

PHARMACOLOGICAL ATTRIBUTES OF NATURAL COMPOUNDS FOR CHOLESTEROL REDUCTION

Abstract

Plant sterols and stanols (phytosterols and stanols) are naturally present compounds found in all plant-based foods. The word Phytosterols corresponds to up to 200 various compounds. The most common present in foods is sitosterol and campesterol. Sitostanol and campestanol, their saturated constituents, are much less abundant. Plant-based oils, nuts, cereal grains, legumes, and fruits and vegetables are all good sources of phytosterols in the diet. Phytosterol glucosides have been discovered to be key structural constituents in the plasma membranes of plant cells, which are assumed to be necessary for plasma membrane enzymes and other proteins to function. It has a similar structure to cholesterol. Despite their structure being similar, the amount of absorption in the body is not the same. Phytosterols are absorbed at a rate of less than 2%, whereas cholesterol is absorbed at a rate of 30 to 60%. Phytosterols are reported to have a variety of bioactive attributes that may influence human health, which has sparked a surge of research in the last decade. The major advantage is that they lower serum cholesterol by partially inhibiting intestinal cholesterol absorption. On average, taking 2g of phytosterols per day decreases the level of cholesterol by 30 to 40% and LDL-cholesterol by 10%. Other reported phytosterol benefits include anti-atherogenic activities as well as immune-stimulating and anti-inflammatory properties, especially beta-sitosterol.

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I. INTRODUCTION

Dyslipidemia is known as a long-term metabolic disorder that is presented by increment total cholesterol level, low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) levels or reduced high-density lipoprotein cholesterol (HDL-C). Dyslipidemia can lead to accumulated cardiovascular disease if not treated properly. According to the World Health Organisation (WHO), elevated plasma cholesterol levels threaten the health of around 40% of the world's population. Statins, the first-line medication treatment, have been linked to an increased risk of muscle soreness, weakness, and depression. Furthermore, it does not affect the risk of atherosclerotic cardiovascular risk in individuals aged 70 and up. Thus, an alternative pathway has been developed such as using a natural compound for serum cholesterol reduction (1). Natural compounds have been applied as complementary medicine all over the world. Several thorough clinical trials have shown that the bioactive components found in herbal medicines are both helpful and harmless in reducing serum lipids. The International Lipid Expert Panel (ILEP) has approved the use of nutraceutical therapies comprising herbal monomers and metabolites as a lipid reduction other than statins in intolerant individuals since they appear to be quite safe and well tolerated. For instance, in major hypercholesterolemic adults, the use of red yeast rice as a serum cholesterol reduction dietary supplement appears to be palatable and safe. Natural compounds have been said to have fewer adverse effects, such as drowsiness(1).

Phytosterols (also known as plant sterols and stanols) are one of the compound alternatives for lowering increased serum TC and LDL-C levels. Phytosterols' serum cholesterol reduction effects were initially found in humans in the 1950s. After that, there are many human studies have found that phytosterols, as incorporated in a range of diets, plant sterols or stanols, esterified to vegetable oil fatty acids lower TG and LDL-C. 2 g/d phytosterols (same amount calculated as free sterols according to 3.3 g/d phytosterol esters) reduced LDL-C levels by around 10% on average. (2). As consumed 2 g/d or greater, the impact appeared to decline, with a small extra benefit at consumption greater than 2.5 g/d. As a result, some nutritional guidelines now include 2 g of phytosterols per day as an extra nutritional choice for reducing increased LDL-C levels. The decrease of intestinal cholesterol absorption is the main mechanism of action for phytosterols' serum cholesterol reduction. Cholesterol absorption is reduced by 30–40% when 2 g of phytosterols are consumed daily(2).

II. SOYBEAN

Soybean has a botanical name which is called *Glycine Max (L.) Merr.* The seeds of the soybean consist of protein, carbohydrates, dietary fiber, vitamins, and minerals. It also contains oil which can be used to produce edible oil. The seed of the soybean is widely used in preparing numerous fresh, fermented, and dried foods. Some soya-based food products are available in the market, such as tofu, soy sauce, soy milk, milk, and so on.

1. Phytoconstituent: Soybeans consist of various phytochemicals which are phenolic acids, isoflavones, saponins, flavonoids, phytosterols, and sphingolipids. The isoflavones can be converted into phytoestrogen which has a similar function as 17β -estradiol and produces weak estrogenic effects. The main isoflavones that are contained in soy products are genistein and daidzein.

- 2. Mechanism of Action:** Soybeans have been found to contain proteins and peptides that have biological activity in reducing serum cholesterol levels. This makes it to be a functional food. Soybean contains two main soy proteins which are β -conglycinin and glycinin. Three cholesterol-lowering peptides can be obtained from glycinin in the soybean which are IAVPGEVA, IAVPTGVA, and LPYP. These peptides can act as the competitive inhibitor of 3-hydroxy-3-methylglutaryl CoA reductase (HMGR) in which HMGR is a rate-limiting enzyme that is involved in the synthesis of cholesterol(3). Besides, these peptides can also increase the uptake of LDL (low-density lipoprotein) in the liver cells (HepG2 cells) via the activation of the LDL receptor-sterol regulatory element-binding protein 2 (SREBP2) pathway(4). These peptides can also decrease the level of cholesterol by causing an increase in the phosphorylation at threonine 173 (Thr173) via the activation of the AMPK pathway. This in turn can lead to the inactivation of the 3-Hydroxy-3-Methylglutaryl-CoA Reductase (HMGCR) through phosphorylation at serine 872(4). By having these actions, soybeans can reduce the cholesterol level in the blood plasma.
- 3. Adverse Effect:** Dietary supplements that contain soy extract are usually safe when it is used for up to six months. There are some side effects of soybean, such as constipation, bloating, and nausea. Besides, some people can also develop allergic reactions towards soybeans, such as rash, itching, and breathing problems.
- 4. Drug Interaction:** Soybeans have been found to contain high levels of tyramine whereby tyramine is involved in the regulation of blood pressure. Monoamine oxidase inhibitors (MAOIs) can interact with tyramine by decreasing the metabolism of tyramine. If high levels of tyramine and MAOIs are taken together, the levels of tyramine will remain high in the body for a long period. Hence, this can eventually increase the risk of a hypertensive crisis. There are some examples of MAOIs that interact with tyramine, such as phenelzine, selegiline, and tranylcypromine (5). Besides, soy can interact with warfarin which is an anticoagulant. Soy can decrease the effects of warfarin. Hence, this can increase the risk of clotting which may lead to serious complications. Moreover, soybean also interacts with levothyroxine in which levothyroxine is used for treating hypothyroidism. Soybeans can decrease the absorption of levothyroxine in infants, but not in adults. Therefore, this can reduce the effect of levothyroxine in infants. As a result, dose adjustment is required when levothyroxine is administered together with soybean.
- 5. Clinical Uses:** There is study found that the isoflavone in soybean can help to reduce the symptoms of menopause, such as hot flush as it can reduce the systolic blood pressure in the early stages of menopause(6). Furthermore, after consuming soy protein, the level of total cholesterol and low-density lipoprotein (LDL) cholesterol can be reduced. However, taking supplements that contain purified soy isoflavones might not be able to reduce the level of total cholesterol and LDL cholesterol. In addition, soy milk is also suitable to be used in people with lactose intolerance. This is because soy milk does not contain lactose. If an infant is unable to digest lactose, then the infant can use a soy-based formula to reduce the symptoms of lactose intolerance including diarrhea and bloating. (7).

III. NUTS

Tree nuts, such as walnuts, hazelnuts, cashew nuts, Brazil nuts, almonds, macadamias, pistachios, and peanuts are foods with unique compositions. These nuts consist of

monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), protein, soluble and insoluble fibers, vitamin E vitamin K, folate, phytosterol compounds, thiamine, minerals such as magnesium, potassium, copper, and so on(8). Due to the presence of unique composition, nuts can bring various health benefits. Some studies found that nuts have a cholesterol-lowering effect. Regular consumption of nuts is not likely to cause obesity, instead, it can also help in weight loss(9).

- 1. Phytoconstituent:** Nuts contain phenols including phenolic acids, flavonoids, and stilbenes. Proanthocyanidins can be found in many nuts, such as almonds, cashews, hazelnuts, pecans, pistachios, peanuts, and walnuts. Some nuts contain α - and β -Carotene, β -cryptoxanthin, lutein, and zeaxanthin(10). Pistachios are rich in lutein and zeaxanthin as well as containing the highest β -carotene levels among the nuts(11). Resveratrol is only found in peanuts and pistachios(10).
- 2. Mechanism of Action:** Nuts do not contain cholesterol, but the fat fraction of the nuts consists of non-cholesterol sterols which belong to phytosterols which are non-nutritive plant components that involves in the structure of the cell membranes of plant cells. Besides, the phytosterols of the nuts can hinder the absorption of cholesterol and thus this helps to reduce the cholesterol level in the blood plasma(12).

There are various nuts available that can reduce the cholesterol level, such as almonds, walnuts, pecan, and pistachios. These nuts contain a high amount of unsaturated fats and a low amount of saturated fats. If the nuts contain a high amount of unsaturated fat, they can increase the amount of high-density lipoprotein (HDL) and decrease the amount of low-density lipoprotein (LDL). If there is a high amount of HDL in the blood plasma, the HDL can carry the LDL away from the arteries to the liver which the liver will remove the LDL from the body. Hence, this eventually can decrease the amount of LDL in the body. However, not all nuts can reduce their cholesterol level. If the nuts contain a high amount of saturated fats, this eventually increases the cholesterol level in the blood. Some nuts are high in saturated fats, such as Brazil nuts, cashews, and macadamia nuts. Therefore, consuming nuts that are high in unsaturated fats and low in saturated fats can reduce the serum cholesterol level.

- 3. Adverse Effect:** Some people might develop acute allergic reactions to peanuts. Allergic reactions toward peanuts and tree nuts can happen when the person is first exposed to them. The allergic reaction might be life-threatening and requires emergency treatment(13).
- 4. Precaution:** When a person is allergic to one tree nut, the person is more likely to have an allergy to other tree nuts. Hence, the person should avoid taking tree nuts unless the person is not allergic to them(13).
- 5. Drug Interaction:** There are drug interactions that occur when some nuts are consumed. For example, cashew nuts can increase the blood sugar level while antidiabetic drugs can decrease the blood sugar level. There are some examples of antidiabetic drugs, such as glimepiride, glyburide, insulin, pioglitazone, glipizide, and so on. Hence, when cashew nut is taken along with antidiabetic drugs, this can decrease the effects of antidiabetic drugs. Therefore, dose adjustment for antidiabetic drugs might be required.

6. Clinical Uses: When the nuts are consumed, it can cause a reduction in oxidative damage, inflammation, vascular reactivity, and platelet aggregation, and improve immune functions. Regular consumption of nuts can be used as adjunctive therapy in the treatment and prevention of various neurodegenerative diseases and age-related brain dysfunction. Consumption of nuts also can alter cognitive performance in humans by inhibiting or reversing the neurodegeneration effects in aging. (Pribis&Shukitt-Hale, 2014). Besides, consumption of nuts can decrease the risk of cardiovascular disease and death. For example, walnuts can improve the risk factor of blood lipids and other cardiovascular disease (14).

IV. ARTICHOKE LEAF

Artichoke (*Cynara cardunculus*) is a plant native to the Mediterranean area. The artichoke leaf is the main part that is extracted to use in medicine. It is mainly used as a hyperlipidemia medication. Some physicians also used it as an alternative therapy for alcohol-induced hangovers, irritable bowel syndrome, liver dysfunction as well as flatulence or vomiting symptoms.

- 1. Mechanism of action:** The phytosterols found in the artichoke leaf cell membrane are structurally similar to the body's cholesterol. Thus, they will compete with the cholesterol absorption in the digestive system and reduce normal cholesterol absorption. Not only that, the artichoke leaf extract (*Cynara scolymus*) is also widely used as a cholesterol-reducing agent. This is because the *Cynara scolymus* will inhibit the HMG-CoA-reductase enzyme in the liver. This enzyme is used by the liver to synthesize cholesterol from mevalonate acid. The artichoke leaf also contains cynarin compounds. This compound can stimulate the production of bile in the liver to store in the gallbladder. Thus, more bile can be used to break down the cholesterol from the food we have eaten and lower the blood cholesterol.
- 2. Dosage:** Artichoke leaf extract is most often used by adults in doses of 320-640 mg by mouth three times daily to reduce the serum cholesterol level.
- 3. Adverse Effect and Contradiction:** Artichoke leaf extract is safe to be taken as a medication for up to 12 weeks. However, prolonged use of overdose of artichoke leaf extract will lead to side effects such as flatulence, diarrhea, abnormal spasms, and pain. Henceforth, the accurate dose should be measured before prescribing this medication to the patients. Physicians should also advise the side effects of artichoke leaf extract to the patients. Besides, the artichoke leaf extract is contraindicated in pregnancy and breastfeeding due to not having enough reliable information. It is also contraindicated in patients that have bile duct obstruction due to it will worsen the condition. Patients that are allergic to artichoke should not be prescribed this medication too.
- 4. Drug Interaction:** The artichoke leaf extract will interact with medications that are metabolized by cytochrome P450 enzymes in the liver such as diazepam, amiodarone, loratadine, and diltiazem. Some studies had shown that artichoke leaf may inhibit the CYP-450 enzyme, thus it will potentiate the side effects of the drugs that are metabolized by the CYP-450 enzyme. Artichoke leaf extract will also interact with antidiabetic drugs such as metformin, this is because artichoke will lower the blood sugar level. If we take

both medications together it will be a high risk of getting hypoglycemia. Furthermore, artichoke leaf extract will also interact with antihypertensive drugs due to artichoke will lower your blood pressure. High risk of hypotension will be caused if we take both medications together.

V. FLAXSEED OIL

Flaxseed oil (*Linum usitatissimum*) is a yellowish oil obtained from the dried seeds of the flax plant by pressing and solvent extraction process. Some research shows that flaxseed oil can improve the health condition of some chronic diseases such as diabetes, menopausal symptoms, several heart diseases as well as serum cholesterol level.

- 1. Dosage:** Flaxseed oil is prescribed at the dose of 1-2 grams by oral route of administration daily for up to 6 months to reduce the serum cholesterol level.
- 2. Mechanism of Action:** Flaxseed oil contains phytosterol that can lower blood cholesterol level as well as prevent atherosclerosis. The phytosterol in flaxseed oil is a type of omega-3 fatty acid which is known as alpha-linolenic acid. The body uses alpha-linolenic acid from flaxseed oil and converts it into small amounts of other fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). These fatty acids can reduce our blood cholesterol level by decreasing the low-density lipoprotein in the blood. Also, the hypolipidemic and anti-inflammation properties of dietary alpha-linolenic acid in flaxseed oil are associated with a reduction in cardiovascular events.
- 3. Clinical Studies:** A study in Japan has shown that alpha-linolenic acid has the effect of reducing blood cholesterol levels. The study involved 15 adults, the participants consumed either flaxseed oil or corn oil once per day with dinner. Researchers measured the participants' cholesterol levels at the start of the study and again 12 weeks later. Those who consumed the corn oil had no change in their cholesterol levels, while those who consumed the flaxseed oil had a significant decrease in low-density lipoprotein.
- 4. Adverse Effect and Contradiction:** When we consume flaxseed oil without drinking sufficient amounts of water, flaxseed oil will cause bloating, flatulence, and diarrhea. Furthermore, flaxseed oil is contraindicated in pregnancy (due to it will increase the risk of giving birth prematurely) and for those who have allergic reactions toward the flaxseed oil. It is also contraindicated two weeks before surgery due to it can decrease blood clotting.
- 5. Drug Interaction:** On the other hand, flaxseed oil has interactions with some drugs such as anticoagulants, antidiabetics, contraceptives, and so on (15). As mentioned above, flaxseed oil will decrease blood coagulation, hence, if it was taken with an anticoagulant drug such as warfarin, it may increase the risk of bleeding. Also, flaxseed will decrease blood pressure. If we consume drugs that will lower your blood pressure such as ACE inhibitors together with flaxseed oil, it may cause hypotension. The same mechanism occurs when we take flaxseed oil with antidiabetic drugs, both flaxseed oil and antidiabetic drug reduce the blood sugar level if we take both together, it may lead to hypotension. Not only that, but flaxseed oil also has an anti-estrogen effect which will interact with contraceptive drugs or estrogen replacement therapy.

VI. RED YEAST RICE

Red yeast rice is a natural compound used in Traditional Chinese Medicine for centuries. It is developed in China and made from a type of fermented rice, *Monascus purpureus*, using a specific mold. Red yeast rice can be added to the daily diet to lower serum cholesterol levels and related lipids, which also helps to reduce the risk for cardiovascular diseases. It is also available as an oral supplement.

- 1. Chemical Constituents:** The chemical constituents of red yeast rice include polysaccharides, flavonoids, amino acids, lignans, sterols, and most importantly monacolin K, which plays an important role in the cholesterol-lowering action of red yeast rice. (Bo Zhu, 2019)
- 2. Uses:** It is mainly used for the reduction of serum cholesterol levels, enhancement of the digestive system, and improvement of the blood circulatory system. It can also be used as an additive, food coloring, and preservative. (Link, 2021) Based on research in the United States, red yeast rice extract given at higher doses (2.4gm/day) can lower total serum cholesterol by almost 20-25%.
- 3. Mechanism of Action:** It is believed that the cholesterol-lowering effect of red yeast rice may be due to the presence of monacolin K in red yeast rice, which is structurally identical to lovastatin, a medicine used to lower cholesterol. It may also be due to the unsaturated fatty acids, isoflavones, and phytosterols contained in red yeast rice. These substances lead to inhibition of the action of the enzyme that produces cholesterol in our body. The primary mechanism of action is through the blocking of the enzyme, 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, which catalyzes the conversion of HMG-CoA to mevalonate in the cholesterol production process in the body. Hence, cholesterol synthesis is inhibited, and the total cholesterol level is reduced. (Cicero, 2019) Based on research done by the American Heart Association, 187 people with mild to moderately high serum cholesterol level has shown a reduction in total serum cholesterol (16%), low-density lipoprotein (LDL) cholesterol (21%), and also triglycerides level (24%) after consumed red yeast rice for some time, then those who took a placebo. It also showed an increment in high-density lipoprotein (HDL) cholesterol levels (14%).
- 4. Dosage:** Red yeast rice is usually prescribed to adults as dietary supplements and the dosage can be very high in TCM. The dosage may be different based on the type of supplement needed by the patient. However, the standardized dosage for red yeast rice extract is 600mg, 2 to 4 times per day.
- 5. Adverse Effects and Contraindications:** Some studies indicate that some people might be unable to tolerate red yeast rice, due to the content of statin like monacolin K, although the amounts of monacolin K might be lower compared to that of statin. (Red yeast rice is not suitable for people younger than 20 years old. Patients with liver diseases or prone to liver disease should not take red yeast rice as well as it may lead to higher-than-normal liver function test results and myopathy due to the presence of the statin-like compound, monacolin K. It is an inhibitor of CYP3A4 enzyme that reduces its metabolism, and the higher plasma level of the medicine increases the risk of liver injuries. However, the side effect is less common in red yeast rice extract as it contains less lovastatin. Red yeast rice should also be avoided in people with thyroid issues, musculoskeletal disorders, and

kidney diseases. It is also contraindicated in pregnant and breastfeeding women. Some of the side effects of red yeast rice include dizziness, heartburn, headache, bloating, and myopathy.

- 6. Drug Interactions:** Patients should avoid taking red yeast rice if they are taking any cholesterol-lowering medications like statins, as both medicines with the same action may lead to enhancement of the action of the drugs and thus increase the risk of liver damage. Other than that, red yeast rice is also contraindicated with anticoagulants like warfarin, aspirin, and clopidogrel. Red yeast rice may reduce the drug's activity and cause excessive bleeding. Furthermore, red yeast rice should not be consumed with grapefruit as well. This is because grapefruit may increase the amount of medicine in the body and increase its action in the body. This may further damage the liver and exacerbate the adverse effects of red yeast rice. To conclude, red yeast rice extract can be considered one of the most effective natural compounds for the treatment of hypercholesterolemia. Its efficacy to lower serum cholesterol is proportional to its monacolin K.

VII. HAWTHORN

Hawthorn, which is also called *Crataegus oxyacantha*, is a plant where flowers, leaves, and berries can be used as medicines for the treatment of congestive heart failure (CHF), chest pain, and irregular heartbeat. (16). The hawthorn berries are rich in nutrients, taste sweet, and have a tart and tangy taste. They have been used in herbal medicines for heart failure, high blood pressure, and anxiety, and to improve digestion since hundreds of years ago.

- 1. Chemical Constituents:** Some of the chemical constituents in hawthorn include amines, pectin, flavonoids, terpenoids, and tannins. Flavonoid and pectin pentasaccharide content of hawthorn are the constituents that make it a great medicine for the reduction of serum cholesterol levels (17).
- 2. Mechanism of Action:** Pectin pentasaccharide is a type of fiber that is involved in the cholesterol synthesis pathway in the body. It is used to improve bile acid biosynthesis and excretion and thus reduce the accumulation of cholesterol in the liver(17). This is due to the inhibition of the gene expression of the 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase enzyme which catalyzes the conversion of HMG-CoA to mevalonate during cholesterol synthesis. The hawthorn pentasaccharide also helps to increase the gene expression of HDL cholesterol, cholesterol 7 α -hydroxylase (CYP7A1), and fecal bile acids. CYP7A1 is an enzyme that catalyzes the bile acids production and cholesterol catabolism process(18).

Furthermore, the pectin pentasaccharide of hawthorn is also found to be useful to promote adiponectin synthesis and activation in white adipose tissue and the liver respectively. Adiponectin secreted by adipocytes is a cytokine that is significant for the regulation of lipid metabolism through binding to the receptors. This facilitates the metabolism of hepatic lipids and hence reduces the total cholesterol in the blood as well(17). Besides that, it is also suggested that the content of ethanol extract in hawthorn can also help in the reduction of lipid levels in the body. This may be due to the presence of flavonoids which have been confirmed to have serum lipid-lowering activity and lipid

metabolism regulation activity by increasing the expressions of lipid metabolism genes in the liver, like HSL, FAS, SREBP-1c and TGH(17).

- 3. Clinical Uses:** Other uses of hawthorn include its positive inotropic activity where it increases the strength of muscular contraction of the heart. This will increase the coronary blood flow to the heart. Hawthorn is also a beta-antagonist which can lead to decreased heart rate, slower atrioventricular conduction, and decreased cardiac workload. It can protect the heart from ischemia reperfusion-induced damage, where tissue damage is caused when the blood supply returns to tissue after a period of ischemia.
- 4. Dosage and Administration:** The dosage of a crude drug of hawthorn is given at 200mg daily. The hawthorn berries can be administered as a dried powder, liquid extract, tincture, solid extract, and syrup. Meanwhile for the leaf and flower of hawthorn, extract, powder, and tincture form are available as well.
- 5. Adverse Effects:** The side effects of hawthorn include nausea and fatigue, sweating, and rashes on the hand. It can also lead to bradycardia and respiratory depression which leads to cardiac arrest and respiratory paralysis.
- 6. Drug Interactions and Contraindications:** The possible drug-drug interaction of hawthorn needs to be aware before taking hawthorn. For example, hawthorn should not be administered with antiarrhythmic medications such as cardiac glycosides, angiotensin-converting enzyme (ACE) inhibitors, and antihypertensive medications. This is due to the potential additive hypotensive effect of hawthorn with antihypertensive medication. Besides, hawthorn is also unsafe to be used for pregnant and breastfeeding women.

VIII. GUGGULIPID

Guggulipid is an ethyl acetate extract of resin known as guggul from the tree *Commiphora wightii*, which is also known as the mukul myrrh tree native to India, Bangladesh, and Pakistan. Gum resin has been used in traditional Ayurvedic medicine for its therapeutic effects in the treatment and management of inflammation and arthritis, as well as obesity and lipid metabolism disorders.

- 1. Chemical Constituents:** The active pharmaceutical component is responsible for managing hyperlipidemia is known as guggulsterone, specifically the isomers E-guggulsterone, and Z-guggulsterone. Guggulsterone [4,17(20)-pregnadiene-3, 16-dione], the active component of guggulipid, is derived from the gum resin of the tree *Commiphora mukul* and has cis- and trans-isomers.
- 2. Mechanism of Action:** Guggulipids act as antagonistic ligands for the bile acid receptors and farnesoid X receptor (FXR), which is an important regulator of cholesterol homeostasis involving the conversion of cholesterol into bile acids (19). These phytosterols inhibit cholesterol synthesis in the liver via antagonism of the said receptor, resulting in hypolipidemic activity. The mechanisms implicated for the lipid-lowering effect of guggulipid are stimulated hepatic lipases and receptor-mediated catabolism of low-density lipoproteins, as well as the suppression of hepatic cholesterol biosynthesis.

- 3. Clinical Uses:** The guggul resin containing guggulipids is primarily used to manage inflammatory conditions such as acne, eczema, and psoriasis. Research studies have reported that guggul is effective in both complementary and alternative treatments for nodulocystic acne, as well as relieving the symptoms associated with eczema and psoriasis such as redness, swelling, itchiness and tenderness. Guggul may manage obesity by promoting weight loss via inducing the breakdown of fat and subsequently the amount of fatty tissue. Further research also suggests that guggul can achieve a similar effect by reducing skinfold thickness and body circumference. Most importantly, guggul is used as the natural treatment for hyperlipidemia as it reduces triglyceride levels, total cholesterol, and low-density lipoproteins (LDL). Long-term administration of guggulsterone isomers shows a significant reduction of LDL-C levels in patients.
- 4. Dosage and Administration:** Guggul supplements are available in a wide range of drug delivery forms such as capsules, powders, and lotions. Oral supplement dosage ranges from 6.25mg to 132mg per day depending on the condition of the patient.
- 5. Adverse Effects:** Guggul is considered relatively safe when taken at the typically recommended dose. Mild side effects may include skin rash, diarrhea, mild nausea, hiccups, and irregular menstrual cycles. Administration of high doses of guggul is associated with liver damage, hence it is advised that patients with hepatic pathology exercise caution when using guggul.
- 6. Drug interactions and Contraindications:** Taking guggul along with medications that are metabolized by liver enzymes may decrease the efficacy and bioavailability of these medications because guggul may potentiate hepatic enzyme metabolism. Likewise, guggul decreases the absorption of beta-blocker propranolol and calcium channel blocker diltiazem, leading to decreased effectiveness of these medications. Guggul also exerts effects on estrogen receptors, causing interactions with hormonal medications such as birth control pills or estrogen-sensitive cancer prophylaxis, hence it is important to note the contraindication in pregnancy. The consideration also takes into account the action of guggul as a uterine stimulant resulting in potential uterine contractions and premature labor. Guggul may decrease blood clotting ability, hence patients undergoing surgery or taking antiplatelets or anticoagulants should avoid usage.

IX. WHEY PROTEIN

Milk is made of two proteins, casein protein, and whey protein. Whey protein can be separated from the casein in milk or formed as a by-product of cheese production. Despite being low in lactose content, whey protein is considered a complete protein as it contains all 9 essential amino acids required for healthy metabolism. It is classified into three primary types based on its constituents namely whey protein concentrate (WPC), whey protein isolate (WPI), and whey protein hydrolysate (WPH). WPC contains low levels of fat and carbohydrates, with the protein percentage within the range of 30%-90%. WPI is at least 90% protein, with the fat and lactose removed from the concentrate, whereas WPH is the pre-digested form of whey protein after partial hydrolysis with improved digestibility and reduced allergen potential.

- 1. Chemical Constituents:** Whey is a complex mixture of globular protein molecules comprising up to 50% beta-lactoglobulin β -LG, 20% of alpha-lactalbumin α -LA, 10% of

immunoglobulins IgG, and up to 6% Bovine Serum Albumin BSA. Whey protein also includes other minor protein or peptide components such as lactoferrin, lactoperoxidase, lysozyme, and growth factors. The most common whey protein product WPI is a powder form with more than 90% by weight of protein, which is produced by ion exchange chromatography or microfiltration, followed by spray drying.

- 2. Mechanism of Action:** Whey protein mechanisms include the promotion of hepatic lipid metabolism, the inhibition of absorption of fatty acid and cholesterol in the intestine, and the increase in the excretion of fecal sterols (20). Whey protein was found to decrease body weight and body fat hence improving lipid profiles. The TG reduction effects of whey protein supplementation can be attributed to the functional components in whey protein. The beta-lactoglobulin protein chains may capture hydrophobic molecules and thus may decrease intestinal lipid absorption. The sphingolipids present in whey protein isolates (WPI) may block lipid absorption by decreasing the absorption of dietary cholesterol and free fatty acids to reduce plasma TG by 58%. Furthermore, an in vitro study reported that amino acids such as leucine, isoleucine, valine, casein, and whey may downregulate gene expression related to cholesterol metabolism and lipogenesis, whereas isoleucine and whey also downregulated gene expression involved in fatty acid transport and cholesterol absorption.
- 3. Clinical Uses:** The primary use of whey protein involves promoting weight loss, increasing muscle mass and strength. Whey protein can boost energy expenditure by 80 to 100 calories per day, and make people automatically eat up to 441 fewer calories per day. In one study, eating 25% of the daily calories in protein cut cravings by 60% and reduced the desire for late-time snacking by half due to increased satiety from the proteins. Studies also have shown that replacing other sources of calories with whey protein, combined with weightlifting, can cause weight loss of about 3.5 kg while increasing lean muscle mass. Whey protein can also lower blood pressure, and blood sugar and reduce symptoms of stress and depression, aside from protecting against cancer, reducing symptoms of hepatitis, increasing bone mineral density, and improving immune function in HIV patients.
- 4. Dosage and Administration:** For whey protein powder form, a commonly recommended dosage is 1 to 2 scoops (around 25 to 50 grams) per day usually after workouts. Patients are recommended to follow the serving instructions on the packaging of whey protein products available in the market. Taking whey protein in addition to a diet already high in protein intake may be unnecessary as the protein requirements are already met.
- 5. Adverse Effects:** Oral administration of whey protein in high doses may cause increased bowel movements, thirst, and bloating. Individuals who are allergic to milk may be specifically allergic to whey. In moderate doses, whey protein does not typically cause any adverse events. However, consuming very high doses can result in cramps, stomach pains, nausea, reduced appetite, fatigue, and headache. Consistent high-dose administration of whey protein is associated with acne manifestation in younger age groups.
- 6. Drug Interactions and Contraindications:** Whey protein might decrease absorption and efficacy of levodopa hence it is advised to not take the two compounds at the same time. Whey protein might decrease the efficacy of quinolone and tetracycline antibiotics. To

avoid this interaction, take antibiotics at least 2 hours before or 4 to 6 hours after whey protein. Whey protein can also decrease the effect of bisphosphonates hence it is advised to take whey protein and bisphosphonates at separate times in a day.

X. DISCUSSION

The role of natural compounds in managing hyperlipidemia via lowering serum cholesterol is significant, especially in the field of traditional medicine. Plant sterols are compounds that can lower serum triglyceride levels, total cholesterol, and LDL-C values in individuals with hyperlipidemia. Among the compounds investigated, guggulipid is one such example that provides hypolipidemic properties in addition to its anti-inflammatory effects. The plant sterols in the form of E-guggulsterone and Z-guggulsterone act on receptors directly involved in the synthesis of cholesterol in the liver. Antagonistic interactions result in the inhibition of cholesterol synthesis and hence allow for the management of hyperlipidemia. Likewise, reduction in the serum cholesterol level can also be achieved via differing mechanisms of action as summarised in the table below.

Some natural compounds possess the same mechanism of action including soybean, artichoke leaf, and red yeast rice. Soybean, artichoke leaf, and red yeast rice can inhibit the 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase enzyme. Besides, nuts, artichoke leaf, and whey protein also have some similarities in terms of the mechanism of action as these three compounds inhibit the absorption of cholesterol in the intestine. Moreover, some nuts and red yeast rice can increase the HDL-cholesterol level in the blood. When there is a high HDL-cholesterol level in the blood, more LDL-cholesterol can be carried by the HDL-cholesterol to the liver to be removed from the body. This eventually can reduce the LDL-cholesterol level in the body. Flaxseed oil can also contribute to the reduction in LDL-cholesterol due to the presence of DHA and EPA. Both artichoke leaf and hawthorn can increase the synthesis of bile acids. Hence, both of them can eventually break down the ingested cholesterol.

In the field of traditional medicine, many traditional medications can manage hyperlipidemia by lowering the serum cholesterol level. Among all the mechanisms of action of the natural compounds/traditional medicines mentioned above, the most suitable natural compound to be prescribed to the public for hyperlipidemia is artichoke leaf extract. This is because artichoke leaf extract can reduce the serum cholesterol level by three mechanisms of action which are, stimulating the bile synthesis, inhibiting the HMG-CoA reductase enzyme in the liver, and antagonist to the cholesterol absorption. Research conducted in Germany showed that taking 1,800 mg of artichoke extract in 450 mg tablets for six weeks brought about an 18.5 percent decrease in total cholesterol and a 22.9 percent decrease in LDL cholesterol (low-density lipoprotein) compared to an 8.6 percent decrease in total cholesterol and 6.3 percent decrease in LDL cholesterol among a control group treated with placebo. The researchers said their findings recommend artichoke leaf extract for treating high cholesterol. Other natural compounds such as red yeast rice and soybean also have the same mechanism of action by inhibiting the HMG-CoA reductase enzyme to prevent cholesterol formation, but artichoke leaf extract can further stimulate the bile secretion in the liver to increase the breakdown of the lipid in the blood which red yeast rice and soybeans couldn't. Besides, if we compare artichoke leaf extract with the hawthorn, both of these natural compounds can stimulate bile secretion. However, hawthorn can lead to several chronic side effects such as bradycardia and respiratory depression, cardiac arrest and respiratory paralysis. The side

effects of artichoke leaf extract are much milder, such as flatulence, diarrhea, abnormal spasms, and pain. The side effects of artichoke leaf extract can even be minimized/avoided if prescribed by an accurate dose and avoid prolonged use of it. To sum it up, the artichoke leaf extract is the best natural compound for serum cholesterol reduction due to its high efficiency and least side effects.

There is a myriad of compounds for serum cholesterol reduction with an extensive history of application in managing signs and symptoms of diseases, yet there are limited human clinical trials for every one of the compounds in determining the safety and efficacy of said component. Constant research and interest in natural compounds have made advancements in the field possible. Whey protein isolates (WPI) are combined with phytosterols (WPS) to form nanoparticles as stabilizers of oil-in-water emulsions. The combination of the two components via non-covalent bonding has altered the nanoparticle structure, conferring outstanding interfacial wettability, emulsification stability, and antioxidant activity. Emulsions with said nanoparticles can reduce lipid digestion hence lowering serum cholesterol levels.

Meanwhile, for hawthorn, the contents of flavonoids, and pectin pentasaccharides are the main constituents in hawthorn that help in cholesterol-lowering activity. Other than reducing total cholesterol, LDL-cholesterol level, and triglycerides level, hawthorn is also widely used for the treatment of cardiovascular diseases, especially heart failure. Moreover, hawthorn can also lower blood pressure in patients with high blood pressure. Based on a research study, after consuming hawthorn extract for four months, there is an obvious reduction in diastolic blood pressure in type 2 diabetes patients. There are also suggestions from some researchers of using hawthorn with heart failure medications as it may potentiate the efficacy of the medications. From these, we can say that Hawthorn has the potential for further research to discover more clinical uses for better treatment options in the future.

Table 1: Mechanism of actions of different natural compounds on serum cholesterol reduction

| Natural Compounds | Mechanism of actions |
|-------------------|---|
| Soybean | 1) Competitively inhibit 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase enzyme. 2) The peptides in soybean increase the uptake of LDL (low-density lipoprotein) in the liver cells via the activation of the LDL receptor-SREBP2 pathway 3) The peptides can also increase the phosphorylation at threonine 173 via the |
| Nuts | 1) Phytosterols of the nuts hinder the absorption of cholesterol 2) Some nuts that have a high amount of unsaturated fats can increase the HDL level and decrease the LDL level. HDL can carry the LDL to the liver so that the liver can remove the LDL from the body |

| | |
|----------------|--|
| Artichoke leaf | <ol style="list-style-type: none"> 1) Phytosterols in the cell membrane of artichoke leaf can compete with cholesterol absorption and reduce normal cholesterol absorption as they have a similar structure to the body's cholesterol. 2) Inhibit HMG CoA- reductase enzyme in the liver 3) Cynarin in the artichoke leaf can stimulate the production of bile in the liver to |
| Flaxseed oil | <ol style="list-style-type: none"> 1) Alpha-linolenic acid from flaxseed oil can convert into fatty acids which are DHA and EPA. These fatty acids can decrease the LDL in the blood. |
| Red Yeast Rice | <ol style="list-style-type: none"> 1) Monacolin K in red yeast rice has a structure identical to lovastatin. 2) block the HMG-CoA reductase enzyme. 3) Increase the HDL-cholesterol level |
| Hawthorn | <ol style="list-style-type: none"> 1) Improve the bile acid biosynthesis and excretion 2) Increase the gene expression of HDL cholesterol, cholesterol 7α-hydroxylase (CYP7A1), and fecal bile acids. 3) Promote the synthesis and activation of adiponectin in white adipose tissue and in the liver respectively 4) Flavonoids present in the ethanol extract of hawthorn can increase the |
| Guggulipid | <ol style="list-style-type: none"> 1) Act as antagonistic ligands for the bile acid receptors and farnesoid X receptors. 2) Stimulate hepatic lipases 3) Stimulate receptor-mediated catabolism of LDL. 4) Suppress the biosynthesis of cholesterol in the liver |
| Whey Protein | <ol style="list-style-type: none"> 1) Promote the metabolism of lipids in the liver 2) Inhibit the absorption of fatty acid and cholesterol from the intestine 3) Increase the excretion of fecal sterols |

XI. CONCLUSION

Phytosterols are a class of nutraceutical substances that have been shown to be an approved remedy for serum cholesterol reduction. When taken in the recommended amounts, phytosterols are clinically safe and well-tolerated, resulting in effective cholesterol reduction. Phytosterols, when used in conjunction with statin medicines, give extra LDL cholesterol reduction that is more beneficial than increasing the statin dose. The natural compounds that we discussed in reducing serum cholesterol are soybean, nuts, artichoke leaf, flaxseed oil, red yeast rice, hawthorn, guggulipid, and whey protein. To examine the effectiveness of phytosterol medication in pregnant and nursing women, more investigation is necessary. Phytosterols can help lower LDL cholesterol levels when used with additional nutrition, lifestyle, or pharmacological approaches. Further therapeutic effects of phytosterols, according to recent findings, include anti-inflammatory, anti-cancer, and immune-regulatory capabilities.

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