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The Management of Hypercholesterolemia with Herbal Medicine

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INTRODUCTION

It is the condition that is characterized by increased concentration of lipids or fats (triglycerides, cholesterol) and low density lipoproteins in the blood and decrease in high density lipoproteins. This increase of lipids in the blood can lead to serious heart diseases and pancreatitis. Most of the time hyperlipidemia has no symptoms and usually it has been diagnosed on routine lab investigation or during secondary investigations held primarily for other symptom or disease. Once baseline lipid levels are determined, they should be checked and controlled for every 3 to 4 months, or at least once a year. Regular aerobic exercise is shown to reduce cholesterol. Discontinuing smoking and avoid or limit consumption of alcohol can also lower cholesterol. The plasma lipid levels recommended by National Cholesterol Education Program (NCEP), ATP (Adult Treatment Panel) III USA the desirable amount of "total Cholesterol" is less than 200 mg/dL, 200-239 mg/dL is borderline range, above or equal to 240 mg/dL is high range and for "triglycerides" normal value is less than 150 mg/dL, 159-199 mg/dL is borderline, 200-499 mg/dL is high, and equal or above than 500 mg/dL is very high. In case of "LDL-Cholesterol" the optimal value is less than 100 mg/dL, near optimal/ above optimal is from 100-129 mg/dL, borderline high is ranges 139-159 mg/dL, high value is 160-189 mg/dL, and very high, and equal or above190 mg/dL. "HDL- Cholesterol" level low is below 40 mg/dL, and high values is equal or above 60 mg/dL" [1]. Table 1 shows the detailed elaboration from NCEP ATP III USA Guidelines:

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The depiction of healthy cholesterol levels and hypercholesterolemia are given in figure 1 and figure 2 where as in healthy cholesterol levels low density lipoproteins, triglycerides and high density lipoproteins have been figured out. In case of hypercholesterolemia low density lipoproteins, high lipoproteins are found in abundance that elicits the causes of hyperlipidemia.

Hypercholesterolemia

1. Mild hypercholesterolemia (borderline-high cholesterol): It is defined as the "total cholesterol in the range of 200 to 239 mg/dL". Epidemiological studies show that levels above 200 mg/dL twice increase risk for heart disease e.g. coronary heart diseases, therefore, the patients with cholesterol levels in the range 200 to 239 mg/dL should be clinically evaluated for risk factors.

2. Moderate hypercholesterolemia: "Plasma cholesterol with the range of 240 to 300 mg/dL and LDL-Cholesterol 160 to 210 mg/dL" is termed as moderate hypercholesterolemia. Normally, this is related to reduced activity of LDL receptors, defects of hepatic cholesterol metabolism, hypothyroidism and complications after menopause [2].

3. Severe hypercholesterolemia (familial

Table 1

Recommended Healthy Levels Ages 2 – 18				
		Desirable	Borderline	High Risk
Total Cholesterol		Less than 170	171-199	200 or more
LDL Cholesterol		Less than 110	111-129	130 or more
HDL Cholesterol		More than 60	36-59	35 or less
Recommended Healthy Levels Ages 19 or older				
	Desirable	Acceptable	Borderline	High Risk
Total Cholesterol	Less than 180	181-199	200-239	240 or more
HDL Cholesterol				
Men	50 or more	45-49	35-44	35 or less
Women	60 or more	55-59	40-54	39 or less
Total Cholesterol / HDL Ratio				
Men	4.0 or less	4.1-5.0	5.1-6.5	6.6 or more
Women	3.3 or less	3.4-4.5	4.6-6.5	6.6 or more
LDL Cholesterol	100 or less	100-129	130-159	160 or more
Triglycerides	Less than 150	150-199	200-499	500 or more
Screening Recommendation				
Blood Cholesterol Levels	199 or less		200 or more	
Screening Frequency	Consult your physician for specific screening guidelines		A complete Cholesterol Panel is recommended. See your physician	
Source: American Heart Association and National Cholesterol Education Program Guidelines: 2008				

hypercholesterolemia):

It refers to the plasma concentration of cholesterol above 300 mg/dL and LDL over 210 mg/dL. It relates inherited defects in the gene encoding of the LDL receptors. Heterozygous familial hypercholesterolemia is usually one in 500 people and manifests clinically with tendon xanthomas and premature coronary heart disease whereas homozygous forms are rare, i.e. one in 1,000,000. Hypothyroidism and nephritic syndrome may be the cause of severe hypercholesterolemia.

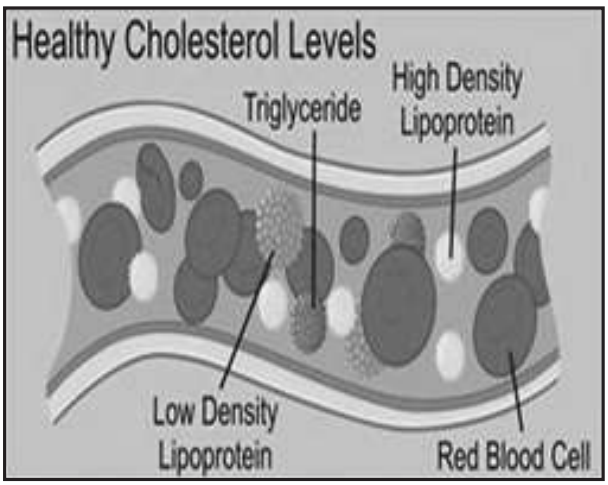

Figure.1 Healthy Cholesterol Levels

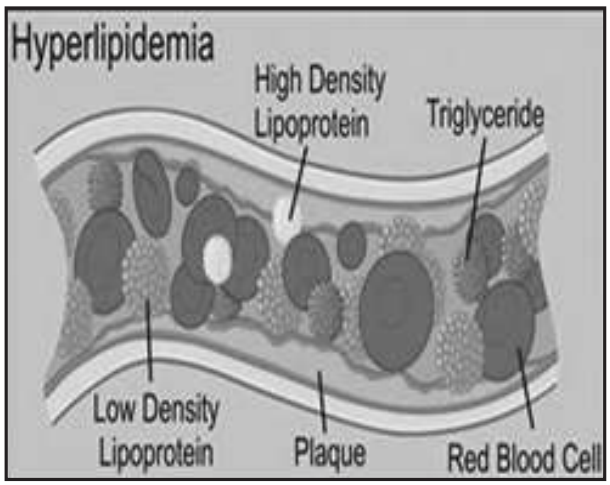

Figure.2 Hypercholesterolemia

In addition, many intervention studies have clearly demonstrated the role of low-density cholesterol (LDL-C) in mortality and morbidity due to heart diseases while high density cholesterol (HDL-C) is considered the good cholesterol helps in reverse cholesterol absorption [3,4].

Hypertriglyceridemia

It refers to increase plasma triglyceride levels over 250 mg/dL, generally in the range of 250 to 500 mg/dL. Endogenous hypertriglyceridemia also called type IV Hypercholesterolemia, which is characterized by increased VLDL, triglycerides. Diet-induces endogenous hypertriglyceridemia due to dietary factors like excessive caloric intake, excessive alcohol intake, stimulates the production of VLDL triglycerides. Primary endogenous hypertriglyceridemia is due to overproduction of VLDL triglycerides or defective lipolysis of VLDL, however, the reasons are poorly understood but insulin resistance could be one explanation. Among all causes the non-insulin dependent diabetes mellitus is common cause and requires good glycemic control to limit secondary hypertriglyceridemia. HMG-CoA is the only choice but their role is not fully established in hypertriglyceridemic diabetics.

Mixed Hypercholesterolemia

It refers to "increase plasma levels of the total cholesterol above than 240 mg/dL and above than 250 mg/dL triglycerides level". Chylomicrons and VLDL are typically increased more than 500 mg/dL in marked hypertriglyceridemia with elevated cholesterol (type V hypercholesterolemia).

Clinical Manifestation

Initially it does not show any symptoms but most of the time it is diagnosed at screening. In its later stages, however, high cholesterol can cause

- Fatty deposits and skin tendon.
- Hepato-splenomegaly.
- Abdominal pain.

Epidemiological evidence

High risk of hypercholesterolemia is present worldwide however it is more so in India and Pakistan. According to a survey carried out in about 3143 adults >40 years of 12 randomly selected communities in Karachi, Pakistan, women were more likely to develop high cholesterol than men. The evidence shows that people living in South Asia have higher readings compared to the data equivalent of living in Europe, China and North America. This index can be used as a marker of the presence of small plates that may progress to rupture and contribute to coronary occlusion and ischemia potential [5].

According to another study "conducted in the department of epidemiology and public health at University College London, UK", the risk of developing cardiovascular disease in adult men belonging to the upper class, fed butter and saturated fats by sedentary with lipid profiles in the upper limits were higher compared to individuals belonging to low socioeconomic class with normal lipid profiles without hypertension in South Asia [6].

Causes of Abnormal Lipid Profiles

Total and LDL Cholesterol: These may raise due to hereditary hypercholesterolemia (types IIa or IIb), taking diets that are high in saturated fats and cholesterol, under active thyroid, poorly controlled diabetes, liver disease, overactive pituitary gland, nephritic syndrome characterized by elevated cholesterol, loss of protein in the urine leading to low levels of protein in the blood and excessive fluid retention causing swelling, anorexia nervosa, certain medications.

These are raised due to variety of factors that includes genetic factors and age usually over age 45 in men and age 55 in women, menopause, lack of physical activity, certain medications e.g., diuretics, immunosuppressant, and corticosteroids. Chronic diseases like diabetes, hypothyroidism, cigarette,

high intake of dietary cholesterol, and obesity.

HDL cholesterol levels: There are some factors that may cause to lower down the level of beneficial cholesterol these includes malnutrition, cigarette smoking, certain medications (beta blockers and anabolic steroids), laziness, polycystic ovarian syndrome [7]. HDL-Cholesterol particle have some basic functions to eliminate the products of LDL due to paraoxonase enzyme [8].

Reverse Cholesterol Transport: HDL-cholesterol are picked up by liver via SRB1 receptors (Scavenger receptor B, class 1) and ApoE receptors, also present in adrenal glands and ovaries, that selectively remove esterified cholesterol from liver. Hepatic cholesterol is then excreted in bile mediated by ABCG5/ ABCG8 transporters. Moreover, cholesterol linked to HDL is exchanged with Triglycerides of VLDL, IDL, and LDL resulting in TG enriched HDL-cholesterol.

Epidemiological studies on HDL-Cholesterol According to one study, "the HDL cholesterol is inversely related to both coronary heart disease and other cardiovascular disease mortality in both sexes". According to study conducted by World Health Organization analyzed the data from 19 countries and showed "an inverse correlation between HDL-cholesterol and mortality due to coronary artery diseases". Framingham study also showed an inverse correlation between HDL-Cholesterol and coronary artery diseases in male and female of different age groups, and also greater risk with HDL-Cholesterol as <40 mg/dl, regardless of LDL-Cholesterol values. Moreover, HDL-Cholesterol above 65 mg/dl provide protection against coronary events, even if LDL-Cholesterol 160 mg/dl.

In Lipid Research Clinics Prevalence Mortality Follow-up Study, it is shown that even 1 mg/dl increase in HDL-Cholesterol is associated with reduction of 3.5 % risk of coronary artery diseases, while HDL-cholesterol <35 mg/dl is associated with 3.7% mortality rate in men and 4.7% in women and the risk is 6 times higher for coronary artery diseases [9].

High triglycerides levels: Hereditary hypercholesterolemia (types I, IIb, III, IV, or V), diets high in calories, especially form sugar and refined carbohydrates, obesity, poorly controlled diabetes, insulin resistance, alcohol use, kidney failure, stress, pregnancy, polycystic ovarian syndrome, hepatitis, lupus, multiple myeloma, and lymphoma.

According to one study, high TG–low HDL-C, the characteristic dyslipidemia seen in insulin-resistant subjects, was at least as powerful predictor of IHD as isolated high LDL-C. The results suggest that efforts to prevent IHD should include intervention against high TG–low HDL-C, and not just against hypercholesterolemia [10].

Classification of triglycerides according to the National Cholesterol Education Program Adult Treatment Panel III is shown in table 2.

Table 2. Classification of triglycerides

1	Normal triglycerides < 150 mg/dL
2	Borderline-high triglycerides 150 - 199 mg/dL
3	High triglycerides 200 - 499 mg/dL
4	Very high triglycerides* = 500 mg/dL

Diagnosis

Diagnosis is done usually by testing lipid profile of the patients after an overnight fasting (10 to 12 hours). Adults with normal lipid profile should have their cholesterol checked after every five years and those who treated should cholesterol levels measured every two to six months and also liver functions tests.

The major risk factors that modify low-density lipoprotein include age, smoking status, hypertension, high-density lipoprotein levels, and family history. The concept of "CHD equivalent" is introduced—conditions requiring the same vigilance used in

patients with coronary heart disease. Patients with diabetes and those with a 10-year cardiac event risk of 20 percent or greater are considered CHD equivalents. Once low density lipoprotein cholesterol is at an acceptable level, physicians are advised to address the metabolic syndrome and hypertriglyceridemia.

Literature Search: Literature Search on herbal medicine has been extensively carriesout however some of the representative hebrs that are utilized are delineated herewith are as follows. *Bombyx mori Cocoon.,Commiphora mukul Engl.,Trigonella foenum-graecum Linn., Origanum vulgare Linn., Rauwolfia serpentine (L.) Benth. ex Kurz.*

Commiphora mukul Engl.: The English and vernacular names of *Commiphora mukul* are Gum-gugul, Salai tree. In Urdu it is termedas Muql, Gugal, Gugar while its botanical name is *Commiphora mukul* and belongs to family Burseraceae.

Figure.3 Leaves

Figure.4 (Gum)

Figure.5 Tree

Chemical Constituents: It contains Z-guggulsterone, E-guggulsterone, Z-guggulsterol, 16-a hydroxy-4-pregnen-3-one, 20a-hydorxy-4-pregnen-3-one, 20 ß-hydorxy-4-pregnen-3-one, guggulsterol –I, guggulsterol-II, guggulsterol-III, 3.5,6-cholestanetriol, 5-hydroxycholestane-3,6-dione, 16,20-dihydroxycholest-4,24-dien-3-one, mukulol, Cembrene-A, Myrcene, Myrcenol, D-xylo-guggultetrol-18, 4,5 dihydro: 8,12 epoxy-1(10)4,7,11-germacratetaen-6-one and ferulic acid [11]. The ketone fraction has the most potent cholesterol lowering components. These are composed of C21 or C27 steroids, with the major components being Z- and E-guggulsterone. It contains resin, volatile oil, and gum. Guggulsterones, the extract isolates ketonic steroid compounds and have the lipid-lowering actions.

Pharmacological Properties: The compounds isolated from *Commiphora mukul* like cembrenoids, a bicyclic diterpene, guggulsterone derivatives, myrrhanonol derivatives, myrrhanol derivatives, and a lignan, inhibit the lipid peroxidation by 79, 57 and 58 % respectively [12]. In a randomized, double blind study *Commiphora mukul* was proved to be hypolipidemic. It may decrease upto 11.7 % the total cholesterol level, 12.5 % the LDL-Cholesterol,12.0 % triglycerides and11.1 % the total cholesterol / HDL-Cholesterol ratio from the post diet levels compared with the placebo group [13].

388 patients were enrolled with different diagnosis in six randomized clinical trials of *Commiphora mukul*, involving, five in India and one in the United States, 4 placebo-controlled and 1 compared guggul with 2 reference compounds reduced the total cholesterol from 10 % to 27 % and significant decrease in lipid peroxide levels[14]. According to another study, guggulsterone, inhibit the LDL oxidation that is mediated by either catalytic copper ions, free radicals that are generated withazo compound 2, 2-azobis-(2-amidinopropane) dihydrochloride (AAPH), or soybean lipoxygenase enzymatically, or the mouse peritoneal macrophages that reducing chances of atherogenesis [15]. In another study of twenty patients of Hypercholesterolemia, purified gum of *Commiphora mukul* in two divided doses of 4.5 gm daily for 16 days reduced serum cholesterol and triglyceride levels at the end of 4th and 8th weeks [16].

Bombyx mori Cocoon: Common name of *Bombyx moriis Abresham*. It is an insect being a primary producer of silk. A silkworm's that preferred white mulberry leaves as food, but it may eat leaves of the other mulberry tree i.e.Morusnigraor or Morusrubra as well as the Osage orange. For reproduction it is completely dependent on humans.

General Uses: It is promising as a reserve for solving a various biological problems [17]. In Unani medicine

it is also known as Abresham Muqirz [18] and is also used in various formulations (Khameera-E- Abresham Sada, Khameera Abresham Hakeem Arshad Wala, Khameera Abresham Oud Saleeb Wala) and these are used for treating various ailments along with the Badranjboyaand Arjan [19,20].The crude extracts has protective role in hyperlipidemia and also have good antioxidant effect and beneficial effects for the management of hyperlipidemia [21]. Several formulations with large or small number of ingredients in Unani pharmacopoeia have been described for treating various ailments. But out of these some of the dosage forms in the Unani medicine have shown better results [22]. It is hot and dry in temperament. It is prescribed as nervine stimulant and also a cardiac tonic. It is an expectorant and can remove surplus 'Balghan' from the blood (Blagam – e – ghairtabaee) [23]. Recently it has been used to treat the, hypertension, heart diseases and palpitations [24].

Rauvolfia serpentina (L.) Benth. ex Kurz Rauvolfia serpentina (L.) Benth. ex Kurz belongs to the family Apocynaceae and also cultivated in Karachi [25,26].

Figure 6. *Bombyx mori Cocoon.*

Chemical Constituents: Rauvolfia root contains almost 50 alkaloids that include reserpine, serpentina, deserpidine, ajmalicine, ajmaline, ajmalidine, sarpagine etc. Among all the principal alkaloid reserpine and rescinnamine in roots are majorly responsible for hypotensive activity [27,28,29,30].It was also reported that the Rauvolfia contains not less than 0.15% of reserpine-rescinnamine group alkaloids, calculated as Reserpine [31,32,33,34]. It was found in previous research study that it contains phytosterol, oleic acid, and unsaturated alcohols, five alkaloids, which were classified by them into

Figure 7. *Rauwolfia serpentina*

two groups; 1) The ajmaline group of three white crystalline, weak bases, ajmaline, ajmalinine, ajmalicine; and 2) the serpentine group of two yellow crystalline stronger bases, serpentine and serpentinine"[35].

Pharmacological Properties: Recent research showed the major use of Rauvolfia roots is in the treatment of mild hypertension. Usually to prevent fluid retention it is given in combination with a diuretic herb that support its activity [36-42]. It was also investigated that rauvolfia root powder is a potent hypolipidaemic agent especially having hypo-triglyceridemic and hypo-cholesterolemic effects with undetectable side effects on liver and cardiac functions. Reserpine in Rauwolfia is powerful alkaloid has not shown any toxicity with same generic name of drugs. It has been used in the treatment of psychic and motor neuronal disorders, that including excitement, anxiety states, insanity insomnia and epilepsy from many centuries. It was reported that the powdered extract of root of Rauwolfia have efficacy to decrease the high blood pressure in experimental animals [43,44]. Medicinally it is an important herb that has widespread spectrum of

therapeutic actions with majorly effective in the treatment of hypertension and psychotic disorders [45,46]. It has unique properties of being slow onset of action but effect is sustained for longtime. By withdrawal of the prescribed medicine there may be chances of occurrence of cardiac and central nervous system effects. The metabolisms of active alkaloids

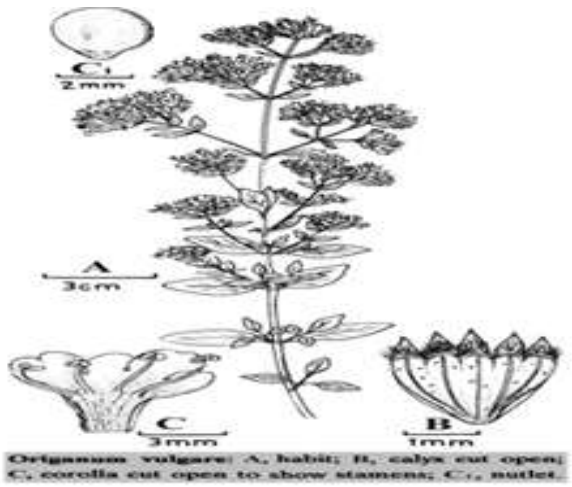

Figure 8. *Origanum vulgare L.*

into inactive compounds occur in liver that are excreted primarily in the urine [47].

Chemical Constituents: The plant contains 0.15-1.0% volatile oil in which chief components includes carvacrol (40-70%), p-cymene (5-10%), gamma-terpinene (8-10%), additionally alpha-pinene, thymol. Other components are flavonoids: including naringin, Caffeic acid derivatives: in particular, rosmaric acid (5%) [48].

Pharmacological Properties: Leaves of Oregano are used as strong anti-hyperglycemic agents described in traditional practitioners [49]. In one research study it was said that the extract of oregano have blood glucose lowering activity without effecting the basal plasma insulin concentrations in normal and streptozotocin (STZ) diabetic rats. The carvacrol principally in aromatic oregano water, is used in gastrointestinal disorders, also reduce blood cholesterol and glucose level and also used for tumor suppressive activities [50]. In one animals study, the animals were treated with the infusion of oregano showed lower blood glucose in comparison with the control group [51]. It is demonstrated in vitro studies that the ability to inhibit the aggregation and adhesion of blood platelets and cholesterol synthesis is due to oregano oil and its constituent substances, such as gamma-terpinene and carvacrol, whereas a decline was noticed in vivo study in the total cholesterol, triglycerides and both the systolic and diastolic readings in hypertension [52].

Trigonella foenum graecum L.: Trigonella foenum - graecum (Linn.) belongs to the family Papilionaceae. It is an aromatic, 30-60 cm tall, annual herb, and cultivated throughout the country [53,54].

Figure 9. *Trigonella foenum-graecum*

Chemical Constituents: The major constituents of T. foenum-graecum are fibers, saponins, flavonoids, flavonoids, polysaccharides and polysaccharides fixed oils and some identified alkaloids i.e .trigonelline and choline [55,56]. Seeds of Fenugreek also contains 45-60% carbohydrates, mainly mucilaginous fiber (galactomannans), 20-30% proteins high in lysine and tryptophan, 5 - 10% fixed oils (lipids), pyridine alkaloids, mainly trigonelline (0.2 - 0.38%), choline (0.5%), gentianine and carpaine, the flavonoids apigenin, quercetin, vitexin and isovitexin, free amino acids, such as 4-hydroxyisoleucine (0.09%), arginine, histidine and lysine, calcium and iron, saponins (0.6 - 1.7%), glycosides yielding steroidal sapogenins, vitamins A, B1, C and nicotinic acid, cholesterol and sitosterol,

and 0.015% volatile oils n-alkanes and sesquiterpenes [57,58]. The seeds gave alkaloids, including trigonelline, carpaine; and saponins, based mainly on the sapogenins, diosgenin and its isomer yamogenin, gitogenin and tigogenin; flavonoids, including vitexin and its glycosides and esters and luteolin; a volatileoil in small quantities. *Pharmacological Properties:* It has been observed that flavonoids possess anti-oxidant activity [59,60,61]. It was also reported that the seeds may raise the anti-oxidant levels. In number of clinical trials it was observed that the seeds have shown the efficacy as a hypoglycemic and anti-diabetic agent with minor or even no toxic manifestations [62,63]. The results indicate that the extract of fenugreek seeds contains antioxidants and protects cellular structures from oxidative damage. These findings provide evidence for the in vivo beneficial effects of the seeds reported in the literature. The antiradical activity could be correlated with the polyphenolic components present in the extract. The results gained by these methods provide some important factors responsible for the antioxidant potential of fenugreek seeds and offer evidence for the large number of in vivo beneficial effects of the seeds reported in the literature [64].

Fenugreek was used for the treating various ailments i. e. wounds, joint pain, chest problems, and gastrointestinal affections. It was used by Traditional Chinese Herbalists for management of renal affections and male reproductive tract affections. It has been used as condiments for food preparation in various part of the world [65]. The seeds are also used as tonic, expectorant, restorative, aphrodisiac, carminative, emmenagogue, and vermifugal properties. The seeds showed effects on serum cholesterol and glucose levels in condition from mild to moderate hypercholesterolemia or diabetes assessed by clinical studies in past.

CONCLUSION

From the above extensive literature search which was carried out with the assistance of a team comprises of professionals like botanist, herbalists, Phytochemists and pharmacologists, it was concluded to add these botanicals in the formulation to produce a drug with the coded name "BIOCOR PLUS" Tablet for the treatment of hypercholesterolemia. The literature search showed enough evidences that supports the inclusion of the herbs and their extracts in the formulation to make it effective to normalize the blood cholesterol level especially considering total cholesterol and LDL-Cholesterol.

The herbs belong to Indo-Pak region, which makes their availability easier, these will be cost effective also and more importantly there were no major toxicity associated with these herbal raw materials and their good efficacy in hypercholesterolemia, makes them ideal candidates to be added into the formulation.

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