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Guggulipid as an adjuvant therapy for Hyperlipidemia: A review

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Abstract
Hyperlipidemia also known as hyperlipoproteinemia is a disorder of abnormally high levels of any or all lipids and/or lipoproteins in the blood. Hyperlipidemia itself usually causes no symptoms but can lead to symptomatic vascular disease, including coronary artery disease (CAD) and peripheral arterial disease. Atherosclerosis being the main complication associated with hyperlipidemia is the leading cause of death in the developed and developing countries like India. Treatment of hyperlipidemia is one of the major approaches towards decelerating the atherogenic process. Guggulipid (GL), an extract of *Commiphora mukul*, has been safely used for thousands of years in the Indian Ayurveda medicine practice for the treatment of different ailments like arthritis, obesity, and other disorders. It has been clinically proven to reduce the levels of harmful serum lipids in the bloodstream. Guggulsterone E and guggulsterone Z which are present in a concentration of 4.0 and 6.0% have been identified as the active ingredients responsible for the maintenance of healthy cholesterol levels. Guggul was introduced as a medicine in 1966, and but approved as a hypolipidemic drug for marketing in India in 1986. In the present paper, an attempt has been made to review the use of guggulipid preparations for hyperlipidemia.

Keywords: guggulipid (GL), hyperlipidemia, atherosclerosis, coronary artery disease, guggulsterone, peripheral arterial disease, guggulsterone E, guggulsterone Z

1. Introduction
The advancement of high-throughput screening and the post-genomic era provided more than 80% of drug substances, which are obtained from natural products or inspired by a natural compound. More than 150 natural product-derived compounds are currently undergoing clinical trials and at least 100 similar projects are in preclinical development. A very modest quantity of the world's plant diversity has been screened extensively for bioactivity so far. Further, more extensive collections of plants based on ethnomedicine knowledge or advanced microbial culture could provide many novel lead molecules in drug discovery. Indian natural products, particularly those from traditional medicinal plants which are reported in classic texts like Ayurveda and Charak Samhita, have contributed towards this boom in drug discovery [1].The current rediscovery process aims to identify a single, pure active constituent from an active extract and a method to estimate it in the crude drug discovery [2]. The demand for plant based medicines, health products, pharmaceuticals, food supplement, cosmetics etc., are increasing in both developing and developed countries, due to the growing recognition that the natural products are non-toxic, have less side effects and easily available at affordable prices [3]. Development of standardized, safe and effective herbal formulations with proven scientific evidence can also provide an economical alternative in several disease areas [4].

1.1 Hyperlipidemia
Major lipids found in the bloodstream are triglycerides, phospholipids, cholesterol and cholesterol esters and free fatty acids. The function of cholesterol is to help carry fat in the body, because fat being insoluble in water cannot travel on its own in the blood stream. Cholesterol associates with fat and protein and comes out of the liver as a lipoprotein. There are several types of lipoproteins for the transport of fatty material in the body such as chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), intermediate density lipoproteins (IDL) and high-density lipoproteins (HDL). Each has a different function in the transport system. VLDL is responsible to carry endogenous triglycerides from the liver into the blood stream and to other parts of the body. Lipoprotein lipase catalyzes triglycerides degradation to generate VLDL remnants which are further degraded by hepatic glyceride hydrolase to generate LDL. It easily adheres along the walls of the arteries and, therefore, called as bad cholesterol. There are different types of HDL like HDL1, HDL2, and HDL3. It is called good cholesterol as it finds and removes stuck LDL of peripheral cells and bring them back to the liver. Hyperlipidemia, the elevation of lipid concentration in plasma, is the manifestation of a disorder in the synthesis and degradation of plasma lipoproteins. Primary type hyperlipidemia can be treated with drugs but the secondary type originating from diabetes, renal lipid nephrosis or hypothyroidism demands the treatment of original disease rather than hyperlipidemia [4, 5].

1.2 Modern drugs for Hyperlipidemia
Modern drugs of the first choice for elevated LDL cholesterol are the HMG-CoA reductase inhibitors, like lovastatin, pravastatin and simvastatin. These drugs are not totally free from side effects particularly when used for prolonged periods. Statin drugs are very effective for lowering LDL

cholesterol levels and have very few immediate short-term side effects. They are easy to administer, have high patient acceptance and have few drug-drug interactions. Patients, who are pregnant, have active or chronic liver disease, or who are allergic to statins shouldn't use statin drugs. The most common side effects are gastrointestinal, including constipation and abdominal pain and cramps. These symptoms are usually mild to severe and generally subside as therapy continues.

Another class of drugs for lowering LDL is the bile acid sequestrants, cholestyramine and colestipol and nicotinic acid (niacin). These have been shown to reduce the risk for coronary heart disease in controlled clinical trials. Both classes of drugs appear to be free of serious side effects. But both can have troublesome side effects and require considerable patient education to achieve adherence. Nicotinic acid is preferred in patients with triglyceride levels that exceed 250 mg/dL because bile acid sequestrants tend to raise triglyceride levels. Other available drugs are gemfibrozil, probucol, and clofibrate. Gemfibrozil and clofibrate are most effective for lowering high triglyceride levels. They moderately reduce LDL cholesterol levels in hypercholesterolemic patients. If a patient does not respond adequately to single drug therapy, combined drug therapy should be considered further to lower LDL cholesterol levels. For patients with severe hypercholesterolemia, combining a bile acid sequestrant with either nicotinic acid or lovastatin has the potential to markedly lower LDL cholesterol. For hypercholesterolemic patients with elevated triglycerides, nicotinic acid or gemfibrozil should be considered as one agent for combined therapy. But these synthetic drugs possess side effects such as bloating, constipation, muscle pain, the progression of cataract, cutaneous flushing, skin disorders nausea, gastrointestinal, hepatobiliary neoplasms and cardiac arrhythmias [6].

The action of most synthetic drugs discussed above is intended to be powerful and singular. In other words, they usually affect a specific problem with a strong action. As the chemicals in these drugs are concentrated, their action is strong and focused. Consequently, they can also produce many side effects [6].

1.3 Plant remedies for Hyperlipidemia

A number of plant preparations such as *Allium sativum, Cicer arientinum, Inula recemosa, Terminalia arjuna, Trigonella foenum-graecum, Commiphora mukul,* green tea, and curcumin have been reported to have hypolipidemic actions. Few of these also, possess certain other beneficial properties like antianginal and antiplatelet actions. Plant preparations contain many compounds that work synergistically on multiple parts of the body. For example, garlic is not only antibacterial, but antifungal, and helps to lower cholesterol. This synergy of chemicals helps to balance the overall activity of the herb. Since the chemicals in herbs are non-specific and unconcentrated, there are generally fewer side effects from herbs than from manufactured drugs [7, 8].

2. Guggulipid

Guggulipid also known as gugulipid, guggulipid or guglipid has a long history of use in Ayurveda. The Atharveda is the earliest reference for its medicinal and therapeutic properties. Detailed descriptions regarding its actions, uses, and indications as well as the varieties of guggul have been described in numerous Ayurvedic treatises including Charaka Samhita (1000 BC), Sushruta Samhita (600 BC) and Vagbhata (7th century AD). In addition, various Nighantus (medical lexicons) were written between the 12th and 14th centuries A.D. that were based on the Ayurvedic literature. It is responsible for reducing fat, indicated for healing bone fracture to inflammation, arthritis, atherosclerosis, obesity, and hyperlipidemia [7]. Guggulipid is a standardized extract prepared from the oleogum resin (gum resin) of *Commiphora mukul,* commonly known as Guggul belonging to the family Burseraceae, is indigenous to India and is also found in Bangladesh and Pakistan. It grows wild in the semi-arid states of Rajasthan, Gujarat, and Karnataka in India. As afore mentioned, GL has been safely used for thousands of years in the Indian Ayurvedic medicine for the treatment of different ailments, including lipid disorders, rheumatoid arthritis, ulcers, osteoarthritis, bone fractures, epilepsy, and obesity [6, 9]. In 1986, GL was granted approval in India for marketing as a lipid lowering drug [10]. Several products of standardized formulations of *Commiphora mukul* are already in human use as cholesterol-lowering agents. The Z- and E-forms of guggulsterone (Gug, 4, 17(20)-pregnadie-3, 16-dione) have been identifed as major active components of GL [6, 11]. GL and its active component z-Gug have been used in many clinical trials that focused on its cholesterol-lowering effect. *Commiphora mukul* has been clinically proven to reduce the levels of harmful serum lipids in the blood stream. The active ingredients responsible for the maintenance of healthy cholesterol levels are the guggulsterones, specifically guggulsterone E and guggulsterone-Z [12, 13].

3. Chemistry

The oleoresin is a yellowish substance with a balsamic odor. The resin is tapped during winter and each guggul tree yields about 700-900 g of resin. The oleoresin contains 0.37% essential oil, containing mainly myrcene, dimyrcene and polymyrcene. Solvent extraction, hydrolysis and column chromatography over silica gel of guggul resin identifies a number of compounds such as diterpene hydrocarbon, a diterpene alcohol, sesamin, guggulsterone-Z, guggulsterone-E, guggulsterol-I, guggulsterone-II and guggulsterone-III, cholesterol, and camphorene [6, 9, 12].

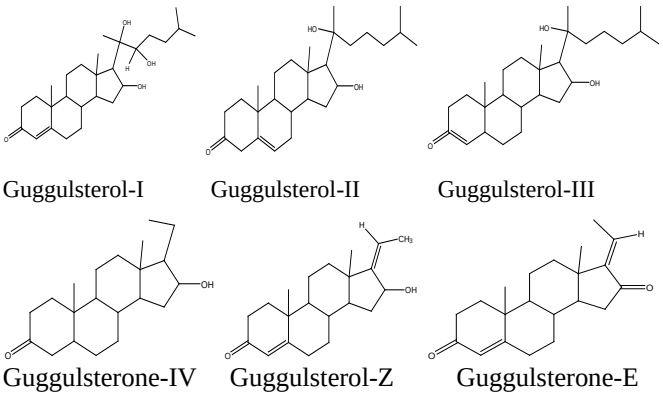

Fig 1: Phytoconstituents of guggul gum resin.

Solvent extraction using ethyl acetate separates the oleo-gum resin into two parts, gum and resin. The gum insoluble in ethyl acetate is chemically characterized as carbohydrate. The resinous portion dissolves in ethyl acetate and possesses both anti-inflammatory and lipid-lowering properties. It was further separated into an acidic, basic and neutral fraction that comprised approximately 45% *w/v*, 0.3% *w/v*, and 95% *w/v* of the ethyl acetate soluble resin, respectively. The basic fraction is devoid of any activity, while acidic fraction possesses lipid lowering activity. The lipid lowering activity is found in a ketonic fraction, which is a complex mixture of chemical compounds belonging to steroids [6, 12, 13, 14]. Among the compounds listed, Z-Guggulsterone and E-Guggulsterone which is present in a concentration of 4.0 and 6.0% are responsible for the hypolipidemic activity of the gum resin. In fact, the hypolipidemic activity of Z and E-Guggulsterone has been determined to be quantitatively comparable to that of the total ethyl acetate of the gum resin [9, 14, 15].

4. Mechanism of action

Prior to 2003, the majority of scientific evidence suggested that guggulipid elicits significant reductions in serum total cholesterol, low density lipoprotein (LDL), and triglycerides, as well as elevations in high-density lipoprotein (HDL). However, most published studies were small and not well designed or reported [16-21]. In August 2003, a well designed trial reported small significant increases in serum LDL levels associated with the use of guggul compared to placebo [22]. No significant changes in total cholesterol, high-density lipoprotein, or triglycerides were measured. These results are consistent with two prior published case reports [23]. Although this evidence provides preliminary evidence against the efficacy of guggul for hypercholesterolemia, due to the precedent of prior research and historical use, further study is necessary before a definitive conclusion can be reached. Initial research reports that guggulsterones are antagonists of the farsenoid X receptor (FXR) and the bile acid receptor (BAR), nuclear hormones which are involved in cholesterol metabolism and bile acid regulation [6, 24, 25]. Thus, the hypolipidemic activity of Guggul could be attributed to the following possible mechanisms include:

- Inhibition of cholesterol biosynthesis,
- Enhancing the rate of excretion of cholesterol,
- Promoting rapid degradation of cholesterol,
- Thyroid stimulation,
- Alteration of biogenic amines,

High-affinity binding and anion exchange. The first three mechanisms, inhibition of cholesterol biosynthesis, enhancing the rate of excretion of cholesterol and promoting rapid degradation of cholesterol are related in that the end result is the elimination of cholesterol. Guggul compounds are antagonist ligands for bile acid receptor called farnesoid X receptor (FXR), which is an important regulator of cholesterol homeostasis. It is likely that this effect accounts for the hypolipidemic activity of these phytosterols. Guggulsterone has the capability of inhibiting oxidative modification of LDL. While Guggulsterone E (GSE) or Z (GSZ) had no effect on FXR activity per se, both compounds statistically and dose-dependently inhibited FXR activation by chenodeoxycholic acid, the most potent of the bile acids activating FXR. This may imply that guggulsterones enhance conversion of cholesterol into bile acids which could be excreted in the feces lowering the liver and body cholesterol level [26, 27].

Guggulsterones have also been found to significantly inhibit activated pregnane X nuclear receptor (PXR) which participates in the production of bile acids in a similar way to that of FXR [26, 27].

Another type of nuclear receptor that may participate in the mechanism of action of GSE and Z is peroxisome proliferator-activated receptor (PPARs). These receptors, like FXR, modulate gene expression in response to a broad spectrum of compounds and may activate several enzymes metabolizing lipids and lipoproteins [26, 27].

5. Pre-clinical studies

The acute toxicity of GSE and Z standardized gum guggul extract was established based on LD_{50} in mice (1600 mg/kg *i.p.*) and LD_{50} (1600 mg/kg, *p.o.*) in mice and rats. Sub-chronic and chronic toxicity studies of gum guggul preparations, performed in rats, beagle dogs and rhesus monkeys, showed that a dose range of 125 to 500 mg/kg body weight, administered orally for 90 and 180 days, did not produce adverse effects and did not alter clinical biochemical or pathological parameters of the tested animals.

Mutagenic and teratogenic studies performed on rats (125 mg/kg, p.o.) and rabbits (100 to 200 mg/kg, p.o.) for 180 days showed no mutagenic effects as indicated by micronucleus and dominant lethality tests respectively.

In experimentally induced hyperlipidemia in rats treated with Triton or fed a high fat diet, the GSE and Z gum guggul preparation in an oral dose of 200 mg/kg, for 14-30 days, caused a statistically significant decrease (30-60%) in serum cholesterol and in serum triglyceride levels (30%). In the same experiments, the hypolipidemic activity of GSE and Z was found comparable to that of clofibrate and nicotinic acid. Oral administration of GSE and Z gum guggul preparation at 50 to 120 mg/kg to hyperlipidemic rabbits or rhesus monkeys for 8-12 weeks resulted in a significant lowering of serum cholesterol (30-40%) and triglycerides (30%) [17, 24].

The GSE and Z gum guggul preparation also prevented the formation of atheroma and contributed to regression of atheromatous lesions in hyperlipidemic rabbits and rhesus monkeys treated orally with 200 mg/kg for 90 days.

It was observed that there was 50% reduction of atheroma in

treated animals as compared to a 60% increase of atheromatous change in untreated animals. In addition blood coagulation parameters (prothrombin time and euglobinlysis time) in treated vs. untreated rabbits returned to normal levels [17, 24].

Administration of GSE and Z gum Guggul in rats, rabbits and monkeys (50-100 mg/kg, p.o.) produced a statistically significant two-fold increase in cholic and deoxycholic acids excreted in feces probably from the conversion of cholesterol.

Studies in vitro and in vivo showed that GSE and Z gum Guggul inhibits cholesterol biosynthesis (at comparable levels to clofibrate), prevents adrenaline-induced free fatty acids release from fat cells (antilipolytic activity), and inhibits adrenaline-induced platelet aggregation [24, 25].

6. Formulation

Gugulipid, an ethyl acetate extract of the oleoresin, standardized at CDRI (The Central Drug Research Institute, Lucknow) has been marketed in India since 1988 as a hypolipidemic agent [28].

Traditionally, Guggul is given in the form of Yog, wherein Guggul is mixed with other drugs along with castor oil or Indian clarified butter. The Yog could also be prepared by cooking the Guggul with water, and other herbal drug powders, popular Ayurvedic formulations containing Guggul are: Yograj Gugguluvati, Shuddha Guggul, Panchamritloh guggulu, Kaishore Guggulu vayi, Triphala Gugglu, and Sinha Gugguluvati [29-33]. The list of *guggul* formulations given in hyperlipidemia along with dose and its ingredients are listed below.

6.1 Himalaya Guggul (Shuddha Guggul/Guggulu)

Himalaya Guggul is a pure herb extract. Guggul or Shuddha Guggul/Guggulu helps to maintain normal cholesterol levels, normal HDL-LDL ratio and triglycycerides levels. Guggul also helps to lose weight. It comes in the form of capsules. Each capsule contains: Shuddha Guggulu (*Commiphora wightii*) oleo-gum-resin extract - 250 mg

Dose: 1 capsule twice a day after meals or as directed by the physician.

6.2 Triphala Guggulu

This classic Ayurvedic preparation combines the detoxifying and rejuvenating actions of triphala with the deeply penetrating and cleansing actions of guggul. It decongests the channels of the body, while scraping natural toxins held within the tissues. This preparation is particularly useful for weight management because it kindles agni (the digestive fire), promotes healthy metabolism, and releases excess kapha from the system. In maintaining overall health, it minimizes the accumulation of toxins in the GI tract, blood, and joints by supporting proper digestion and elimination.

Triphala Guggulu comprises of 5 herbs- Amalaki, Haritaki, Vibhitaki, Pippali and Shuddha Guggulu. In combination, these herbs help to remove toxins from the digestive tract, soft tissues, and joints along with maintaining normal cholesterol levels and a healthy weight. Each 250 mg tablet contains:

- Shuddha Guggulu (*Commiphora mukul*) : 138.88 mg
- Amalaki fruit (*Emblica officinalis*) : 27.77 mg
- Vibhitaki fruit (*Terminalia bellerica*) : 27.77 mg
- Haritika fruit (*Terminalia chebula*) : 27.77 mg
- Pippali fruit (*Piper longum*) : 27.77 mg

Dose: 1 to 4 Tablets (250 mg to 1g) in the morning and evening with milk or as directed by the Physician.

6.3 Yogaraj Guggul

This synergistic combination of herbs is particularly adept at clearing excess vata from the body, especially when it is lodged in the musculoskeletal system. It is powerfully detoxifying and rejuvenating and it has a special affinity for the joints, muscles and nerves. Guggul helps this preparation to scrape and eliminate natural toxins from the joints and muscle tissues as it rejuvenates and strengthens the skeletal and neuromuscular systems overall. [9]. The Main ingredients of Yogaraj Guggulu are: Shuddha Guggulu(Commiphora mukul), Chitrak root (Plumbago zeylanica), Musta root (Cyperus rotundus), Amalaki fruit (Emblica officinalis), Vibhitaki fruit (Terminalia belerica), Haritaki fruit (Terminalia chebula), Pippali fruit and root (Piper longum), Ajowan seed (Carum copticum), Vidanga fruit (Embelia ribes), Gokshura fruit (Tribulus terrestris), Black Cumin seed (Nigella sativa), Ajamoda seed (Trachysspermum roxb.), Cumin seed (Cuminum cyminum), Devdaru (Cedrus deodara), Chavya herb (Piper cubeba), Cardamom seed (Elettaria cardamomum), Rasna herb (Pluchea lanceolata), Rock salt, Coriander seed (Coriandrum sativum), Ginger (Zingiber officinale), Black Pepper fruit (Piper nigrum), Cinnamon bark (Cinnamomum zeylanica), Ushira herb (Vetiveria zizanoides), Yavakshar (Hordeum Vulgare), Talisa leaf (Abies webbiana), Tejpatra herb (Cinnamomum tamala).

Dose: 1 to 2 tablets, twice a day with lukewarm water or milk or as directed by the physician.

6.4 Kaishore Guggulu

This preparation is especially balancing for pitta, particularly when it is disturbing the musculoskeletal system. Its main ingredients: guduchi, triphala, and trikatu-when combined with guggul, create a powerful detoxifying and rejuvenating combination aimed primarily at removing deep-seated pitta from the tissues. It also acts to nourish and strengthen the system, supporting the overall health and proper function of the joints, the muscles, and the connective tissue.

6.5 Punarnavadi Guggulu

This formula is very useful for clearing excess kapha from the urinary system, kidneys, heart, and joints. Its main ingredients; punarnava, triphala, and trikatu-when combined with guggul, create a powerful detoxifying and rejuvenating combination that supports the healthy elimination of liquids, thereby balancing the water element in the body and releasing deep-seated kapha from the tissues. It also supports the lymph and blood and encourages healthy circulation and comfortable movement of the joints.

6.6 Kanchanar Guggulu

This combination of herbs is primarily used to address deep-seated kapha imbalances and is particularly supportive of the thyroid gland and the lymphatic system. Kanchanar is a very astringent herb that helps to clear the moist, stagnant qualities of kapha. When mixed with triphala, trikatu, and guggul, the

combination is powerfully detoxifying and removes excess kapha from the tissues. Future accumulation of kapha is also minimized by this formula because it kindles agni (the digestive fire) and promotes healthy elimination.

6.7 Gokshuradi Guggulu

This compound has a strong affinity for the genitourinary tract, strengthening and toning the kidneys, the bladder, the urethra, and the reproductive organs, while balancing vata, pitta, and kapha. Its main ingredient, gokshura, is renowned for its rejuvenating action on the kidneys, the prostate, and the reproductive system. This formula, which also contains guggul, triphala, and trikatu, is very effective at detoxifying and balancing the urinary ststem.

6.8 Simhanad Guggulu

This formula is specifically geared toward detoxifying and rejuvenating the joints and is balancing for vata and kapha; in excess, it may aggravate pitta. It combines the scraping and rejuvenating qualities of guggul with the potent cleansing capacity of castor oil and triphala, allowing it to remove natural toxins from the joints, blood, and GI tract. The soothing and lubricating qualities of the herbs then work to nourish and strengthen the joint tissues, supporting proper function and mobility. This preparation also promotes healthy digestion and elimination for improved overall health.

7. Guggul Research and Clinical Studies

Numerous studies have been undertaken to research the benefits of guggul. Guggul's benefits with regards to cholesterol, HDL-LDL ratio and fat metabolism have been published in various medical journals.

The one of the communication reports the findings of multicentric clinical trials carried out with Guggulipid, a new antihyperlipidemic agent, in primary hyperlipidemic cases at seven centres in India coordinated by and in collaboration with the Central Drug Research Institute (CDRI), Lucknow. Phase I clinical study, carried out at CDRI in 35 normal human volunteers established the safety of Guggulipid after a single oral dose (200-2400 mg). On multiple dose administration at 400 mg tds for 4-6 weeks in 20 patients of primary hyperlipidaemia, gugulipid was found to be safe and devoid of adverse effect on haematological and biochemical parameters and electrocardiogram. The fall of serum cholesterol 14.13% was observed in 80% patients [16, 18].

A pilot study to evaluate the efficacy of Guggulipid in primary hyperlipidemic patients was carried out at K.G. Medical College, Lucknow with a dose of 500 mg three times a day for 6 weeks in 22 patients; Guggulipid produced an average fall in serum cholesterol and triglycerides of 16.48% and 25.98% respectively21. The second study at the same centre on 19 primary hyperlipidemic patients for a period of 12 weeks showed a fall in serum cholesterol and triglycerides by 14.21% and 30.7% respectively which was highly significant. In both studies the lipid levels started to fall within a 2-4 week of starting gugulipid and statistically significant lowering persisted after 6-8 week of drug withdrawal. No side-effects were observed except in one patient who developed mild gastro-intestinal symptoms which did not necessitate withdrawal of the drug [16-18].

In double-blind crossover trial, the percentage lowering both of serum cholesterol and triglycerides were less variable with drugs. Guggulipid showed an edge over clofibrate in cholesterol-lowering effect and clofibrate over guggulipid in case of triglycerides, although percentage fall in both groups was not significantly different [16].

The effect of guggulipid on serum cholesterol and triglycerides is comparable to that of other hypolipidemic agents. Clofibrate, nicotinic acid and cholestyramine lowered serum cholesterol by 6-12, 10-17 and 20-27% respectively. Beta-sitosterol produced reduction in cholesterol by 10-15%. Clofibrate and nicotinic acid lowered triglyceride levels by 20-25% and 26% respectively. HDL-cholesterol level has been shown to be strongly but inversely correlated with coronary artery disease risk. In the present study a significant increase in HDL cholesterol was found in responders to guggulipid therapy. Clofibrate has been reported to cause a rise in HDL-cholesterol but in this study this was not confirmed. Lowering of LDL-cholesterol was found with both drugs which could be directly due to a decrease in serum cholesterol by diet and drugs. In this study a reduction in the ratio of LDL-C/HDL-C and TC/HDL-C was observed, more with guggulipid than with clofibrate in 45 patients. Larger sample studies have shown that reduction in total cholesterol and/or in low-density lipoprotein cholesterol/or an elevation in high-density lipoprotein cholesterol results in amelioration in cardiovascular end points [16, 18, 22].

8. Conclusion

Commiphora mukul has become a vital subject of research due to the presence of numerous pharmaceutically valuable bioactive agents. Although no other natural product is as effective as guggulsterone against treatment of multiple ailments including lipid and cholesterol lowering activity but there is a need to evaluate the complexity of different bioactive components present in the oleo-gum resin by rigorous assessment of the mechanism of drug action, pharmacokinetics, metabolism, effective concentration, ratio of impurities, bioavailability and bibliographic data which will reveal the safety and efficacy of the drug after a long-term experience. Therefore, cost effective and easily available drug delivery systems like Guggul some having no toxicity can be established on a large scale. Molecular mechanisms underlying guggulsterone action must be elucidated precisely so that various pharmaceutical applications of guggulsterone including anti-cancerous and cardio-protective properties can be used for saving thousands of lives annually. Although Guggul is an important and valuable drug for cholesterol lowering, chemical analysis revealed that the insoluble extact (prepared by using petroleum ether, alcohol and ethyl acetate) does not contain any beneficial biological activity rather it may be toxic for animals and cause some allergic effects like skin rashes and gastrointestinal discomfort. Finally, it is observed that no data on bioavailability, metabolism, and pharmacokinetics of *guggulipid i*n animal models or humans are currently available. The knowledge of these basic parameters is needed for proper evaluation of the clinical findings with *guggulipid* and other formulations of guggul.

Conflicts of interest: There are no conflicts of interest.

9. References

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