	-8.3	-10	-7.6	-6.8	-8.4	-8.6	-8.6	-10.9	-8.9	-8	-9.5	-8.1	-11	-8.4	-9	-8.9	-8.6	-8.9	-8.6	-8.3	-7.8	-6.3	-6.1	-9	-7.8	-8.2	-8.1	-11.1	-9.8	-8.5	-325.9
ljm048CID10557731.pdbqt	-9.7	-8.6	-8.1	-8.4	-9.5	-8.4	-8.2	-7.5	-9.1	-9.8	-7.3	-7.7	-8.3	-8.3	-8	-9.8	-9.2	-9.2	-8.9	-9.3	-7.2	-9	-9	-9	-8.5	-8.9	-8.1	-6.4	-7.8	-5.1	-5.4	-9.1	-9.5	-8.8	-9.4	-9.2	-10.2	-8.8	-322.7
ljm049CID85185010.pdbqt	-9.5	-9.4	-8.1	-9.3	-9.1	-8.3	-8	-8.6	-8.3	-8.8	-7.1	-8.2	-8.3	-10.5	-7	-9	-8.5	-9.9	-8.5	-9.2	-8.2	-8.6	-8.4	-9.4	-9.1	-8.6	-8.6	-6.1	-5.3	-5	-5	-9.2	-7.3	-8.6	-7.3	-8.6	-10.2	-8.9	-316
ljm050CID10350826.pdbqt	-7.8	-9.7	-9.1	-8.2	-8.7	-8	-8.1	-8.5	-9.3	-9.3	-7.8	-7.2	-7.9	-8.5	-8.1	-9.5	-9.3	-9.6	-10	-9.4	-7.8	-8.7	-8.3	-8.5	-7.9	-8.4	-8.7	-7.1	-7.7	-5.9	-5.5	-8.9	-9.7	-9.5	-7.7	-10.4	-10.8	-9	-324.5
Grand Total	-484	-492.3	-410.6	-423.5	-440.6	-438.1	-429.1	-412.5	-440	-469.6	-397.9	-388.7	-430.2	-463.4	-452	-503	-444.6	-468.1	-490.6	-452.7	-434	-436.5	-453.2	-426	-441.8	-448.9	-442.2	-360.4	-370.2	-288.1	-290.2	-476.6	-411.1	-423.7	-420	-502.8	-477.6	-417.9	-16452.7

Sum of AFFINITY	Column Labels																	
Row Labels	p011lpaB	p021lpbB	p031n8sA	p041hlgA	p051hlgB	p066e7kA	p076e7kB	p086oazA	p094x9yA	p104gqqA	p114z49A	p124z49B	p136nnaA	p146nnaB	p156g79S	p164iraA	p175v54A	p186bqgA
Icy001CID13854.pdbqt	-4.5	-4.2	-4.2	-4.9	-4.8	-4.8	-4.4	-4	-4.2	-4.2	-3.9	-4.6	-4.3	-4.5	-4.3	-4.4	-4.7	-4.5
Icy002CID7361.pdbqt	-4.6	-4.6	-4.4	-4.5	-4.7	-4.5	-4.2	-4.1	-4.1	-4.9	-4	-4.8	-4.2	-4.3	-4.3	-4.4	-4.7	-4.5
Icy003CID12508287.pdbqt	-4.5	-4.6	-4.2	-4.9	-5.2	-4.3	-4.2	-4.1	-4.6	-4.3	-4	-4.9	-4.6	-4.7	-4.8	-4.7	-5	-4.7
Icy004CID5318017.pdbqt	-4.5	-4.6	-4.1	-5.2	-5.4	-4.5	-4.2	-4.2	-4.5	-4.4	-4	-4.8	-4.8	-4.6	-4.8	-4.7	-4.7	-4.7
Icy005CID5364517.pdbqt	-4.7	-4.6	-4.3	-5.2	-5.4	-4.3	-4.3	-4.2	-4.6	-4.4	-4.1	-5	-4.7	-4.5	-4.9	-4.7	-4.6	-4.8
Icy006CID71349956.pdbqt	-4.8	-4.5	-4.2	-5	-5.2	-4.2	-4.2	-4.1	-4.6	-4.2	-3.9	-3.9	-4.4	-4.8	-4.8	-4.7	-4.7	-4.6
Icy007CID5367536.pdbqt	-4.7	-4.5	-4.2	-5	-5.2	-4.4	-4.1	-4.1	-4.6	-4.3	-4	-3.9	-4.6	-4.9	-4.7	-4.7	-4.8	-4.8
Icy008CID543123.pdbqt	-4.7	-4.4	-4	-5	-5.2	-4.2	-4.2	-4.1	-4.5	-4	-4	-4	-4.4	-4.7	-4.5	-4.5	-4.9	-4.7
Icy009CID23264402.pdbqt	-4.8	-5	-4.8	-5	-5.7	-4.7	-4.7	-4.6	-5	-4.7	-4.6	-6.3	-5	-5.3	-5.1	-5	-5.8	-5.2
Icy010CID798.pdbqt	-5.8	-5.9	-5.4	-5.8	-6.2	-5.3	-5.3	-5	-5.6	-5.5	-4.8	-4.7	-5.6	-6	-5.7	-6.3	-6	-5.6
Icy011CID6998.pdbqt	-6.2	-5.6	-5.4	-5.6	-5.9	-5.1	-5	-5.3	-5.2	-5.4	-4.5	-5	-5.4	-5.9	-5.5	-5.9	-5.8	-5.5
Icy012CID7409.pdbqt	-6.1	-5.8	-5.5	-5.6	-5.7	-5.1	-5.1	-5.1	-5.5	-5.5	-4.8	-5.6	-5.5	-5.5	-5.5	-6	-6.1	-5.8
Icy013CID181575.pdbqt	-5.4	-5.1	-4.7	-5.2	-6	-4.9	-4.8	-4.9	-4.7	-4.9	-4.5	-4.8	-4.9	-5.4	-5.2	-5.2	-5.6	-5.6
Icy014CID7708.pdbqt	-6.4	-5.8	-5.1	-5.9	-6.3	-5.6	-5.3	-5.4	-4.9	-5.4	-4.7	-4.8	-5.4	-5.5	-5.6	-5.9	-6	-5.5
Icy015CID17000.pdbqt	-5.4	-5.9	-5.4	-5.9	-6.6	-5.5	-5.6	-5	-5.5	-5.6	-5	-5	-5.6	-6	-5.5	-5.9	-6.6	-6.2
Icy016CID7711.pdbqt	-6.1	-5.9	-5	-6.2	-6.5	-5.7	-5.5	-5.7	-5.3	-5.4	-4.8	-5	-5.6	-5.9	-5.8	-6.1	-6.1	-5.6
Icy017CID1188.pdbqt	-6.3	-6.2	-6	-5.7	-6	-5.7	-5.7	-5.4	-5.5	-6.5	-5.1	-5.7	-5.7	-6	-5.6	-6.5	-5.6	-5.7
Icy018CID638011.pdbqt	-5.9	-5.6	-5	-5.8	-6.5	-5.4	-5.3	-5.4	-4.9	-5.5	-5.1	-4.6	-5.5	-5.7	-5.5	-6.1	-6	-6.5
Icy019CID5366264.pdbqt	-5.8	-5.4	-5	-5.5	-6	-5	-5	-5	-5.3	-5.3	-4.8	-4.9	-5.3	-5.8	-5.7	-5.5	-6.2	-5.8
Icy020CID17100.pdbqt	-6.1	-6.6	-5.9	-6.3	-6.4	-6	-5.8	-6.1	-5.9	-5.8	-5	-5.2	-6.3	-6.7	-6.3	-6.5	-6.9	-6.5
Icy021CID101115.pdbqt	-5.9	-6.2	-5.5	-5.8	-6.6	-5.4	-5.3	-4.8	-5.5	-5.9	-4.8	-4.8	-5.3	-6.2	-5.4	-5.6	-6.4	-5.6
Icy022CID1549018.pdbqt	-7	-6.3	-5.4	-6.8	-7.4	-6	-6	-6	-5.7	-5.9	-5.3	-5.4	-6.3	-6.3	-6.1	-6	-6.8	-6.9
Icy023CID80220.pdbqt	-6.6	-6.3	-5.5	-5.9	-6.6	-6.1	-5.9	-5.7	-5.9	-6.1	-5.6	-6.1	-5.7	-6.3	-5.8	-6.2	-6	-5.2
Icy024CID439378.pdbqt	-5.6	-5.1	-4.9	-5.1	-5.4	-5.1	-5.4	-5.2	-4.9	-5.3	-4.3	-4.5	-5.5	-5.6	-5.3	-5.7	-5.4	-5.6
Icy025CID5429.pdbqt	-6.7	-6.8	-5.4	-6	-6.2	-6.1	-5.9	-5.4	-6.4	-6.5	-5.6	-6.2	-6	-6.3	-6	-6.2	-6.3	-6
Icy026CID2153.pdbqt	-6.1	-6.5	-5.7	-6.2	-6.4	-6	-6.2	-5.5	-5.6	-6.3	-5.4	-6.2	-5.5	-6.2	-5.8	-6.2	-5.5	-5.8
Icy027CID5319748.pdbqt	-5.5	-5.2	-4.3	-5.2	-5.5	-5	-5.4	-4.9	-4.4	-5.1	-4.4	-4	-5.2	-5.4	-5.2	-5.4	-5.4	-5.1
Icy028CID2519.pdbqt	-6.5	-6.7	-5.6	-6.5	-6.8	-5.6	-5.7	-5.7	-5.6	-6.3	-5.4	-6.5	-5.3	-6.4	-6.1	-5.9	-5.1	-5.7
Icy029CID11019926.pdbqt	-6.9	-6.9	-6.2	-6.3	-6.6	-6	-6.3	-5.7	-6.1	-6.8	-5.5	-5.8	-6.1	-6.6	-6.5	-6.9	-6.2	-6
Icy030CID5352456.pdbqt	-7	-6.6	-5.2	-6.4	-6.4	-6.6	-6.2	-5.8	-5.4	-6.4	-4.6	-5	-6.4	-6.4	-6.2	-6.7	-6.5	-6.9
Icy031CID6430825.pdbqt	-7.6	-6.8	-6	-5.9	-6.3	-6.6	-6.6	-6.1	-6.2	-6.8	-6.1	-5.7	-6.9	-7	-6.6	-7.2	-7.6	-7.7
Icy032CID5321925.pdbqt	-6.8	-6.7	-6.1	-6	-6.8	-6	-6.3	-5.8	-6.5	-7	-6.2	-6.1	-6.6	-7.8	-6.6	-7	-7.8	-7.3
Icy033CID73160.pdbqt	-9	-9.2	-7.4	-7.6	-7.5	-7.9	-8	-7.5	-8.5	-8.6	-6.6	-6.6	-8.3	-8.7	-8.5	-8.6	-8.4	-8.2
Icy034CID72276.pdbqt	-8.3	-9.3	-7.3	-7.6	-7.6	-8.1	-8	-7.2	-8.5	-8.4	-6.6	-6.7	-8.1	-8.6	-8.8	-8.8	-8.7	-8.4
Icy035CID6050.pdbqt	-5.8	-5.9	-5	-5.4	-5.5	-5.1	-6	-5	-5.1	-6	-4.8	-5.3	-5.7	-6.5	-5.9	-5.7	-6.3	-6.3
Icy036CID72277.pdbqt	-7.9	-9	-7.1	-7.3	-7.5	-8.3	-8.2	-7.2	-8.3	-8.4	-6.5	-6.6	-8.4	-9.2	-8.7	-8.8	-6.7	-8.1
Icy037CID65084.pdbqt	-8.7	-9	-7.1	-7.9	-7.9	-8	-7.7	-7.3	-8.4	-8.5	-6.8	-6.6	-8.7	-8.5	-8.7	-8.3	-8.3	-8.2
Icy038CID1794427.pdbqt	-8.2	-8.6	-7.3	-7.6	-7.4	-7.9	-6.9	-7.1	-7.8	-8.7	-6.6	-7.1	-8.1	-8.7	-8.9	-8.3	-8.4	-7.3
Icy039CID5326970.pdbqt	-9.3	-10	-8.5	-8	-8.2	-8.5	-8.4	-8	-8.6	-10	-7.9	-7.2	-8.5	-9.6	-9.2	-10.9	-8.6	-10.7
Icy040CID13889661.pdbqt	-9	-10.2	-8.2	-7.6	-8.4	-8.6	-8.3	-8.3	-8.8	-9.2	-7.6	-7.3	-9.1	-10.2	-9.1	-11	-11.3	-10.2
Icy041CID65064.pdbqt	-9.4	-8.6	-8.6	-8.9	-8.4	-8.5	-8.1	-7.8	-9.1	-9.4	-8	-7.4	-8.7	-9.6	-10.1	-9.9	-9.5	-9.1
Icy042CID107905.pdbqt	-9.3	-9	-8.2	-8.6	-7.4	-7.7	-8.1	-7.2	-8.7	-9.5	-7.9	-7.4	-9	-9.3	-9.8	-10.2	-7.5	-9.3
Icy043CID65056.pdbqt	-8	-7.9	-8	-9	-8.7	-7.9	-7.5	-7.4	-9.4	-8.7	-6.5	-7	-8.2	-9.1	-10.7	-10.2	-10.1	-7.5
Icy044CID44256700.pdbqt	-8.2	-8.5	-7.9	-7.6	-7.8	-7	-7	-7.4	-8.8	-8.6	-7.6	-7.2	-8.5	-8.8	-9	-9.9	-7.4	-9.3
Icy045CID199472.pdbqt	-8.3	-8.9	-8.2	-8	-8	-8.5	-8.6	-7.4	-9.3	-9.8	-7.8	-7.3	-8.1	-8.8	-11	-9.8	-10.7	-9
Icy046CID5280804.pdbqt	-7.9	-7.9	-7.5	-7.8	-7	-7.7	-8.1	-7.6	-8.8	-9	-7.5	-6.7	-8.4	-8.7	-7.2	-8.6	-8.7	-8.7
Icy047CID531649.pdbqt	-8.5	-8.4	-8	-7.3	-7.2	-7.6	-7.9	-7.6	-8.8	-8.9	-7.5	-6.6	-8.5	-8	-7.1	-9.4	-7.6	-9.1
Icy048CID5280489.pdbqt	-10.2	-9.2	-7.8	-8.8	-8.9	-8.5	-9.3	-9.1	-8.7	-10.2	-8.2	-8.1	-7.9	-8.8	-8.2	-8.9	-9.3	-9.9
Icy049CID135438671.pdbqt	-8.8	-10	-9.2	-9.4	-9.4	-8.3	-8.4	-8.7	-11	-9.7	-7.7	-7.9	-10	-8.9	-8.5	-11.4	-8.8	-8.9
Icy050CID5487342.pdbqt	-8.3	-8.1	-7.9	-8	-8.5	-8.5	-7.7	-8.4	-8.9	-10	-8	-7.4	-8.5	-9.9	-9.4	-10.3	-8.6	-7.7
Icy051CID15922818.pdbqt	-8.6	-10	-8.6	-9.1	-8.5	-7.2	-8.9	-9	-9.9	-9.4	-7.4	-7.5	-9	-10.6	-8.8	-11.3	-9.5	-7.7
Icy052CID5487343.pdbqt	-8.4	-9	-7.8	-8.7	-8.7	-8.3	-8.2	-8.5	-9.2	-10.2	-7.8	-7.9	-9.1	-9.6	-9	-10	-8.5	-9.2
Icy053CID442543.pdbqt	-8.1	-8.4	-9.6	-8.8	-8.4	-7.7	-8.7	-8.3	-9.5	-9.7	-7.6	-7.7	-9.1	-9.2	-8.3	-6.8	-8.5	-8.2
Icy054CID14520989.pdbqt	-10.3	-9.4	-9	-8.9	-9.1	-8.1	-8.4	-7.7	-8.6	-8.8	-8	-7.8	-8.6	-8.4	-8.4	-7.8	-8.7	-8.9
Icy055CID10843814.pdbqt	-8.2	-8.1	-8	-8	-8.2	-8.2	-8	-8.3	-9	-8.3	-6.7	-7.4	-8.6	-8.3	-7.7	-6.9	-9	-8.2
Icy056CID11953922.pdbqt	-7.8	-7.5	-7.5	-8.5	-8.5	-8	-7.8	-7.8	-9.1	-8.2	-7	-6.9	-8.4	-7.7	-7.6	-5.8	-8	-8.3
Ihh001CID3893.pdbqt	-5.9	-5.7	-4.8	-4.9	-5.8	-5.2	-5.1	-5	-4.9	-5.6	-5	-4	-5.6	-5.7	-5.8	-5.3	-5.5	-5.7
Ihh002CID11005.pdbqt	-6.4	-5.7	-4.7	-5.1	-5.3	-5	-5.2	-5.2	-4.6	-5.8	-4.6	-4.3	-5.6	-5.7	-5.1	-5.6	-5.8	-5.9
Ihh003CID985.pdbqt	-6	-6	-4.5	-4.6	-5.3	-5.3	-5.1	-4.9	-5.2	-5.6	-5	-4.3	-5.7	-6	-5.6	-5.5	-5.8	-6.2
Ihh004CID5280961.pdbqt	-9.7	-8.8	-7.1	-7.7	-7.3	-8.5	-8.8	-9	-8.1	-8.2	-6.3	-6.6	-8.4	-8.9	-8.7	-9.2	-8.5	-8.6
Ihh005CID5280863.pdbqt	-9.4	-9.5	-7.7	-7.3	-7.4	-8.4	-8.4	-8	-8.4	-8.2	-6.5	-6.9	-8.1	-8.8	-9.1	-9.2	-8.7	-8.6
Ihh006CID10467.pdbqt	-6	-6.1	-4.8	-4.9	-5.5	-5.3	-5.4	-5	-5	-6	-5.5	-4.2	-6.1	-6	-5.2	-5.8	-6.9	-6.3
Ihh007CID5280681.pdbqt	-8.9	-9.2	-7.3	-7.7	-7.6	-7.5	-7.8	-7.2	-7.8	-8.4	-7	-6.6	-8.1	-8.9	-8.9	-8.4	-7.1	-7.7
Ihh008CID5281654.pdbqt	-9.2	-9.2	-7.7	-7.2	-7.5	-8.2	-8.2	-7.8	-8.5	-8.3	-6.8	-6.8	-8.7	-9.8	-9.3	-8.8	-8.8	-8.6
Ihh009CID92797.pdbqt	-7	-6.5	-5.8	-6.4	-6.3	-5.8	-6.2	-5.5	-6.6	-6.8	-5.5	-5.4	-7.2	-6.9	-6.9	-6.5	-6.6	-6
Ihh010CID146515.pdbqt	-9.4	-8.4	-6.9	-7.4	-8.4	-8	-8.2	-7.6	-7.8	-9.7	-6.4	-6	-8.9	-7.3	-8.8	-9.7	-9.9	-9.5
Ihh011CID222284.pdbqt	-9.2	-9.4	-8	-7.3	-7.5	-8.7	-7.9	-8.1	-8.3	-9.4	-7.9	-6.5	-8.1	-9.7	-9.2	-10.6	-8.3	-10.5
Ihh012CID5321398.pdbqt	-9.2	-9.2	-8.3	-7.8	-8	-8.9	-9	-7.9	-8.3	-9.8	-7.7	-8	-9.2	-8.7	-8.8	-10.1	-7.7	-9.9
Ihh013CID72326.pdbqt	-7.9	-8.9	-8.2	-7.4	-7.5	-7.4	-7.5	-7.2	-8.5	-10.2	-7.4	-7.5	-8.7	-7.9	-8	-10	-9	-7.7
Ihh014CID9846221.pdbqt	-8.9	-9	-9	-8.4	-8.8	-9.6	-9.5	-8.5	-9.4	-9.1	-8.9	-8	-9.4	-8.7	-8.5	-9.8	-8.8	-9
Ihh015CID11968944.pdbqt	-9.4	-8.9	-7.9	-9.3	-8.3	-8.2	-8.9	-8.8	-8.4	-9.5	-7.9	-7.9	-8.7	-9.5	-9.4	-11.2	-8.7	-9.6
Ihh016CID5318767.pdbqt	-9.1	-9.1	-8.5	-9.1	-8.9	-8.3	-7.5	-7.4	-8.7	-10.9	-7.3	-7.7	-8.7	-8.8	-7.6	-10.1	-8.8	-10.5
Ihh017CID5280805.pdbqt	-8.9	-8.3	-8.5	-9.3	-9.1	-7.4	-8.3	-7.5	-9.1	-9.4	-7.9	-7.9	-7.8	-9.1	-7.5	-10	-8.5	-7.9
Ihh018CID5282155.pdbqt	-8.2	-8.3	-7.4	-7.5	-7.6	-6.6	-8.2	-7.3	-8.2	-8.7	-6.6	-7	-7.9	-8.5	-8	-8.7	-9.9	-7.3
Ihh019CID6728944.pdbqt	-8.4	-9	-8.1	-7.8	-7.8	-8.4	-8	-8.3	-8.2	-9.1	-7.7	-7.8	-9.1	-8.7	-7.3	-10.4	-8.2	-9
Ihh020CID46936193.pdbqt	-8.6	-9.1	-9.4	-7.7	-8.5	-8.6	-8.2	-8.1	-9.5	-9	-8.1	-7.5	-8.4	-8	-7.6	-10.3	-8.4	-8.3
Ihh021CID17751019.pdbqt	-8.1	-8.3	-8.1	-8.6	-8.2	-8.2	-7.7	-7.9	-8.8	-9.5	-8	-8.1	-8.7	-9	-7.6	-10	-8	-8.3
Ihh022CID102004842.pdbqt	-8.3	-8.5	-7.4	-7.7	-7.6	-8.2	-8.3	-7.8	-9.3	-8.7	-7.8	-7.6	-9.4	-8.9	-8.9	-8.6	-9	-8.1
Ihh023CID14103656.pdbqt	-9.1	-8.8	-8.8	-8.5	-8.5	-7.9	-8.1	-7.7	-9.3	-10.4	-8.2	-7.4	-9	-8.9	-8	-8	-10	-9.3
Ihh024CID102120183.pdbqt	-9.1	-9.1	-8.5	-8.6	-9.3	-8.2	-8.2	-8.2	-10.3	-9.9	-8.2	-8.3	-9.7	-9	-8.1	-8.6	-9.5	-9.6
Ihh025CID13326387.pdbqt	-8.8	-8.8	-8.6	-8.5	-8.7	-9.2	-7.6	-7.7	-9	-9.5	-7.7	-7.4	-9.3	-8.8	-7.7	-7.5	-8.9	-10.2
Ihh026CID21607811.pdbqt	-8.4	-8.7	-8.5	-8.7	-8.8	-7.6	-7.9	-8	-9.8	-9.5	-7.4	-7.1	-9.1	-9.1	-7.7	-7.3	-9.1	-10.1
Ihh027CID188384.pdbqt	-8.7	-8.2	-8.3	-9	-9	-8.1	-8.4	-8.1	-9.5	-8.7	-8.3	-7.7	-8.9	-8.5	-8.1	-7.6	-10.7	-9.6
Ihh028CID101538997.pdbqt	-9.1	-10.7	-8.7	-10.4	-10.7	-7.9	-8.9	-8.9	-9.9	-9.9	-7.3	-8.2	-9.7	-9.3	-7.8	-9.4	-9.8	-9
Ihh029CID122097.pdbqt	-9	-10.2	-8.5	-9.9	-10.1	-7.7	-8.4	-8.4	-9	-9.6	-7.7	-7.5	-9.2	-8.3	-7.7	-8.9	-9.4	-8.7
Grand Total	**-634.3**	**-636.6**	**-572.3**	**-599.4**	**-613.9**	**-582.1**	**-585.2**	**-565.2**	**-616.4**	**-644.2**	**-534**	**-535.6**	**-617.5**	**-638.3**	**-611.2**	**-651.4**	**-637.2**	**-632.7**

Row Labels	p196bqhA	p206dzzA	p216dgoA	p226dgoB	p233e00D	p245zmdA	p253h8oA	p263h8rA	p273h8xA	p283v6oA	p293v6oB	p306e2pC	p316e2pD	p325nx2A	p336b3jR	p345vexA	p355vexB	p365i6xSM	p374xp4SM	p384xptSM	Grand Total
Icy001CID13854.pdbqt	-4.6	-4.7	-4.2	-4.1	-4	-4.2	-4.4	-4.6	-4.4	-3.6	-3.8	-2.9	-2.9	-4.1	-4	-4.7	-4.7	-4.5	-4.4	-4.6	-162.8
Icy002CID7361.pdbqt	-4.5	-4.1	-4.3	-4.2	-4.5	-4.7	-4.4	-4.6	-4.4	-3.6	-3.8	-2.9	-3.1	-4.2	-3.9	-5.1	-5.1	-5.1	-4.3	-4.7	-165.3
Icy003CID12508287.pdbqt	-4.8	-4.9	-4.5	-4.4	-4.4	-4.6	-4.4	-4.7	-4.6	-3.8	-4	-3.1	-3.3	-4.5	-4.1	-4.4	-4.6	-4.6	-4.9	-5.2	-170.1
Icy004CID5318017.pdbqt	-4.9	-4.6	-4.4	-4.4	-4.3	-4.8	-4.5	-4.8	-4.6	-3.7	-3.7	-3.2	-3.3	-4.6	-4.1	-4.5	-4.6	-4.8	-5.2	-5.5	-171.2
Icy005CID5364517.pdbqt	-4.7	-4.7	-4.4	-4.4	-4.4	-4.3	-4.5	-4.6	-4.6	-3.8	-4	-3.1	-3.2	-4.5	-4.5	-4.4	-4.6	-4.7	-5	-4.3	-170
Icy006CID71349956.pdbqt	-4.8	-4.9	-4.3	-4.4	-4.3	-4.2	-4.4	-4.8	-4.6	-3.7	-3.9	-3.2	-3.4	-4.5	-4.3	-4.5	-4.4	-4.5	-4.9	-4.3	-167.1
Icy007CID5367536.pdbqt	-4.8	-4.9	-4.6	-4.6	-4.5	-4.3	-4.6	-5	-4.6	-3.7	-3.8	-3.1	-3.3	-4.5	-4	-4.6	-4.7	-4.9	-5.1	-5.6	-170.7
Icy008CID543123.pdbqt	-4.4	-4.8	-4.3	-4.3	-4.4	-4.4	-4.3	-4.8	-4.3	-3.5	-3.9	-3	-3.3	-4.3	-4	-4.4	-4.4	-4.6	-4.8	-4.1	-164.3
Icy009CID23264402.pdbqt	-4.9	-5	-4.8	-4.5	-5.1	-4.4	-4.9	-5.2	-4.9	-3.9	-4	-3.2	-3.4	-4.9	-4.3	-4.9	-5	-5.5	-5.2	-5.9	-185.2
Icy010CID798.pdbqt	-6.2	-6.2	-5.7	-5.8	-5.4	-4.9	-5.4	-5.7	-5.4	-4.2	-4.7	-3.7	-3.7	-5.8	-5.4	-5.4	-5.3	-6	-6.6	-6.7	-208.7
Icy011CID6998.pdbqt	-6	-5.6	-5.1	-5.3	-5.1	-5.3	-5.5	-5.7	-5.5	-4.3	-4.5	-3.7	-3.7	-5.4	-4.6	-5.2	-5.4	-6	-5.9	-6.3	-202.3
Icy012CID7409.pdbqt	-6.1	-6.2	-5.5	-5.5	-5.4	-5.6	-5.3	-5.5	-5.3	-4.5	-4.6	-3.8	-3.9	-5.9	-5	-5.3	-5.3	-5.8	-6.2	-6.4	-206.9
Icy013CID181575.pdbqt	-5.6	-5.3	-5.1	-5.1	-5	-5.4	-4.8	-5.1	-4.8	-4.1	-4.3	-3.7	-3.8	-5	-5.3	-4.8	-5.4	-5.7	-5.6	-4.7	-190.4
Icy014CID7708.pdbqt	-5.8	-5.6	-5.5	-5.4	-5.4	-5.2	-5.4	-5.9	-5.5	-4.2	-4.6	-3.6	-3.7	-5.5	-4.9	-5.1	-5.2	-5.6	-6.3	-6.4	-204.3
Icy015CID17000.pdbqt	-6.5	-6.2	-5.5	-5.7	-5.4	-5.4	-6.1	-5.5	-6.1	-4.2	-4.6	-3.7	-3.9	-6	-5.2	-5.9	-5.9	-5.8	-6.1	-5.5	-211.4
Icy016CID7711.pdbqt	-6.1	-6.1	-5.6	-5.6	-5.7	-5.5	-5.7	-5.8	-5.7	-4.4	-4.7	-3.8	-4.1	-5.5	-5.1	-5.4	-5.5	-5.8	-6.5	-5	-209.8
Icy017CID1188.pdbqt	-6	-5.8	-5.5	-5.9	-5.5	-5.4	-6.5	-6.8	-6.3	-4.7	-4.8	-3.9	-3.7	-5.7	-5.2	-5.8	-6.4	-5.8	-6.1	-5.2	-215.9
Icy018CID638011.pdbqt	-6.1	-6.4	-5.6	-5.2	-5.3	-5.6	-5.5	-5.7	-5.4	-4.1	-4.6	-4	-4.1	-5.5	-5	-5	-5.4	-5.9	-6.2	-5.4	-206.3
Icy019CID5366264.pdbqt	-5.8	-5.8	-5.8	-5.5	-5.4	-5.1	-5	-5.2	-5	-4.1	-4.6	-3.7	-3.9	-5.9	-5.3	-5.2	-5.3	-6	-5.8	-5.1	-200.8
Icy020CID17100.pdbqt	-6.9	-6.6	-5.9	-6.4	-6.2	-6.2	-6	-6.2	-6	-5	-5.4	-4.1	-4.2	-6.3	-5.6	-5.8	-5.8	-6.9	-7	-5.8	-228.6
Icy021CID101115.pdbqt	-5.7	-6.2	-5.1	-5.7	-5.7	-5.1	-6.2	-6.1	-6.2	-4.4	-4.6	-3.6	-3.5	-6	-5	-6.1	-6.1	-5.8	-6.2	-5.5	-209.8
Icy022CID1549018.pdbqt	-6.7	-5.4	-6.4	-6	-5.5	-5.3	-5.7	-5.6	-5.7	-4.4	-4.4	-3.9	-4.4	-7	-5.5	-5.9	-5.7	-6.8	-6.2	-5.4	-223.5
Icy023CID80220.pdbqt	-6.3	-5.8	-5.8	-5.6	-5.8	-5.6	-6.4	-6.9	-6.4	-4.8	-4.8	-4.2	-3.6	-5.8	-5.4	-5.9	-6.2	-6.2	-6.1	-5.5	-220.6
Icy024CID439378.pdbqt	-5.3	-5.2	-4.6	-5.4	-5.4	-5.5	-5.7	-5.6	-5.7	-4.5	-4.3	-3.5	-3.4	-5	-4.2	-5.3	-5.3	-5.3	-5.3	-4.9	-193.3
Icy025CID5429.pdbqt	-6.3	-6.1	-5.9	-6.3	-6.1	-5.4	-6.5	-6	-6.5	-4.8	-5	-3.9	-3.6	-5.7	-5.3	-5.8	-5.9	-6.2	-6.4	-5.4	-223.1
Icy026CID2153.pdbqt	-6	-6.1	-5.9	-5.7	-5.6	-5.6	-6.7	-5.6	-6.7	-4.8	-5.2	-3.8	-3.6	-6	-5.3	-6.2	-6.1	-6	-6	-5.3	-219.3
Icy027CID5319748.pdbqt	-5.3	-5.3	-5.4	-5.3	-5.3	-4.3	-5.5	-5.1	-5.5	-3.7	-4.3	-3.4	-3.5	-5.1	-4.6	-5	-4.8	-5.4	-5.4	-4.3	-187.1
Icy028CID2519.pdbqt	-6.4	-6	-6.2	-6.6	-5.8	-5.5	-6.4	-6	-5.7	-4.7	-4.8	-3.7	-3.6	-5.9	-5.6	-5.4	-5.4	-6.1	-5.9	-5.6	-218.7
Icy029CID11019926.pdbqt	-6.9	-6.2	-6.4	-6.2	-6.8	-5.6	-6.9	-6	-6.6	-5.1	-5.3	-4.1	-4	-5.9	-5.4	-5.9	-5.8	-6.6	-6.1	-6	-231.2
Icy030CID5352456.pdbqt	-6.9	-5.9	-5.4	-5.7	-6.4	-5.4	-6.7	-6.3	-6.6	-4.3	-5.4	-3.5	-4.5	-6.1	-6.1	-5.7	-5.9	-7.3	-6.9	-5.8	-227.5
Icy031CID6430825.pdbqt	-7.2	-7.3	-6.8	-7.1	-6.4	-5.8	-6.2	-6.4	-6.2	-5.3	-5	-4.1	-4.4	-6.9	-6.1	-6.8	-6.9	-7	-6.7	-5.9	-244.2
Icy032CID5321925.pdbqt	-7.8	-7.6	-5.6	-7.4	-7.4	-5.7	-5.9	-6	-5.9	-5.4	-5.4	-4.2	-4.2	-7.9	-5.9	-7.3	-7.4	-7.3	-7	-6.5	-247.2
Icy033CID73160.pdbqt	-8.6	-9.1	-8.2	-8.6	-8.5	-7.7	-8.3	-7.7	-8.3	-6.6	-6.9	-5.2	-5.2	-8.1	-7.4	-8.3	-8	-9.7	-8.7	-6.8	-301
Icy034CID72276.pdbqt	-8.6	-9.4	-8.5	-7.3	-8.5	-7.7	-8.2	-8.1	-8.2	-6.5	-7.2	-5.5	-5.2	-8.1	-6.9	-7.9	-8.2	-9	-8.8	-7.3	-300.1
Icy035CID6050.pdbqt	-6.1	-5.7	-5	-5.5	-6.8	-5.8	-5.4	-5.3	-5.9	-4.4	-4.4	-3.9	-3.7	-5.9	-5.3	-5	-5.6	-6.2	-5.8	-5	-208
Icy036CID72277.pdbqt	-8.4	-9.1	-8.5	-7.8	-8.6	-7.6	-7.7	-7.8	-7.7	-6.4	-7.4	-5.4	-5	-7.6	-7	-7.8	-7.7	-8.5	-8.2	-7.2	-293.6
Icy037CID65084.pdbqt	-8.1	-7.5	-8.1	-8.4	-7.9	-6.8	-7.8	-7.5	-7.8	-5.9	-6.9	-5.5	-5.1	-8	-7.3	-8.2	-8.1	-8.7	-8.3	-6.7	-293.2
Icy038CID1794427.pdbqt	-8.3	-9.2	-7.7	-7.9	-8.5	-6.5	-7.9	-8	-7.7	-6.1	-6.8	-5.2	-4.9	-7.5	-7.4	-6.8	-7.1	-9	-8.8	-6.7	-288.9
Icy039CID5326970.pdbqt	-10.5	-10.6	-8	-8.9	-8.7	-7.2	-7.6	-8.9	-7.6	-7.3	-7.2	-5.2	-5.2	-10.2	-8.2	-8.4	-8.5	-7.5	-10.2	-8.9	-324.9
Icy040CID13889661.pdbqt	-10.9	-11	-7.3	-8.9	-9.3	-7.5	-8.7	-9.2	-8.7	-7.5	-7.6	-5.4	-5.3	-10.6	-8.9	-7.8	-8.3	-10	-10.3	-9.1	-334.7
Icy041CID65064.pdbqt	-10.1	-9.8	-7.5	-8.2	-9	-7.8	-8.2	-8.4	-8.2	-6.3	-7.4	-5.6	-5.1	-8.5	-8.1	-8.6	-9.1	-10	-9.3	-8.4	-322.7
Icy042CID107905.pdbqt	-10	-8.5	-6.9	-7.7	-9.3	-7.8	-8.1	-8.4	-8.1	-6.7	-7.2	-5.5	-5.1	-8.3	-8	-7.1	-7.7	-9.5	-9.2	-7.6	-310.8
Icy043CID65056.pdbqt	-9.8	-8.6	-6.9	-9	-8.4	-8.3	-7.9	-8.5	-8	-6.9	-6.7	-5.9	-5	-8.7	-8	-8	-8.4	-10.9	-9.1	-7.9	-312.7
Icy044CID44256700.pdbqt	-9.1	-8	-8.5	-7.8	-8.3	-7.6	-8	-8.3	-8	-6.5	-6.8	-5.8	-5.5	-7.9	-8.3	-7.8	-8.4	-10.8	-7.8	-7.7	-303.4
Icy045CID199472.pdbqt	-9.5	-8.3	-7.4	-8	-8.1	-8.4	-8.6	-8.8	-8.6	-6.7	-7.5	-5.5	-5.4	-8.2	-7.9	-8.6	-9	-10.3	-8.2	-7.5	-318
Icy046CID5280804.pdbqt	-8.1	-7.8	-7.3	-8.9	-8.5	-7.3	-7.7	-8	-7.7	-6.8	-6.6	-5.2	-5.1	-7.8	-8.5	-7.7	-7.7	-8.9	-7.8	-7.4	-294.6
Icy047CID531649.pdbqt	-8.8	-9	-6.8	-8.1	-8.6	-7.1	-8.1	-7.9	-8.1	-6.2	-6.5	-5.6	-5.1	-7.8	-8.1	-8.2	-7.7	-9.1	-8.4	-7.5	-296.7
Icy048CID5280489.pdbqt	-9.8	-8.3	-7.8	-10.2	-8.5	-7.7	-7.7	-7.6	-7.8	-7.7	-7.7	-6	-6	-10.6	-9.2	-9.1	-9.3	-10.1	-9	-8.4	-328.5
Icy049CID135438671.pdbqt	-9.4	-8.8	-7.8	-9.3	-8.9	-8.6	-10.5	-10.4	-10.4	-7.9	-8.5	-6.3	-6	-10.2	-8.9	-8.4	-9.3	-9.3	-9.9	-9.4	-343.2
Icy050CID5487342.pdbqt	-10.7	-11	-8.1	-8.4	-9.3	-8.1	-9.1	-9.3	-9.1	-7.9	-7.4	-6	-5.7	-9.7	-8	-8	-8.5	-10.6	-10.2	-8.3	-327.5
Icy051CID15922818.pdbqt	-11	-8.7	-7.4	-7.2	-8.2	-8.5	-9.1	-9.4	-9.1	-6.1	-7.6	-5.8	-6.5	-9.5	-8.3	-9.1	-7.9	-10.3	-8.8	-8.8	-328.3
Icy052CID5487343.pdbqt	-10.8	-9.4	-8	-8.3	-9.5	-8	-9.2	-9.4	-9.2	-8.2	-7.5	-6	-5.7	-9.5	-8.6	-9.3	-9.2	-10.8	-9.7	-8.1	-332.5
Icy053CID442543.pdbqt	-8.7	-9.5	-7	-8.4	-8.7	-9.3	-9.1	-9.3	-9.1	-7.7	-7.1	-4.9	-5.2	-10.5	-9	-8.9	-9.1	-9.6	-9.8	-10.3	-323.8
Icy054CID14520989.pdbqt	-9.2	-9.9	-7.4	-7.9	-9.4	-9	-8.9	-10	-8.9	-7.9	-7.5	-5.9	-6	-10	-10.1	-8.1	-8.4	-9.6	-9.9	-8.8	-327.7
Icy055CID10843814.pdbqt	-8	-9.1	-7.3	-7.8	-8.4	-8	-8.5	-8.3	-8.6	-7	-6.8	-5.6	-5.5	-10.1	-9.1	-8.5	-7.2	-7.9	-9.3	-9.7	-305.8
Icy056CID11953922.pdbqt	-7.8	-6.9	-6.9	-6.6	-7.2	-7.4	-8.1	-8.1	-8.1	-7	-7.1	-4.8	-5.1	-7.8	-8.8	-7.7	-7.4	-7	-8.7	-7.4	-286.3
Ihh001CID3893.pdbqt	-5.1	-4.5	-5.1	-5.2	-4.6	-5.5	-5.4	-5	-5	-3.7	-4.7	-3.4	-3.5	-4.9	-4.4	-4.3	-4.6	-5.9	-5.5	-5	-190.8
Ihh002CID11005.pdbqt	-5.9	-5.9	-5.9	-5.2	-4.9	-5.2	-5.2	-4.8	-4.4	-3.8	-4.3	-3.1	-3.3	-5.3	-5.2	-5.1	-4.7	-5.6	-5.6	-5	-194
Ihh003CID985.pdbqt	-5.8	-6.2	-5.6	-5.3	-4.9	-3.9	-5.1	-4.9	-4.8	-3.9	-4	-3.3	-3.9	-5.4	-5.4	-4.6	-4.8	-6.1	-5.1	-5.1	-194.7
Ihh004CID5280961.pdbqt	-8.4	-8.7	-8.5	-7.4	-7.3	-8.2	-7.9	-8	-7.9	-7.2	-7.5	-5	-4.9	-8.3	-7.4	-7.9	-8	-8.3	-9.5	-7	-301.7
Ihh005CID5280863.pdbqt	-8.3	-9.1	-8.9	-8.5	-7.2	-8	-8.2	-7.7	-8.2	-6.5	-7.5	-5.1	-5.3	-8.3	-7	-7.9	-7.7	-8.7	-9	-6.7	-302.4
Ihh006CID10467.pdbqt	-5.6	-4.9	-4	-5.3	-5.9	-4.1	-4.5	-4.8	-4.9	-4.1	-4.1	-3.4	-3.2	-5.9	-5.1	-4.7	-5.1	-6.2	-5.5	-4.9	-196.2
Ihh007CID5280681.pdbqt	-8.3	-8.8	-8.3	-7.6	-8.2	-8.1	-7.5	-7.7	-7.5	-6.2	-6.4	-5.3	-5.1	-8.2	-7.2	-7.8	-7.6	-8.5	-8.3	-6.6	-291.3
Ihh008CID5281654.pdbqt	-8.2	-9.2	-8.4	-8.6	-7.3	-7.4	-8	-7.4	-8.1	-6.7	-7.1	-5.3	-5.2	-8.1	-7.1	-7.6	-7.5	-8.9	-8.9	-6.7	-301.1
Ihh009CID92797.pdbqt	-6.1	-6.1	-5.2	-5.6	-5.6	-5.5	-6.6	-6.6	-6.4	-5.3	-5.1	-4.5	-4	-5.6	-5.5	-6.2	-6	-6.4	-6.2	-5.8	-228.2
Ihh010CID146515.pdbqt	-10.5	-10.5	-8.6	-7.8	-9.1	-8	-8.2	-8	-8.3	-5.4	-5.9	-5.9	-6.6	-9.1	-8.3	-6.6	-8.1	-10.7	-9.1	-7	-310
Ihh011CID222284.pdbqt	-10.3	-7.9	-6.6	-8.5	-8.8	-7.1	-7.7	-7.4	-7.7	-6.7	-7	-5.2	-5.3	-10.3	-8	-8.7	-7.8	-7.2	-10	-8.5	-311.3
Ihh012CID5321398.pdbqt	-9.7	-8.3	-8.8	-9.8	-8.1	-8.4	-8.6	-8.9	-8.5	-7.4	-7.5	-5.6	-5.6	-9.6	-7.5	-8.7	-7.8	-9.9	-9	-7.7	-321.9
Ihh013CID72326.pdbqt	-9.3	-8	-7.1	-8.7	-8.9	-7.1	-8.1	-7.8	-8.1	-7.3	-6.5	-5.4	-5.1	-10	-8.2	-7.6	-7.7	-8	-9.8	-8.2	-303.8
Ihh014CID9846221.pdbqt	-10.1	-9	-7.8	-9.4	-9.5	-7.6	-7.7	-7.7	-7.7	-8.3	-6.9	-6.4	-6.2	-9.5	-9.2	-8.6	-8.8	-8.4	-10.7	-8.8	-329.6
Ihh015CID11968944.pdbqt	-9.6	-9.4	-7.6	-9.1	-8.5	-8.1	-8.7	-8.3	-8.7	-7.5	-7.1	-5.9	-5.7	-9.7	-8.2	-9.1	-8.9	-9.2	-9.7	-8.4	-327.9
Ihh016CID5318767.pdbqt	-10.4	-8.4	-7.3	-7.9	-8.1	-8.4	-8.9	-8.7	-8.9	-7.3	-7.6	-6.3	-5.4	-9.6	-8.7	-7.9	-7.8	-8.8	-8.8	-8.5	-320.7
Ihh017CID5280805.pdbqt	-8.8	-8.8	-7.4	-7.8	-9.1	-8.6	-8.7	-9	-8.5	-7.3	-7.6	-5.4	-5.1	-9.8	-8.6	-7.7	-8.1	-9.2	-8.2	-8.3	-314.4
Ihh018CID5282155.pdbqt	-8.6	-7.9	-7.4	-7.6	-8.1	-7.2	-8	-8.3	-8	-6.5	-7.3	-5	-5	-8.2	-8.2	-7.8	-8.2	-8.2	-9.2	-7.7	-294.3
Ihh019CID6728944.pdbqt	-8.8	-8.8	-7.2	-8.1	-8.7	-8.9	-7.9	-8.5	-7.9	-6.9	-7.2	-5.5	-5.5	-8.4	-9.1	-8.5	-8	-9	-9.7	-8.1	-312
Ihh020CID46936193.pdbqt	-9.3	-8.7	-7.5	-8.4	-9.5	-7.6	-8.9	-8.8	-8.5	-6.9	-7	-5.9	-5.8	-9.8	-8.9	-8.1	-9.3	-10.7	-9.6	-8.8	-321.3
Ihh021CID17751019.pdbqt	-10.5	-8.6	-7.3	-7.3	-8.4	-7.9	-8.5	-8.5	-8.5	-7.5	-7.3	-5.3	-5.2	-8.9	-8	-8.2	-8.4	-8.2	-8.6	-8.5	-310.7
Ihh022CID102004842.pdbqt	-8.8	-8.9	-7.4	-8.6	-8.9	-8.4	-8.8	-8.9	-8.8	-6.9	-6.7	-5.5	-5.3	-9	-7.8	-7.6	-7.7	-9.1	-10.2	-8.5	-311.9
Ihh023CID14103656.pdbqt	-8.4	-10	-7.7	-8	-9.5	-8.9	-8.2	-8.7	-8.2	-7.7	-7.8	-6.4	-5.8	-9.9	-9.3	-8.8	-8.5	-8.4	-10.1	-8.6	-324.8
Ihh024CID102120183.pdbqt	-10.2	-10	-7.8	-9.3	-9.4	-9.1	-8.7	-8.6	-8.7	-8.2	-7.6	-6.5	-6.2	-11.1	-9.8	-8.4	-8.6	-9	-10.9	-8.5	-337
Ihh025CID13326387.pdbqt	-8.6	-9.8	-7.4	-8.8	-8.9	-8.5	-8.1	-8.5	-8.4	-7.4	-7.4	-6.1	-5.3	-9.6	-9.4	-8.2	-8	-9.2	-10.3	-8.9	-320.7
Ihh026CID21607811.pdbqt	-8.8	-10	-7.5	-8.9	-9.2	-8.5	-8.5	-8.1	-8.5	-7.7	-7.3	-6.2	-5.6	-9.5	-9.4	-8	-8.1	-7.8	-10.3	-8.8	-319.5
Ihh027CID188384.pdbqt	-8.8	-8.7	-7.6	-7.8	-9.3	-7.9	-8.1	-7.8	-8.1	-7.9	-7.9	-5.9	-5.6	-11	-8.9	-9.3	-9.5	-8.5	-9.9	-9.4	-323.3
Ihh028CID101538997.pdbqt	-8.5	-9.7	-8.4	-8.2	-9.3	-8.4	-9.3	-8.6	-8.9	-7.7	-8.3	-6	-6	-11.5	-10	-8.8	-8.4	-9.8	-11.1	-9.7	-342.2
Ihh029CID122097.pdbqt	-8.1	-8.2	-7.4	-7.6	-8.3	-8.2	-8.9	-8.7	-8.9	-7.5	-7.8	-5.6	-5.4	-10.9	-9.3	-8.6	-8.4	-8.8	-10.5	-9.7	-325
Grand Total	**-654.4**	**-637.7**	**-562.1**	**-595.1**	**-610.5**	**-568.7**	**-601.7**	**-605.1**	**-599.6**	**-494.9**	**-511.5**	**-401.4**	**-395.9**	**-642.4**	**-582.6**	**-586.3**	**-592.4**	**-650.5**	**-659.8**	**-587.1**	**-22447.2**

順天堂藥廠股份有限公司
SUN TEN PHARMACEUTICAL CO., LTD.
地址： 台北市 100 羅斯福路二段 11 號 3 樓
3F, No. 11 Roosevelt Rd., Sec. 2, Taipei 100, Taiwan ROC
TEL: 886-2-2395-7070 FAX: 886-2-2321-1926
http://www.sunten.com.tw

Certificate of Analysis

Chinese Product Name(中文品名) : 減肥方
English/Pharmaceutical Name(英文名/學名) : Herbal Formulation for Obesity Trial
Batch No. (批號) : 091906
Dosage Form(劑型) : Capsule

Items	Test Results
1. General Description 性狀	#0 Capsules with brown caps and milky white bodies with Sun Ten logo and filled with brown granules.
2. Loss on Drying 乾燥減重	4.65 %
3. Water Extractive 水抽提物含量	50.39 %
4. Dilute-Alcohol Extractive 稀醇抽提物含量	53.54 %
5. Total Ash 總灰分含量	8.15 %
6. Acid-Insoluble Ash 酸不溶性灰分含量	0.43 %
7. Assay 含量測定 Chrysophanol EC(Epicatechin) Caffeine EGCg(Epigallocatechin gallate) Ecg(Epicatechin gallate) Rutin	 0.0317 mg/g 10.89 mg/g 31.24 mg/g 52.34 mg/g 13.63 mg/g 62.09 mg/g
8. Identification 鑑別 Semen Cassiae 決明子 Flos Sophorae 槐花	 Positive（dark absorptive at Rf =0.20,0.30,0.42.） 陽性（Rf 值於 0.20，0.30，0.42 處有暗色吸收斑點） Positive（dark absorptive at Rf =0.44.） 陽性（Rf 值於 0.44 處有暗色吸收斑點）
9. Weight Variation 重量差異	481~517 mg/cap
10. Average Weight 平均重量	499 mg/cap

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Chinese Product Name(中文品名) : 減肥方
English/Pharmaceutical Name(英文名/學名) : Herbal Formulation for Obesity Trial
Batch No. (批號) : 091906
Dosage Form(劑型) : Capsule

Items	**Specifications**
11. Disintegration 崩散度	15 minutes.
12. Total Heavy Metals 總重金屬檢驗	Less than 50ppm
13. Microbial Tests: 微生物檢驗	
E. Coli 大腸桿菌	Nil
Salmonella 沙門氏菌	Nil
Enterobacteria 腸內菌	< 10CFU/g
Total Aerobic Microbial Count 總生菌數	300CFU/g
Yeast and Mould 酵母菌及黴菌總數	20CFU/g

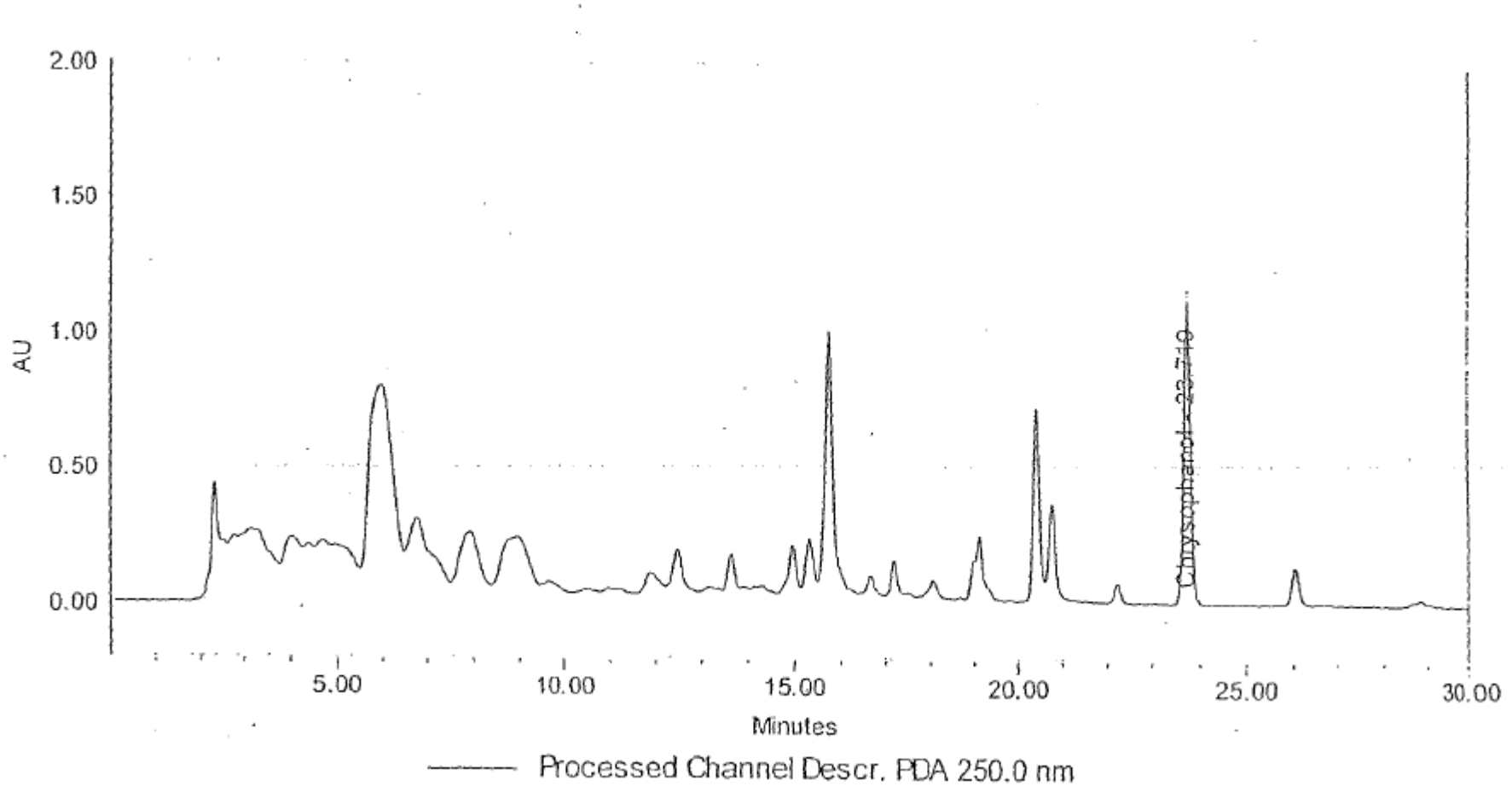
Authorized by: _____ **Date:** _____

SU, Kuei Chin
Chief of QC

Product : 決明子飲片 (Jue Ming Zi raw herb)

Lot No. : A417N

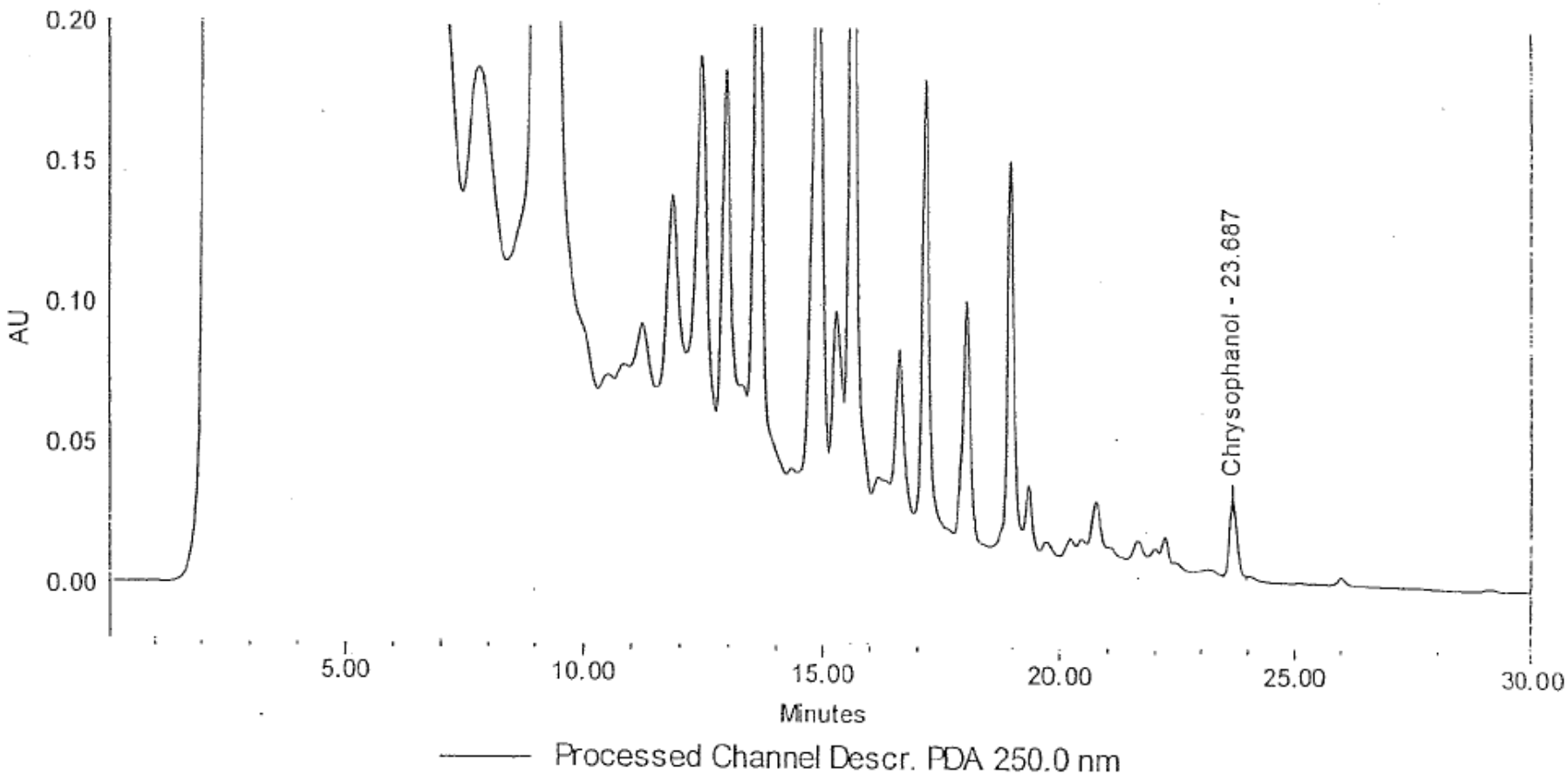
Date Acquired : 2007/6/11, 15:37:35



Product : 外貿 Xue XP 粉 (Extract)

Lot No. : RY7023008-Jue Ming Zi

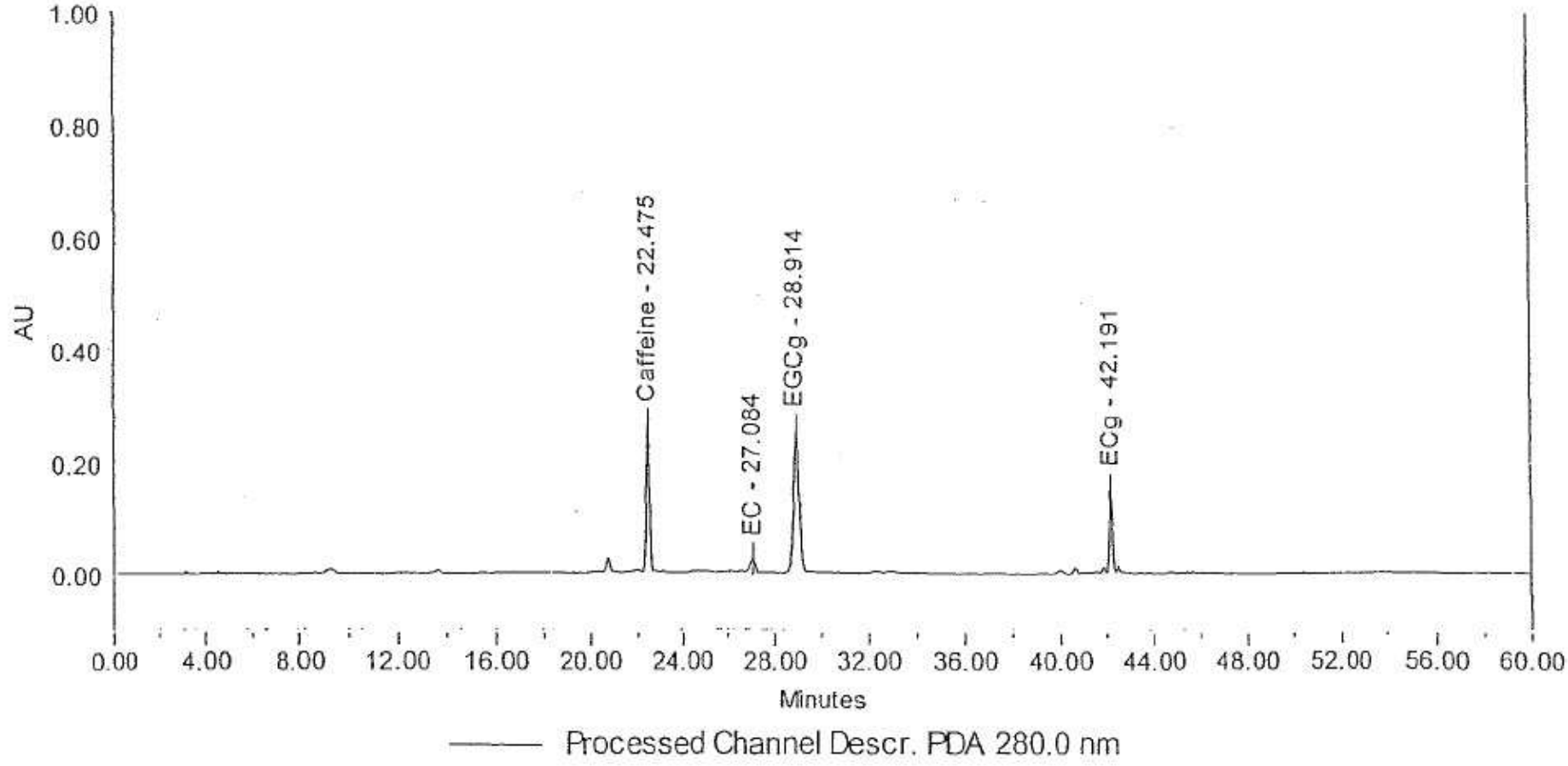
Date Acquired : 2007/6/11, 16:18:47



Product : 綠茶飲片 (Green Tea raw herb)

Lot No. : Z918N

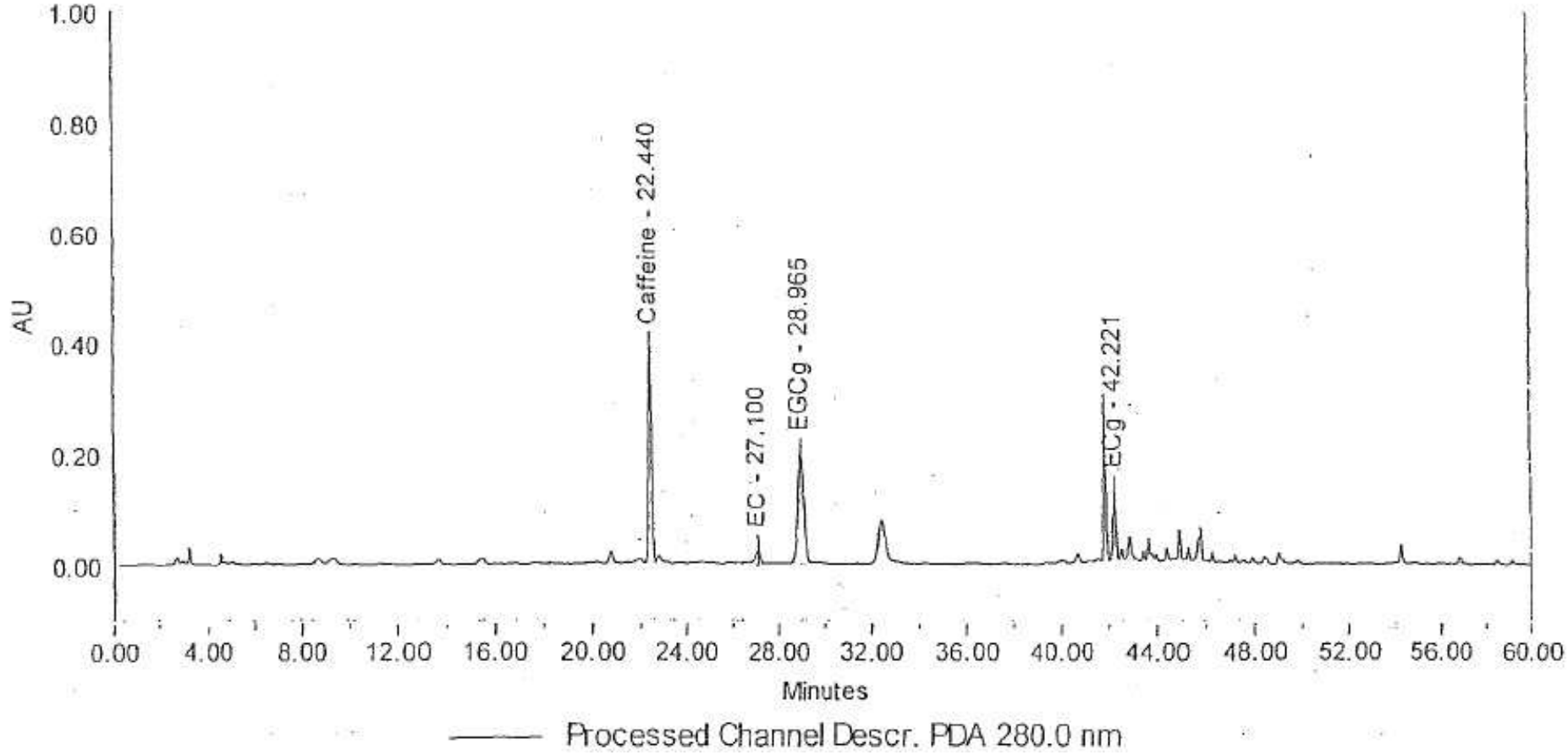
Date Acquired : 2007/5/22, 01:14:16



Product : 外貿 Xue XP 粉 (Extract)

Lot No. : RY7023008-Green Tea

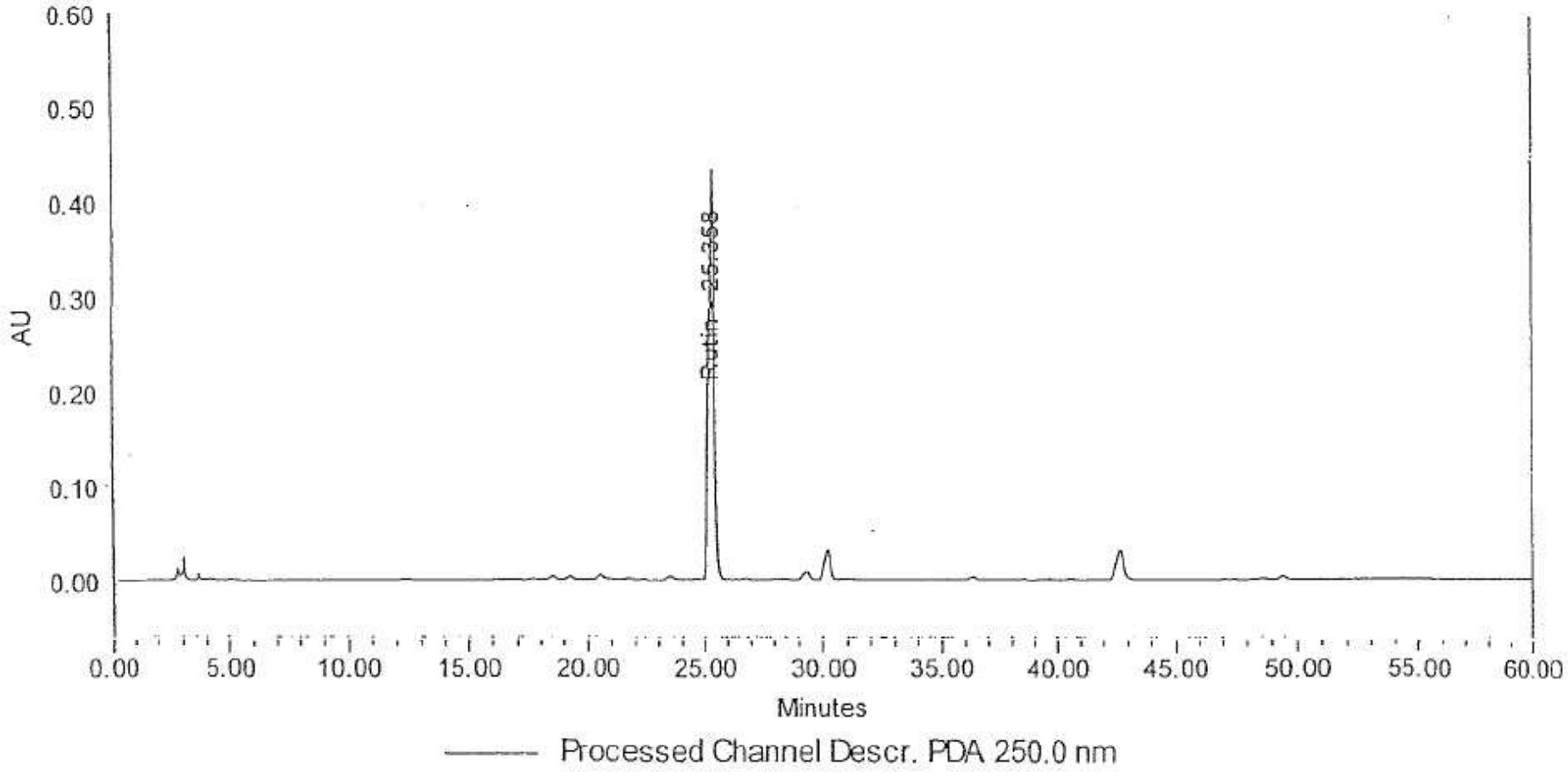
Date Acquired : 2007/5/21,16:22:08



Product : 槐花飲片 (Huai Hua raw herb)

Lot No. : R960515

Date Acquired : 2007/5/24, 22:23:09



Product : 外貿 Xue XP 粉 (Extract)

Lot No. : RY7023008-Huai Hua

Date Acquired : 2007/5/21,16:59:21