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Therapeutic Hypolipidemic Activity Of Traditional Polyherbal Formulations

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Abstract
Hyperlipidemia, particularly elevated low-density lipoprotein (LDL) cholesterol, is a major risk factor for atherosclerosis and cardiovascular diseases, which remain the leading cause of global mortality. Although several synthetic antihyperlipidemic drugs are available, their long-term use is often associated with adverse effects and limited patient compliance. This review aims to provide a comprehensive overview of traditional polyherbal formulations used in the management of hyperlipidemia, with a focus on their phytoconstituents, therapeutic potential, and mechanisms of action.
Relevant literature was collected from scientific databases including PubMed, Scopus, and Web of Science, focusing on studies related to polyherbal formulations with antihyperlipidemic activity. Various traditional formulations such as Arogyavardhini vati, Navaka Guggulu, and formulations containing *Trigonella foenum-graecum*, *Ziziphus lotus*, and *Commiphora wightii* have demonstrated significant lipid-lowering effects. These formulations act through multiple mechanisms, including inhibition of HMG-CoA reductase, antioxidant activity, and modulation of lipid metabolism pathways. Polyherbal formulations represent a promising alternative to conventional therapies due to their multi-targeted action, natural origin, and relatively lower side effects. However, further standardization, clinical validation, and mechanistic studies are required to establish their safety, efficacy, and global acceptance.
Hyperlipidemia, Polyherbal formulations, Antihyperlipidemic activity, Medicinal plants, Lipid metabolism

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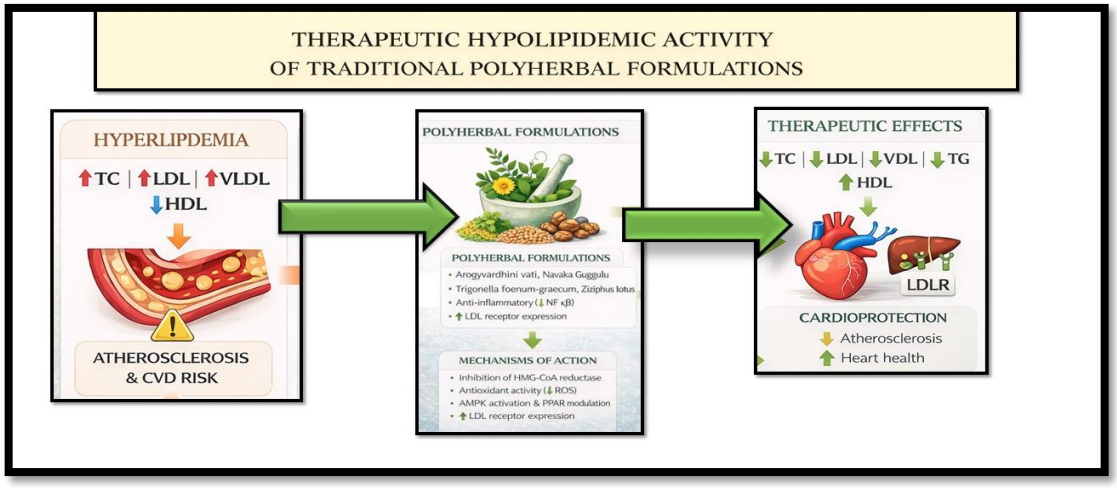
Graphical Abstract:



Graphical Abstract: Polyherbal formulations reduce TC, LDL, VLDL, and TG while increasing HDL, thereby improving lipid profile and providing cardioprotective effects.

Introduction

Hyperlipidaemia and obesity are major global health concerns that have been linked to increasing incidence of cardiovascular diseases, diabetes, and metabolic disorder. Based on global health estimates, overweight and obesity are responsible for millions of deaths each year because of ill health. Roughly 44% of diabetes cases, 23% of ischemic heart disease, and a considerable proportion of cancers occurred due to excessive body weight [1,2]. As these conditions continue to rise, there is an urgent requirement for the counter measures targeting lipid and other risk factors. Hyperlipidemia (hypercholesterolemia) is defined by elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein cholesterol (VLDL-C) and/or decreased high-density lipoprotein cholesterol (HDL-C). The alterations in lipids promote the genesis of atherosclerosis, which in turn is responsible for coronary artery disease, stroke and other cardiovascular complications [3,4]. When lipids build up in the arterial walls, it triggers inflammation and oxidative stress, contributing to plaque formation and vascular injury. Lipid regulation are essential for cardiovascular diseases and overall health, and fat mobilization is one of them. Currently, various synthetic antihyperlipidemic drugs such as statins, fibrates, niacin, and bile acid sequestrants are commonly used for the management of hyperlipidemia. These compounds work by affecting cholesterol biosynthesis, lipid metabolism or the inhibition of lipids absorption from the gut. While these drugs are very effective, their use is frequently associated with side effects over time, such as hepatotoxicity, myopathy, and gastrointestinal or renal effects [5,6]. Moreover, challenges like low patient adherence, resistance to medications, and expensive treatment options restrict their broad application in clinical settings. Lately, there has been a great attention on natural products and herbal medicines as safer options to control hyperlipidemia. Since ancient times, medicinal plants have been used as a remedy for the treatment of various metabolic disorders due to their therapeutic efficacy, cost-effectiveness and relatively less side-effects [7,8]. The Polyherbal formulations gain importance because of their synergistic effect which enables them to act on more than one biological target [9]. In complex diseases like hyperlipidemia, which act on multiple pathways, use of multi-targets drugs is especially useful. Polyherbal formulations contain various plants that act together to give their pharmacological action. The lipid lowering effects of these formulations involve various mechanisms of action including inhibition of HMG-CoA reductase, modulation of lipid metabolism, antioxidant and anti-inflammatory effects [10,11]. They also regulate important signaling pathways, which include AMP-activated protein kinase and peroxisome proliferator-activated receptors that are often crucial for lipid and glucose homeostasis [12]. The therapy potential of these phytoconstituents is additionally attributable to their ability to contain flavonoids, alkaloids, saponins, tannins, etc. Several medicinal herbs like Trigonella foenum-graecum (Fenugreek), Commiphora Wightii (Guggulu), Emblica Officinalis (Amla) and Terminalia arjuna have been well documented for their lipid-lowering properties. These plants can not only lower lipids in serum but exhibit antioxidant and cardioprotective activity to prevent oxidative damage and improve vascular functions [13,14]. Moreover, the formulations containing various medicinal herbal plants have shown promising outcomes during experimental as well as clinical studies, thus exhibiting their antihyperlipidemic potential. In spite of their anticipated therapeutic potentials, there are a number of problems associated with polyherbal systems. The phytochemical variability, lack of standardization, insufficient clinical validation, and quality control issues hinder these applications [15]. Thus, their safety and efficacy are established by means of scientific validation, standardization and regulatory evaluation. To tackle these issues, advanced analytical methods and pharmacological approaches are now being employed to better understand the medicinal action of herbal formulations. Through this review, we collate and critically analyze the scientific evidence on traditional polyherbal formulations used in the management of hyperlipidemia. The analysis examines their phytoconstituents, mechanisms of action, therapeutic efficacy, and advantages over traditional therapies. Moreover, it is necessary to explore the potential of traditional knowledge coupled with modern science for the discovery of safe, effective and cheap remedies for hyperlipidaemia and allied metabolic disorders [16].

2.Methods

An exhaustive and systematic literature search was performed to obtain relevant information on antihyperlipidemic activity of traditional polyherbal formulations. The peer-reviewed research articles, review articles, and experimental studies related to hyperlipidemia, medicinal plants, and polyherbal formulations were thoroughly searched for in various scientific databases PubMed, Scopus, Web of Science and Google Scholar (46–50). The studies were selected as per defined inclusion and exclusion criteria. The studies which were carried out on the polyherbal formulation, plant-derived phytoconstituents and their lipid-lowering potential were included in the review. Both in vitro as well as in vivo experimental studies along with the available clinical investigations were taken into account

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for acquiring proper understanding regarding their therapeutic potential [36-40]. Articles that did not deal with antihyperlipidemic activity directly, were not scientifically validated and were either published in non-reviewed material, was excluded. During the literature search process, the keywords such as "hyperlipidemia," "polyherbal formulations," "antihyperlipidemic activity," "medicinal plants," and "lipid metabolism" were used individually as well as in combination. Boolean operators were used to refine the search strategy and to make the hits more specific. The collected articles were screened, critically examined, and compiled to obtain details regarding various traditional polyherbal formulations and mechanisms of action [48–50].

3. Overview of Traditional Polyherbal Formulations: To collect relevant information pertaining to traditional polyherbal formulations showing antihyperlipidemic activity, a detailed and systematic review of the literature was conducted. A variety of scientific databases including PubMed, Scopus, Web of Science, and Google Scholar were searched extensively for peer-reviewed research papers, reviews, and experimental studies related to hyperlipidaemia, medicinal plants and polyherbal formulations [46–50]. Selection of studies was done on defined criteria of inclusion and exclusion. The review included studies on polyherbal formulations, plant derived phytoconstituents and lipid lowering activity. Both these formal and informal, lab-based and field experiments can be very helpful in understanding their use in practice and assessing their effectiveness. To Enhance the Quality and Reliability of Data, Exclusion Criteria of Articles Not Reporting Antihyperlipidemic Activity, Not Scientifically Validated, and Not Peer-Reviewed Were Assumed. The literature search process utilized relevant keywords like hyperlipidaemia, polyherbal formulations, antihyperlipidaemic activity, medicinal plants, and lipid metabolism employed one at a time or in combination. Boolean operators were thus used to optimize the search strategy and its specificity. The selected articles were screened, critically analysed, and compiled to present a detailed analysis of traditional polyherbal formulations and the mechanism of action [48–50].

Table 1: List of Herbal formulation

Sr. No.	Herbal Formulation	Manufacturer / Source	Herbal Ingredients (Part Used)	Therapeutic Actions	Toxicity & Stability	Reference
1	Arogyavardhini Vati	Maharshi Ayurveda	*Picrorrhiza kurroa, Terminalia chebula, T. bellerica, Emblica officinalis, Commiphora wightii*	Reduces TC, TG, LDL; increases HDL; antioxidant (↓MDA, ↑GSH)	Safe and effective in dyslipidemia	[36,37]
2	Navaka Guggulu	SKM (Ayush Care)	*Commiphora wightii*	Antihyperlipidemic, anti-obesity	Aged (Purana) formulation more effective	[28,36]
3	*Trigonella foenum-graecum* Extract	Extract	Fenugreek seed extract	Reduces lipid profile, anti-obesity	Safe, no major side effects	[26,38]
4	Polyherbal Extract (*Ricinus, Ziziphus, Capparis*)	Extract	*Ziziphus lotus, Ricinus communis, Capparis decidua*	Inhibits HMG-CoA reductase; lowers TC, TG	Effective in experimental models	[16,29]
5	Reosto (Herbomineral)	Himalaya	*Terminalia arjuna, Withania somnifera, Commiphora wightii*, others	Reduces plasma lipids; cardioprotective	Safe with good efficacy	[38,41]
6	Hridayarnava Rasa	Dabur	Tamra Bhasma, Triphala, *Solanum nigrum*	Reduces TC, TG, VLDL	Safe and non-toxic	[37,42]
7	Shanmei Capsule	TCM formulation	*Crataegi folium*	Regulates lipid metabolism via PPAR-α	No toxicity (computational validation)	[48,49]
8	*Ziziphus lotus* Extract	Extract	*Ziziphus lotus* fruits	Antioxidant and antihyperlipidemic	Safe herbal extract	[29,34]
9	Fenugreek + Aloe Vera Formulation	Extract	*Trigonella foenum-graecum* + Aloe vera	Improves lipid profile and body weight	Effective in HFD models	[26,39]
10	Kumbhajatu	Ayurvedic Rasashala	*Symplocos racemosa, Nardostachys jatamansi, Careya arborea*, Shilajit	Reduces LDL and VLDL	Safe formulation	[35,40]
11	OB-6 Polyherbal Formulation	Alpspure	*Cassia angustifolia, Nigella sativa, Phyllanthus amarus, Zingiber officinale*	Reduces triglycerides	Effective with good safety	[31,36]
12	Medohara & Lekhaniya Dravyas	Ayurvedic classical	Multiple herbal drugs	Antihyperlipidemic, metabolic regulation	Safe and effective	[11,15]

Many traditional herbal formulations are available as antihyperlipidemic medicine of which thirteen reported and potent formulations showing therapeutic hypolipidemic activity **have been reviewed (Table 1)**.

3.1 Arogyavardhini vati [5]

Arogyavardhini is a well-known Ayurvedic polyherbal formulation composed of many medicinal plant ingredients like Picrorrhiza kurroa (Kutki), Terminalia chebula (Haritaki), Terminalia bellerica (Bibhitaka), Emblica officinalis (Amalaki), Commiphora wightii (Guggulu), Ricinus communis (Eranda), Azadirachta indica (Neem) and mineral ingredients such as purified mercury (suddha rasa), sulfur (gandhaka suddha), iron (lauha bhasma) mica (abhraka bhasma) and copper (tamra bhasma) etc. This formulation has traditionally been utilized in Ayurveda for the management of liver disorders, jaundice, and various skin diseases due to its detoxifying and hepatoprotective properties [11,13]. Recent research has shown that Arogyavardhini vati reduced oxidative stress and improved lipid profiles in patients suffering from dyslipidaemia. It has been said to reduce malondialdehyde (MDA) and to elevate glutathione (GSH), which alludes to very strong anti-oxidative capacity. The formulation also significantly reduces serum total cholesterol, triglycerides, and LDL while increasing HDL. These effects are due to its capacity to modify lipid metabolism and decrease lipid peroxidation, thus suggesting its possible use against hypercholesterolemia and cardiovascular disorders [36–38].

3.2 Navaka guggulu[6]

Navaka Guggulu is a standardised polyherbal formulation of Ayurveda containing primarily Guggulu (Commiphora wightii) as its key active ingredient. Traditionally, it is used in the management of Medoroga (hyperlipidemia), Sthaulya (obesity), and other Kaphaja disorders due to lipid-lowering and metabolic regulatory actions. As per classical Ayurvedic texts, fresh (Naveena) Guggulu is Brimhana (anabolic or body mass-increasing) while aged (Purana) Guggulu is Atilekhana (scraping or lipid-reducing). The preparation is known as Vyoshadi Guggulu, Dashanga Guggulu and Trayushnadi Guggulu in different classic texts [11,15]. Navaka Guggulu has significant antihyperlipidemic efficacy: clinical and experimental studies. For an evaluation of the comparative efficacy, patients with hyperlipidemia were selected, total 40. Divided into two groups and given Navaka Guggulu prepared from fresh Guggulu and aged Guggulu (2 g twice daily for 8 weeks). According to the data, tridoshajwarakutaj 3-Year-old guggulu prepared formulation shows better therapeutic effects than fresh sample as the cholesterol level shows an 8.94% reduction while triglycerides shows a 22.76% decrease and VLDL shows a 23.10% decrease. The increased efficacy of aged Guggulu may be due to its improved lipid-lowering and metabolic activity, thus supporting hyperlipidemia and obesity [28,36,38].

3.3 Ethanolic extract of *Trigonella foenum* graecum

The ethanolic extract of Trigonella foenum-graecum (fenugreek) seeds has been extensively studied for its antihyperlipidemic potential and is usually prepared in a liquid dosage form. The medicinal herb fenugreek is prepared by mixing fenugreek seeds in alcohol with Aloe vera leaf juice and ascorbic acid. The fenugreek seed is the dried seed of Trigonella foenum graecum. The extract of fenugreek has 20% w/w ethanolic extract of fenugreek seeds. It is incorporated in Aloe vera leaf juice and stabilizer 0.5% w/v ascorbic acid. The high lipid diet-induced obese and hyperlipidemic animal studies revealed antihyperlipidemic and antiobesity effects of the aloe vera-based herbal formulation. Results of experimental studies show that the formulation significantly reduces serum total cholesterol, triglycerides and low-density lipoprotein (LDL) levels and improves high-density lipoprotein (HDL) levels. The bioactive phytoconstituents found in fenugreek, including saponins, flavonoids and alkaloids are responsible for the lipid-lowering activity of fenugreek which helps in improving insulin sensitivity and altering lipid metabolism. In addition, body weight loss and overall improvement in the lipid profile were better than standard treatment in animals receiving the formulation. Findings from the study indicate that the ethanolic extract of Trigonella foenum-graecum could be a potential natural remedy for hyperlipidemia and obesity [26,31,38–40].

3.4 Hydro-alcoholic extract of *Ricinus Communis* L., *Zizyphus jujuba* Lam., and *Capparis decidua*

A new study has evaluated the antihyperlipidemic activity of a hydro-alcoholic extract of a polyherbal formulation containing Ricinus communis, Zizyphus jujuba, and Capparis decidua. The formulation is prepared in equal quantity of powdered plant material and extraction through a hydro-alcoholic solvent (ethanol and

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water) at controlled temperature (60–70° C). The potential of this extract to lower lipid levels was studied on a Triton WR-1339-induced hyperlipidemic rat model and a high-fat-diet-induced hyperlipidemic rat model. The hyperlipidemic rats were given the extract by mouth at doses of 200 and 400 mg/kg, which lowered the levels of elevated serum and hepatic cholesterol and triglyceride significantly. Moreover, the extract exhibited a significant reduction in the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. It helps lessen the synthesis of endogenous cholesterol and enhance lipid metabolism. The results in general revealed that the hydro-alcoholic polyherbal extract exhibited a highly effective anti-hyperlipidemic activity in experiment models. Thus the extract would be a good natural therapeutic agent for hyperlipidemia [16,29,36–38].

3.5 Reosto (herbomineral formulation)

Reosto is a branded herbomineral formulation that has been tested on Triton WR-1339-induced hyperlipidemic rats for its hypocholesterolemic and antihypertriglyceridemic activities. The composition involves a range of medicinal plant and mineral components. It incorporates Terminalia arjuna, Withania somnifera, Commiphora wightii, Sida cordifolia, Vanda roxburghii along with Godanti bhasma and Kukkutandatvak bhasma. These constituents exhibit a wide range of pharmacological activities including lipid-lowering, antioxidant, cardioprotective and anti-inflammatory. Experimental studies indicate Reosto lowers plasma cholesterol and triglyceride levels, which improves the lipid profile of hyperlipidemic conditions. The bioactive compounds' synergistic action may have contributed to the observed antihyperlipidemic activity. For example, Commiphora Wightii has proven effects regarding inhibiting atherosclerosis and lowering lipid levels. Similarly, Withania Somnifera exhibits antioxidant and immunomodulatory effects. Terminalia Arjuna is famous for exhibiting anti-heart attack and lowering lipid levels. The therapeutic efficacy is enhanced by the combined action of flavonoids and phytosterols through a multi-target action. Reosto can be used as an effective adjunct management of hyperlipidemia and consequent cardiovascular disorders because of its multi-component and multi-targeted mechanism of action [31,36–38,41].

3.6 Hridayarnava Rasa (an Ayurvedic herbo-metalo-mineral formulation)

Hridayarnava Rasa is helpful in the management of lipid disorders due to its property. The main ingredient of the medicine contains Tamra bhasma, which is burnt copper purified through Panchamrita as well as Kajjali which is black sulphide of mercury. It is finely crushed with the decoction of Triphala as well as the juice of Solanum nigrum Linn. The therapeutic efficacy of Saffron is related to its unique combination of herbal and mineral components. Thus, it is helpful in metabolic and cardiovascular disorders. Experimental studies showed that Hridayarnava Rasa has potent antihyperlipidemic activity in diet-induced hyperlipidemic animals. The composition lowers increased total cholesterol, triglycerides and VLDL, thereby improving the lipid profile. The impact seen might be as a result of constituent modulating lipid metabolism and also reducing oxidative stress due to the synergistic action. The results of Hridayarnava Rasa administration in experimental animals indicate its promising potential as a traditional therapeutic agent for managing hyperlipidemia [37,41,42].

3.7 Shanmei Capsule

Shanmei Capsule is a herbal medicine that is used for obesity, hyperlipidemia and other similar conditions in traditional Chinese medicine. Recent research has examined its molecular mechanism through network pharmacology and molecular docking analyses. The formulation contains several bioactive agents, as identified 59 candidate active compounds. The biological targets of these compounds were assessed to create an interaction network of 330 nodes (59 compounds and 271 targets) and 928 interaction edges indicating the multi-target nature of the formulation. The utilization of network pharmacology and molecular docking methods revealed that Shanmei Capsule acts against hyperlipidemia via PPARs and other pathways. A multi-component and multi-target interaction leads to lipid regulating activity which helps in metabolic modulation. As a multi-target drug for the treatment of hyperlipidaemia, Shanmei Capsule appear to possess a marked therapeutic potential, with applicability in traditional and modern integrative medicine. [46,48–50].

3.8 Extract of Ziziphus lotus:

Ziziphus lotus (L.) Lam is extracted with water. The research on fruits has been done on these properties. This extract is rich in flavonoids and contains significant levels of phenolic compounds. Research conducted on the effect of Ziziphus lotus extracts on serum lipid showed that it reduced total cholesterol, triglycerides and low-density lipoprotein (LDL) while also enhancing high-density lipoprotein (HDL) levels. The high phenolic and flavonoid content of the extract is responsible for its antioxidant activity, thereby preventing free radical damage and any lipid peroxidation. In protection cellular structure atherosclerosis progression, the compound extract minimizes oxidative stress. Considering the above data, the aqueous extract of Ziziphus lotus has great potential as an agent for natural therapy. Furthermore, it can also be used as a dietary supplement for hyperlipidaemia and related disorders [29,34,36].

3.9 Vital plant

Another important polyherbal formulation with significant lipid-lowering activity contains the combination of essential oils and bioactive components present in medicinal plants. This formulation comprises Petroselinum crispum (Parsley), a plant of diuretic properties and containing apiole, with a stimulatory effect; Mentha × piperita (Peppermint) and Carum carvi (Caraway) which are used for gastrointestinal discomfort; and Rhamnus frangula (Alder buckthorn), which contains anthraquinone glycosides with weak laxative properties. This polyherbal combination reduces the body weight gain and lipid profile of hyperlipidemia-induced (high-fat diet) HFD animal models as established through experimental studies. The formulation is shown to lower plasma total cholesterol and low-density lipoprotein levels with reduced levels of alanine transaminase and atherogenic index indicating improvement in liver function as well as cardiovascular risk. The therapeutic effects revealed during the experiment may be because of positive interaction between the phytoconstituents which are mainly enhancing lipid metabolism, diuresis and reducing oxidative stress. These results hint at the promise of such polyherbal formulations as an effective natural treatment for hyperlipidemia and associated metabolic diseases [31,36,39–40].

3.10 Liquid solution (extract *Trigonella foenum-graecum* L.) with aloe vera juice

An aqueous formulation prepared from the ethanolic extract of Trigonella foenum-graecum (fenugreek) seeds was prepared by dissolving the extract in the leaf juice of Aloe vera. We examined this formulation for antihyperlipidemic potential in high fat diet (HFD)-induced hyperlipidemic animal models. The study results indicated that the animals of HFD group exhibited significantly elevated lipid profiles compared to the normal control. The above herb-alternative fenugreek formula reduced the total cholesterol, triglyceride and low-density lipoprotein (LDL) levels and also increased the high-density lipoprotein (HDL) levels markedly. The formulation has also been effective in decreasing body weight gain due to a high-fat diet. This formulation has greater therapeutic efficacy because of the presence of fenugreek saponins and flavonoids which regulate lipid metabolism and metabolic balance. The research in the given experiment confirms that fenugreek-based formulation holds a great promise towards natural management of hyperlipidemia and obesity [26,31,38–40].

3.11 Kumbhajatu

Kumbhajatu is the marketed Ayurvedic polyherbal formulation. It is prepared by Ayurvedic Rasashala, Pune. It is made of four ingredients only. They are Symplocos racemosa (Lodhra), Nardostachys jatamansi (Jatamansi), Careya arborea (Kumbhi) and Shilajit (Asphaltum). The preparation is generally administered in a powder and suspended in distilled water and evaluated at different doses for its activity. Experimental investigations including acute oral toxicity tests showed that Kumbhajatu is safe and well tolerated. In addition, it has been shown to reduce plasma levels of low-density lipoprotein (LDL) and very low-density lipoprotein cholesterol (VLDL-C). The formulation that lowers lipid levels conversely aids in cardiovascular health since increased high-density lipoprotein or HDL-C levels are known to provide protective effects against coronary artery diseases or CAD. The therapeutic effect may be due to the additive effects of the phytoconstituents which collectively modify lipid metabolism and reduce cardiovascular risk. Kumbhajatu could be used as a natural agent for hyperlipidemia management which is supported by these findings to be effective and safe [35,36,40].

3.12 OB-6 (polyherbal formulation) : Another multiherbal formulation with considerable antihyperlipidemic activity comprises a mixture of six medicinal plants-i.e., Cassia angustifolia, Nigella sativa, Phyllanthus amarus, Emblica officinalis, Zingiber officinalis, and Terminalia chebula. The extract of this formulation was prepared and put through a number of pharmacological evaluations of lipid lowering. Experimental studies have shown that this polyherbal formulation significantly improves the lipid profile parameters. Significantly, it decreases serum triglyceride (TG) levels and can ultimately enhance lipid metabolism in comparison to standard-treated groups. The posts show healling effects for the present of bioactive phytoconstituents, which help in lipid, anti-oxidant and metabolic modulation. These results indicate that this formulation may be useful in the management of hyperlipidaemia and metabolic dysfunctions [31,36,38–40].

3.13 Medohara and Lekhaniya dravyas:[17]

The classical texts of Ayurveda i.e. Charaka, Sushruta and Vagbhata described the Lekhaniya Gana (group of scraping or lipid reducing drugs) and enumerated various drug groups with therapeutic potential in metabolic disorders. In sum, these classical texts mention a wide array of herbs with Medohara properties that are traditionally used in the management of Medodushti and Santarpanottha Vikara. A thorough examination and compilation of these herbal medications revealed

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several plant-based actions with various therapeutic activities such as anti-hyperlipidemic, anti-oxidant, and anti-inflammatory ones [11,15]. Scientific studies have recently further confirmed that polyherbal formulations (PHFs) exert their effects by multiple mechanisms with several targets and pathways. The formulations show lipid-lowering action due to inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase which is the rate limiting enzyme in cholesterol biosynthesis exhibiting statin like effects [16–18]. Moreover, the lipid profile was improved by a significant reduction in the levels of total cholesterol, triglyceride, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) in the serum, with a gradual increase in high-density lipoprotein (HDL) levels (36–40). Moreover, formulations of multi-herb preparations modulate important metabolic as well as signalling pathways like AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptors (PPARs) which control lipid metabolism as well as insulin sensitivity. These also determine chronic inflammation pathways such as nuclear factor kappa B (NF-κB), thus ameliorating chronic inflammation and improving metabolic health. These multi-targeted activities suggest that PHFs may serve as potential therapeutic agents in the management of hyperlipidemia and associated metabolic disorders [19,20,24,46–48].

4. Mechanisms of Action

Antihyperlipidemic actions of traditional polyherbal formulations act through the interplay of various mechanisms that have a role in regulating lipid homeostasis and preventing cardiovascular disorders. These mixtures contain a variety of bioactive phytoconstituents with flavonoids, alkaloids, saponins, glycosides, phenols etc. that act on multiple molecular targets involved in lipid metabolic and oxidative stress [31–35]. A major action involves blocking the enzyme activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. This rate-limiting hepatic cholesterol biosynthetic enzyme was shown to cholesterol lowering by statins in vivo almost 30 years ago. Inhibition of this enzyme reduces endogenous cholesterol synthesis, leading to decreased levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in the blood. Due to the Natural Origin of Polyherbal Formulations, They can have Lesser side Effects Compared with Statins, which has an almost Similar Mechanism of Action [16-18]. In addition, some phytoconstituents in these formulations enhance expression of liver LDL receptors which further speeds up clearance of LDL from blood. The reduction of the cholesterol synthesis and increasing the lipid clearance results in a significant antihyperlipidemic effect of polyherbal formulations [19,36–38].

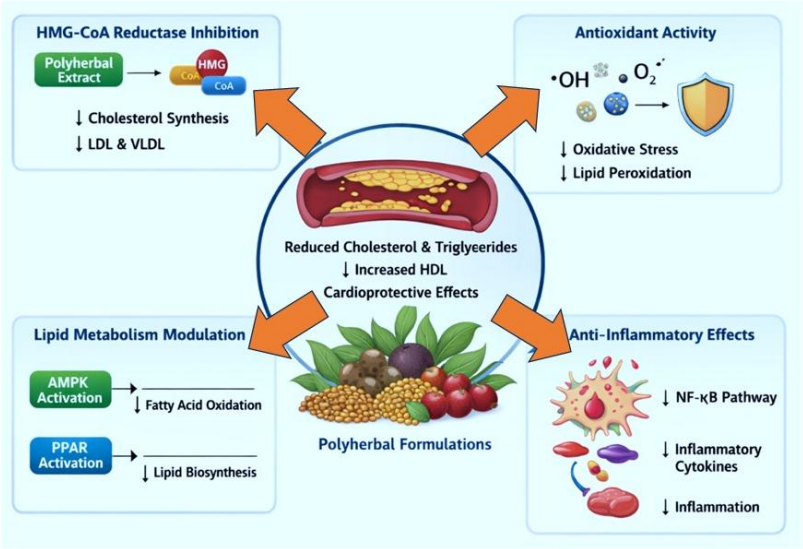

Figure 1: Mechanism Of Action

Polyherbal formulation also contains potent antioxidant that contributes to its antihyperlipidemic activity. The oxidation of low-density lipoprotein (LDL) particles and resultant foam cell formation is vital in atherosclerosis' initiation and progression. Atherosclerosis is the leading cause of death worldwide. Antioxidant phytoconstituents such as flavonoids and polyphenols present in these formulations scavenge reactive oxygen species (ROS) and diminish lipid peroxidation and cell damage. The stabilization of atherosclerotic plaques and improvement of endothelial function are also linked to this action. Moreover, the formulations modulate AMPK and PPARs, the critical enzymes involved in lipid homeostasis. Most polyherbal formulations target these enzymes as the regulators of lipids energy metabolism in human being. AMPK activation enhances fatty acid oxidation and inhibits lipid synthesis while PPARs are transcription factors that regulate gene expression involved in lipid transport, storage, and catabolism. Through these mechanisms, polyherbal formulations improve lipid utilization, hinder triglyceride accumulation and increase the levels of HDL [19,20,36–40]. In addition, these formulations show significant anti-inflammatory activity which is mediated through their action on signalling pathwasy like nuclear factor kappa B (NF-κB). Metabolic disorders and cardiovascular diseases are primarily due to chronic inflammation. Polyherbal formulations inhibit the release of pro-inflammatory cytokines and mediators, thereby preventing vascular inflammation and atherogenic plaque formation. The action of some phytoconstituents interfering with the activity of pancreatic lipase reduces absorption of dietary lipid into the body, 38 which in turn reduces intestinal lipid absorption activities [23–25,36–38]. The action of these mechanisms leads to a significant improvement in the parameters of the lipid profile leading to a decline in total cholesterol, triglycerides, low-density lipoprotein, very low-density lipoprotein and an increase in high-density lipoprotein. Using multiple target sites can enhance efficacy and decrease side effects. Using such polyherbal formulations is a promising safer alternative to Conventional Antihyperlipidemic Drugs [36–40,46–48].

5. Discussion

In recent years, polyherbal formulations have attracted remarkable interest due to their multi-targeted therapeutic action and natural origin. These formulations incorporate multiple bioactive phytoconstituents that have been shown to have the potential to act on diverse molecular targets implicated in lipid metabolism and regulation of the cardiovascular system, unlike conventional single-drug formulations. The simultaneous modulation of key pathways including cholesterol biosynthesis, lipid absorption, oxidative stress and inflammation results in enhanced overall therapeutic efficacy. Inclusion of the presence of various phytochemicals, such as flavonoids, alkaloids, saponins, and tannins, endows them with broad-spectrum pharmacological activities [11–15,31–35]. Compared to conventional antihyperlipidemic agents like statins and fibrates, polyherbal formulations have several advantages. The long-term use of synthetic drugs, despite their efficacy in reducing lipid levels, is implicated in the development of side effects such as hepatotoxicity, myopathy, GI disturbances and renal complications. Herbal formulations, being natural and used for centuries, are usually safer than chemical formulations. Additionally, due to synergism, co-administration is possible at lower effective doses, minimising toxicity and improving compliance. Another important benefit of polyherbal formulations is the management of various components of metabolic disorders other than lipids. The formulations improve the lipid profile and possess antioxidant, anti-inflammatory and cardioprotective properties. These combined effects will further result in improved vascular function and attenuation of atherosclerosis. Moreover, their affordability, easy access, and cultural suitability make them especially important for developing nations; a region where cardiovascular illness burden is increasing rapidly [21–24; 36–40].

6. Challenges and Future Directions

Although polyherbal formulations can demonstrate therapeutic efficiency, there are many issues that need to be resolved for their wider acceptance. One of the primary limitations is the absence of standardization and quality control. Differences in the plant source, geographical condition, harvesting practice, and extraction techniques can have a substantial impact on the phytochemical profile of any herbal preparation. Hence, there is a need to establish protocols and use sophisticated techniques, in order to ensure quality and reproducibility of these formulations [51-55]. One more essential challenge is a shortage of well-designed clinical trials. Despite various in vitro and in vivo studies proving the antihyperlipidemic potential of different polyherbal formulations, large-scale clinical trials are urgently

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needed to evaluate their safety, efficacy, and pharmacokinetics in human beings. In addition, thorough mechanistic studies are essential to understand the intricate molecular interactions and signaling pathways underlying their therapeutic actions [36–40,56–58]. In future studies, modern scientific techniques such as molecular docking, network pharmacology, and systems biology should be an integral part of understanding the multi-target mechanisms of polyherbal formulations. By following these computational and systems-level approaches for herb–target interaction studies, rational design of drugs can be achieved. Also, development of newer drug delivery systems, like nanoparticle, phytosome, liposomal formulations, can enhance the bioavailability, stability and targeted delivery of beneficial phytoconstituents [41–45,46–50]. The acceptance of herbal formulations into global health care systems is also affected by regulatory hindrances and lack of harmonized guidelines. Documentation of safety, efficacy and quality that meets international regulatory requirements is essential for their global recognition and incorporation into EBM [52–54]. The combining of traditional knowledge with current pharmacotherapy in polyherbal formulations is debated on the future. One novel approach in these combinations is the allopolyherbal formulation (APHF) which includes mixing herbal drug with the conventional drug like statin or anti-diabetic. This strategy seeks to lower the dosage of synthetic drugs to mitigate their side effects and increase therapeutic efficiency [30,36]. The formulation technologies such as nanoliposomal systems and phytosomes are currently being explored for improving the pharmacokinetics and therapeutic efficacy of herbal drugs. The use of computational tools like molecular docking and bioinformatics is also gaining attention for predicting interactions between herbs and between herb and drugs, as well as elucidating their modes of action [43–45,49–50]. Standard HPTLC and other chromatographic techniques for standardization of herbal formulations is another important aspect. The item must be subjected to rigorous safety tests to ensure that it is free from heavy metal, pesticides and microbial toxins. These steps are important to gain the global clinical acceptance of polyherbal formulations [51–55]. Significant Ingredients of Polyherbal Formulations. Many medicinal plants are studied for their hypolipidemic activity and are widely used in polyherbal formulations. The serum triglycerides as well as total cholesterol are reduced by Trigonella foenum-graecum (fenugreek) along with enhanced insulin sensitivity. Ginger (Zingiber officinale) helps improve lipid metabolism and lowers levels of LDL cholesterol. The study showed the hypolipidemic and hypoglycaemic properties of Aegle marmelos (bael) along with protection against metabolic complication. Turmeric (Curcuma longa), above all the active ingredient curcumin, acts as an important antioxidant and lipid-lowering agent as it reduces cholesterol and LDL levels and inhibits damage induced by oxidative stress.

7. Conclusion

This review aims at compiling the therapeutic hypolipidemic potential of some important traditional polyherbal formulations for use in hyperlipidaemia and related CVDs. The data collected show these formulations can lower fats and lipids due to the presence of different medicinal plants and compounds having various modes of action. The main mechanisms include inhibition of the enzyme HMG-CoA reductase, enhancing lipid metabolism, antioxidant effect, and modulating important signaling pathways, such as AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptors (PPARs). The combined impacts of this leads to a fall in serum total cholesterol, triglycerides, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and an increase in high-density lipoprotein (HDL), thereby improving cardiovascular health. Polyherbal formulations exhibit additional benefits beyond their hypolipidemic activity, including anti-inflammatory, antioxidant, cardioprotective etc. benefits that enhance their therapeutic potential. The interaction of phytoconstituents acts on multiple biological targets, enabling these complex hyperlipidemia formulations to target metabolic disorders at multiple activities to act. In addition, their natural origin, cost-effectiveness, and comparatively lower incidence of adverse effects make them a significant advantage over conventional synthetic drugs, especially for long-term therapy. Although these results are promising, many limitations should be addressed before these formulations are accepted in modern clinical practice. The absence of standardization in herbal products, fluctuations in phytochemical nature, and limited quality control represent the remaining problems. Further research shows that although many experimental studies indicate their efficacy, there are no large-scale, well-designed clinical trials to validate their safety and therapeutic effectiveness in humans. Subsequent sshould establish standardized formulations, conduct thorough clinical trials, and evaluate pharmacokinetic and toxicological profiles. The use of advanced scientific approaches (molecular docking; network pharmacology; metabolomics; nanotechnology based drug delivery systems) may also help in unraveling the mechanisms of action of these formulations and improve the bioavailability and targeted delivery. Harmonisation in regulations and standard guidelines at the global level is equally important for use in evidence. To sum up, the treatment of hyperlipidemia by the use of conventional polyherbal formulations is promising and sound. Through continuing scientific validation and proper standardization and technological advancement, these formulations can truly create a bridge between traditional medicine and modern pharmacotherapy. They offer a safe, effective, and sustainable therapeutic option for the prevention and treatment of lipid-altering disorders.

Ethics approval and consent to participate

Not applicable

Declaration of competing interests

We wish to confirm that there are no known conflicts of interest associated with this manuscript.

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