The Use of Traditional Chinese Medicine Herbs and Formulas in the Treatment of Hyperlipidemia, and their effect on Blood Glucose Levels and Liver Function: A Qualitative Research Synthesis.

By

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A capstone project

Presented in partial fulfillment of the requirements for the

Doctor of Acupuncture and Oriental Medicine Degree

Yo San University

Los Angeles, California

April 2016

Approval Signature Page

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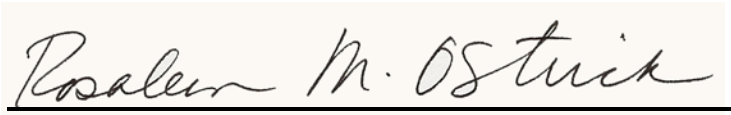

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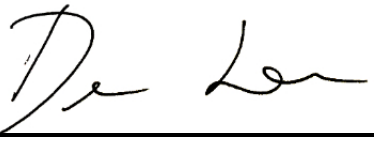

Jan 31, 2016

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Abstract

Hyperlipidemia is a metabolic disease characterized by elevated blood lipid levels. It has been linked to an increased risk for cardiovascular diseases like stroke and heart attack, and is often associated with other chronic conditions like type 2 diabetes, insulin resistance, and obesity. The current standard of care, statin drugs, have a poor patient compliance rate, often due to statin side effects that include liver damage as well as new onset type 2 diabetes. Chinese herbal medicine is commonly used in Eastern countries to treat hyperlipidemia as well as diabetes and liver diseases. This study aims to identify whether frequently prescribed formulas and herbs for hyperlipidemia can effectively lower lipid levels while also regulating blood glucose levels and promote healthy liver function. **Methods:** UCLA Biomedical Library databases and PubMed were searched for current prescription trends for antihyperlipidemic herbs and formulas to identify the most commonly used herbs for this disease. The most commonly prescribed formula and five of the most commonly prescribed herbs were cross-referenced for hepatoprotective and antidiabetic properties, as well as side effects and documented herb-drug interactions. **Results:** Research showed that many of the herbs prescribed for hyperlipidemia also have positive effects on blood glucose levels, insulin resistance, and liver health. Documentation of side effects and herb-drug interactions are still few, and issues arose due to the lack of standardization of plant compounds and combinations of plant compounds studied, quality control, and methods of extraction. Further studies with these limitations in mind are needed to evaluate the efficacy of herbal formulas for the treatment of hyperlipidemia and its associated comorbidities.

Acknowledgments

I would like to thank my advisor, Rosaleen Ostrick, for her willingness to jump on board at the last minute, and all her hard work and patience. She worked with me through all the challenges and last-minute deadlines, which I know included several late nights of editing and improving my work, and who supported and encouraged me to the bittersweet end.

I also would like to thank my advisor, Dr. Daniel Weber for finding the time in his busy schedule to review my lengthy drafts on short-term notice, and for providing me with valuable feedback and key ideas in terms of East-West integration that helped me refine this paper. Both instilled in me a new love for pursuing research that will be able to incorporate Chinese medicine principles into clinical western research parameters that will hopefully help advance TCM in the medical field.

I would also like to express my gratitude to Dr. Andrea Murchison, who played an integral part in helping me get through this program, and who managed to encourage me through injury and sickness. To my best friends, Veronica Rogers, Meg Cranston, and Charmaine Johansen, who kept me motivated and helped me through the dark and uninspired times. To the many amazing teachers who ignited my passion for this medicine, David Cohen, Jiling Hu, Huabing Wen, Ed Shaheen, Paul DesRosier, and Yuhong Chen. And of course a big thank you to my parents, without whom this entire journey wouldn't have been possible.

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Chapter 1: Introduction

Background

Hyperlipidemia is a metabolic syndrome which presents with elevated levels of one or more lipids or lipoproteins in the blood (Mahamuni, Khose, Menaa, & Badole, 2012). High levels of these lipids, especially elevations of low-density lipoproteins (LDL), which are high in cholesterol, have been linked with an increased risk of cardiovascular disease (CD). According to Kalant, Grant, and Mitchell (2007), more than 60% of men who presented with coronary artery disease were also diagnosed with hyperlipidemia. High lipid levels are a contributing factor to atherosclerosis and increase your risk of heart disease, stroke, and other CD. Diabetes, insulin resistance, as well as obesity are conditions often associated with hyperlipidemia and hypercholesterolemia (Sham et. al, 2014).

Hyperlipidemia and hypercholesterolemia are a common problem in the United States (Pejic & Lee, 2006). According to the Center for Disease Control and Prevention (CDC), 73.5 million adults have elevated low-density lipoprotein (LDL) levels. Of those with high LDL levels, less than one in three adults have their elevated levels controlled, and less than half are receiving medical treatment for their condition (CDC, 2015). The American Heart Association (AHA), in its 2015 Statistical Update for Hearth Disease and Stroke Statistic, states that more than 100 million American adults over the age of 20 have total cholesterol levels that are greater than 200 mg/dL, and almost 31 million have levels above 240 mg/dL (AHA, 2015). Lipid abnormalities can either be primary or secondary. The primary form of hyperlipidemia is inherited, while the secondary form is a result of dietary choices, excessive alcohol intake, certain drugs, or diseases like diabetes or hypothyroidism (Sham et al. 2014). Obesity was associated with hyperlipidemia in children (Lai et al., 2001).

Cholesterol is a waxy, fatty substance that functions as a precursor to steroid hormones and bile salts, and it also plays a vital role in cell membrane construction (Boon, Colledge, Walker 2006). Since it is insoluble in the aqueous plasma, it is converted into lipoproteins which consist of a center containing cholesterol and triglycerides, and an outer structure of various proteins and phospholipids, which is more water soluble. LDL particles are responsible for transporting cholesterol to the appropriate tissues (Boon et al. 2006), and c,ells take up cholesterol through LDL receptors on their surface. This is called the receptor-dependent pathway. The reverse cholesterol pathway uses HDL particles to bind to the LDL particles to transport them back to the liver, hence removing them from circulation. The remaining circulating LDL is prone to oxidization (Kalant, Grant, Mitchell, 2007), and once oxidized, cannot be eliminated via normal pathways. Instead, macrophages take up oxidized LDL particles to form foam cells in the intima of the vessels, which contributes to the atherosclerotic process (Boon et al., 2006).

Hypercholesterolemia is diagnosed by testing for total cholesterol levels, LDL levels, HDL levels, and triglyceride levels. According to the National Institute for Health, recommended lipid levels in patients without comorbidities like existing CD or diabetes are (2001):

Total Cholesterol:	< 200 mg/dL
LDL levels:	< 100 mg/dL
HDL levels:	> 60 mg/dL
Triglycerides:	< 150 mg/dL

Dietary and lifestyle modifications are usually the first recommended course of treatment, and if these modifications do not bring about the necessary changes in LDL concentrations, drug therapy is the second line of treatment (Kalant et al., 2007). Statin drugs are the most-prescribed

group of cholesterol-lowering drugs. According to an NCHS Data Brief (2014), 93% of all adults that have been prescribed a cholesterol-lowering medication were using statin drugs, and the overall rate of statin use increased from 18% to 26%. The latest recommendations by the AHA, which were published in 2013, have veered away from fixed LDL target levels for everyone, and recommend statin therapy for four groups of people: patients who have clinical evidence of atherosclerosis and cardiovascular disease, patients whose primary LDL levels are above 190 mg/dL, diabetics between the ages of 40 – 75 with LDL levels of 70 – 189 mg/dL, and 40 – 75 year olds with LDL levels of 70 – 189 mg/dL who have a 10-year-risk of CVD of > 7.5% (Stone et al., 2013). Under these new guidelines, an additional 13 million American adults would be eligible for statin therapy (Pencina et al. 2014).

According to a consumer brief by the FDA (2014), side effects of statins include cognitive impairments like confusion and memory loss, potential for muscle damage, liver damage, and new onset type 2 diabetes. Since hepatic complications are rare, regular liver function tests are not recommended anymore. However, the FDA advised patients to be on the lookout for symptoms of impaired hepatic function like loss of appetite, right upper quadrant discomfort, and yellowing of skin or dark urine, and to contact their doctor immediately if any of these should occur (FDA, 2014).

Cederberg et al. (2015) concluded in their study "statin treatment increased the risk of type 2 diabetes by 46%, attributable to decreases in insulin sensitivity and insulin secretion." These findings were dose dependent for simvastatin and atorvastatin (Cederberg et al., 2015). Thorsten, Hendrik, Andersen, Rossing and Jensen (2015) looked at the relationship between statin use and increase in Hemoglobin A1c (HbA1c) in patients with type 1 diabetes, and found that "statin use was independently and significantly associated with higher HbA1c levels. They

caution that while no causal relationship can be established from the study, patients with type 1 diabetes may "need to revisit dose of insulin when starting statin treatment." Okuyama et al. (2015) argue that statins may actually stimulate atherosclerosis and heart failure due to the fact that statins inhibit the synthesis of vitamin K2, which protects the arteries from calcifications and hardening, and through its inhibition of CoQ10, which impairs ATP generation and may have negative effects on cardiovascular function.

Patient compliance is another issue with statins. Toth (2010) pointed out that almost half of all patients discontinued their statin drugs within a year. According to Maningat, Gordon, and Breslow (2013), this number is compounded by the fact that "adherence decreases with time." They also listed adverse reactions as the most common reason patients discontinued their statin therapy.

There are also questions regarding the efficacy of statins, especially in a primary prevention model. In a letter to the editor, Redberg and Katz (2012) pointed out that a Cochrane analysis concluded that statins should be prescribed to patients of low cardiovascular risk only with caution. This was based on the fact that authors of this study, while finding "a small reduction in all-cause mortality associated with statin use", also observed "evidence of selective reporting of outcomes, failure to report adverse events, and inclusion of patients with cardiovascular disease (Redberg and Katz, 2012)."

Mosca (2012), in her editorial comment in the Journal of the American College of Cardiology, pointed out several shortcomings of current studies on statin efficacy. She claims that of the studies included in a meta-analysis by Kostis et al., almost all of the studies were funded by pharmaceutical companies. She also argues that the JUPITER trial had a follow-up period that was too short to be applied to primary prevention models, and that due to the

increased risk of type 2 diabetes, safety for long-term preventative statin treatments still needs to be established (Mosca, 2012). McCormack, Vandermeer, and Allen (2013) explain that many studies use the relative risk reduction model rather than the absolute risk reduction model. Based on their analysis, statin drugs "seem to have roughly a 1 in 200 effect on overall mortality in primary prevention."

Traditional Chinese Medicine and Hyperlipidemia

Traditional Chinese medicine (TCM) and its herbal products are commonly used in Eastern countries to treat hyperlipidemia (Chu, Shih, Yang, Chen, & Chu, 2015). Sham et al. (2014) state that TCM has gained popularity and public recognition for the treatment of hyperlipidemia due to its low costs, effectiveness, and low occurrence of side. While hyperlipidemia in itself is not a diagnosis according to TCM, and being a relatively recent biomedically-defined condition or risk factor for other disease, O'Brien (2010) states that various authors have, in general reported that three to eight syndrome differentiations according to Zang-Fu Theory could be applied to patients diagnosed with hypercholesterolemia. O'Brien and colleagues (2009) found up to 15 different TCM syndromes (patterns of disharmony) in hypercholesterolemic Australians who were otherwise healthy (O'Brien et al., 2009). Bob Flaws describes a total of eight different patterns found in people diagnosed with hypercholesterolemia, along with eight different formulas to treat these patterns (2001). According to Xie et al. (2012), *Phlegm and Blood Stasis* are two predominant patterns seen in patients diagnosed with hyperlipidemia. The concept of these patterns and pathogens will be further explored and explained in Chapter Two.

TCM and Chinese herbs have also been widely used in the treatment of type 2 diabetes (Dharmananda, 2002), which indicates that some Chinese herbs are effective in regulating blood

glucose levels.

In China, patients are often treated with a combination therapy of pharmaceutical drugs and herbal medicines. One study by Zhu et al. (2015) looked at the effect of combining fenofibrate (FF), a chemical drug used in the treatment of hyperlipidemia, with an aqueous extract of Wu Wei Zi (*Schisandrae Fructus*), and found that this combination reduced the amount of liver injury caused by FF in mice fed with a high-cholesterol diet.

Objectives of the Study

The objective of this study is to see if Chinese herbs and formulas that are frequently prescribed in Taiwan and China for treatment of hyperlipidemia are effective at lowering cholesterol and LDL levels, and also have positive effects on blood glucose levels, insulin resistance, and liver function. It is hypothesized that Chinese herbs and herbal formulas offer a viable treatment option for hypercholesterolemia while also preventing some of the more severe side effects seen with statins drug treatments, particularly new onset type 2 diabetes and liver damage. This study will look at the most prescribed formula for hypercholesterolemia in Taiwan and five frequently prescribed individual herbs for hypercholesterolemia, and then examine their effects on lipid levels, blood glucose levels, insulin resistance, and liver health, as well as possible interactions with pharmaceuticals and reported side effects.

Definition of Terms:

Adverse Reactions: A term to describe any unwanted or dangerous effect that can include feelings of discomfort as well as forms of toxicity that are associated with a drug (Tarloff, 2012).

Alanine Transaminase (ALT): A liver enzyme which is present in abnormally high levels in the blood in the presence of liver disease (Merriam-Webster, 2016).

Aspartate Aminotransferase (AST): A liver enzyme which is present in abnormally high levels in the blood in the presence of liver disease or liver damage (Medline Plus, 2015).

***Blood Stasis*:** In TCM, *Blood Stasis* is a lack of proper blood flow and circulation, resulting in conditions presented by sharp pain. It is associated with Western medical conditions like angina and myocardial infarction. There is also an association with *Blood Stasis* and *Phlegm*, since *Phlegm*, if blocking arteries, can cause blood to stagnate (Maciocia, 1989; O'Brien, 2010).

Cardiovascular Disease (CD): Heart disease and cardiovascular disease are often used interchangeably. However, CD generally describes a condition in which blood vessels are blocked, hardened, or narrowed, which in turn can lead to heart attacks (Mayo Clinic, 2014).

Chinese medicinal herbs: One of the many facets of Traditional Chinese Medicine (TCM) which uses more than 450 substances, mostly plants, but also animal and mineral substances that are prescribed either singly, or as an ingredient in a multi-substance formulation (AACMA, 2016).

Chinese Medicine (CM): A system of health care originating from China and other parts of East Asia that includes a variety of modalities, including acupuncture, herbs, massage, exercise, qi gong, and dietary as well as lifestyle modifications (AACMA, 2016).

Cholesterol: A waxy, fatty substance which functions as a precursor to bile salts and steroid hormones, and a necessary element cell wall integrity (NIH/Medline Plus, 2016).

***Dampness*:** In TCM, *Dampness* is a pathogen which is either internally produced by a weakened digestion, or which is contracted by being exposed to damp environments. It usually presents

with feelings of heaviness, dizziness, excessive discharges (nasal, vaginal, etc.), edema, and other fluid accumulations (Maciocia, 1989).

Diabetes: A metabolic disorder characterized by elevated blood glucose levels, insulin resistance and/or lack of insulin production, and most commonly due to either autoimmune disorders (type 1 diabetes), or due to other factors, which often include heredity, overeating, and under-exercising (type 2 diabetes) (Shier, Butler & Lewis, 2004).

Dyslipidemia/Hyperlipidemia: A condition characterized by elevation of one or more plasma lipids, like cholesterol, triglycerides, or LDL that contributes to the development of atherosclerotic plaques (Goldberg, 2015).

Foam Cells: Foam cells are a hallmark sign of atherosclerosis, and are an accumulation of macrophages that are loaded with oxidized LDL (Valledor, Lioberas & Celada, 2015).

HDL: high density lipoprotein which is mostly comprised of proteins and is responsible for transporting LDL and cholesterol back to the liver; also called the "good" cholesterol (Boon, Colledge, Walker, 2006).

Hemoglobin A1C (HbA1c): An indicator for blood sugar control. The HbA1c test measures the amount of hemoglobin that is glycated, and a high level of HbA1c is indicative of poor blood glucose control (Mayo Clinic, 2016).

Hepatoprotective: Hepatoprotective compounds are able to diminish damage done to the liver and liver cells by toxic agents (Shamsi-Baghbanan H, Sharifian A, Esmaeili S, 2014).

High Blood Glucose/Hyperglycemia: Elevated levels of sugar or glucose in the blood due to the body's inability to produce adequate amounts of insulin, excess intake of sugars, or inability of cells to take up glucose due to insulin resistance (NIH/MedlinePlus, 2016).

HMG-CoA reductase: a rate-controlling enzyme involved in cholesterol synthesis in the liver (Boon, Colledge, & Walker, 2006).

Hypercholesterolemia: An increase in plasma cholesterol levels only (Goldberg, 2015).

Insulin: A hormone that assists in transporting blood glucose from the blood circulation into cell through insulin receptors for the cells to use as fuel (Shier, Butler, & Lewis, 2004).

Insulin Resistance (IR): One of the features of diabetes type 2, in which cells cannot take up glucose, and glucose metabolism as well as storage are impaired (Kumar et al., 2007).

***Kidney*:** In TCM, the *Kidney* organ system plays a vital role in fluid metabolism as well as reproductive function, and a weakness of this system can lead to fluid accumulations like edema (Maciocia, 1989; O'Brien, 2010).

LDL: Low density lipoprotein which is mostly comprised of cholesterol and some triglycerides and which is responsible for transporting cholesterol to the target tissues; also called the "bad" cholesterol (Boon, Colledge, Walker, 2006).

Lipids: Non-polar molecules that are insoluble in water, but soluble in non-polar environments like alcohol and chloroform, like fats and waxes. Cholesterol is one example of a lipid (Boon, Colledge, Walker, 2006).

Lipoproteins: A small particle consisting of proteins and fat that carry lipids like cholesterol and other hydrophobic substances through the blood (Weinrauch, 2014).

***Liver*:** In TCM, the term *Liver* corresponds to the functioning of an entire organ system, and not the anatomical organ. The functions of this system are to promote circulation in the body and regulating blood volume. Lack of said regulatory functions can lead to pain and menstrual disorders, and can also contribute to the *stagnation of fluids* which in turn contribute to

Dampness and *Phlegm* accumulations. Physical movement will support the *Liver* system's circulatory function (Maciocia, 1989; O'Brien, 2010).

Liver Enzymes: A group of enzymes found in the liver which are released into the blood when liver injury occurs, and can be measured via blood test to assess liver health. Alanine transaminase (ALT) and aspartate aminotransferase (AST) are two examples (Martin Laura, 2015).

***Phlegm*:** In TCM, *Phlegm* is attributed to impaired digestion, and hence a result of metabolic disorders of the body's fluids. It is also seen as a progression of *Dampness*, a further condensation of *untransformed fluids*. There is *substantial* and *insubstantial* phlegm. *Substantial phlegm* is *phlegm* that can be seen, like yellow nasal discharge. *Insubstantial phlegm* is an internal pathogen which can result in blocked blood vessels and blood circulation, and is often associated with serious diseases like like cancer, heart disease, stroke, and atherosclerosis (Kong et al., 2014; Maciocia, 1989).

***Spleen*:** In TCM, the *Spleen* relates to the organ system that governs digestion and the *transformation of food and fluids* into nutrition the body can use, similar to the function of the whole epigastria, including stomach, duodenum, liver, gallbladder, and pancreas in Western medicine. If the *Spleen* is not transforming correctly, fluids accumulate and result in *Dampness and Phlegm* (Maciocia, 1989; O'Brien).

Statin: The most commonly prescribed pharmaceutical drug for the treatment of hyperlipidemia, which is an HMG-CoA reductase inhibitor and through this action blocks the synthesis of cholesterol in the liver (Kalant, Grant, Mitchell, 2007).

TCM Pattern: TCM pattern differentiation identifies specific disease expression mainly based on a set of presenting symptoms in individual patients so as to correctly guide treatments (Lu C, Zha Q, Chang A et al., 2009; O'Brien, 2010).

Total Cholesterol (TC): The total amount of cholesterol, calculated by adding LDL plus HDL plus 20% of the triglyceride levels (American Heart Association, 2012).

Traditional Chinese Medicine (TCM): A system of health care originating from China and other parts of East Asia that includes a variety of modalities, including acupuncture, herbs, massage, exercise, qi gong, and dietary as well as lifestyle modifications (AACMA, 2016).

Yin/Yang Theory: Yin and Yang theory is the basis of TCM theory, and describes two opposing forces. While the concept of Yin refers mostly to qualities like cold, dark, rest, and matter, the concept of Yang refers mostly to qualities like heat, light, activity, and energy. The harmonious balance between these two opposites is what constitutes good health (Maciocia, 1989; O'Brien, 2010).

For the purpose of this paper, TCM organ systems and pattern diagnoses are in italics to differentiate them from the Western definitions of these terms.

Chapter 2: Literature Review

Overview

This chapter will begin with an introduction to how hyperlipidemia is defined and diagnosed in traditional Chinese medicine (TCM), and will then examine current prescription trends for hyperlipidemic formulas and herbs. The rest of this section will focus on the most-prescribed formula for hyperlipidemia in Taiwan, as well as five of the most commonly prescribed single herbs in Taiwan and China. Each section will discuss the herbs and formulas used, their TCM indications and functions based on Chen and Chen (2004, 2009) as well as potential actions for lowering blood lipid levels, regulating blood glucose level and insulin resistance, and their effects on liver health. Potential side effects of the herbs and potential interactions with western medications will also be discussed. The chapter will end with a literature integration section that will sum up the reviewed literature and establish the need for a prospective randomized clinical trial to establish the efficacy of TCM hyperlipidemic formulas in lipid reduction, and antidiabetic as well as hepatoprotective functions in a human cohort.

Hyperlipidemia and TCM

Hyperlipidemia is a fairly recent, biomedical diagnosis for a condition that often has no symptoms; it is a risk factor for other medical conditions. There is not the historical precedence of treatment over hundreds of years as has been the case with other diseases or conditions (O'Brien, 2010). Flaws (2001) explains that based on the symptoms presented by patients diagnosed with hyperlipidemia, patients can fit into many different disease patterns, which all depend on the symptoms and signs with which the patient presents. Obesity, one symptom a patient with high cholesterol could present with, would be diagnosed as *fei pang* (*fatty fatness*),

and a patient presenting with heart disease and chest pain would be diagnosed with *Xiong bi* (*chest impediment*) (Flaws, 2001). Since there are no historical records of the treatment of hyperlipidemia with Chinese medicine (CM), clinical definitions of etiology as well as pathogenesis are recent developments. According to O'Brien (2010), the literature reports that patients diagnosed with hyperlipidemia typically fit into three to eight different TCM syndromes. However, a study in hypercholesterolemic Australians who were otherwise 'healthy' found over 15 different TCM syndromes (O'Brien et al., 2009). This prompted the researchers to question the applicability of syndrome differentiation to hypercholesterolemia as the syndromes may have simply reflected the range of syndromes present at the time or their constitutional pattern (O'Brien, 2010; O'Brien et al., 2009). *Spleen*, *Liver*, and *Kidney* are mentioned as the main organ networks involved in the pathology, while the *Heart* is associated because of its circulatory function. Pathogenesis is mostly attributed to *Dampness*, *Phlegm*, and *Blood Stasis* (O'Brien, 2010), and treatment to lower blood lipid levels "must focus on *dissolving Damp*, *eliminating Phlegm*, and *invigorating blood circulation*" (Lotus Institute, 1998).

Considering that hyperlipidemia is associated with Cardiovascular disease (CD) (Kalant et al., 2007), and is often attributable to poor dietary (high fat and sugar diets) and lifestyle choices (lack of exercise) (Sham et al., 2014), it is possible to see a correlation between the TCM patterns, which include inadequate digestion (*Spleen*), lack of blood circulation due to inactivity (*Liver*), as well as the build-up of foam cells (*Phlegm*) which impair free flow of blood.

In *The Treatment of Modern Western Diseases with Chinese Medicine*, Flaws (2001) identifies eight different patterns for patients diagnosed with hyperlipidemia. All these patterns are diagnosed based on their presenting symptoms, along with a biomedical diagnosis of

hyperlipidemia, and they describe similar mechanisms observed by O'Brien (2010) about common TCM pathologies and organ systems involved.

Chinese Herbal Prescription Trends for Hyperlipidemia

In Taiwan, Xue Fu Zhu Yu Tang has emerged as the most commonly prescribed formula for the treatment of hyperlipidemia, with Jia Wei Xiao Yao San being the second most-prescribed formula (Chu et al., 2015). Among the single herbs, Shan Zha-(*Crataegi Fructus*), was the most prescribed single herb, and Dan Shen (*Salviae Miltiorrhizae Radix)* and Shan Zha (*Crataegi Fructus*) were the most prescribed pair of herbs. In terms of single herb and formula combination, Xue Fu Zhu Yu Tang modified with Dan Shen (*Salviae Miltiorrhizae Radix)* took the first place (Chu et al., 2015). A complete list of the most-prescribed herbal formulas and single herbs is shown in
Table 1.

Xie, Zhao, and Du (2012) looked at TCM formulas that have been approved in mainland China for treatment of hyperlipidemia by the Chinese State Food and Drug Administration (CSFDA), and extracted the 29 most frequently prescribed herbs out of these formulas. While XFZYT was not one of the formulas approved by the CSFDA, four of the components of XFZYT were on the list of most-prescribed herbs extracted from these formulas; Chuan Xiong (*Rhizoma Chuanxiong),* Hong Hua (*Flos* Carthami), Chai Hu (*Radix* Bupleuri), and Gan Cao (*Radix Glycyrrhizae*). A list of the 13 most-prescribed herbs from this study is shown in Table 2. They also looked at which categories these herbs can be group into, and found three basic approaches: herbs that promoted digestion and excretions, like Shan Zha (*Fructus Craetegi)* and Ze Xie (*Rhizoma Alismatis)*; herbs with strong influence on the cardiovascular system, like Dan

Shen (*Salvia Miltiorrhize)* and Chuan Xiong (*Rhizoma Chuanxiong)*; and nourishing and tonifying herbs, like Ren Shen (*Radix Ginseng)* and Huang Qi (*Radix Astragalus)* (Xie, Zhao, Du 2012). These categories overlap with some of the mechanisms identified by Western medicine in regards to hyperlipidemia, namely absorption of lipids through digestion, and impaired cardiac function.

Sham et al. (2014) reviewed nine single herbs for their hyperlipidemic actions, which included Ze Xie (*Rhizoma Alismatis),* Huang Lian (*Rhizome Coptidis),* Shan Zha (*Fructus Craetegi),* Ren Shen (*Radix Ginseng),* San Qi (*Radix Notoginseng),* Hong Qu (*Red Yeast Rice),* Ge Gen (*Radix Puerariae),* Da Huang (*Radix and Rhizoma Rhei),* and Dan Shen (*Radix Salvia Miltiorrhizae).* They also looked at TCM formulas which have shown to have effects on blood lipid levels. These included Dang Gui Bu Xue decoction, Dan Shen Ge Gen formula, Er Xian decoction, Ling Gui Zhu Gan decoction, Sheng Mai Yin, Turtle Jelly, and Xue Fu Zhu Yu decoction.

Since there are no studies examining current trends in herbal prescriptions for hyperlipidemia in the United States, one clinical manual textbook that was published in the United States was included in the herb selection process for this study. *The Clinical Manual of Oriental Medicine: An Integrative Approach* (2006) by the Lotus Institute of Integrative Medicine includes contemporary formulations by Dr. John Chen, who holds doctorate degrees in pharmacology as well as TCM. Dr. John Chen is considered an expert in the field of TCM, and is currently an herbal consultant for the California State Oriental Medical Association, and is on the review and editorial committees for American Herbal Pharmacopoeia, the University of Arizona Integrative Medicine Program, and the American Academy of Medical Acupuncture (TCM Kongress, 2016). While the Lotus Institute clinical reference is widely used as a clinical

reference due to the in-depth information on research and pharmacological actions of the formulas listed, it has to be mentioned that they also sell these formulas through Evergreen Herbs.

*The Clinical Manual of Oriental Medicine: An Integrative Approach (*2006*)* lists two formulas for the treatment of hyperlipidemia: Cholisma, and Cholisma ES. Both are formulas designed by Chen incorporating classical TCM principles as well as modern research on pharmacological actions (Lotus Institute, 2006, p.293-304). Cholisma contains Cang Zhu (*Rhizoma Atractylodis)*, Dan Shen (*Radix Salviae Miltiorrhizae)*, Ge Gen (*Radix Puerariae)*, He Shou Wu (*Radix Polygoni Multiflori)*, He Ye (*Folium Nelumbinis)*, Hu Zhang (*Rhizoma Ploygoni Cuspidati)*, Jiao Gu Lan (*Rhizoma seu Herba Gynostemmatis)*, Ju Hua (*Flos Chrysanthemi)*, Jue Ming Zi (*Semen Cassiae)*, Shan Zha (*Fructus Crataegi)*, Yi Yi Ren (*Semen Coicis)*, Ze Xie (*Rhizoma Alismatis)*, and Zi Mu Xu (*Herba Medicago Sativa)*, and is aimed at treating high cholesterol and triglyceride levels as well as hypertension with arteriosclerosis and atherosclerosis. Cholisma ES, which is designed to treat high cholesterol and triglyceride levels along with fatty liver and obesity, contains Da Huang *(Radix et Rhizoma Rhei)*, Dan Shen (*Radix Salviae Miltiorrhizae)*, Ge Gen (*Radix Puerariae)*, Hai Zao (*Sargassum)*, Huang Qin (*Radix Scutellariae)*, Jue Ming Zi (*Semen Cassiae)*, Shan Zha (*Fructus Crataegi)*, Yin Chen Hao (*Herba Artemisiae Scopariae)*, Yu Jin (*Radix Curcumae)*, and Ze Xie *(Rhizoma Alismatis)* (Lotus Institute, 2005, p.293-304).

Based on these data and the included studies, this study will focus on the Chinese herbal formula Xue Fu Zhu Yu Tang, along with all its individual herbal ingredients. The additional single herbs discussed in this study were found in all four of the included sources, and include Shan Zha (*Fructus Crataegi)*, Dan Shen (*Radix Salviae Miltiorrhrizae)*, Da Huang (*Radix et*

Rhizome Rhei), Ze Xie (*Radix Alsimatis),* and Ge Gen (*Radix Puerariae).* For this selection process, the single herbs examined in the three articles included were listed for the final selection process, so were all the herbs contained in both Lotus Institute (2006) formulas, since these formulas were specifically designed for the biomedical diagnosis of hyperlipidemia. A complete list can be seen in Table 4.

Xue Fu Zhu Yu Tang

Xue Fu Zhu Yu Tang (XFZYT), also called "Drive Out Stasis in the Mansion of Blood Decoction", is a *Blood-invigorating* formula that first appeared in 1830 in *Yi Lin Gai Cuo (Corrections of Errors Among Physicians)* by Wang Qing-Ren (Chen, 2009). According the Chen (2009), XFZYT has antiplatelet, anticoagulant, cardiovascular, and antihyperlipidemic effects, and he lists a total of 18 conditions for which XFZYT has been used in studies as a treatment modality. These include among others: Cardiac ischemia, bradyarrhythmia, hepatitis, vascular headaches, phlebitis, stroke, cerebral atherosclerosis, and hyperlipidemia. It consists of 11 herbs: Tao Ren (*Semen Persicae),* Hong Hua (*Flos Carthami),* Di Huang (*Radix Rehmaniae),* Dang Gui (*Angelica Sinensis),* Chi Shao (*Radix Paeoniae Rubra),* Chuan Xiong (*Radix Chuanxiong Lingustici),* Chai Hu (*Radix Bupleuri),* Zhi Qiao/Zhi Ke (*Fructus Citri Aurantii),* Jie Geng (*Radix Platycodonis),* Chuan Niu Xi (*Radix Cyathulae),* and Gan Cao (*Radix et Rhizoma Glycyrrhizae)* (Chen, 2009).

Effects on hyperlipidemia

Song et al. (2013) investigated the antihyperlipidemic actions of XFZYT compared to simvastatin. Sixty rats were randomly divided into six groups. One group was fed a normal diet;

the other five groups were fed a high-fat diet to induce hyperlipidemia. After four weeks, the hyperlipidemic rats were treated with simvastatin (SIM), low (XF1), medium (XF2) and high (XF3) dosages of XFZYT, and one group was left untreated. They found that both the simvastatin as well as the XFZYT groups showed significant reduction in total cholesterol levels and LDL levels, while also presenting with significantly increased HDL levels after seven weeks of treatment. The results can be found in Table 5. Moreover, they also found that while the control group showed an increase in the hepatic index of 34.52%, the hepatic indexes of the treated groups were reduced by 19.95% in the SIM group, 23.72% in the XF3 group, 14.31% in the XF2 group, and 6.11% in the XF1 group. The authors concluded that XFZYT might effectively address hepatic steatosis seen in hyperlipidemia (Song et al., 2013).

Liao et al. (2014) looked at a total of six randomized controlled clinical trials. Three of these compared simvastatin use alone to simvastatin plus XFZYT, two compared the effects of XFZYT alone to a group of patients using inositol nicotinate, and one group compared XFZYT alone to Xuezhikang, a common Chinese patent derived from red yeast rice. The XFZYT groups consistently performed better than the control groups, however, the authors point to several problems with the studies. While all studies claimed to be randomized, there were no details of randomization methods. There were also issues with differences in baselines, allocation concealment, and blinding methods. The authors concluded that while XFZYT may be effective at lowering blood lipid levels, further investigation is necessary due to the high probability of bias (Liao et al., 2014).

Zhang and Cheng (2005) analyzed the hypercholesterolemic extracts of XFZYT in order to identify major lipid-lowering constituents of the formula. Seventeen compounds were identified in total; nine of those were clearly identified, while the other eight were only

tentatively identified. The clearly identified compounds were oxypaeoniflorin, amygdalin, albiflorin, Paeoniflorin, ferulic acid, naringin, hesperidin, senkyunolide I, and neohesperidin. The authors reported that some of the isolated compounds had been shown to be effective at lowering LDL levels in previous studies, while others were not. However, they also point out that these compounds have been found in other plant extracts that have been shown to lower cholesterol levels, with the example of citrus juice which contains certain phenolic compounds that significantly inhibit atherosclerosis and lower lipid levels (Zhang & Cheng, 2005). A previous study by the same authors from 2004, in which a water extract of XFZYT was divided into six fractions which were then individually and combined examined for their ability to decrease LDL levels, concluded that the synergy between compounds cannot be overlooked. Single fractions that did not have any effect on lowering lipid levels would profoundly lower them when combined (Zhang & Cheng, 2004).

Effects on cardiovascular disease

Clinically, XFZYT has been used frequently to treat cardiovascular disease in Asian countries; Hung et al. (2015) found that XFZYT was the second-most prescribed TCM formula in the treatment of ischemic heart disease in their population-based study in Taiwan. Studies have shown that XFZYT has multiple mechanisms by which it affects cardiovascular health, and that it has positive effects on cardiovascular blood flow, including increased coronary blood flow and improved microcirculation, as well as reduction of blood lipid levels and aggregation of platelets (Wang et al., 2013). In their review to evaluate XFZYT in the treatment of patients with Angina Pectoris, Yi et al. (2014) looked at 14 studies, which included patients with stable as well as unstable angina pectoris. All trials were randomized controlled studies, and primary outcome

measures were improvements in the symptoms of angina pectoris, as well as improvement in ECG, and some considered blood lipid levels (HDL, LDL, TC, and TG). The two groups compared were patients on traditional antianginal medications (TAM) alone and patients on TAM combined with XFZYT. The TAM and XFZYT combination group showed better results in ECG improvement, and also presented with a significant increase in HDL levels and decrease in LDL and triglyceride levels (Yi et al., 2014). Better effects in improving ECG as well as relieving symptoms of angina by XFZYT combined with conventional angina medications was also noted by Yang et al. (2014).

Effects on hypertension

XFZYT has also been found effective in treating hypertension. Pengqian Wang et al. (2015) compared 15 studies with 1364 patients with hypertension, and found that all of them reported improvement in symptoms as well as a significant reduction in blood pressure. They also pointed out that XFZYT had marked antihyperlipidemic effects and improved total cholesterol levels as well as LDL levels, and stated that XFZYT has shown to have multiple positive effects on cardiovascular function with no side effects. Previous studies have also shown XFZYT to induce endothelial progenitor cell formation as well as hasten tube formation (Dong et al., 2010; Song et al. 2012).

Effects on hepatic function

While there are no studies in regards to XFZYT's effect on insulin resistance and blood glucose levels, one article pointed to its efficacy in inhibiting liver fibrosis in mice. Zhou et al. (2014) compared actions of a chemical drug for treatment of liver fibrosis, Sorafenib, to the effects of XFZYT. They found that both had beneficial effects on liver enzyme levels and were

able to reduce alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBil). XFZYT was also able to decrease inflammation, and inhibited the progression of fibrosis. Moreover, while previous studies have pointed to XFZYT's ability to induce angiogenesis, this study found that the formula showed an antiangiogenic effect in hepatocytes. They point out that recent studies have implicated that XFZYT has a beneficial effect on non-alcoholic fatty liver pathologies, and several of the herbs contained in the formula exhibited hepatoprotective properties. Dang Gui was found to have anti-oxidant effects on rat livers, and extracts of Gan Cao and Di Huang showed to have hepatoprotective effects, hence indicating that XFZYT may be able to improve liver function (Zhou et al., 2014).

Tao Ren

Tao Ren (*Semen Persicae)* is a commonly used herb in the *Blood invigorating* and *Stasis removing* category, which describes herbs that are used to promote blood circulation. Indications include gynecological conditions, and traumatic injuries. Tao Ren is also known to have laxative effects. According to Chen & Chen (2004), Tao Ren has exhibited effectiveness in dissolution of thrombi, has anti-inflammatory effects, and has shown to improve symptoms and hematology in schistosomal cirrhosis. Due to its anti-coagulant effect, Tao Ren has the potential to increase the effect of anticoagulant medications like Warfarin, and should hence only be used with extreme caution in patients on anticoagulant or antiplatelet medications (Chen & Chen, 2004).

One study done by Liu et al. (2012) examined the effects of the herbal combination of Tao Ren and Hong Hua and its effect on promoting blood circulation. They state that abnormalities in hemorrheology have been observed in patients with hyperlipidemia. Tao Ren and Hong Hua combination showed multiple effects on hemorrheology: it decreased whole blood

viscosity, plasma viscosity, packed cell volume, and also prolonged thrombin time, thromboplastin time, prothrombin time, and lowered fibrinogen content (Liu et al., 2012).

There were no studies found about effects on cholesterol and other blood lipids.

Hong Hua

Hong Hua (*Flos Carthami)* is another herb in the *Blood invigorating* and *Stasis-removing* category. Indications include gynecological issues, abdominal masses, joint pain, dermatological disorders, and chest pain (Chen & Chen, 2004). Pharmacological effects include cardiovascular effects with low doses having an inotropic effect on the heart, antiplatelet properties, and CNS suppression. According to Chen & Chen (2004), Hong Hua has shown to be effective in relieving chest pain in coronary artery disease, and effected improvements in ECG. Just as in the case of Tao Ren, due to its blood circulation enhancing effect Hong Hua should be used with caution in patients on Warfarin or other anticoagulants.

Zhou et al. (2014) found that Hong Hua has wide-reaching therapeutic effects. Besides having anticoagulant and antithrombotic effects, Hong Hua has also been found to have a protective effect on myocardial and cerebral ischemia as well as on endothelial cell structure. Noteworthy is the anti-fibrotic effect on hepatic cells and its ability to protect the liver from oxidative stress, which indicates that Hong Hua has potential as an herbal medicine in the treatment of liver disease (Zhou et al., 2014). Zhou at al. also point to a study by Asgary et al. from 2012 on the anti-diabetic effects of hydroalcoholic extract of Hong Hua. That study found that Hong Hua was similar in its positive effect on fasting blood sugar, cholesterol, LDL, and insulin levels as glibenclamide, which was given as the standard drug; both managed to bring levels of these markers to near normal. They also pointed out that the extract of Hong Hua

"appeared non-toxic as evidenced by normal levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) (Zhou et al., 2014).

While Hong Hua is thought to be of low toxicity, Zhou et al. (2014) mentioned an increase of reported side effects, especially since Hong Hua has gained popularity as a coloring and flavoring agent. At higher dosages of 1.2 mg/kg/day, Hong Hua showed teratogenic effects, and there is also evidence that it has a toxic effect on mouse testicular tissue (Zhou et al. 2014).

Di Huang

Di Huang (*Radix Rehmanniae)* is an herb in the *Heat-clearing* and *Blood-cooling* category. Herbs in this category generally have a strong anti-inflammatory and anti-pathogenic actions. Indications include fever, dry mouth and tongue, delirium, gastrointestinal or excessive menstrual bleeding as well as *xiao ke* (*wasting and thirsting*) disorders, which is considered diabetes in Western medicine (Chen & Chen 2004). Pharmacological effects include anti-inflammatory, cardiotonic, antihypertensive, hemostatic, hepato-protective, diuretic and antibiotic effects. Chen & Chen mention no herb-drug interactions or adverse reactions under toxicology (2004).

Di Huang has also displayed effects on glucose-stimulated insulin secretion, and it was found that extract of Di Huang was able to enhance insulin secretion by improving glucose sensing (Park et al., 2008, p. 347), and that this extract was also able to increase beta-cell proliferation. Xie and Du (2011) pointed out that Di Huang is one of the main herbs in many of the formulas used to treat diabetes. One of its compounds, Catalpol, has hypoglycemic effects, and its oligosaccharides have also presented with significant glucose-lowering effects. Their review article states that some of the regulatory effects of Di Huang on glucose metabolism have

to do with its stimulation of insulin secretion and its ability to regulate insulin resistance and ability to stimulate glucose uptake (Xie & Du, 2011).

No studies were found about hypolipidemic effects of Di Huang.

Dang Gui

Dang Gui (*Angelica Sinensis)* is a traditional Chinese herb in the *Blood-tonifying* category. These herbs, while also being able to treat anemias, work more by supporting the production of blood indirectly, by supporting TCM organ systems involved in the production of blood. Indications include blood deficiencies of *Heart* and *Liver*, which present with anemia, dryness of skin, nails, and hair, dizziness, palpitations, blurred vision, and insomnia. It also possesses *Blood moving* properties, and is indicated especially for menstrual disorders and traumatic injuries as well as painful syndromes associated with numbness. Additionally, it is indicated for constipation as well as its ability to treat cough and dyspnea (Chen & Chen, 2004). Pharmacological effects relevant to this study are cardiovascular effect, antiplatelet activities, and hepatoprotective as well as anti-inflammatory properties. Chen & Chen mention clinical studies that showed Dang Gui to be effective in treating arrhythmias, ischemic stroke, and liver disease. It is also mentioned that Dang Gui has shown to treat acetaminophen-induced liver damage due to its ability to stimulate hepatocyte generation. Since Dang Gui possesses *Blood-moving* properties, caution is warranted in prescribing this herb to patients on anticoagulant and antiplatelet medications (Chen & Chen, 2004).

Wang et al. (2015) established that polysaccharides from Dang Guihave hypoglycemic as well as hypolipidemic effects. Pre-diabetic and diabetic mice were given either metformin or Dang Gui polysaccharides (DGP). The authors found that high doses of DGP significantly

lowered fasting blood glucose levels in the pre-diabetic mice, an effect which was not significant with lower doses. Treatment for a duration of four weeks with DGP also normalized fasting insulin levels, and improved insulin resistance. The same held true for the diabetic mice, but reduction in fasting blood glucose level was significantly less than with metformin. When the researchers looked at serum lipid profiles in both the diabetic and pre-diabetic groups, they found that DGP had significantly decreased levels of total cholesterol, but had little effect on serum triglyceride levels, and that the cholesterol-lowering effects were dose-dependent (Wang et al., 2015). Moreover, Wang et al. observed fatty liver changes in both pre-diabetic and diabetic mice, and noted that these changes were alleviated by treatment with DGP. Hua et al. (2014) examined polysaccharides derived from four differently processed samples of Angelica Sinensis (AS): charred AS, parched AS with soil, AS parched with wine, and AS parched with sesame oil. They concluded that charred AS had the best hepatoprotective effects out of the four (Hua et al., 2014).

In regards to herb-drug interactions, Chen at al. (2013) found that while animal studies did not show prothrombin time (PT) to be affected by Dang Gui when used alone, after three days of treatment with Dang Gui in conjunction with Warfarin, PT values dropped significantly. They also cite a study from Heck et al. (2000) which reported a sudden increase in international normalized ratio (INR) levels in a female patient who took Dang Gui once or twice daily. After discontinuing Dang Gui, the patient's INR levels returned to normal. Chen et al. also pointed out that Dang Gui induced CYP2D6 activity in the liver which is also an enzyme involved in drug metabolism, hence cautioning about possible herb-drug interactions (Chen et al., 2013).

Chi Shao

Chi Shao (*Radix Paeoniae Rubrae)* is an herb that is often used to invigorate blood. While Chen & Chen (2004) list Chi Shao in the category of *Heat-clearing* and *Blood-cooling* herbs, Bensky (2004) lists it under *Blood-invigorating* herbs. According to Chen & Chen (2004), Chi Shao is indicated in conditions of hot *Blood* which leads to bleeding, as well as for gynecological conditions, bruises from traumatic injuries, and post-stroke hemiplegia. Pharmacological actions include antiplatelet properties, cardiovascular and antispasmodic effects. Chen & Chen also list studies in which Chi Shao showed to be effective in treatment of coronary artery disease, cerebral thrombosis, and cor pulmonale (2004). As previously noted, due to the blood-moving properties, Chi Shao has the potential to interact with anticoagulant and antiplatelet therapies.

Zhang, Yang, and Yu (2015) examined the effects of Paeoniflorin, an active compound found in Chi Shao, and found that it significantly lowered total cholesterol and LDL levels. However, triglyceride levels were not affected. Paeoniflorin was also able to restore liver function in mice with elevated serum ALT and AST levels due to the long-term high-fat diet, and was able to reduce lipid inclusions in hepatic steatosis in size and number (Zhang, Yang & Yu, 2015).

No articles were found about hypolipidemic effects of Chi Shao.

Chuan Xiong

Chuan Xiong (*Rhizoma Ligustici Chuanxiong)* is a classical Chinese herb in the *Blood-invigorating* and *Stasis-removing* category. According to Chen & Chen (2004), therapeutic actions include OB/Gyn as well as pain issues. Pharmacological effects include dilation of blood vessels, lowering of blood pressure as well as increased coronary blood perfusion, antiplatelet

and anticoagulant properties. Chen & Chen list one study where Chuan Xiong improved symptoms of chest pain in angina, and as with all *Blood-moving* herbs, cautions of interactions with antiplatelet and anticoagulant medications. Side effects were not noted (2004).

Kang et al. (2015) found that administration of Chuanxiong capsule, which consists of Chuan Xiong and Dang Gui, to hyperlipidemic mice with atherosclerosis was able to significantly decrease the atherosclerotic indexes and reduce plaque areas, while also improving blood levels of Triglycerides (TG), TC, and LDL, while having no effect on HDL levels.

Chai Hu

Chai Hu (*Radix Bupleuri),* while being in an herbal category that treats common colds and other viral infections, also has the added actions of spreading *Liver qi* and *relieving Liver qi stagnation*. In Western terms, this translates into the *Liver* system's function of promoting circulation and movement in the body, which includes circulation of blood, processing of emotions, and regulation of peristalsis. Chen & Chen (2004) state that pharmacological effects of Chai Hu include anti-inflammatory, hepatoprotective, cholagogic, and antihyperlipidemic effects. They list several case studies in which supported the argument for Chai Hu's hepatoprotective actions, which included treatment of infectious hepatitis, liver cirrhosis, as well as hyperlipidemic effects (2004). Moreover, Chen & Chen note that "Chai Hu has very low toxicity."

Chai Hu is the active ingredient in Xiao Chai Hu Tang, a traditional Chinese formula used among others in the treatment of liver disease. Zheng et al. (2013) looked at the individual ingredients of this formula, and explained that Chai Hu seemed to improve liver function, hence preventing fibrosis, and it seemed to be able to "enhance the liver antioxidant defense systems."

Saikosaponins are an active ingredient of Chai Hu, and have shown to reduce liver inflammation and also block the production of pro-inflammatory cytokines in the liver (Zheng et al., 2013).

Regarding side effects, Lee, Wang, and Chen (2011) looked at the relationship between liver damage in chronic hepatitis infection and treatment with Chai Hu containing products. They explained that formulas containing Chai Hu were frequently prescribed for chronic hepatitis. A significantly high relationship was found between the administration of Chai Hu containing herbal products and liver damage. This damage was found to be dose-dependent: dosages of more than 19 g of Chai Hu in hepatitis patients increased their risk for liver damage (Lee, Wang & Chen, 2011).

No studies were found about hypolipidemic effects of Chai Hu.

Zhi Qiao/Zhi Ke

Zhi Ke (*Fructus Aurantii)*, or Zhi Qiao, which is an alternate spelling, is a *Qi-regulating* herbs that is mostly indicated for abdominal distension and gastrointestinal disorders. Chen & Chen (2004) list cardiovascular as well as antiplatelet effects, which also bring with it the caution of using this herb in patients on anticoagulants and antiplatelet medicine.

Studies on Zhi Ke that fit the search criteria were not found.

Jie Geng

Jie Geng (*Radix Platycodoni)* is a classical Chinese herb used for *resolving phlegm* and *regulating the Lungs*. In Western terms, this translates into herbs that are used in respiratory infections. Its indications also include dispelling pus, and raising qi, and it is used as an herb to guide the actions of other herbs to the upper areas of the body. Chen & Chen (2004) state that

effects of Jie Geng include cardiovascular effects (lowering blood pressure, heart rate, and respiratory rates, and dilation of blood vessels), as well as anti-inflammatory, gastrointestinal, and antidiabetic properties. According to the study listed, alcohol extract of Jie Geng lowered blood glucose levels and attenuated sharp increases of plasma glucose levels after meals.

Lee et al. (2014) studied the anti-diabetic effects of a concentrated saponin fraction extracted from Jie Geng. The authors found that Jie Geng was able to lower fasting blood glucose levels as well as hemoglobin A1C (HbA1c) levels in mice. The saponin fraction also improved insulin levels, and was able to "modulate hepatic glucose-regulating enzyme activities." While it was able to reduce serum free fatty acids and triglyceride levels, Jie Geng was found to have no effect on total cholesterol levels (Lee et al., 2014). Another study by Hwang et al. (2013) found levels of hepatic triglycerides, TC and LDL cholesterol were significantly decreased in high fat diet rats treated with Jie Geng saponins. Long-term consumption of Jie Geng was found to decrease body weight and insulin resistance (Lee et al. 2012; Cho, Yoon, & Yang, 2013). Multiple articles point to Jie Geng's positive effect on liver health and ability to prevent liver fibrosis (Choi et al. 2013; Hwang et al. 2013; Chen et al 2015).

Chuan Niu Xi

Chuan Niu Xi (*Radix Cyathulae)* is another herb in the *Blood- invigorating* and *stasis-removing* category. According to Chen & Chen (2004), therapeutic actions include gynecological conditions, pain due to trauma, abnormal bleeding, urinary dysfunctions, and weakness of Liver and Kidney leading to low back and knee pain and weakness. Pharmacological effects on cholesterol and blood glucose levels, and cardiovascular and liver health are not recorded (Chen & Chen, 2004).

Gan Cao

Gan Cao (*Radix Glycyrrhizae*) is an herb that is often used in formulas to *harmonize* all other ingredients in the formula. In western terms, this harmonizing of ingredients translates into Gan Cao's ability to negate some of the toxicities of other drugs (Chen & Chen, 2004). Indications include, but are not limited to, digestive issues, palpitations, arrhythmias and irregular pulse, insomnia, mental-emotional issues, cough, pain, and poisoning, since it is an antidote against various kinds of toxins (Chen & Chen, 2004). Pharmacological effects mentioned in this book pertinent to this study include anti-inflammatory, antiarrhythmic, gastrointestinal, antispasmodic, hepatoprotective and antihyperlipidemic effects. One study mentioned by Chen & Chen found that Gan Cao "reduced the damage to and death of liver cells, reduced inflammatory reaction, promoted regeneration of liver cells, and decreased the risk of liver cirrhosis and necrosis" (2004). However, Chen & Chen also list several contraindications and herb-drug interactions. Gan Cao is contraindicated for high dosages and prolonged usage in patients with edema, kidney disorders, hypokalemia, hypertension, and congestive heart failure. Due to its mineralocorticoid effects, it may also interact with corticosteroids, and should be used in caution with Digoxin (Chen & Chen, 2004).

Sil, Ray, and Chakraborti (2015) state that Glycyrrhizin, an active compound from Gan Cao, "has been reported to ameliorate insulin resistance, hyperglycemia, dyslipidemia, and obesity in rats with metabolic syndrome." Their study showed that glycyrrhizin indeed reduced weight gain, lowered blood glucose and insulin levels, and was also able to reduce the amount of liver enzymes. Li et al. (2014) found in their review article that glycyrrhizic acid, derived from Gan Cao, showed inhibition of liver damage, but points out that due to its inductive effect on the

enzyme CYP3A, which is one of the enzymes used in the synthesis of certain medications, clinicians should pay attention to side effects, especially with narrow therapeutic index drugs. Jung et al. (2016) determined that Gan Cao might have protective effects against alcohol-induced liver damage, which they attribute to Gan Cao's anti-inflammatory and antioxidant properties. Xie and Du (2010) state that roasted Gan Cao was better than raw Gan Cao at improving glucose tolerance, and that Glycyrin, a compound of Gan Cao, has shown to significantly lower blood sugar levels.

Dan Shen

Dan Shen (*Radix Salviae Miltiorrhizae)* is a Chinese herb in the *Blood-invigorating* and *stasis-removing* category. According the Chen & Chen (2004), therapeutic actions include gynecological disorders like abdominal pain, dysmenorrhea and irregular periods, epigastric and chest pain, traumatic injuries, sores and abscesses, and palpitations and insomnia. Pharmacological effects pertinent to this study include reduction of blood pressure, dilation and increased blood flow to the coronary arteries, antiplatelet, anticoagulant and thrombolytic actions, as well as hepatoprotective properties. One study mentioned by Chen & Chen reported normalization of liver function in 22 patients with chronic hepatitis. Due to its effect on coagulation and platelets, Dan Shen is contraindicated or indicated for use with highest caution for patients on anticoagulant, antiplatelet, or digoxin therapies (Chen & Chen, 2004).

Several studies point to the antidiabetic effect of salvianolic acid, which is an extract derived from Dan Shen. Huang et al. (2015) found that administration of salvianolic acid B (SAB) to diabetic mice significantly reduced fasting blood glucose levels, blood insulin levels, and significantly increased insulin sensitivity indexes. They also found that SAB was able to

significantly lower total cholesterol and LDL levels while increasing HDL levels. These effects were found to be dose-dependent. Yang et al. (2011) found that SAB also seems to be able to inhibit LDL oxidation in hypercholesterolemic rabbits. Qiang et al. (2015) found that salvianolic acid A (SAA) was able to lower fasting and regular blood glucose levels, while also reducing 24-hour food and water intake, which pointed to SAA being able to alleviate some of the symptoms of diabetes like polydipsia and increased food intake.

Some of these effects seem to be limited to extracts of Dan Shen. Van Poppel et al. (2015) tested a water extract of Dan Shen and its effects on cardiovascular risk factors. They concluded that the water extract had no effects on HDL, and found that total cholesterol as well as LDL cholesterol levels were slightly higher after the treatment. However, they did point out that only two out of the twenty participants were diagnosed with Blood Stasis, a key pattern indicated for treatment with Dan Shen.

Shan Zha

Shan Zha (*Fructus Crataegi),* also known as Hawthorn berry, is in the category of *digestive* herbs, and its indications include promotion of healthy digestion, especially the digestion of meats and greasy foods. It also has the action of activating blood circulation so it is indicated for pain, and it is used for treatment of cardiovascular disease, including hypertension, coronary artery disease, angina, and hypercholesterolemia (Chen & Chen, 2004). Pharmacological effects mentioned are cardiotonic, vasodilating, antihypertensive, antihyperlipidemic, and gastrointestinal functions. Studies and research listed includes studies on angina where administration of Shan Zha lead to improvement in ECG, and on hyperlipidemia, where two studies showed decreases in cholesterol levels after administration of Shan Zha (Chen

& Chen, 2004). Herb-drug interactions listed are for Digoxin, since both Digoxin and Shan Zha have cardiotonic effects. It is also stated that Shan Zha, due to its sour nature, is not suitable for patients with stomach ulcers or gastric hyperacidity.

In their paper *Hawthorn*, Chang el al. (2002) listed the effects of Shan Zha as cardiotonic, antiarrhythmic, hypotensive, hypolipidemic, and antioxidative. They also state that in clinical trials, no significant side effects had been reported, but point to the potentiating effects Shan Zha can exert on various drugs used for cardiovascular health, including digitalis, beta-blockers, and other hypotensive drugs. There is a lot of literature pointing to the lipid-lowering effects of Shan Zha. Niu et al. (2011) found that the use of Shan Zha as a food supplement in mice fed with a high fat diet significantly improved total cholesterol levels, while exerting no such effect on normally fed mice. Kwok et al. (2010) found that dietary supplementation with Shan Zha was found to lower LDL levels, while increasing HDL levels. They also found that the addition of Shan Zha to a regular diet provided hepatoprotective effects and alleviated some of the negative effects that are associated with a high cholesterol diet. It also showed an ability to reduce oxidative stress in the liver and lessen the fatty liver development. Kwok et al. (2010) concluded that consuming a powder derived from Shan Zha showed an overall improvement in the functioning of the hepatic and cardiovascular systems, and that this is an important factor in the treatment of hyperlipidemia-related cardiovascular complications.

Jurikova et al. (2012) also found that extracts of Shan Zha effectively lowered blood lipid levels, and also found it decreased fatty deposits in the liver of mice. Moreover, Shan Zha reduced accumulations of cholesterol in the liver, mainly by supporting cholesterol degradation and suppressing cholesterol synthesis. However, they pointed out that when they tested a mixture of compounds extracted from Shan Zha, lipid-lowering results were very significant, whereas

each of the single compounds did not assert such a strong result.

There is also evidence that Shan Zha has the ability to lower blood glucose levels and improve insulin resistance. Shih et al. (2013) found that extract from Shan Zha was able to reduce blood glucose levels in mice, and suggested that Shan Zha at higher doses might improve insulin resistance. Chowdhury et al. (2014) found that various extractions of Shan Zha were able to delay the absorption of carbohydrates by affecting alpha-glucosidase, which is responsible for breaking down carbohydrates. Delayed absorption of carbohydrates leads to extra time for the pancreas and beta-cells to produce enough insulin to digest the entire meal. They also found that Shan Zha's inhibitory effect on PTP1B, a major regulator in insulin and leptin signaling and thought to be a factor in insulin resistance, making the herb a promising food supplement in the management of diabetes.

Sham et al. (2014) noted that some of the most frequent side effects in the administration of Shan Zha included symptoms such as dizziness, nausea, gastrointestinal bleeding, circulatory issues, and rashes. They also pointed out that many of these cases did not provide the necessary data to establish a definite link between the adverse effects and the herb (Sham et al. 2014).

Ge Gen

Ge Gen (*Radix Puerariae)*, like Chai Hu, is an herb often used to treat pathogenic infections like viruses. According to Chen & Chen (2004), Ge Gen is effective for common colds and other externally contracted pathogens, and it is used for the promotion of the eruption of measles, hydrating the body in case of fevers, stopping diarrhea, as well as for treating hypertension with headache, stiff neck, tinnitus and dizziness. Pharmacological effects listed by Chen & Chen include cardiovascular, antiplatelet, antihypertensive, and antidiabetic functions.

Due to its blood glucose lowering effects, Chen & Chen advise usage of Ge Gen only with caution in patients who are taking insulin or other antidiabetic medications, as well as caution in patients on anticoagulant and antiplatelet therapies (Chen & Chen, 2004).

Ge Gen exerts anti-diabetic as well as lipid-lowering effects. Wu et al. (2013) found that puerarin, an extract from Ge Gen, was found to effectively lower blood glucose levels as well as to reduce triglycerides, total cholesterol, and LDL levels. Wong et al (2011) found that puerarin and Ge Gen extract were able to decrease blood glucose and insulin levels, and found that administration of a 0.2% Ge Gen extract for two months as part of a normal diet induced weigh loss, and lowered fasting blood glucose (FBG), TC, and insulin levels. Zhou et al. (2014) also found that puerarin was able to prevent oxidative stress to the islet cells, and was able to relieve insulin resistance while also lowering triglyceride and total cholesterol levels (Zhou et al., 2014; Prasain et al. 2012). Puerarin was also found to have a protective effect on the liver after injury was induced by alcohol, and was found to improve leptin signaling transduction which resulted in positive effects on non-alcoholic fatty liver disease (Wei, Chen and Xu, 2014). However, Sham et al. (2014) reported that Ge Gen flavones had estrogen-like effects similar to those observed in estrogen-treated rats, and hence recommend this to be considered when prescribing Ge Gen.

Ze Xie

Ze Xie (*Rhizoma Alismatis)* is a traditional Chinese herb in the *water-regulating* and *damp-resolving* category, and is often used as a diuretic due to its *regulation of water transformation*. Chen & Chen (2004) mention antihyperlipidemic and antihypertensive pharmacological actions, and list a study indicating Ze Xie's ability to reduce high cholesterol

and triglyceride levels in patients. Due to its diuretic effect, Ze Xie should be avoided in patients on diuretic medications to avoid a synergistic effect of these substances (Chen & Chen, 2004).

Tian, Chen and Zhao's (2014) review article assessed the pharmacological activities of Ze Xie, and found it exhibited hypolipidemic as well as hypoglycemic effects in animal models, and Jang et al. (2015) found Ze Xie to be effective at preventing hepatic steatosis by alleviating endoplasmic reticulum stress. Side effects reported by Sham et al. (2014) were related to over dosage of Chai Hu in chronic hepatitis B patients, and were correlated with hepatotoxicity as well as nephrotoxicity. Dan et al. (2011) evaluated the hypolipidemic effects of Ze Xie in mice with high-fat diet induce hyperlipidemia. Their results showed significant decreases in serum as well as liver cholesterol levels and triglycerides, and also found an elevation in HDL levels. Moreover, they found adipose vacuole changes in Ze Xie-treated mice as well as decreases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which resembled the liver values in healthy control mice. Overall, they concluded that one of the effects of Ze Xie were to decreasing the synthesis of cholesterol by the liver.

Da Huang

Da Huang (*Radix et Rhizoma Rhei)* is an herb in the *downward draining* and *purging category*, and has been classically used for digestive disorders leading from diarrhea to dysentery. It also *purges fire*, *clears heat and detoxifies*, *activates Blood circulation*, *removes stasis*, and *clears damp-heat* while promoting diuresis (Chen & Chen, 2004). Due to its strong purgative effect, it is contraindicated for patients who are not constipated or suffering from *Blood stagnation*, and should be used in caution in patients with impaired digestion. Chen & Chen (2004) mention adverse reactions due to overdosing which include diarrhea, nausea,

vomiting, dizziness, borborygmus, and abdominal pain. Pharmacological effects include hepatoprotective, cholagogic, and cardiovascular effect. Chen & Chen (2004) list one study in which Da Huang was effective in reducing high triglyceride levels. Cardiac Glycosides are listed under herb-drug interactions. According to Chen & Chen, the usage of Da Huang over longer periods of times may cause a loss of potassium, which in turn can affect medicaitons like digoxin and lead to toxicity (2004).

Rhein, an anthraquinone and extract of Da Huang, has been found to reduce blood cholesterol, triglyceride and LDL levels (Sham et al., 2014). While these effects were similar to the simvastatin group, its inhibitory effect on HMG-CoA was weaker than that of the statin drug. It was however found to decrease body and fat weight, lower hepatic lipid levels, improve insulin resistance, and was able to regulate alanine aminotransferase levels and reverse fatty liver symptoms (Sham et al., 2014). They noted only mild side effects in most patients, including diarrhea. Due to the purgative effect of Da Huang, overdose symptoms include severe diarrhea which can subsequently lead to fluid and electrolyte loss. Xie and Shang (2014) studied the extraction process of Da Huang, and found that the concentration, extraction time and ethanol amounts significantly affected the extraction of anthraquinones from Da Huang, but also confirmed the lipid-lowering effects of the herb and its ability to prevent LDL oxidation. They found that ethanol extraction of Da Huang resulted in higher anthraquinone content than water extraction, and that a two-time extraction in a solution of 70% ethanol for 60 minutes had the optimal effects.

Li et al. (2016) examined the effects of Emodin, another constituent extracted from Da Huang, and found it to be effective in reducing body weight, appetite, and blood lipid levels, and also effective in improving fasting blood glucose levels and insulin sensitivity. Moreover,

Emodin was found to positively affect lipid levels in liver and adipose tissues in animal models. Arvindekar et al. (2015) looked at effects of various extracts from Da Huang, and found that emodin, rhein, chrysophanol and physcion were all able to lower blood glucose levels in animal models.

Side Effects and Herb-Drug Interactions

With TCM becoming popular world-wide, risk of side effects and interactions with drugs need to be established. Teschke et al. (2015) looked into reports of herbal hepatotoxicity. In their selective literature review, they found a number of reports on liver toxicity for TCM herbs. Reported cases were found for Chai Hu (28), Da Huang (1), Gan Cao (1), and Ge Gen (2) and Pueraria Thunbergiana (6), and for Ze Xie (1). They also included reported causality assessments for TCM in cases of documented liver toxicity, and listed Da Huang (highly probably), Gan Cao (probably), Ge Gen (highly probably), and Ze Xie (highly probable). However, the authors pointed to several challenges in determining causality. For one, the possibility of herbal misidentification, contamination and adulteration were mentioned. Other concerns were quality standard regulations for standardization (Teschke et al., 2015; Zhang et al., 2012). Another problem listed by Teschke et al. was that determining whether the liver damage was actually caused by the herbs rather than other factors had challenges. Finding appropriate diagnostic levels of ALT and AST was necessary to prevent including patients with nonspecific diseases (2015). Also, since a positive re-exposure test is an important step in verifying the toxicity was actually caused by the herbs, and these tests in this case are usually unintentional and not planned, data are often of poor quality (Teschke et al., 2015). In another article form 2014, Teschke found that hepatotoxicity was reported in several patients being treated with formulation

containing Chai Hu, including Xiao Chai Hu Tang, Da Chai Hu Tang, and Long Dan Xie Gan Tang in Taiwan for hepatitis B infections (HBV). He listed one case of a 45-year-old man from Hong Kong who was suffering from chronic HBV infection, and who died due to acute liver and organ failure after using Da Huang, which was deemed to be due to herbal hepatotoxicity. Gan Cao was found to be the most likely culprit in hepatotoxicity in a 46-year-old male from Hong Kong with chronic HBV, and the patient fully recovered after discontinuation of Gan Cao. Ge Gen was also suspected in being the cause for toxic hepatitis in two female patients in Korea (Teschke, 2014).

However, in a study, which compared the effects of fenofibrate vs. the effects of a combination of fenofibrate and pulp from Wu Wei Zi (*Schizandrae Fructus),* Zhu et al. (2015) found that the herbal combination had a marked hepatoprotective effects, demonstrated by the decrease in ALT levels. The study also suggests that the herb-drug combination increased hepatic glucose-lowering effects.

Studies on herb-drug interactions are still few. One study by Lau et al. (2013) found that Di Huang (*Radix Rehmanniae)* has an effect on CYP3A4. Li et al. (2014) found that Gan Cao (*Radix Glycyrrhizae)* induced CYP3A enzymes, and Wong et al. (2011) reported that Ge Gen (*Radix Puerariae)* had inductive effects on CYP enzymes 1A2, 2B1, 2E1, and 3A, while also inhibiting CYP2D4. Since enzymes in the CYP450 system play an important role in the metabolism of pharmaceutical drugs, these are indicative of possible herb-drug interactions.

Literature Review Integration

Hyperlipidemia is a condition often treated with TCM and herbs in Asian countries. Many studies and reviews have been done on the hyperlipidemic effects of herbs and herbal

formulas, as well as current prescription trends for antihyperlipidemic herbs and formulas (Chu et al., 2015; Xie, Zhao & Du, 2012). This study is trying to fill a gap in the literature by looking at most prescribed herbs and formulas for hyperlipidemia, and then explore whether these formulas and herbs also possess anti-diabetic and hepatoprotective qualities, since both of these are adverse reactions caused by the leading western treatment approach to hyperlipidemia, statin drugs. Several of the herbs investigated were shown to be effective in blood glucose regulation (Liu et al., 2014; Tian et al., 2014; Wong et al., 2011), and hepatoprotective actions are documented as well (Jung et al., 2016; Zheng et al., 2013; Chen & Chen, 2004). Since side effects as well as herb-drug interactions are an important criterion, this study also explored information regarding side effects for the particular herbs in this study (Teschke et al., 2015; Teschke, 2014), as well as some relevant drug interactions (Lau et al., 2013).

Chapter 3: Methods

The goal of this study was to evaluate whether herbs and herbal formulas commonly prescribed for the treatment of hyperlipidemia are effective at lowering cholesterol and LDL levels, regulating blood glucose levels and insulin resistance, and whether these herbs and formulas also display hepatoprotective qualities. Recorded side effects and herb-drug interactions were also examined in order to evaluate safety. This chapter will explain the research methodology used to determine which formulas and herbs were included in this Capstone research process.

Designation of Methodology

This study uses the method of qualitative research synthesis focused on the following questions:

- Which formulas and herbs are commonly prescribed for the treatment of hyperlipidemia?
- What are the effects of these herbs on lipid levels?
- What is known about the effects these herbs and formulas have on blood glucose levels, insulin resistance, and on liver function?
- What are the major side effects and herb-drug interactions of these herbs?
- Can these herbs and formulas also address diabetes and liver function which are two comorbidities often associated with hyperlipidemia, and which are also two documented side effects of statin drugs?

The qualitative research approach was selected for this study because it allowed the researcher to use inductive reasoning to gain an in-depth understanding of the current use of herbal formulas

for hyperlipidemia, and to draw conclusions from studies on the efficacy of these commonly prescribed herbs on lipid and glucose metabolism, liver function, and potential side effects as well as herb-drug interactions.

A hypothesis was developed, and then a systematic literature synthesis was performed to compile and analyze information. Qualitative rather than quantitative analysis was used because studies included for this paper include a mixture of clinical trials, population-based surveys as well as review articles which examined various aspects of herbs and formulas included in this study. The qualitative method therefore allowed the researcher to go beyond numerical presentation in interpreting the data found (Green & Britten 1998). It is the hope of this researcher that if the researcher's hypothesis was correct, a quantitative research study, such as a randomized clinical trial, may be pursued in order to further explore the use of Chinese herbal formulas and herbs for hyperlipidemia while also preventing some of the side effects seen with the current standard of care, which is treatment with statin drugs.

Search Strategy

1. The search was conducted in 2015, and databases used were the UCLA Biomedical library database and PubMed searches.
2. For the initial search, in order to establish commonly used herbs and formulas for hyperlipidemia, the search of "hyperlipidemia" with "Chinese herbal medicine" was performed and resulted in 37 articles. The search of "hyperlipidemia" with "Chinese herbs" resulted in 20 articles.

3. These articles were further limited to articles that focused on general prescription trends of herbs and formulas for hyperlipidemia. Five articles qualified, and three of these were selected. Of the two articles eliminated, one focused on red rice yeast as their primary herb of interest, which was excluded because it contains active ingredients similar to that of statins (University of Maryland Medical Center, 2015), and the other focused on only one formula and did not explore overall prescription trends.
4. Since none of these articles mentioned any American studies, one clinical manual published in the United States was included in the herb selection process: *Clinical Manual of Oriental Medicine 2nd Edition* by the Lotus Institute of Integrative Medicine (2006). All herbs that were contained in the two formulas Dr. John Chen composed for the Lotus Clinical manual were included (see Table 4).
5. These herbs were then compared to the herbs listed in the three articles found on prescription trends, and herbs that were mentioned in all four sources were included. Two articles examined formula prescription trends, and one formula, Xue Fu Zhu Yu Tang (XFZYT), was mentioned in both articles, and was hence included (see Table 4).
6. The secondary search focused on identifying articles and studies relating to antihyperlipidemic, antidiabetic, side effects, herb-drug interactions, and hepatoprotective functions of XFZYT, the single herbs included in this formula, as well as the five single herbs determined in the initial selection process. Searches were often limited to the herb name only, since very few articles emerged in English language, and filters applied were "10 years" and "English language". The resulting articles were only included if information regarding the above mentioned parameters were included. The total number of articles that qualified to be included was 48.

Search Terms

Hyperlipidemia, hypercholesterolemia, Chinese herbs, Chinese herbal medicine, herbal medicine, traditional medicine, diabetes, insulin resistance, hepatoprotective, liver function, blood glucose, dyslipidemia, side effects, adverse reactions, herb-drug interactions, Xuefu Zhuyu, Xue Fu Zhu Yu, Tao Ren, Semen Persicae, Hong Hua, Flos Carthami, Chuan Xiong, Ligusticum, Di Huang, Radix Rehmanniae, Dang Gui, Angelica Sinensis, Chi Shao, Paeoniae Rubrae, Chai Hu, Radix Bupleuri, Zhe Ke, Zhe Qiao, Fructus Amarantii, Gan Cao, Radix Glycyrrhizae, Niu Xi, Cyathula Root, Jie Geng, Radix Platycodi, Dan Shen, Salvia Miltiorrhiza, Shan Zha, Fructus Crataegi, Ge Gen, Radix Puerariae, Da Huang, Radix and Rhizome Rhei, Ze Xie, Rhizoma Alismatis.

Inclusion & Exclusion Criteria

- English language only
- Due to the limited full-text articles available in English on this subject, review articles and studies in human, animal, and in vitro models were included.
- For the initial search for prescription trends, only articles published in the past five years were included to assess the latest trends.
- Research on individual herbs and XFZYT was limited to articles published in the past 10 years.
- Abstracts in English for articles in published only in Chinese were not included since abstract information couldn’t be verified and further examined.

- Articles that focused on herb combinations were excluded unless every herb included in these combination products were subject to this study. This was necessary to make sure all pharmacological actions recorded were associated with the herbs examined by this study, and not the adjunct herbs in the herbal combinations.

Data Analysis

Data extracted were tabulated in table form to identify prescription patterns, establish most-used herbs and formulas, and to establish which herbs showed effects on the included parameters. Tables can be found in Chapter 4: Results, and in the Appendices**.**

Human Research Ethical Considerations

Since this study is in the format of a literature review, and the researcher did not interact with any of the participants in the studies used for this project, no informed consent was needed. The proposal for the current study was reviewed by the Yo San University IRB and was ruled exempt. See Appendix five.

Chapter 4: Results

Overview

The objective of this study was to determine whether TCM formulas and herbs that are frequently prescribed for hyperlipidemia can effectively lower blood lipid levels, while also preventing some of the side effects we see in the current standard of care, which is treatment with statin drugs. Statin drugs have shown to cause new onset type 2 diabetes in some patients (Cederberg et al., 2015), and can also cause issues with liver health (FDA, 2014). Since there are no current studies examining the effects of antihyperlipidemic herbs and formulas on lipid levels as well as blood glucose levels and liver health, this study aims to close this gap.

The results are organized by the pharmacological actions examined in this study: hypolipidemic and atherosclerotic effects, anti-diabetic effects, hepatoprotective actions, and side effects and herb-drug interactions. Any results for XFZYT are examined first, followed by the individual ingredients in the formula. The most prescribed single herbs will be listed last in each section. Table 11 summarizes the findings sorted by pharmacological action:

Table 11

Hypolipidemic Effects	Antidiabetic Effects	Hepatoprotective Effects
Chi Shao	Chi Shao	Chai Hu
Chuan Xiong	Da Huang	Chi Shao
Da Huang	Dan Shen	Dang Gui
Dan Shen	Dang Gui	Gan Cao
Dang Gui	Di Huang	Ge Gen
Gan Cao	Gan Cao	Hong Hua
Ge Gen	Ge Gen	Jie Geng
Hong Hua	Hong Hua	XFZYT
Jie Geng	Jie Geng	Ze Xie
Shan Zha	Shan Zha	
Ze Xie	Ze Xie	
XFZYT		

Herbs sorted by pharmacological effects.

Hypolipidemic and Atherosclerotic Effects

In regards to the hypolipidemic and atherosclerotic effects of XFZYT and its components as well as the other single herbs included, many have shown to be effective in lowering lipid levels as well as improving atherosclerotic indices. The effects documented in the studies reviewed are shown in Table 5 (herbs contained in XFZYT are highlighted in red).

XFZYT was mentioned in a total of four studies. Three of these studies (Song et al., 2012; Liao et al., 2014; Want, Xiong & Li, 2015) found that the formula reduces total cholesterol (TC) levels as well as LDL levels. Two of them (Song et al., 2012; Liao et al., 2014) also found that XFZYT was able to increase HDL levels, with Song et al. (2012) finding that these effects were dose-dependent. Table 6 shows the results of this study in terms of changes in TC, LDL, and HDL levels in hyperlipidemic rats after seven weeks of treatment with simvastatin (SIM), high-dose (XF3), medium-dose (XF2), and low-dose (XF1) of XFZYT (Song et al., 2012).

Table 6:

Column1	SIM	XF3	XF2	XF1
TC	51.40%	54.24%	46.70%	34.77%
LDL	47.80%	48.47%	39.90%	29.60%
HDL	49.81%	42.16%	N/A	N/A

Song et al. (2011)

One study (Wang, Xiong & Li, 2015) stated that the formula was able to lower triglyceride (TG) levels as well, and the article by Liao et al. (2014) also mentioned that XFZYT was able to enhance simvastatin's ability to lower LDL levels. Chu at al. (2015) also noted that XFZYT was found to decrease the risk of atherosclerosis.

Dang Gui was mentioned in two studies (Wang et al., 2015; Kang et al., 2015). Both studies reported that Dang Gui was effective at reducing TC and TG concentrations, and Wang et al. (2014) found these actions to be dose-dependent. Kang et al. (2015) studied Dang Gui in combination with Chuan Xiong, and found this combination decreased atherosclerotic indices ($p < 0.05$) as well as reduced atherosclerotic plaque areas ($p < 0.01$). Hong Hua, another herb in XFZYT, was found to normalize cholesterol and LDL levels by Zhou et al. (2014).

Chuan Xiong was mentioned in two articles (Xie, Zhao & Du, 2011; Kang et al., 2015). Both studies found Chuan Xiong to be able to lower TC, TG, and LDL levels. Kang et al. (2015), however, used a combination of Chuan Xiong with Dang Gui. This combination significantly decreased TC, TG, and LDL ($p < 0.05$). In addition, Kang et al. (2015) also reported decreased atherosclerotic indices ($p < 0.05$) and plaque areas ($p < 0.01$). Jie Geng appeared in three studies (Chen et al., 2015; Hwang et al., 2012; Lee et al., 2014). All three studies found Jie Geng to be able to lower TG levels, two (Chen et al., 2015; Chen et al., 2015) stated that it was able to lower TC levels, and Hwang et al. (2012) also found Jie Geng to be effective at lowering LDL levels. Chi Shao was found to improve hyperlipidemia by lowering LDL and TC levels, however, effects on TG levels were not noted.

Five articles were found on Shan Zha's effects on blood lipid levels (Xie, Zhao & Du, 2011; Jurikova et al., 2012; Kwok et al., 2010; Niu et al., 2011; Chang & Zuo, 2002). Four of these (Xie, Zhao & Du, 2011; Jurikova et al., 2012; Kwok et al., 2010; Chang & Zuo, 2002) reported Shan Zha's effect on lowering LDL levels, and three articles found Shan Zha effective at lower TC levels (Xiao, Zhao & Du, 2011; Jurikova et al., 2012; Kwok et al., 2010) and at lowering TG levels (Xiao, Zhao & Du, 2011; Jurikova et al., 2012; Chang & Zuo, 2002). Niu et al. (2011) stated that Shan Zha improved hypertriglyceremia and hypercholesterolemia, and

Jurikova et al. (2010) reported that Shan Zha prevented LDL oxidization, increased LDL receptor activity, and prevented cholesterol accumulations in the liver as well as suppressed cholesterol synthesis.

Da Huang appeared in four studies (Xie, Zhao & Du, 2011; Sham et al., 2014; Li et al., 2016; Xie & Shang, 2014). Three of these (Xie, Zhao & Du, 2011; Li et al., 2016; Xie & Shang, 2014) reported Da Huang to be effective at lowering TC, TG, and LDL levels. Sham et al. (2014) reported Da Huang to have an inhibitory effect on HMG-CoA, similar to the effects of statins. In regards to HDL levels, Xie, Zhao & Du (2011) found Shan Zha to raise these levels, while Li et al. (2016) found no effects on HDL levels, and Xie & Shang (2014) reported a reduction in HDL levels.

Ze Xie was mentioned in three articles (Xie, Zhao & Du, 2011; Sham et al., 2014; Tian et al., 2014). Two studies mentioned its ability to lower TG levels (Xie, Zhao & du, 2011; Tian et al., 2014), one mentioned an increase in HDL levels (Tian et al., 2014), and Sham et al. (2014) reported that Shan Zha decreased liver synthesis of cholesterol and was also able to lessen lipid peroxidation.

Five articles examined various actions of Dan Shen (Xie, Zhao & Du, 2011; Sham et al., 2014; Van Poppel et al., 2015; Yang et al, 2011; Huang et al., 2015). Sham et al. (2014) and Yang et al. (2011) both noted Dan Shen's ability to inhibit LDL oxidization, Xie, Zhao & Du (2011) and Huang et al. (2015) both noted Dan Shen's ability to increase HDL levels while lowering TC levels, and while Huang et al. (2015) observed Dan Shen being able to lower TG levels, Huang et al. (2015) found it to lower LDL levels. Van Poppel et al. (2015) looked at the water extract of Dan shen, and found it to have no effects on any blood lipid levels.

Ge Gen was mentioned in six articles (Xie, Zhao & Du, 2011; Sham et al., 2014; Wei, Chen, & Xu, 2014; Zhou, Zhang & Peng, 2014; Wong et al., 2011; Wu et al., 2013). Four of these noted Ge Gen's ability to lower TC and TG levels (Xie, Zhao & du, 2011; Zou, Zhang & Peng, 2013; Wong et al, 2011; Wu et al., 2013), two also found it effective in lowering LDL levels (Xie, Zhao & du, 2011; Wu et al, 2013). Sham et al. (2014) looked at some of the mechanisms and found that Ge Gen promoted cholesterol and bile acid excretion in the liver, and Wei, Chen & Xu (2014) noted an overall hypocholesterolemic effect of the herb. Table 8 shows the studies and results found for hypolipidemic and anti-atherosclerotic effects.

Table 8

HERBS/FORMULA	**ACTIONS**
XFZYT	Song et al. (2012) • Reduced TC & LDL levels • Increased HDL levels (dose-dependent) Liao et al. (2014) • Lowers TC & LDL levels • Enhanced simvastatin's efficacy in lowering LDL • Increased HDL levels Wang, Xiong, Li (2015) • Lowered TC, TG, and LDL Chu et al. (2015) • Decreased risk of atherosclerosis
Dang Gui	Wang K et al. (2014) • Reduced serum TC & TG concentrations (dose-dependent action) Kang et al. (2015) – studied with Chuan Xiong • Decreased TG, TC, and LDL • Decreased atherosclerotic index • Reduced atherosclerotic plaque areas
Hong Hua	Zhou X et al. (2014) • Normalized cholesterol & LDL
Shan Zha	Xie, Zhao & Du (2011) • Lowered TC, TG, and LDL Jurikova et al. (2012)

	• Prevented LDL oxidization • Increased LDL receptor activity • Reduced TC, LDL, and TG • Prevented cholesterol accumulation in liver • Suppressed cholesterol synthesis Kwok CY et al. (2010) • Lowered LDL and TC & increased HDL • Normalized atherosclerotic index Niu et al. (2011) • Improved hypertriglyceremia & hypercholesterolemia Chang & Zu0 (2002) • Lowered LDL and TG
Da Huang	Xie, Zhao & Du (2011) • Lowered TC, TG, and LDL levels • Raised HDL Sham et al. (2014 • Inhibited HMG-CoA Li J et al. (2015 • Lowered TC, TG, and LDL (dose-dependent) • No changes in HDL • Decreased hepatic TC and TG levels Xie & Shang (2014) • Reduced TC, TG, LDL & HDL levels
Ze Xie	Xie, Zhao & Du (2011) • Lowered TC and TB Sham et al. (2014) • Decreased liver synthesis of cholesterol • Lessened lipid peroxidation & activated antioxidant enzymes Tian, Chen & Zhao (2014) • Decreased cholesterol and TG in serum and liver • Increased HDL levels
Dan Shen	Xie, Zhao & Du (2011) • Lowered TC and TG • Raised HDL Sham et al. (2014) • Inhibited LDL oxidation Van Poppel et al. (2015) • No effect on lipids or blood pressure Yang TL et al. (2011) • Inhibited LDL oxidization Huang et al. (2015) • Lowered TC and LDL • Increased HDL (dose-dependent)
Ge Gen	Xie, Zhao & Du (2011) • Lowered TC, TG, and LDL Sham et al. (2014) • Promoted cholesterol and bile acid excretion in liver

	Wei, Chen & Xu (2014) • Hypocholesterolemic effects Zhou YX, Zhang & Peng (2014) • Lowered TG & TC levels Wong KH et al. 2011 • Reduced TC and TG levels Wu et al. 2013 • Lowered TG, TC, and LDL levels
Chuan Xiong	Xie, Zhao & Du (2011) • Lowered TC, TG, and LDL levels Kang et al. (2015) (with Dang Gui) • Decreased TG, TC, and LDL levels • Decreased atherosclerotic index & plaque areas
Jie Geng	Chen T et al. (2015) • Downregulated TC and TG in liver Hwang YP et al. 2012 • Lowered TC, TG, and LDL levels Lee JS et al. 2014 • Decreased TG
Chi Shao	Zhang, Yang, & Yu 2014 • Improved hyperlipidemia • Lowered LDL & TC levels • No observed effect on TG

Summary of findings for hypolipidemic and anti-atherosclerotic effects

Antidiabetic Effects

While XFZYT wasn't mentioned in any articles in terms of effects on blood glucose levels (BG) and insulin resistance (IR) or insulin sensitivity (IS), many of the herbs it contains did. Dang Gui was mentioned by Wang et al. (2014) as having fasting BG levels lowering effects which were found to be dose-dependent, and as being able to correct insulin resistance. Hong Hua was found by Zhou et al. (2014) to normalize fasting BG levels, as well as normalizing insulin levels and normalizing the size of the islets of Langerhans. Gan Cao displayed insulin and BG level reducing actions, as well as being able to reduce weight gain by Sil, Ray & Chakraborti (2015).

Jie Geng was mentioned in three articles (Lee et al., 2012; Hwang et al, 2012; Lee et al, 2014). Lee et al. (2012) found it was able to improve insulin resistance and obesity, Lee et al. (2014) found it to lower BG levels and improve glucose and insulin tolerance, and Hwang et al (2012) noted that it was able to decrease body weight as well as liver weight. Di Huang enhanced glucose-stimulating insulin secretions in a study by Park et al. (2008), which they attributed to its ability to improve glucose sensing. Chi Shao was found to improve hypercholesterolemia and improve IR (Zhang, Yang & Yu, 2014).

Ge Gen appeared in five studies (Prasain et al., 2012; Wei, Chen & Xu, 2014; Zhou, Zhang & Peng, 2014; Wong et al., 2011; and Wu et al., 2013). Three of those noted Ge Gen's ability to lower BG levels (Zhou, Zhang, Peng, 2014; Wong et al., 2011; Wu et al., 2013), and two mentioned Ge Gen's ability to improve insulin responsiveness (Prasain et al., 2012; Zhou, Zhang & Peng, 2014). Wei, Chen & Xu (2014) noted Ge Gen was able to enhance glucose uptake as well as glucose-stimulated insulin secretions, and Wu et al. (2013) also stated Ge Gen showed effects on lowering body weight.

Da Huang was examined in two of the studies (Li et al., 2016; Arvindekar et al., 2015). Both found Da Huang to be effective at lower BG levels, and Li et al. (2016) also pointed to its ability to decrease body weight while improving insulin sensitivity. Ze Xie was found to increase glucose update by Tian et al. (2014). Shan Zha was labeled as "potentially anti-diabetic" by Chowdhury et al. (2014), And Shih et al. (2013) found it to reduce BG levels, and indicated that it may improve insulin resistance at mid- to high doses. Dan Shen was mentioned in two studies (Qiang et al., 2015; Huang et al., 2015) which both noted Dan Shen's effects on lowering fasting BG levels. Qiang et al. (2015) found it to be able to lower BG in both type 1 and type 2 diabetes,

and Huang et al. (2015) also found it increased insulin sensitivity and reduced blood insulin levels. The summary of results can be found in Table 9.

Table 9

HERBS	ACTIONS
Dang Gui	Wang K et al. 2014 • Decreased FBG level (dose-dependent) • Ameliorated insulin resistance
Hong Hua	Zhou X et al. 2014 • Normalized FBG • Normalized insulin • Normalized size of islets of Langerhans
Gan Cao	Sil, Ray & Chakraborti, 2015 • Reduced weight gain • Reduced BG and Insulin
Ge Gen	Prasain et al, 2012 • Improved glucose and insulin responsiveness Wei, Chen & Xu, 2014 • Enhanced glucose uptake • Enhanced glucose-stimulated insulin secretions Zhou YX, Zhang, Peng (2013) • Lowered BG • Improved insulin resistance Wong KH et al. 2011 • Decreased BG and insulin levels Wu et al. 2013 • Reduced BG levels • Reduced body weight
Jie Geng	Lee CE et al. 2012 • Ameliorated insulin resistance • Ameliorated obesity Hwang YP et al. 2012 • Decreased body weight and liver weight Lee JS et al. 2014 • Lowered BG levels • Improved glucose and insulin tolerance
Di Huang	Park et al. 2008 • Enhanced glucose-stimulated insulin secretion by improving glucose sensing
Chi Shao	Zhang, Yang, & Yu (2014) • Improved hyperglycemia • Improved insulin resistance

Da Huang	Li J et al. (2015) • Decreased body weight • Reduced FBG • Improved insulin sensitivity Arvindekar et al. (2015) • Reduced BG
Ze Xie	Tian, Chen & Zhao (2014) • Increased glucose uptake
Shan Zha	Chowdhury et al. (2014) • Potentially anti-diabetic Shih et al. 2013 • Reduced BG levels • May improve insulin resistance at middle and high doses
Dan Shen	Qiang G et al. 2015 • Lowered FBG and BG in type 1 and type 2 diabetes Huang et al. 2015 • Lowered FBG at mid and high doses • Increased insulin sensitivity and reduced blood insulin levels

Summary of results for antidiabetic effects.

Hepatoprotective Effects

XFZYT as well as many of the individual herbs were found to have hepatoprotective effects. XFZYT was examined in three studies (Chu et al., 2015; Song et al., 2012; and Zhou et al., 2014). Decreases in the risk of developing fatty liver disease due to a high fat diet were noted by Chu et al. (2015), and Song et al. (2012) also found that XFZYT was able to reduce hepatic steatosis. Zhou et al., (2014) found that XFZYT was able to decrease ALT, AST, and TBil levels, and also inhibited the progression of hepatic fibrosis with an anti-angiogenic effect on fibrotic liver tissue and by decreasing inflammation.

Dang Gui was found to alleviate fatty liver changes by Wang et al. (2014), and Hua et al. (2014) examined the effects of polysaccharides extracted from various preparations of Dang Gui, and found the polysaccharides from charred Dang Gui to be the most effective at displaying hepatoprotective effects. Zhou et al. (2014) noted that Hong Hua has an antifibrotic effect on the liver. Gan Cao was also found to have hepatoprotective properties by three studies (Sil, Ray &

Chakraborti, 2015; Li et al., 2014; Jung et al., 2016). Sil, Ray & Chakraborti (2015) found Gan Cao was able to lower ALT, ALP and AST levels, Jung et al. (2016) mentioned its protective effect against alcohol-induced liver damage, and Li et al. (2014) listed Gan Cao as an herb with hepatoprotective properties.

Chai Hu was found to prevent fibrosis and improve liver function while also enhancing the antioxidant defense system and inhibiting liver inflammation and fibrosis (Zheng et al., 2013), but Lee, Wang and Chen (2011) found a dose-dependent correlation between Chai Hu-containing formulas and hepatotoxicity, especially in Hepatitis B patients. Formulas containing more than 19 g of Chai Hu were found to be the most likely to induce hepatotoxicity.

Jie Geng displayed the ability to lower ALT and AST levels in studies by Chen at al. (2015) and Choi et al., 2012. Chen et al. (2015) also mentioned its ability to improve liver histological changes, and Hwang et al. (2012) found it to have a regulatory effect on hepatic lipogenesis, and to prevent infiltrations of fatty tissue in the liver. Zhang, Yang & Yu (2014) found that Chi Shao had multiple hepatoprotective effects by decreasing ALT and AST levels, improving overall liver function, and by being able to lower hepatic fatty infiltrations.

Ge Gen was mentioned to be hepatoprotective by Sham et al. (2014), and Wei, Chen & Xu (2014) found while it was able to reduce ALT and AST levels, Ge Gen displayed no effects on ALP levels. Ze Xie was described as being able to prevent hepatic steatosis by Jang et al. (2015), but Tian et al. (2014) found that it is possibly hepatotoxic as well as nephrotoxic. Shan Zha was able to decrease fatty deposits in studies on mice by Jurikova et al. (2012). Summary of results can be seen

in Table 10.

Table 10

HERBS/FORMULAS	ACTIONS
XFZYT	Chu et al. 2015 • Decreased risk of fatty liver disease induced by high fat diet Song et al. 2012 • Decreased lipid droplets and ameliorated hepatic steatosis Zhou et al. 2014 • Decreased ALT, AST, and TBil levels • Decreased inflammatory or necroinflammatory foci • Inhibited progression of hepatic fibrosis • Antiangiogenic effects in fibrotic liver tissue
Dang Gui	Hua et al. 2014 • Hepatoprotective effect best with polysaccharides from charred Dang Gui Wang et al. 2014 • Alleviated fatty liver changes
Hong Hua	Zhou et al. 2014 • Antifibrotic effect on liver
Ge Gen	Sham et al. 2014 • Hepatoprotective Wei, Chen & Xu (2014) • Reduced ALT and AST • No changes in ALP
Gan Cao	Sil, Ray & Chakraborti, 2015 • Lowered ALT, ALP, and AST Li J et al 2014 • Hepatoprotective Jung et al. 2016 • Protective against alcohol-induced liver damage
Chai Hu	Lee, Wang, and Chen 2011 • Dose-dependent hepatotoxicity of Chai Hu-containing formulas Zheng N et al. 2013 • Prevented fibrosis and improved liver function • Enhanced antioxidant defense system • Inhibited liver inflammation and fibrosis
Jie Geng	Chen et al. 2015 • Downregulated ALT & AST • Attenuated liver histological changes Choi JH et al. 2012 • Downregulated AST and ALT Hwang YP et al 2012 • Regulated hepatic lipogenesis • Prevented fatty infiltration in liver

Chi Shao	Zhang, Yang & Yu, 2014 • Decreased ALT and AST levels • Attenuated hepatic adipose infiltration • Improved liver function
Ze Xie	Jang et al. 2015 • Prevented hepatic steatosis pathogenesis Tian, Chen & Zhao 2014 • Possible hepatotoxicity and nephrotoxicity
Shan Zha	Jurikova et al. 2012 • Decreased fatty deposits in mouse livers

Summary of results for hepatoprotective properties.

Side Effects and Drug-Herb Interactions

Studies on side effects and drug-herb interactions were limited. Liao et al. (2014) found that some patients on XFZYT reported GI discomfort, fatigue, headaches, and dizziness, but these side effects were also found in the medication group. Wang, Xiong & Li (2015) reported nausea and dry cough as patient-reported side effects of XFZYT. Dang Gui was documented as having interactions with Warfarin (Chen et al, 2013); a female patient who was concurrently taking Warfarin and Dang Gui experienced a significant increase in INR levels, which went back into therapeutic ranges after Dang Gui was discontinued. Zhou et al., (2014), while noting that Hong Hua was non-toxic, also pointed to an increase in reported side effects, mostly due to the fact that Hong Hua had recently gained popularity in being used as a natural coloring agent. They noted that it was found to have teratogenic effects, had toxic effects of testicular tissue in mice, and in one report “caused a significant decrease in seminiferous tubule diameter, seminiferous epithelial weight, and maturation arrest.” Gan Cao was found to have no toxic effects by Sil, Ray & Chakraborti (2015), and Lee, Wang & Chen (2011 reported dose-dependent hepatotoxic effects of Chai Hu-containing formulas.

Ge Gen was suggested to be used in caution in certain patients by Liao et al. (2014) because it was found to have an estrogen-like effect, not only on lipid metabolism, but also on adipose tissue. Wong et al. (2011) examined Ge Gen's effect on CYP enzymes, and found it to be inductive of CYP1A2, CYP2B1, CYP2E1, AND CYP3A, and to have an inhibitory effect on CYP2D4. These effects have to be considered when prescribing Ge Gen to patients on drugs which are metabolized by any of the enzymes (Wong et al., 2011). Da Huang was reported as an herb with no significant cytotoxicity by Li et al. (2016), and Tian et al. (2014) reported that Ze Xie might be hepato- and nephrotoxic. Summary of results can be seen in Table 11.

Table 11

HERBS	ACTIONS
Hong Hua	Zhou X et al. 2014 • Non-toxic • teratogenic effects • evidence of toxic effect on mouse testicular tissue • caused a significant decrease in seminiferous tubule diameter, seminiferous epithelial weight and maturation arrest
Dang Gui	Chen XP et al. 2013 • Documented interaction with Warfarin
XFZYT	Liao et al. 2014 • GI discomfort, fatigue, headache, dizziness Wang, Xiong, & Li 2015 • Nausea, dry cough
Ge Gen	Sham et al. 2014 • Estrogen-like effect on lipid metabolism and adipose tissue Wong KH et al. 2011 • Induces CYP1A2, CYP2B1, CYP2E1, CYP3A • Inhibits CYP2D4
Gan Cao	Sil, Ray & Chakraborti 2015 • No toxic effects
Chai Hu	Lee, Wang & Chen 2011 • Dose-dependent hepatotoxicity of Chai Hu-containing formulas
Da Huang	Li J et al. 2015 • No significant cytotoxicity
Ze Xie	Tian, Chen & Zhao 2014 • Possible hepatotoxicity and nephrotoxicity

Summary of results for side effects and herb-drug interactions.

Chapter 5: Discussion

Summary of Findings

The objective of this study was to evaluate the efficacy of hypolipidemic herbs and formulas on blood lipid levels, blood glucose levels and insulin resistance, and on hepatic function. Side effects as well as herb-drug interactions were reviewed as well. A total of 48 articles qualified to be included. These articles had significant variations in study design, outcome reporting, methodology, participants, inclusion and exclusion of pattern differentiation, and results reported.

Many of the herbs and formulas prescribed for hyperlipidemia that were included in this project are in fact effective at lowering blood lipid levels, and also have positive effects on BG levels, IR, and hepatic function. This indicates that treatment with Chinese herbal formulas could offer a viable treatment alternative for patients who cannot or will not take statins. However, the inconsistencies in study design, especially surrounding uniformity of various extracts of plants used and the methods used for extraction, as well as the lack of adequately designed human trials implies that more research is warranted. A deeper understanding also needs to be gained regarding side effects as well as herb-drug interactions.

Discussion of Findings

The number of prescriptions for statin drugs are on the rise (“NCHS Data Brief”, 2014; Pencina et al., 2014), and patient compliance remains poor (Toth, 2010; Maningat et al., 2013), mainly due to side effects that range from liver damage and cognitive issues to an increased risk of new onset type 2 diabetes (Cederberg et al., 2015; FDA, 2014). There are also questions regarding the use of statin drugs in a preventative model, with Mosca (2012) stating that safety

has yet to be established for long-term preventative use in patients without CD, and Redberg and Katz (2012) stating that a Cochrane review reported that statins should only be used with caution in a primary prevention model. Considering that hyperlipidemia is often treated with herbs in Eastern countries (Chu et al., 2015; Sham et al., 2014), and most studies examined found no toxicity, or only mild side effects (Zhou X et al., 2014; Sil et al., 2015, Liao et al., 2014; Wang et al, 2015, Li et al., 2016), herbal treatment of hyperlipidemia may present a viable treatment option for patients who cannot or will not take statins.

In this study, XFZYT and its herbal ingredients, as well as the five single herbs reviewed, were effective not only at lowering lipid levels, but also at regulating BG levels and IR, and many were shown to have hepatoprotective functions as well. In fact, based on the information discovered, XFZYT in itself covers all of the reviewed functions: it was reported to decrease atherosclerosis (Chu et al., 2015), decrease the risk of fatty liver and liver fibrosis (Song et al., 2014; Chu et al., 2015), reduce TC and LDL levels while increasing HDL levels (Song et al., 2014), decreased ALT, AST and TBil levels (Zhou et al., 2014), and was found to enhance the lipid-lowering effects of Simvastatin (Liao et al., 2014). The side effects that were reported were mostly mild (GI discomfort, headaches, dizziness, fatigue, and dry cough), and these also occurred in the medicated control groups (Liao et al., 2014; Wang et al., 2015). One of its ingredients, Chai Hu, had mixed results in the studies reviewed. While one found that Chai Hu is commonly prescribed for its positive effects on liver function (Zheng et al., 2013), another study found a dose-related correlation between formulas with high doses (19g or more) of Chai Hu and hepatotoxicity (Lee, Wang, & Chen, 2011). These observations were made in patients with chronic hepatitis B infections, and Chai Hu was always part of a multi-herb formula.

XFZYT is also one of the top prescribed formulas in Taiwan for ischemic heart disease (Hung et al., 2015), and several of the studies included in this project pointed to its ability to support healthy cardiovascular function (Chu et al., 2015, Hung et al., 2015). These pharmacological actions were also confirmed in studies looking at the ingredients of XFZYT. Dang Gui, for example, was found to be hepatoprotective while also reducing fasting blood glucose (FBG) and TC levels, ameliorating IR, and alleviating fatty liver changes (Hua et al. 2014; Wang et al., 2014). Jie Geng was found to have wide therapeutic actions ranging from regulating hepatic lipogenesis and reducing ALT, AST, TC, and LDL to attenuating IR and facilitating weight loss (Chen et al., 2015, Choi et al., 2012; Hwang et al., 2012, Lee C et al., 2012). Considering that obesity is often a factor seen in hyperlipidemia, Jie Geng shows promise to treat many of the comorbidities associated with elevated lipid levels. Other noteworthy pharmacological actions that need to be investigated further are the mention of Hong Hua's ability to normalize the size of islets of Langerhans (Zhou X et al., 2014), and Chuan Xiong's potential at decreasing atherosclerosis while reducing the size of plaques (Kang et al., 2015).

Due to the effects some of XFZYT's ingredients have on coagulation times and blood viscosity, however, this formula is not recommended for patients who are on anticoagulant and antiplatelet medications, since its mechanisms resembles that of these drugs and may lead to enhanced drug actions (Chen & Chen, 2001). Moreover, interactions have been reported (Chen et al., 2013), and herbs and formulas with blood moving and hence blood circulation enhancing properties are generally contraindicated to be used with anticoagulants (Chen & Chen, 2004 & 2009).

Of the single herbs studied, Ge Gen was of particular interest due to its wide range of therapeutic actions. This herb shows promise not only at lowering TC and LDL levels while

raising HDL levels (Xie, Zhao, & Du, 2011), but also because of its hepatoprotective effects and ability to reduce serum ALT and AST levels (Wei, Chen, & Xu, 2014). Some of the cholesterol-lowering effects might be due to its ability to promote cholesterol and bile acid excretion (Sham et al., 2014). Moreover, Ge Gen showed potential in being able to regulate BG levels and IR, as well as possibly leading to weight loss (Wu et al., 2013). However, Ge Gen has been found to exhibit estrogen-like effects on lipid metabolism, which might be problematic in some female patients. It has also been found to affect CYP enzymes (CYP1A2, 2B1, 2E1, 3A, AND 2D4) that are involved in drug synthesis, which makes it more likely to have interactions with drugs metabolized by these enzymes (Wong et al., 2011).

Several of the single herbs studied, such as Shan Zha, Dan Shen, and Ze Xie, show promise in inhibiting LDL oxidation, which is a key factor in the formation of foam cells and atherosclerosis (Jurikova et al., 2012; Yang et al., 2011; Sham et al., 2014). These effects should be studied further, since a reduction in size and number of foam cells can alleviate some of the risks associated with hyperlipidemia. Another interesting observation was that the aqueous extract of Wu Wei Zi was able to moderate the liver injury induced by the treatment of fenofibrate (FF) in hyperlipidemic mice (Zhu et al., 2015). This shows that herb-drug interactions can have positive effects as well, and the combinations of herbs with pharmaceutical drugs might be able to negate some of the more serious side effects.

What became apparent after reviewing these articles and studies was that there are still many factors that need to be understood and incorporated into designing studies to examine the efficacy of CM herbal formulas. While all studies included discussed pharmacological effects of herbs, there was no consistency in the preparation and compounds of the herbs used. The efficacy and pharmacological actions vary greatly with different extraction methods, and both

the type of extraction medium (ethanol, water, glycerin, etc.) and the concentration of the extraction medium (i.e. 80% ethanol solution vs. 70% ethanol solution) was shown to be of importance (Xie & Shang, 2014). Some of these issues might be the reason there was conflicting information regarding herbs and pharmacological actions identified. For example, Chai Hu was listed both as possibly hepatoprotective and possibly hepatotoxic. For Da Huang, one study found it to be able to raise HDL levels, one observed no changes in HDL, while a third found it to lower HDL levels. Moreover, the preparation of the herbs used before compounds were extracted (i.e. charred, untreated, parched with wine) also affected pharmacological efficacy and effects (Hua et al., 2014). While some studies focused on a single compound of an herb, like platycodin D from Jie Geng (Chen et al., 2015), others used whole herb extracts which resulted in multiple compounds, like saponins, inulin, and oligosaccharides from Jie Geng (Choi et al., 2013). This again is an issue since combined compounds will have different pharmacological effects than single ones. Several of the studies pointed to the fact that there is a synergy between the different compounds extracted from a whole herb or whole herb formula that effects the pharmacological actions of the herbs or formulas studied. Zhang and Cheng (2005) found that while the single compounds extracted did not exert a strong hypolipidemic effect, a combination of these compounds did. This makes it clear that we cannot only study herbs by understanding their individual compounds, but we also need to consider often unquantifiable synergistic actions between these isolates.

Limitations of the Current Study

There were several limitations with this study. First of all, due to the lack of full articles available in English, studies of all types were included: Review articles, human trials,

population-based studies, animal, in vivo, and in vitro studies. The majority of the studies on single herbs and formulas were in animal models, which cannot freely be translated into effects in the human body. Many of the review articles summarized results, rather than including specific biomarkers, and often lacked pertinent information about study design, participants, and outcome markers. The original articles were not in English and therefore could not be referenced. Some authors pointed to a high probability of researcher bias, and poorly described randomization methods. Also, many of the articles lacked pertinent information regarding participants and study designs, and standardization in terms of outcome measures, extraction methods, and types of extracts or compounds used. Some studies tested whole herbs used as a food supplements, others tested single extracts of the herbs. The extraction methods were often not described, or they varied widely from water extraction to ethanol and methanol extractions, and concentrations of extraction mediums were not uniform, or not mentioned at all. A list of the extraction methods can be found in Appendix 8.

Gagnier et al. (2006) addressed this issue of inadequate reporting of herbal interventions, and issued recommendations for good reporting practices, which cover herb product name (i.e. Latin name for each ingredient), the characteristics of the herbs studied (i.e. part(s) of the herb used, or method of extraction), dosage regimens and quantitative descriptions (i.e. dose and length of administration, and factors used to determine these), qualitative testing (i.e. description of testing for contaminants or chemical analysis), information on placebo or control group used, and information on the practitioners that are part of the study.

Moreover, issues arose due to different compositions of XFZYT. The study from Zhang & Chen (2005) claimed to have identified major constituents of XFZYT, but they only included six (Chi Shao, Chuan Xiong, Zhi Ke, Hong Hua, Tao Ren, and Chai Hu) of the 11 herbs that are

traditionally found in this formula. While this gives us some understanding of which compounds are found in XFZYT, it is far from complete. With the studies for Ge Gen, different variations of the same species were tested (Japanese vs. Chinese Pueraria), and it was sometimes unclear which one was used. The number of articles included in this project were also limited by the fact that many of the individual herbs included were studied as part of a formula that contained herbs not discussed in this study, and hence had to be excluded.

An important limitation emerged regarding pattern differentiation. While some studies used pattern differentiation in their inclusion requirements, others ignored this altogether and limited their criteria for enrollment to western biomedical diagnoses. The importance of correct pattern identification in TCM was supported by the fact that the studies which included pattern differentiation generally had better results than the ones who relied exclusively on western biomedical diagnoses.

Recommendations for Future Research

Based on the information reviewed in this article, it has become apparent that the way we test efficacy of CM herbal formulations needs to be refined. There are five main factors that need to be considered, based on the findings of this study:

1. Pattern differentiation along with biomedical diagnosis
2. Standardization of whole herb formula composition
3. Standardization of extraction methods and extracts used
4. Synergistic actions between multiple plant compounds
5. Herb-drug interactions

Future research needs to be designed that takes all these factors into consideration, while also being quantifiable in terms of western research requirements. Due to the overall low side effects, a study in a human cohort can be considered for primary prevention of hyperlipidemia. Since the formula discussed in this project, XFZYT, is specifically indicated for Blood Stasis patterns, the inclusion and exclusion criteria should include:

- Primary prevention setting
- No or limited medications (due to lack of documented herb-drug interactions)
- No history of CD
- No current diagnosis of diabetes
- Age under 70
- Recent biomedical diagnosis of hyperlipidemia
- Current TCM diagnosis of Blood Stasis

Measures of outcome should be evaluated using these biomarkers:

- TC
- LDL
- HDL
- FBG
- HgA1c
- ALT & AST

In regards to formula composition, pattern-specific as well as disease-specific herbs should be included. Pattern-specific formulas and herbs address the diagnosed TCM pattern of the disease. Disease-specific herbs and extracts address specific western diseases or biochemical pathways associated with these diseases based on research. Guidelines could be as followed:

- XFZYT (pattern-specific whole herb formula, including all 11 herbs)
- Disease-specific whole herb modification (i.e. Ge Gen)
- Disease-specific herbal extract – standardized in extraction method

Since studies indicated that pattern differentiation might play an important role in the best outcome of herbal treatments, further studies should include these parameters. Witt et al. (2014) discussed guidelines for Comparative Effectiveness Research (CER) for CM, and they pointed out that CM pattern differentiation seems to be a relevant factor especially in CM herbal therapies. Their recommendations include establishing databases, the use of clinical health records to start identifying common pattern diagnoses and interventions, and clinical trials designed to examine the complexities of the combined CM interventions.

One way to get a better understanding of TCM patterns associated with specific diseases, like hyperlipidemia, could be established by creating a data base to collect case studies by TCM practitioners of patients with defined biomedical diseases. This database could track the biomedical diagnosis, TCM pattern diagnosis, and symptoms and parameters upon which these diagnoses were based. This would eventually enable the medical community to evaluate other pattern-specific herbal formulas for their efficacy in treating western diseases.

Due to the poor understanding of herb-drug interactions, further studies to examine herb effects on the CYP450 system, which is involved in drug synthesis, are necessary. Further

studies are also necessary to understand some of the synergistic effects single compounds exhibit when combined.

Conclusion

This study established that XFZYT holds promise in treating hyperlipidemia while also controlling blood glucose levels and insulin resistance, and at being hepatoprotective. However, due to the lack of standardization of extracts studied, and the fact that synergistic functions of herbal formulas that cannot be fully understood yet play an important role in pharmaceutical effects exerted and efficacy, further studies are necessary to evaluate the formula's full potential.

TCM formulas and herbs have a broad spectrum of therapeutic actions. The complex and non-linear nature of pattern identification in TCM, and the fact that the same biomedically defined disease can present with multiple TCM patterns, make the design of studies to evaluate the efficacy and pharmacological actions of herbal formulas difficult. The reductionist methods of western science stand in stark contrast to the interdependent holism of TCM. Evaluation of the efficacy, pharmacological actions, and safety of TCM herbal formulas in a primary care setting, require an approach that combines understanding and studying the specific indications from standardized extracts, with the inclusion of these extracts in whole herb formulas, in order to allow for the synergistic effects that cannot be quantified at this point. A better understanding of single extracts, whole herb formulas, and positive as well as negative interactions between herbs and drugs will give practitioners alternatives for patients who cannot tolerate drugs, like statins for hyperlipidemia, due to side effects.

References

AACMA (Australian Acupuncture & Chinese Medicine Association LTD), (retrieved January 13, 2016a). *Chinese Herbal Medicine.* Retrieved from http://www.acupuncture.org.au/health_services/chinese_herbal_medicine.aspx

AACMA (Australian Acupuncture & Chinese Medicine Association LTD), (retrieved January 13, 2016b). *Traditional Chinese Medicine.* Retrieved from http://www.acupuncture.org.au/Health_Services/Traditional_Chinese_Medicine.aspx

American Heart Association (2014). *What your cholesterol levels mean.* Retrieved from http://www.heart.org/HEARTORG/Conditions/Cholesterol/AboutCholesterol/What-Your-Cholesterol-Levels-Mean_UCM_305562_Article.jsp#.VsFhWsfaRUQ

Arvindekar, A., More, T., Payghan, P. V., Laddha, K., Ghoshal, N., & Arvindekar, A. (2015). *Evaluation of anti-diabetic and alpha glucosidase inhibitory action of anthraquinones from Rheum emodi.* Food & Function, 6, 2693-2700.

Bensky, D., & Barolet, R. *Chinese Herbal Medicine: Formulas & Strategies.* 1990. Seattle: Eastland Press.

Bensky, D., Clavey, S.& Stoeger, E. (2004). *Chinese Herbal Medicine Materia Medica: 3rd Edition.* Seattle: Eastland Press.

Boon, N. A., Colledge, N. R., Walker, B. R., & Hunter, J. A. A. (2006). Davidson's Principles & Practice of Medicine, 20th edition. Toronta, Canada: Elsevier.

Cai, H., Lian, L,, Wang, Y., Yu, Y., & Liu, W. (2014). *Protective effects of Salvia miltiorrhiza injection against learning and memory impairments in streptozotocin-induced diabetic rats.* DOI: 10.3892/etm.2014.1919

CDC (2015) *High Cholesterol Facts.* Retrieved from

http://www.cdc.gov/cholesterol/facts.htm

Cederberg, H., Stancakova, A., Yaluri, N., Modi, S., Kuusisto, J., & Laakso, M. (2015). *Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6-year follow-up study of the METSIM cohort.* Diabetologia, 58, 1109 – 1117, DOI 10.1007/s00125-015-3528-5

Chang, Q., Zuo, Z., Harrison, F., & Chow, M. S. S. (2002). *Hawthorn.* Journal of Clinical Pharmacology, 42, 605-612

Chang, W., Zhang, M., Meng, Z., Yu, Y., Yao, F., Hatch, G. M., & Chen, L. (2015). *Berberine treatment prevents cardiac dysfunction and remodeling through activation of 5'-adenosine monophosphate-activated protein kinase in type 2 diabetic rats and in palmitate-induced hypertrophic H9c2 cells.* European Journal of Pharmacology, 769, 55 – 63.

Chen, J., & Chen, T. (2004) *Chinese Herbal Formulas and Applications.* City of Industry, CA: Art of Medicine Press, Inc.

Chen, J., & Chen, T. (2009) *Chinese Medical Herbology and Pharmacology.* City of Industry, CA: Art of Medicine Press, Inc.

Chen, T., Gao, J., Xiang, P., Chen, Y., Ji, J., Xie, P., Wu, H., Xiao, W., Wei, Y., Wang, S., Lan, L., Ji, H., & Yan, T. (2015) *Protective effect of platycodin D on liver injury in alloxan-induced diabetic mice via regulation of Treg/Th17 balance.* International Immunopharmacology, 26, 338-348.

Chen, X., Li, W., Xiao, X., Zhang, L., & Liu, C. (2013). *Phytochemical and pharmacological studies on Radix Angelica Sinensis.* Chinese Journal of Natural Medicines, 11(6), 0577-0587.

Cho, S. H., Yoon, Y., & Yang Y. (2013). *The evaluation of the Body Weight Lowering Effects of Herbal Extract THI on Exercising Healthy Overweight Humans: A Randomized Double-Blind, Placebo-Controlled Trial.* Hindawi Publishing Corporation: Evidence-Based Complementary and Alternative Medicine, Article ID 758273, 8 pages.

Chowdhury S.S., Islam M.N., Jung H.A., & Choi J.S (2014) *In Vitro antidiabetic potential of the fruits of Crataegus pinnatifida.* Research in Pharmaceutical Sciences, 9(1), 11 – 22

Choi, J. H., Jin, S. W., Kim, H. G., Khanal, T., Hwang, Y. P., Lee, H. J., Choi, C. Y., Chung, Y. C., Lee, Y. C., & Jeong, H. G. (2013). *Platycodi Radix attenuates dimethylnitrosamine-induced liver fibrosis in rats by inducing Nrf2-mediated antioxidant enzymes.* Food and Chemical Toxicology, 56, 231-239.

Chu, S., Shih, W., Yang, Y., Chen, P., & Chu, Y. (2015). *Use of traditional Chinese medicine in patients with hyperlipidemia: A population-based study in Taiwan.* Journal of Ethnopharmacology, 168, 129 – 135

Dan, H., Wu, J., Peng, M., Hu, X., Song, C., Zhou, Z., Yu, S., & Fang, N. (2011). *Hypolipidemic effects of Alismatis rhizome on lipid profile in mice fed high-fat diet.* Saudi Med J, 32(7).

Dharmananda, S. (2002). Treatment of Diabetes with Chinese Herbs and Acupuncture. Internet Journal of the Institute for Traditional Medicine and Preventative Care.

Durrington Paul (2003). *Dyslipidemia.* The Lancet, 362.

Edwards, J. E., Brown, P. N., Talent, N., Dickinson, T. A., & Shipley, P. R. (2012) *A review of the chemistry of the genus Crataegus.* Phytochemistry 79 (2012) 5 – 26

Fasinu, P. S., Bouic, P. J., & Rosenkranz, B. (2014). *An overview of the evidence and*

mechanisms of herb-drug interactions. Frontiers in Pharmacology, 3 (69).

FDA Expands Advice on Statin Risk (DATE). Retrieved from http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm293330.htm

Flaws, B., & Sionneau, P. (2005). *The Treatment of Modern Western Medical Diseases with Chinese Medicine: A Textbook and Clinical Manual, Expanded Edition.* Boulder, Colorado: Blue Poppy Press.

Gagnier, J.J., Boon, H., Rochon, P., Moher, D., Barnes, J., & Bombardier, C. (2006). *Reporting randomized, controlled trials of herbal interventions: An elaborated CONSORT statement.* Annals of Internal Medicine, 144, 364-367.

Gao, D., Wu, L., Jiao, Y., Kaptchuk, T. J., Chen, W., Chen, Y., Lu, B., Song, J., & Chen, K. (2010). *The Effect of Xuefu Zhuyu Decoction on in vitrol Endothelial Progenitor Cell Tube Formation.* Chin J Integr Med., 16(1): 50. Doi:10.1007/s11655-010-0050-y.

Gao, Z., Xu, H., Shi, D., Wen, C., & Liu, B. (2012). *Analysis on outcome of 5284 patients with coronary artery disease: The role of integrative medicine.* Journal of Ehtnopharmacology, 141, 578 – 583

Goldberg, A.C. (2015). *Dyslipidemia (Hyperlipidemia).* Merck Manuals, Professional Version. Retrieved from https://www.merckmanuals.com/professional/endocrine-and-metabolic-disorders/lipid-disorders/dyslipidemia

Green & Britten (1998). *BMJ 316,1230*

Gu, Q., Paulose-Ram, R., Burth, V. L., & Kit, B. K. (2014). *Prescription Cholesterol-lowering Medication Use in Adults Aged 40 and Over: United States, 2003 – 2012.* NCHS Data Brief, No. 177. U.S. Department of Health and Human Services.

Harvard Men's Health Watch, Volume 19, Number 2 (2014) *Statin side effects: How common are they?* Retrieved from www.health.harvard.edu

Hasani-Ranjbar, S., Nayebi, N., Moradi, L., Mehri, A., Larijani, B., & Abdollahi, M. (2010). *The Efficacy and Safety of Herbal Medicines Used in Treatment of Hyperlipidemia; A Systematic Review.* Current Pharmaceutical Design, 16, 2935 – 2947

Hu, M., Zeng, W., & Tomlinson, B. (2014). *Evaluation of a Crataegus-Based Multiherb Formula for Dyslipidemia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial.* Hindawi Publishing Corporation: Evidence-Based Complementary and Alternative Medicine, Vol. 2014, Article ID 365742, 9 pages. http://dx.doi.org/10.1155/2014/365742

Hua, Y., Xue, W., Zhang, M., Wei, Y., & Ji, P. (2013). *Metabonomics study on the hepatoprotective effects of polysaccharides from different preparations of Angelica Sinensis.* Journal of Ethnopharmacology, 151, 1090-1099.

Huang, M., Wang, P., Xu, S., Xu, W., Xu, W., Chu, K., & Lu J. (2015) *Biological activities of salvianolic acid B from Salvia miltiorrhiza on type 2 diabetes induced by high-fat diet and streptozotocin.* Pharmaceutical Biology, 53(7), 1058-1065.

Hung, Y., Tseng, Y., Hu, W., Chen, H., Li, T., Tsai, P., Chen, H., Huang, M., & Su F. (2015). *Demographic and Prescribing Patterns of Chinese Herbal Products for Individualized Therapy for Ischemic Heart Disease in Taiwan: Population-Based Study.* PLoS ONE 10(8): e0137058. Doi: 10.1371/journal.pone.0137058

Hwang, Y. P., Choi, J. H., Kim, H. G., Khanal, T., Song, G. Y., Nam, M. S., Lee, H. S.,

Chung, Y. C., Lee, Y. C., & Jeong, H. G. (2013). *Saponins, especially platycodin D, from Platycodon grandiflorum modulates hepatic lipogenesis in high-fat rats and high glucose-exposed HepG2 cells.* Toxicology and Applied Pharmacology, 267, 174-183.

Irwig L, Irwig J, Trevena L, & Sweet M (2008). *Smart Health Choices: Making Sense of Health Advice.* London: Hammersmith Press. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK63647/

Jang, M. K., Han, Y. R., Nam, J. S., Han, C. W., Kim, B. J., Jeong, H. S., Ha, K.T., & Jung, M. H. (2015). *Protective Effects of Alisma Orientale Extract against hepatic steatosis via inhibition of endoplasmic reticulum stress.* International Journal of Molecular Sciences, 16, 26151-26165.

Jensen M.T., Anderson H.U., Rossing P., & Jensen J.S. (2016). *Statins are independently Associated with Increased HbA1c in Type 1 Diabetes – The Thousand and 1 Study.* Diabetes Research and Clinical Practice, http://dx.doi.org/101016/j.diabres.2015.10.022

Jung, J.C., Lee, Y.H., Kim, S., Kim, K.J., Kim, K.M., Oh, S., & Jung, Y.S. (2016). *Hepatoprotective effects of licorice, the root of Glycyrrhiza uralensis Fischer, in alcohol-induced fatty liver disease.* BMC Complementary and Alternative Medicine, 16,19.

Jurikova, T., Sochor, J., Rop, O., Mlcek, J., Ball, S., Szekeres, L., Adam, V., & Kizek, R. (2012). *Polyphenolic Profile and Biological Activity of Chinese Hawthorn (Crataegus pinnatifida BUNGE) Fruits.* Molecules, 17, 14490 – 14509; doi:10.3390/molecules171214490

Kalant, H., Grant, D. M., Mitchell, J. (2007). Principles of Medical Pharmacology, 7th Edition, (pp 466 – 482). Toronto: Elsevier Canada.

Kang, Q., Liu, W., Liu, H., & Zhou M. (2015). *Effect of Compound Chuanxiong Capsule on Inflammatory Reaction and PI3K/Akt/NF-kappaB signaling Pathway in Atherosclerosis.* Hindawi Publishing Corporation: Evidence-Based Complementary and Alternative Medicine, Vol 2015, Article ID 584596, 9 pages.

Kong, W., Wei, J., Abidi, P., Lin, M., Inaba, S., Li, C., Wang, Y., Wang, Z., Si, S., Pan, H., Wang, S., Wu, J., Wang, Y., Li, Z., Liu, J. & Jiang J.D. (2004). *Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins.* Nature Medicine, 10(12), doi: 10.1038/nm1135

Kumar, V., Abbas A. K., Fausto N., & Mitchell R. N. (2007). Robbins Basic Pathology, 8th edition. Philadelphia, PA: Saunders Elsevier.

Kwok, C.Y., Wong, C. N.Y., Yau, M. Y. C., Yu P. H.F., Au, A. L. S., Poon, C. C. W., Seto, S. W., Lam, T. Y., Kwan, Y. W.,& Chan, S. W. (2010). *Consumption of dried fruit of Crataegus pinnatifida (hawtorn) suppresses high-cholesterol diet-induced hypercholesterolemia in rats.* Journal of Functional Foods 2, 179 – 186

Lai, S. W., Ng, K. C., Lin, H. F., & Chen, H. L. (2001). *Association Between Obesity and Hyperlipidemia Among Children.* Yale Journal of Biology and Medicine, 74, 205-210

Lau C, Mooiman K.D., Maas-Bakker R.F., Beijnen J.H., & Schellens J.H.M. (2013). *Effect of Chinese Herbs on CYP3A4 activity and expression.* Journal of Ethnopharmacology, 149: 543-549.

Lee, C.H., Wang, J.D., Y Chen, P.C. (2011). *Risk of Liver Injury Associated with Chinese Herbal Products Containing Radix bupleuri in 639,779 Patients with Hepatitis B Virus Infection.* PLoS ONE, Volume 6, Issue 1, e16064.

Lee, C.E., Hur, H.J., Hwang, J.T., Sung, M.J., Yang, H.J., Kim, H.J., Park, J.H., Kwon,

D.Y., & Kim, M.S. (2012). *Long-Term Consumption of Platycodi Radix Ameliorates Obesity and Insulin Resistance via the Activation of AMPK Pathways.* Hindawi Publishing Corporation: Evidence-Based Complementary and Alternative Medicine, Vol. 2012, Article ID 759143, 11 pages.

Lee, J.S., Choi, M.S., Seo, K.I., Lee, J., Lee, H.I., Lee, J.H., Kim M.J., & Lee, M.K. (2014). *Platycodi radix saponin inhibits alpha-glucosidase in vitro and modulates hepatic glucose-regulating enzyme activities in C57BL/KsJ-db/db mice.* Arch. Pharm. Res., 37, 773-782.

Li, J.Y., Cao, H.Y., Liu, P., Cheng, G.H., & Sun, M.Y. (2014). *Glycyrrhizic Acid in the Treatment of Liver Diseases: Literature Review.* Hindawi Publishing Corporation: BioMed Research International, Vol. 2014, Article ID 872139, 15 pages.

Li, J., Ding, L., Song, B., Xiao, X., Qi, M., Yang, Q., Yang, Z., Tang, X., Wang, Z., & Yang, L. (2016). *Emodin improves lipid and glucose metabolism in high fat diet-induced obese mice thorugh regulating SREBP pathway.* European Journal of Pharmacology, 770: 99-109.

Liao, J., Tian, J., Li, T., Song, W., Zhao, W., & Du, J. (2014) *Xuefuzhuyu decoction for hyperlipidemia: a systematic review and Meta-analysis of randomized clinical trials.* Journal of Traditional Chinese Medicine 2014 August 15;34(4): 411-418.

Liu, J., Zhang, H.J., Ji, B.P., Cai, S.B., Wang, R.J., Zhou, F., Yang, J.S., & Liu, H.J. (2014). *A diet formula of Puerariae radix, Lycium barbarum, Crataegus pinnatifida, and Polygonati rhizome alleviates insulin resistance and hepatic steatosis in CD-1 mice and HepG2 cells.* Food & Function, 5, 1038

Liu, L., Duan, J., Tang, Y., Guo, J., Yang, N., Ma, H., Shi, X. (2011). *Taoren-Honghua*

herb pair and its main components promoting blood circulation through influencing on hemorrheology, plasma coagulation and platelet aggregation. Journal of Ethnopharmacology, 139, 381-387.

Liu Z.L., Liu J.P., Zhang A.L., Wu Z., Ruan Y., Lewith G., & Visconte D. (2011) *Chinese herbal medicines for hypercholesterolemia (Review).* The Cochrane Library, 7.

Lu C., Zha Q., Chang A., He Y., & Lu A. (2009). *Pattern differentiation in Traditional Chinese Medicine can help define specific indications for biomedical therapy in the treatment of rheumatoid arthritis.* Journal of Alternative Complementary Medicine, 15(9), 1021-5

Maciocia, G. (2005). *The Foundations of Chinese Medicine.* Elsevier Churchill Livingstone: Philadelpia.

Mahamuni, S. P., Khose, R. D., Menaa, F., & Badole, S. L. (2012). *Therapeutic approaches to drug targets in hyperlipidemia.* Biomedicine 2 (2012) 137 – 146

Maningat, P., Gordon, B.R., & Breslow, J.L. (2013). *How Do We Improve Patient Compliance and Adherence to Long-Term Statin Therapy.* Curr Atheroscler Rep., 15(1): 291. Doi:10.1007/s11883-012-0291-7.

Martin Laura (2015). NIH/Medline Plus. Retrieved from https://www.nlm.nih.gov/medlineplus/ency/article/003472.htm

Mayo Clinic (2016). *A1C test.* Retrieved from *http://www.mayoclinic.org/tests-procedures/a1c-test/home/ovc-20167930*

Mayo Clinic (2014). *Heart Disease.* Retrieved from http://www.mayoclinic.org/diseases-conditions/heart-disease/basics/definition/con-20034056

McCormack, J., Vandermeer, B., & Allan, G.M.l (2013). *How Confidence*

Intervals become confusion intervals. BMC Medical Research Methodology, 2013(13), 134, DOI: 10/1186/1471-2288-13-134

Medline Plus (2015). *Aspartate aminotransferase (AST) blood test.* Retrieved from https://www.nlm.nih.gov/medlineplus/ency/article/003472.htm

Merriam-Webster Medical Dictionary, *Alanine Aminotransferase.* Retrieved on Jan. 14, 2016 from http://www.merriam-webster.com/medical/alanine%20aminotransferase

Mosca, L. (2012). *Controversy and Consensus About Statin Use.* Journal of the American College of Cardiology, 59(6).

National Institutes of Health (2001) *Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Executive Summary.* Retrieved from http://www.nhlbi.nih.gov/files/docs/guidelines/atp3xsum.pdf

National Institutes of Health/Medline Plus (retrieved January 15, 2016). *Cholesterol.* Retrieved from *https://www.nlm.nih.gov/medlineplus/cholesterol.html*

National Institutes of Health/Medline Plus (retrieved January 15, 2016). *Hyperglycemia.* Retrieved from https://www.nlm.nih.gov/medlineplus/hyperglycemia.html

Niu C.S., Chen C.T., Chen L.J., Cheng K.C., Yeh C.H., & Cheng J.T. (2011). *Decrease of Blood Lipids Induced by Shan-Zha (Fruit of Crataegus pinnatifida) is Mainly Related to an Increase of PPAR-alpha in Liver of Mice Fed High-Fat Diet.* Morm Metab Res, 2011(43): 625 – 630. Stuttgart/New York: Georg Thieme Verlag KG.

O'Brien, K.A. (2010). *Alternative Perspectives: How Chinese Medicine Understands Hypercholesterolemia.* Hindawi Publishing Corporation, Cholesterol, 2010, Article ID 723289, 9 pages, doi: 10.1155/2010/723289.

O'Brien, K.A., Abbas, E., Zhang, J., Guo, Z.X., Luo, R., Bensoussan, A., & Komesaroff,

P.A. (2009). *An Investigation into the Reliability of Chinese Medicine Diagnosis According to Eight Guiding Principles and Zang-Fu Theory in Australians with Hypercholesterolemia.* The Journal of Alternative and Complementary Medicine, 15(2), 259-266. DOI: 10.1089/acm.2008.0204

Okuyama, H., Langsjoen, P.H., Hamazaki, T., Ogushi, Y., Hama, R., Kobayahsi, T., & Uchino, H. (2015). *Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms.* Expert Review of Clinical Pharmacology, 8(2)

Qiang, G., Yang, X., Shi, L., Zhang, H., Chen, B., Zhao, Y., Zu, M., Zhou, D., Guo, J., Yang, H., Zhang, L., & Du, G. (2015). *Antidiabetic Effect of Salvianolic Acid A on Diabetic Animal Models via AMPK Activation and Mitochondrial Regulation.* Cell Physiol Biochem, 36, 395-408.

Park, S.M., Hong, S.M., Sung, S., Lee, J.E., & Kwon, D.Y (2007). *Extracts of Rehmanniae radix, Ginseng radix and Scutellariae radix improve glucose-stimulated insulin secretion and beta-cell proliferation through IRS 2 induction.* Genes Nutr, e, 347-351, DOI 10.1007/s12263-007-0065-y

Pejic, R.N., Lee, T. (2006). *Hypertriglyceridemia.* Journal of the American Board of Family Medicine, 19(3), 310-316.

Pencina, M.J., Navar-Boggan, A.M., D'Agostino, R.B., Williams, K., Neely, B., Sniderman, A.D., & Peterson, E.D. (2014). *Application of New Cholesterol Guidelines to a Population-Based Sample.* N Engl J Med, 2014(370), 1422-1431.

Prasain, J.K., Peng, N., Rajbhandari, R., & Wyss J.M. (2012). *The Chinese Pueraria root extract (Pueraria lobota) ameliorates impaired glucose and lipid metabolism in obese mice.* Phytomedicine; 20(1), 17-23. Doi: 10.1016/j.phymed.2012.09.017.

Pu, X., Fan, W., Yu, S., Li, Y., Ma, X., Liu, L., Ren, J., & Zhang, W. (2015) *Polysaccharides from Angelica and Astragalus exert hepatoprotective effects against carbon-tetracholride-induced intoxication in mice.* Can. J. Physiol. Pharamcol., 93: 39-43. Dx.doi.org/10.1139/cjpp-2014-0331.

Rouhi-Boroujeni, H., Rouhi-Boroujeni, H., Heidarian, E., Mohammadizadeh, F., & Rafieian-Kopael, M. (2015) *Herbs with anti-lipid effects and their interactions with statins as a chemical anti-hyperlipidemia group drugs: A systematic Review.* ARYA Atheroscler, 11(4), pp. 244 – 251

Sea, L.C., &McPherson, M.L. (2012). *Pharmacokinetics and pharmacodynamics changes associated with aging and implications for drug therapy.* Clinical Geriatric Medicine, 28, 273 – 286

Sham, T.T., Chan, C.O., Wang, Y.H., Yang, J.M., Mok, D.K.W., & Chang, S.W. (2014). *A Review on the Traditional Chinese Medicinal Herbs and Formulae with Hypolipidemic Effect.* Hindawi Publishing Corporation, BioMed Research International, Volume 2014, Article ID 925302, 21 pages, http://dx.doi.org/10.1155/2014/925302.

Shamsi-Baghbanan H., Sharifian A., Esmaeili S., & Minaei B. (2014). *Hepatoprotective Herbs, Avicenna Viewpoint.* Iranian Red Crescent Medical Journal, 16(1), e12313.

Shier, D., Butler, J., & Lewis, R. (2004). *Hole's Human anatomy and Physiology.* New York: McGraw-Hill.

Shih, C.C., Lin, C.H., Lin, Y.J., & Wu, J.B. (2013). *Validation of the Antidiabetic and Hypolipidemic Effects of Hawthorn by Assessment of Gluconeogenisis and Lipogenesis Related Genes and AMP-Activated Protein Kinase Phosphorylation.* Hindawi Publishing Corporation: Evidence-Based Complementary and

Alternative Medicine, Vol. 2013, Article ID 597067, 12 pages. http://dx.doi.org/10.1155/2013/597067

Sil, R., Ray, D., & Chakraborti, A.S. (2015). *Glycyrrhizin ameliorates metabolic syndrome-induced liver damage in experimental rat model.* Mol Cell Biochem 409: 177-189.

Song, J., Chen, W.Y., Wu, L.Y., Zheng, L.P., Lin, W., Gao, D., Kaptchu, T.J.K., & Chen, K.J. (2012). *A Microarray Analysis of Angiogenesis Modulation Effect of Xuefu Zhuyu Decoction on endothelial Cell.* Chin J Integr Med., 18(7): 502-506. Doi: 10.1007/s11655-012-1143-6.

Song, X., Wang, J., Wang, P., Tian, N., Yang, M.,& Kong Lingyi (2013). *H NMR-based metabolomics approach to evaluate the effect of Xue-Fu-Zhu-Yu decoction on hyperlipidemia rats induced by high-fat diet.* Journal of Pharmaceutical and Biomedical Analysis, 78 – 79, 202 – 210

Stagnitti, M.N. (2008). *Trends in Statins Utilization and Expenditures for the U.S. Civilian Noninstitutionalized Population, 2000 and 2005.* Statistical Brief #205, Agency for Healthcare Research and Quality. Retrieved from http://meps.ahrq.gov/mepsweb/data_files/publications/st205/stat205.pdf

Statin Side Effects: Weigh the benefits and risks (2013). Mayo Clinic. Retrieved from http://www.mayoclinic.org/diseases-conditions/high-blood-cholesterol/in-depth/statin-side-effects/art-20046013

Stone, N.J., Robinson, J., Lichtenstein, A.H., Bairey , M.C.N., Blum, C.B., Ecke, R.H.I., Goldberg, A.C., Gordon, D., Lloyd-Jones, D.M., McBride, P., Schwartz, J.S., Shero, S.T., Smith Jr., S.C., Levy, D., Watson, K., Wilson, P.W.F., Eddleman, K.M., Jarrett,

N.M., LaBresh, K., Nevo, L., & Wnek, J. (2013). *2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults*. Retrieved from http://circ.ahajournals.org/

Tan Y., Kamal, M.A., Wang, Z.Z., Xiao, W., Seale, J.P., & Qu, X. (2011). *Chinese herbal extracts (SK0506) as a potential candidate for the therapy of the metabolic syndrome.* Clinical Science, 120, 297 – 305

Tarloff, J.B. (2012). *Adverse Drug Reactions.* Merck Manual, Professional Edition. Retrieved from http://www.merckmanuals.com/professional/clinical-pharmacology/adverse-drug-reactions/adverse-drug-reactions

TCM Kongress (2016) *Chen, John (USA).* Retrieved from www.tcm-kongress.de.en/programm/referent-921.htm

Teschke, R., Zhang, L., Long, H., Schwarzenboeck, A., Schmidt-Taenzer, W., Genthner, A., Wolff, A., Frenzel, C., Schulze, J., & Eickhoff, A. (2015). *Traditional Chinese Medicine and herbal hepatotoxicity: a tabular compilation of reported cases.* Annals of Hepatology, 14(1), 7-19

Teschke, R. (2014). *Traditional Chinese Medicine Induced Liver Injury.* Journal of Clinical and Translational Hepatology, 2, 80-94.

Tian, T., Chen, H., & Zhao, Y.Y. (2014). *Traditional uses, Phytochemistry, pharmacology, toxicology and quality control of Alisma orientale (Sam.) Juzep: A review*. Journal of Ethnopharmacology, 158, 373-387.

Tseng, S.H., Chien, T.Y., Chen, J.R., Lin, I.H., & Wang, C.C. (2011) *Hypolipidemic*

Effects of Three Purgative Decoctions. Hindawi Publishing Corporation, Evidence-Based Complementary and Alternative Medicine, Volume 2011, Article ID 249254, 10 pages, doi: 10.1093/ecam/nep178

Thorsten, M., Hendrik, J.. Andersen, U., Rossing, P., & Jensen, J.S. (2015). *Statins are Independently Associated with Increased HbA1c in Type 1 Diabetes – The thousand and 1 Study*. Diabetes Research and Clinical Practice, http://dx.doi.org/10.1016/j.diabres.2015.10.022

Top 100 Most Prescribed, Top Selling Drugs (2014). Medscape Medical News. Retrieved from http://www.medscape.com/viewarticle/825053

Toth P.P. (2010). *Drug Treatment of Hyperlipidaemia: A guide to the Rational Use of Lipid-Lowering Drugs.* Drugs 2010: 70 911 0: 1363 – 1379

University of Maryland Medical Center (2015). *Red Yeast Rice.* Retrieved from https://umm.edu/health/medical/altmed/supplement/red-yeast-rice

Van Poppel, P.C.M., Breedveld, P., Abbink, E.J., Roelofs, H., Van Heerde, W., Smits, P., Lin, W., Tan, A.H., Russe, F.G., Donders, R., Tack, C.J., & Rongen, G.A. (2015) *Salvia Miltiorrhiza Root Water-Extract (Danshen) Has No Beneficial Effect on Cardiovascular Risk Factors. A Randomized Double-Blind Cross-Over Trial.* PLOS ONE, DOI: 10.1371/journal.pone.0128695.

Valledor, A.F., Lioberas, J., & Celada, A. (2015) *Macrophage Foam Cells.* DOI: 10.1002/9780470015902.a0020730.pub2, retrieved from http://www.els.net/WileyCDA/ElsArticle/refId-a0020730.html

Wang, H.J., & Chiang, B.H. (2012). *Anti-diabetic effect of a traditional Chinese medicine formula.* Food Funct., 3, 1161.

Wang, J., Yang, X., Chu, F., Chen, J., He, Q., Yao, K., Teng, F., Gao, Y., Xing, Y., Wu, A., & Xing, Y. (2013) *The Effects of Xuefu Zhuyu and Shengmai on the Evolution of Syndromes and Inflammatory Markers in Patients with Unstable Angina Pectoris after Percutaneous Coronary Intervention: A randomized Controlled Clinical Trial.* Hindawi Publishing Corporation: Evidence-Based Complementary and Alternative Medicine, Volume 2013, Article ID 896467, 9 pages.

Wang, K., Cao, P., Shui, W., Yang, Q., Tang, Z., & Yu, Z. (2015) *Angelica sinensis polysaccharide regulates glucose and lipid metabolism disorder in prediabetic and streptozotocin-induced diabetic mice through the elevation of glycogen levels and reduction of inflammatory factors.* Food and Function, 6, 902

Wang, P., Xiong, X., & Li, S. (2015). *Efficacy and Safety of a Traditional Chinese Formula Xuefu Zhuyu Decoction for Hypertension.* Medicine, 94(42).

Wei, S.Y., Chen, Y., & Xu, X.Y. (2014). *Progress on the pharmacological research of puerarin: a review.* Chinese Journal of Natural Medicines, 12(6), 0407-0414.

Weinrauch, L. (2014). *Lipoprotein-a.* Medline Plus. Retrieved from https://www.nlm.nih.gov/medlineplus/ency/article/007262.htm

Witt, C.M., Aickin, M., Cherkin, D., Che, C.T., Elder, C., Flower, A., Hammerschlag, R., Liu, J.P., Lao, L., Purrough, S., Ritenbaugh, C., Rubin, L.H., Schnyder, R., Wayne, P.M., Rafferty Withers, S., Zhao-Ziang, B., Young, J., Berman, B.M. & Collaborators (2014). *Effectiveness guidance document (EGD) for Chinese medicine trials: a consensus document.* Trials, 15, 169.

Woo K.S., Yip Thomas W.C., Chook P., Kwong S.K., Szeto C.C., Li June K.Y.,

Yu A.W.Y., Cheng W.K.F., Chan T.Y.K., Fung K.P., & Leung P.C. (2013). *Cardiovascular Protective Effects of Adjunctive Alternative Medicine (Salvia Miltiorrhiza and Pueraria lobate) in High-Rest Hypertension.* Hindawi Publishing Corporation: Evidence-Based Complementary and Alternative Medicine, Vol. 2013, Article ID 132912, 8 pages.

Wong, K.H., Li, G.Q., Li, K.M., Razmovski-Naumovski, V., & Chan, K. (2011). *Kudzu Root: Traditional uses and potential medicinal benefits in diabetes and cardiovascular disease.* Journal of Ethnopharmacology, 134: 584-607.

Wu, K., Liang, T., Duan, X., Xu, L., Zhang, K., & Li, R. (2013). *Anti-diabetic effects of puerarin, isolated from pueraria lobota (Wild.) on streptozotocin-dibetogenic mice through promoting insulin expression and ameliorating metabolic function.* Food and Chemical Toxicology, 60, 341-347.

Xie, H.C., & Shang, J. (2014). *Study on the extraction process of total anthraquinones in Radix et Rhizoma Rhei and their Antilipidemic Effects.* Afr J Tradit Complement Altern Med, 11(2), 358-362.

Xie W & Du L. (2011). *Diabetes is an inflammatory disease: evidence from traditional Chinese medicines.* Diabetes, Obesity and Metabolism, 13, 289-301.

Xie, W., Zhao, Y., & Du, L. (2012). *Emerging Approaches of traditional Chinese medicine formulas for treatment of hyperlipidemia.* Journal of Ethnopharmacology, 140, 345 – 367

Xu, H., Xu, H., & Ryan, D. (2009). *A Study of the Comparative Effects of Hawthorn Fruit Compound and Simvastatin on Lowering Blood Lipid Levels.* The American Journal of Chinese Medicine, 37(5), 903 – 908

Yang, T.L., Lin, F.Y., Chen, Y.H., Chiu, J.J., , Shiao, M.S., Tsai, C.S., Lin, S.J., & Chen, Y.L. (2011). *Salvianolic acid B inhibits low-density lipoprotein oxidation and neointimal hyperplasia in endothelium-denuded hypercholesterolaemic rabbits.* J Sci Food Agric, 91, 134-141.

Yang, X., Xiong, X., Yang, G., & Wang, J. (2014). *Chinese patient medicine Xuefu Zhuyu capsule for the treatment of unstable angina pectoris: A systematic review of randomized controlled trials.* Complementary Therapies in Medicine, 22, 391-399.

Yi, G.Z., Qiu, Y.Q., Xiao, Y., & Yuan, L.X. (2014). *The Usefulness of Xuefu Zhuyu Tang for Patients with Angina Pectoris: A Meta-Analysis and Systematic Review*. Hindawi Publishing Corporation: Evidence-Based Complementary and Alternative Medicine, Volume 2014, Article ID 521602, 11 pages.

Yin J., Xing, H., & Ye, J. (2008). *Efficacy of Berberine in Patients with Type 2 Diabetes*. Metabolism., 57(5), 712 – 717 .

Zhang, H.J., & Cheng, Y.Y. (2006). *An HPLC/MS method for identifying major constituents in the hypocholesterolemic extracts of Chinese medicine formula 'Xue-Fu-Zhu-Yu decoction'*. Biomedical Chromatography, 20: 821-826.

Zhang, L., Yang, B., & Yu, B. (2015). *Paeoniflorin Protects against Nonalcoholic Fatty Liver Disease Induced by a High-Fat Diet in Mice.* Biol. Parm. Bull., 38, 1005-1011.

Zhang, T.T., & Jiang, J.G. (2012). *Active ingredients of traditional Chinese medicine in the treatment of diabetes and diabetic complications.* Expert Opinion on Investigational Drugs, 21(11), 1625 – 1642

Zhao, H.L., Sui, Y., Qiao, C.F., Yip, K.Y., Leung, R.K., Tsui, S.K., Lee, H.M., Wong, H.K., Zhu, X., Siu, J.J., He, L., Guan, J., Liu, L.Z., Xu, H.X., Tong, P.C., & Chan J.C. (2012).

Sustained antidiabetic effects of a Berberine-containing Chinese herbal medicine through regulation of hepatic gene expression. Diabetes, 61(4):933-43. doi: 10.2337/db11-1164. Epub 2012 Mar 6.

Zheng, N., Dai, J., Cao, H., Sun, S., Fang, J., Li, Q., Su, S., Zhang, Y., Qiu, M., & Huang, S. (2013). *Current Understanding on Antihepatocarcinoma Effects of Xiao Chai Hu Tang and Its Constituents.* Hindawi Publishing Corporation: Evidence-Based Complementary and Alternative Medicine, Vol. 2013, Article ID 529458, 14 pages.

Zhou, X., Tang, L., Xu, Y., Zhou, G., & Wang, Z. (2014). *Towards a better understanding of medicinal uses of carthamus tinctorius L. in traditional Chinese medicine: A phytochemical and pharmacological review.* Journal of Ehtnopharmacology, 151, 27-43.

Zhou, Y.N., Sun, M.Y., Mu, Y.P., Yang, T., Ning, B.B., Ren, S., Chen, J.M., & Liu, P. (2014). *Xuefuzhuyu decoction inhibition of angiogenesis attenuates liver fibrosis induced by CCl_4 in mice.* Journal of Ethnopharmacology, 153, 659-666.

Zhou, Y.X., Zhang, H., & Peng, C. (2014). *Puerarin: A Review of Pharmacological Effects.* Phytotherapy Research, 28, 961-975.

Zhu, P.L., Pan, S.Y., Zhou, S.F., Zhang, Y., Wang, X.Y., Sun, N., Chu, Z.S., Yu, Z.L., & Ko, K.M. (2015). *Effects of combined dietary supplementation with fenofibrate and Schizandrae Fructus pulp on lipid and glucose levels and liver function in normal and hypercholesterolemic mice.* Drug Design, Development and Therapy, 2015(9), 923-935

Appendix 1: Most prescribed formulas and herbs in Taiwan

Herbal Formula	Single Herb
Xue Fu Zhu Yu Tang	Shan Zha – *Fructus Crataegi*
Jia Wei Xiao Yao San	Dan Shen – *Radix Salvia Miltiorrhizae*
Fang Feng Tong Sheng San	He Shou Wu – *Radix Polygoni Multiflori*
Da Chai Hu Tang	Ze Xie – *Rhizoma Alismatis*
Zhi Bai Di Huang Wan	Jue Ming Zi – *Semen Cassiae*
Liu Wei Di Huang Wan	Da Huang – *Radix et Rhizoma Rhei*
Yin Chen Wu Ling San	Chuan Qi – *Radix Notoginseng*
Tian Ma Gou Teng Yin	Ge Gen – *Radix Puerariae*
Shu Jing Huo Xue Tang	Cao Jue Ming – *Semen Celosiae*
Ma Zi Ren Wan	Huang Qi – *Radix Astragali*

Table 1: Chu et al., 2015: Most prescribed herbal formulas and single herbs in Taiwan for the treatment of hyperlipidemia.

Appendix 2:

Most Used Single Herbs in Antihyperlipidemic Formulas approved in China.

Rank	**Herb**
1	Shan Zha – *Fructus Crataegi*
2	He Shou Wu – *Radix Polygoni Multiflori*
3	Ze Xie – *Rhizoma Alismatis*
4	Jue Ming Zi – *Semen Cassiae*
5	Dan Shen – *Radix Salvia Miltiorrhizae*
6	Da Huang – *Radix et Rhizoma Rhei*
7	He Ye – *Folium Nelumbinis*
8	Yin Chen Hao – *Herba Artemisiae Scopariae*
9	Ge Gen – *Radix Puerariae*
10	Gou Qi Zi – *Fructus Lycii*
11	San Qi – *Radix Notoginseng*
12	Huang Qi – *Radix Astragali*
13	Chuan Xiong – *Rhizoma Chuanxiong*

Table 2: Xie, Zhao, and Du (2011) – most used single herbs in antihyperlipidemic formulas approved in China.

Appendix 3: Single herb selection table

Chu et al.	Sham et al.	John Chen	Xie et al.
Shan Zha - 5	**Ze Xie**	Cang Zhu	**Shan Zha**
Dan Shen - 5	Huang Lian	**Dan Shen**	He Shou Wu
He Shou Wu	**Shan Zha**	**Ge Gen**	Jue Ming Zi
Ze Xie - 5	Ren Shen	He Shou Wu	**Da Huang**
Jue Ming Zi	San Qi	He Ye	**Ze Xie**
Da Huang - 5	Red Yeast Rice	Hu Zhang	**Dan Shen**
San Qi	**Ge Gen**	Jiao Gu Lan	He Ye
Ge Gen -5	**Da Huang**	Ju Hua	San Qi
Cao Jue Ming	**Dan Shen**	Jue Ming Zi	**Ge Gen**
Huang Qi		**Shan Zha**	Chuan Xiong
		Yi Yi Ren	Hong Hua
		Ze Xie	
		Zi Mu Xu	
		Da Huang	
		Hai Zao	
		Huang Qin	
		Yin Chen Hao	
		Yu Jin	

Table 3: Most-Used single herbs for treatment of hyperlipidemia based on studies included.

Appendix 4: Most used formulas to treat hyperlipidemia

Chu et al.	Sham et al.
Xuefu Zhuyu	Danggui Buxue
Jia Wei Xiao Yao	Danshen-Gegen
Fang Feng Tong Sheng	Erxian
Da Chai Hu Tang	Ling Gui Zhu Gan
Zhi Bai Di Huang	Shengmai Yin
Liu Wei Di Huang	Turtle Jelly
Yin Chen Wu Ling	Xuefu Zhuyu Tang
Tian Ma Gou Teng Yin	
Shu Jing Huo Xue Tang	
Ma Zi Ren Wan	

Table 4: Most-used formulas for the treatment of hyperlipidemia

YO SAN UNIVERSITY
OF TRADITIONAL CHINESE MEDICINE

January 22, 2016

Claudia Laufer
4601 Beethoven St.
Los Angeles, CA 90066

Dear Claudia,

Your research proposal has been approved, with no additional recommendations effective through February 15, 2016.

Should there be any significant changes that need to be made which would alter the research procedures that you have explained in your proposal, please consult with the IRB coordinator prior to making those changes.

Sincerely,

Ed Mervine
IRB Coordinator

13315 W Washington Blvd, Los Angeles 90066

Appendix 6: Table 6

Column1	SIM	XF3	XF2	XF1
TC	51.40%	54.24%	46.70%	34.77%
LDL	47.80%	48.47%	39.90%	29.60%
HDL	49.81%	42.16%	N/A	N/A

Changes in total cholesterol (TC), LDL, and HDL levels in hyperlipidemic rats after 7 weeks of treatment with simvastatin (SIM), and high (XF3), medium (XF2) and low (XF1) dose XFZYT (Song et al., 2013).

Appendix 7: Table 7

Authors	Year	Herb/Formula	Type	Actions Identified
Chu et al.	R 2015	XFZYT	rats	induce endothelial progenitor cell angiogenesis
				hastens tube formation in capillary vessels
				potentiates neuroprotection against thromboembolic stroke
			animal	decreased risk of atherosclerosis
				decreased risk of fatty liver disease induced by high fat diet
Song et al.	S 2012	XFZYT	rats	reduced TC and LDL levels
				increase HDL levels (dose-dependent)
				decreased lipid droplets & ameliorate hepatic steatosis
Zhou et al.	S 2014	XFZYT	mice	decreased ALT, AST, and TBil levels
				decrease in inflammatory or necroinflammatory foci
				inhibition of progression of hepatic fibrosis
				antiangiogenic in fibrotic liver tissues
Hua et al.	S 2014	Dang Gui	mice	hepatoprotective effect - Charred Dang Gui polysaccharides
Wang K et al.	S 2014	Dang Gui	mice	decrease in FBG level (dose dependent)
				ameliorated insulin resistance (IR)
				reduced serum TC & TG concentrations (dose dependent)
				reduced only TC, not TB in diabetic mice
				alleviated fatty liver changes
Zhou X et al.	R 2014	Hong Hua	rats	inhibit platelet aggregation
			n/a	antifibrotic effect on liver
				normalizes FBS, cholesterol, LDL, insulin, size of islets of Langerhans.
				non-toxic
Chen XP et al	R 2013	Dang Gui	n/a	documented interaction with warfarin
Liao et al	R/M 2014	XFZYT	human	lowers TC and LDL levels
				enhanced simvastatin's efficacy in lowering LDL
				increased HDL levels
				SE: GI discomfort, fatigue, headache, dizziness
Xie, Zhao, Du	R 2011	Shan Zha	mixed	Lowered TC, TG, and LDL
		Da Huang	mixed	Lowers TC, TG, LDL

				Raised HDL
		Ze Xie	animal	Lowers TC, TG
		Dan Shen	mixed	Lowers TC, TG
				Raised HDL
		Ge Gen	mixed	Lowers TC, TG, LDL
				Raised HDL
		Chuan Xiong	mixed	Lowered TC, TG, LDL
				Raised HDL
Sham et al	R 2014	Ze Xie	n/a	decreases liver synthesis of cholesterol
				Lessens lipid peroxidation, activates antioxidant
				enzymes
		Ge Gen	n/a	promotes cholesterol and bile acid excretion
				in liver
				estrogen-like effect on lipid metabolism and
				adipose tissue
				hepatoprotective
		Da Huang	n/a	inhibits HMG-CoA
		Dan Shen	n/a	inhibits LDL oxidation
Liu L et al	S 2011	Tao Ren	rats	decrease whole blood viscosity, plasma viscosity,
		& Hong Hua		packed cell volume
				prolonged thrombin time, thromboplastin time,
				prothrombin time
Sil, Ray, Chakraborti	S 2015	Gan Cao	rats	no toxic effect
				reduced weight gain, BG, insulin, TG
				lowered ALT, ALP, AST
Li J et al	R 2014	Gan Cao		hepatoprotective
				induces CYP3A (interactions)
Jung et al	S 2016	Gan Cao	mice	protective against alcohol-induced liver damage
Prasain et al	S 2012	Ge Gen	mice	improved glucose and insulin responsiveness
Wang, Xiong, Li	M2015	XFZYT	human	lowered TC, TG, and LDL
				SE: nausea, dry cough
Lee, Wang, Chen	M 2011	Chai Hu	human	dose-dependent hepatotoxicity of Chai Hu-
				containing formulas
Zheng N et al	R 2013	Chai Hu	n/a	prevent fibrosis, improve liver function.
				enhances antioxidant defense system
				inhibits liver inflammation and fibrosis
Chen T et al	S 2015	Jie Geng	mice	downregulates ALT, AST, TC, TG in liver
				attenuates liver histological changes.
Choi JH et al	S 2012	Jie Geng	rats	downregulates AST, ALT

Hwang YP et al	S 2012	Jie Geng	rats	regulates hepatic lipogenesis
				decreased body weight and liver weight
				lowered TC, TG, LDL levels
				prevented fatty infiltration in livers
Lee CE et al	S 2012	Jie Geng	mice	ameliorated insulin resistance (IR)
				ameliorated obesity
Lee JS et al	S 2014	Jie Geng	mice	lowered BG
		& Dang Gui		improved glucose and insulin tolerance
				decreased TG
Park et al	2007	Di Huang	rats	enhanced glucose-stimulated insulin secretion
				by improving glucose sensing
Kang et al	S 2015	Chuan Xiong	mice	decreased TG, TC, LDL
				decreased atherosclerotic index, reduced
				plaque areas
Zhang, Yang, Yu	S 2014	Chi Shao	mice	improved hyperglycemia, insulin resistance,
				hyperlipidemia, & LIV fx.
				lowered LDL, TC, TG was same
				decreased ALT, AST levels
				attenuates hepatic adipose infiltration
Wei, Chen, Xu	R 2014	Ge Gen	animal	hypocholesterolemic effect
				enhances glucose uptake
				enhanced glucose-stimulated insulin secretion
				reduced ALT and AST, but not ALP
Zhou YX, Zhang, Peng	R 2014	Ge Gen	animal	lowered BG, improved insulin resistance
				lowered TG, TC levels
Wong KH et al	R 2011	Ge Gen	animal	decreased BG and insulin levels
				reduced body weight, FBG, TC, TG, insulin levels
				SE: induces CYP1A2, CYP2B1, 2E1, 3A,
				inhibits CYP2D4
Wu et al	S 2013	Ge Gen	mice	reduces blood glucose levels
				reduces body weight
				lowers TG, TC, LDL
Li J et al	S 2015	Da Huang	mice	no significant cytotoxicity
				decreased body weight
				lowered TC, TG, LDL, (dose dependent),
				no change in HDL
				reduced FBG, improved insulin sensitivity
				decreased hepatic TC and TG
Xie, Shang	S 2014	Da Huang	mice	reduced TC, TG, LDL, HDL

Arvindekar et al	S 2015	Da Huang	rats	reduced blood glucose
Jang et al	S 2015	Ze Xie	in vivo	prevents hepatic steatosis pathogenesis
			/in vitro	
Tian, Chen, Zhao	R 2014	Ze Xie	animal	decreased cholesterol and triglycerides in serum
				and liver
				increased HDL levels
				increased glucose uptake
				SE: possible hepatotoxicity and nephrotoxicity
Chowdhury et al	S 2014	Shan Zha	in vitro	potentially anti-diabetic
Shih et al	S 2013	Shan Zha	mice	reduced blood glucose levels
				may improve insulin resistance at middle &
				high doses
Jurikova et al	R 2012	Shan Zha	mixed	prevents LDL from oxidation
				decreases in fatty deposits in mouse livers
				reduces TC, LDL, TG
				prevents cholesterol accumulation in liver
				suppresses cholesterol synthesis
				increased LDL receptor activity
Kwok CY et al	S 2010	Shan Zha	rats	lowered LDL and TC, increased HDL
				normalized atherosclerotic index
Niu et al	S 2011	Shan Zha	mice	improved hypertriglyceremia and
				hypercholesterolemia
				high doses
Chang, Zuo	R 2002	Shan Zha	human	lowered LDL and TG.
van Poppel et al	S 2015	Dan Zhen	human	no effects on lipids, blood pressure
Yang TL et al	S 2011	Dan Shen	rabbits	inhibits LDL oxidation
Qiang G et al	S 2015	Dan Shen	rats	lowered FBG and fed blood glucose levels in
			& mice	type 1 and type 2 diabetes
Huang et al	S 2015	Dan Shen	rats	lowers FBG at mid an high doses
				increased insulin sensitivity and reduced
				blood insulin
				lowered TC and LDL, increased HDL
				(dose dependent)

Table 7: Data extraction from qualifying articles in regards to antidiabetic, hypolipidemic, and hepatoprotective properties, and side effects and herb-drug interactions.

Appendix 8

Authors	Year/Type	Herb	Extraction or Extract information
Arvindekar et al.	S 2015	Da Huang	Anthraquinones
Chen et al.	S 2015	Jie Geng	Platycodin D (extract)
Choi et al.	S 2013	Jie Geng	Whole herb extract in water
Chen X et al.	R 2013	Dang Gui	Various
Chu et al.	R 2015	XFZYT	n/a
Chowdhury et al.	S 2014	Shan Zha	Methanol extract
Chang, Zuo	R 2002	Shan Zha	n/a
Hua et al.	S2014	Dang Gui	Water & ethanol, various preparations of Dang Gui
Huang et al.	S 2015	Dan Shen	Salvianolic acid B
Hwang et al.	S 2013	Jie Geng	Platycodin D, water extraction
Jang et al.	S 2015	Ze Xie	Methanol extract
Jung et al.	S 2016	Gan Cao	Aqueous methanol extract
Jurikova et al.	R 2012	Shan Zha	Various compounds
Kwok et al.	S 2010	Shan Zha	Whole fruit as food supplement
Kang et al.	S 2015	Chuan Xiong & Dang Gui	n/a
Lee C et al.	S 2012	Jie Geng	Ethanol
Lee J et al.	S 2014	Jie Geng	Ethanol & water
Li j et al.	S 2016	Da Huang	n/a
Lee, Wang, Chen	M/R 2011	Chai Hu	n/a
Li j et al.	R 2014	Gan Cao	n/a
Lau et al.	S 2013	Di Huang	Ethanol
Liu et al.	S 2012	Tao Ren & Hong Hua	Water
Liao et al.	R 2014	XFZYT	n/a
Niu et al.	S 2011	Shan Zha	Ethanol
Prasain et al.	S 2012	Ge Gen	Whole herb powdered
Park et al.	S 2008	Di Huang	Ethanol
Qiang et al.	S 2015	Dan Shen	Salvianolic acid A
Song et al.	S 2013	XFZYT	Water
Sham et al.	R 2014	Ze Xie	n/a
Shih et al.	S 2013	Shan Zha	Methanol & water
Sil, Ray, Chakraborti	S 2015	Gan Cao	n/a
Teschke et al.	R 2015	Various	n/a
Teschke	R 2014	Various	n/a
Tian, Chen, Zhao	R 2014	Ze Xie	n/a
Van Poppel et al.	S 2015	Dan Shen	Water
Authors	**Year/Type**	**Herb**	**Extraction or Extract information**
Wong et al.	R 2011	Ge Gen	n/a, variations in species
Wu et al.	S 2013	Ge Gen	n/a

Wei, Chen, Xu	R 2014	Ge Gen	n/a
Wang, Xiong, Li	M 2015	XFZYT	n/a
Wang K et al.	S 2015	Dang Gui	Water
Xie & Shang	S 2014	Da Huang	Various → preparation affected therapeutic effects.
Xie, Zhao, Du	R 2011	Shan Zha	n/a
Yang et al.	S 2011	Dan Shen	Salvianolic acid B, water & ethanol
Zhou, Zhang, Peng	R 2014	Ge Gen	n/a
Zhang Y, Yang, Yu	S 2014	Chi Shao	Paeoniflorin
Zheng et al.	R 2013	Chai Hu	n/a
Zhou X et al.	R 2014	Hong Hua	n/a
Zhou et al.	S 2014	XFZYT	Water

Extractions methods/extracts used in studies.

Appendix 9: Curriculum Vitae

Education

- **DAOM in Healthy Aging and Integrative** **2014 – current**
  Yo San University, Los Angeles, CA
- **MA in Traditional Chinese Medicine** (with highest honors) **2006 – 2014**
  Yo San University, Los Angeles, CA
- **Psychology** **1996 - 1999**
  Antioch University, Los Angeles, CA
- **AA in Journalism** (with highest honors) **1992 – 1994**
  Santa Monica College, Santa Monica, CA

Work Experience

- **Acupuncturist & Herbalist,** Private Practice, Los Angeles, CA **2010 - current**
  Specializing in Pain Management, Autoimmune Diseases, Digestive Disorders, and Women's Health.
- **Teaching Faculty,** Yo San University, Los Angeles, CA **2011- current**
  Teaching Acupuncture Points Anatomy & Energetics, and Points Practice classes.
- **Clinical Supervisor,** Being Alive, Hollywood & Yo San Clinic, L.A. **2016 - current**
  Supervise interns and direct treatments, advise on proper patient intake, charting, needling, patient follow up, and other issues related to treatments.
- **Clinical Externship,** Wise & Healthy Aging, Santa Monica, CA **2014 - current**
  Treated patients 65 years and older, focus on gastrointestinal health, musculoskeletal pain conditions, and respiratory diseases.
- **Clinical Internship,** Yo San University Clinic, Los Angeles, CA **2009 - 2010**
  Treated patients under supervision using acupuncture, herbs, nutrition, electro-stimulation, tuina, moxibustion, and exercise.
- **Clinical Externship,** Being Alive, West Hollywood, CA **2009 - 2010**
  Treated patients with HIV and HIV-related illnesses.
- **Kindergarten Teacher's Assistant,** Ocean Charter School, CA **2006 - 2007**
  Assisted teacher in all daily tasks including cooking, story-telling, playtime and playground supervision, conflict resolution between students, and communication with the parents.

Work Experience, continued

- **Fine Artist & Art Teacher,** CM Laufer Art, Venice, CA **1999 – 2007**

  Created contemporary artwork, sold art at Fine Art Fairs throughout the country. Taught adult and children's therapeutic arts classes.

- **Purchasing Manager**, Encore Software, Los Angeles, CA **1996 – 1999**

  Maintained inventory and ordered supplies for software production, warehouse and shipping departments.

- **Editor, Tutor, Translation Services,** Self-employed, CA **1992 - 1996**

  Editor-in-chief at Santa Monica College Corsair, tutored students in English and various other subjects, translated documents from English to Germany and vice versa.

- **Journalist & Editor-in-Chief,** Radio Gong, Germany **1991 – 1992**

  Attended press conferences, wrote news, edited sound-bites, planned daily news and entertainment programming, interviewed music celebrities, hosted evening music show

- **Graphic Artist,** Sebald Druck & Verlag, Germany **1986 - 1991**

  Supervised production of German magazine *Petra*, including color corrections, page design, managed written and photo contributions, acted as liaison between clients and production department.

Teaching Experience

- **Acupuncture Anatomy & Energetics** **2015 - current**

  Yo San University, Los Angeles, CA

- **Acupuncture Points Practice** **2011 - current**

  Yo San University, Los Angeles, CA

- **Qi Gong & Tai Chi Stress Management Techniques** **2011 - current**

  Various Locations

- **Creating Medicinal Food Gardens for Common Health Issues** **2014 - current**

  Various Locations

- **Healthy Nutrition/Eating with the Seasons** **2012 - current**

  Various Locations

Skill Highlights

- Acupuncture, Cupping, Gua Sha, Moxibustion, Auricular Therapy, Scalp Acupuncture, Tuina Massage, Rehabilitation Therapies, Chinese Herbs, Nutritional Therapies, Master Tung Acupuncture, Tai Chi & Qi Gong Exercises.

Professional Development

- Internship for herbal studies with Matt Van Benschoten
- John Chen Herbal Classes / E-Lotus.org
- Daniel Weber Seminars on Immunology, Oncology, Psychology
- Dr. Young Master Tung
- Esther Su Master Tung / E-Lotus.org
- Brad Whisnant Master Tung/ E-lotus.org
- Addictions and the Brain

Interests

- Cooking and Baking, developing healthy versions of comfort food, teaching patients about eating right on a budget and easy healthy cooking for busy adults.
- Gardening, especially growing medicinal plants and food.