Medicinal Plants and Nutraceuticals as Lipid Lowering Agents: A Review

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Abstract

Hypercholesterolemia is the kingpin risk factor for the development and progression of atherosclerosis and associated cardiovascular diseases. Several epidemiological, clinical, genetic and experimental studies indicate that Indian medicinal plants have potent effects in treating the disease with less side effects. Thus an attempt to review major Indian medicinal plants with hypocholesterolemic effect was done. In addition, the use of nutraceuticals as a possible alternative to the conventional drug-based therapy for hypercholesterolemia was also presented. More research and studies in evaluating the beneficial effects of not only Indian medicinal plants but also nutraceuticals are the need of the hour which will help to utilize the Indian biodiversity and traditional knowledge for prospecting novel compounds as pharmacologically effective products to manage hypercholesterolemia and allied clinical manifestations.

Introduction

Cardiovascular diseases (CVD) are continuing as the major cause of morbidity and mortality irrespective of geographic realm (Yeates *et al.,* 2015). Hike in lipid level in blood remains as a major risk factor for many diseases including coronary artery disease (CAD) and atherosclerosis (Ruan *et al.,* 2018; Petrie *et al.,* 2018). Thus, it is not surprising that the major consequence of hypercholesterolemia is atherosclerosis. The word “atherosclerosis” comes from the ancient Greek words where "*sclerosis*” means hardening and “*athere*” is gruel or accumulation of lipid. The notable earmark of atherosclerosis is the accumulation of lipid deposits (mainly cholesterol) in macrophages located not only in large but also in medium sized arteries. Atherosclerosis is the most common CVD and manifestations associated with it, such as stroke and acute myocardial infarction (AMI), continue to be the leading causes of morbidity globally (Roth *et al*., 2017). Atherosclerotic cardiovascular disease (ACD) includes two major conditions *viz*. ischemic heart disease (IHD) and cerebrovascular disease (mainly ischemic stroke). IHD and stroke are the world’s first and third causes of death, respectively, causing 247.9 deaths/100,000 persons in 2013, representing 84.5% of cardiovascular deaths and 28.2% of all-cause mortality (Pagidipati and Gaziano, 2013; Mc Namara *et al.,* 2019). Other less prevalent complexities of atherosclerosis include atherosclerosis of the aorta and peripheral vascular disease.

Drugs for hyperlipidemia

Currently, antihyperlipidemic drugs contain five major classes that include statins, fibric acid derivatives, bile acid binding resins, nicotinic acid derivatives and drugs that inhibit cholesterol absorption (Schaiff *et al.,* 2008; Karalis *et al.,* 2012). Statin therapy is the cornerstone in the treatment of dyslipidemia. Numerous researchers and pharmaceutical companies are involved in this field of fighting for dyslipidemia and several promising results are also witnessed. Table 1 illustrates common drugs for treating dyslipidemia currently in practice across the world.

Sl. No.	Drugs	Effects
	Statins	
1.	Lovastatin (10-80 mg)	Decrease TG
2.	Simvastatin (5-40 mg)	Decrease LDL
3.	Atorvastatin (10-80 mg)	Increase HDL
4.	Rosuvastatin (5- 20 mg)	TG generally not effected
	Bile acid binding resins	
5.	Cholestyramine (4-16 mg)	Decrease LDL
6.	Colestipol (5-30 mg)	Increase HDL
	Fibric acid derivatives	
7.	Gemfibrozil (1200 mg)	Decrease TG
8.	Bezafibrate (600)mg	Decrease LDL
9.	Fenofibrate (200 mg)	Increase HDL
	Nicotinic acid derivatives	
10.	Niacin(2-6 gm)	Decrease LDL Increase HDL
	Cholesterol absorption inhibitors	
11.	Ezetimibe (10 mg)	Decrease cholesterol

Table 1: Common drugs for treatment of cholestrol

Plants as lipid lowering agents

According to World Health organization (WHO) 80% of the people in developing countries still rely on traditional plant based medicines, for their primary health care needs (Chatfield *et al.,* 2018). India is well known for its rich traditional systems of medicines like, Ayurveda, Siddha and Unani coupled with ethnomedicine treasure trove. Though, several modern drugs currently in practice lower blood cholesterol level, people are looking for safer alternatives and the search for new drugs capable of reducing and regulating serum cholesterol level has gained interest resulting in numerous reports on significant activities of natural agents (Littleton *et al.,* 2012; Cabral and Klein, 2017). Chemical principles from natural sources have become much simpler and have contributed significantly to the development of novel drugs. The medicinal properties of plants are due to presence of myriad of constituents like saponins, tannins, alkaloids, alkenyl phenols, glycol-alkaloids, flavonoids, sesquiterpenes lactones, terpenoids and phorbol esters (Pagliaro *et al.,* 2015; Yoo *et al.,* 2018). Among them some act as synergistic and enhance the bioactivity of other compounds.

The Indian subcontinent is a diverse emporium of medicinal plants that are used in traditional medical treatments, where traditional communities alone are using around 7,000 - 7,500 plants as therapeutic agents (Mohanraj *et al.,* 2018). The Indian Vedas also describes the widespread use of herbal products and aqueous extract of different plant parts for curing different diseases, even at that time. Currently using hypolipidemic drugs are associated with so many adverse effects which are not seen with herbal preparations. Plant parts or plant extract are sometimes even more promising than known hypolipidemic drugs. Table 2 illustrates the mode of lipid lowering activity of plant extracts.

Sl. No.	Mode of lipid lowering activity
1.	regulates the expression of blood lipid-related genes and improves lipid metabolism
2.	reduce the synthesis of endogenous lipids such as triglyceride (TG) and cholesterol (TC)
3.	inhibition of absorption of exogenous lipids
4.	increase the activity or amount of enzymes that affect lipid metabolism
5.	anti-lipid peroxidation, scavenging free radicals
6.	reduce insulin resistance and promote lipid metabolism
7.	inhibits platelet aggregation, improves blood rheology abnormalities, and reduces blood viscosity

Table 2: Mode of lipid lowering activities of plant extracts

Potential Indian medicinal plants

India is an emporium of rich traditional systems of medicines like Ayurveda, Siddha and Unani. Moreover, the country accounts for a deluge of living traditions of ethnomedicine which is practicing now also by tribal people (Sharma *et al.,* 2016). Majority of modern drugs lowers blood cholesterol either by inhibiting endogenous synthesis or by lowering cholesterol absorption from the intestine (Reshma *et al.,* 2018). Search for safer alternatives, and the search for new drugs capable of reducing and regulating serum cholesterol level has gained momentum recently resulting in numerous reports on significant activities of natural agents where major are given in Table 3.

Sl. No.	Plant	Lipid lowering potential	References
1.	*Allium cepa* (Family: Alliaceae)	Hypolipidemic	Vidyavati *et al.,* 2010; Lata *et al.,* 1991
2.	*Allium sativum* (Family: Alliaceae)	Diallyl disulphide (DADS) and S-allylcysteines (SAC) showed hypocholesterolemic activity	Aleru *et al.,* 2016; Lachhiramka and Patil, 2016
3.	*Semecarpus anacardium* (Family: Anacardiaceae)	Cholesterol mobilization from liver and prevention of deposition in peripheral tissues	Vinayagam *et al.,* 2012; Sharma *et al.,* 1995
4.	*Coriandrum sativum* (Family: Apiaceae)	enhance degradation of cholesterol to faecal bile acids and neutral sterols	Kousar *et al.,* 2011; Joshi *et al.,* 2012
5.	*Commiphora mukul* (Family: Burseraceae)	decrease hepatic steroid production, ultimately increasing the catabolism	Shaik and Khan, 2018; Siddiqui and

		of plasma LDL-C.	Mazumder, 2012
6.	*Terminalia arjuna* (Family: Combretaceae)	increased hepatic clearance of cholesterol, down regulation of lipogenic enzymes and inhibition of HMG-CoA reductase	Subramaniam *et al.*, 2011; Patil *et al.*, 2010
7.	*Emblica officinalis* (Family: Euphorbiaceae)	prevent LDL oxidation; decrease synthesis of cholesterol and enhanced reverse cholesterol transport by elevating HDL-C level	Zahid *et al.*, 2018; Santoshkumar *et al.*, 2013
8.	*Phyllanthus niruri* (Family: Euphorbiaceae)	inhibition of hepatic cholesterol biosynthesis, increased excretion of bile acids and enhanced plasma LCAT activity	Khanna *et al.*, 2002; Paithankar *et al.*, 2011
9.	*Cicer arietinum* (Family: Fabaceae)	Hypolipidemic	Harini *et al.*, 2015; Ali, 2016
10.	*Cyamopsis tetragonoloba* (Family: Fabaceae)	decrease in serum cholesterol particularly LDL increase in HDL	Roopa and Saraswathi, 1983; Pande *et al.*, 2012
11.	*Glycyrrhiza glabra* (Family: Fabaceae)	elevating HDL-cholesterol levels	Maurya *et al.*, 2009; Visavadiya and Narasimhacharya, 2006
12.	*Trigonella foenum-graecum* (Family: Fabaceae)	Hypolipidemic	Nader, 2019; Sharma *et al.*, 1990
13.	*Ocimum sanctum* (Family: Labiateae)	Rising bile acids synthesis using cholesterol as precursor, and antioxidative activity	Husain *et al.*, 2015; Suanarunsawat *et al.*, 2011
14.	*Moringa oleifera* (Family: Moringaceae)	increase the excretion of fecal cholesterol inhibiting the absorption of cholesterol	Jain *et al.*, 2010; Gururaja, 2016
15.	*Sesamum indicum* (Family: Pedaliaceae)	reducing LDL, triacylglycerol and increasing HDL	Biswas *et al.*, 2010; Sedigheh *et al.*, 2013
16.	*Capsicum annuum* (Family: Solanaceae)	Reduction in rise of liver cholesterol and brought enhanced faecal excretion of both free cholesterol	Baek *et al.*, 2013 Sanati *et al.*, 2018

		and bile acids	
17.	*Withania somnifera* (Family: Solanaceae)	hypolipidaemic activities increasing HDL	Udayakumar *et al.*, 2009: Kaur, and Kaur, 2017
18.	*Curcuma longa* (Family: Zingiberaceae)	block lipid accumulation, thus preventing hypercholesterolemia higher hepatic cholesterol-7a-hydroxylase activity	Myung *et al.*, 2015: Kim and Kim, 2010
19.	*Apium graveolans* (Family: Apiaceae)	reducing serum total cholesterol, triglycerides, LDL and increasing HDL	Mansi *et al.*, 2009: Perumalraja and Sharief, 2013
20.	*Pterocarpus marsupium* (Family: Leguminosae)	Reduce serum triglyceride, total cholesterol, LDL, and low-density lipoproteins -cholesterol without any significant effect on the level of HDL	Maruthupandian and Mohan, 2011; Qadeer *et al.*, 2018

Table 3: List of major Indian medicinal plants with lipid lowering activities

Nutraceuticals as lipid lowering agents

The term nutraceutical coined in 1989 by Stephen DeFelice combines the words 'nutrient' (a nourishing food or food component) with 'pharmaceutical' (a medical drug), and indicates that these products have a potential application in pathological conditions, and hence should be treated in a similar way to pharmaceuticals (Gupta *et al.*, 2010; Nasri *et al.*, 2014). In short, nutraceuticals are 'a food or part of a food that provides medical or health benefits, including the prevention and/or treatment of disease'. Nutraceuticals can effectively reduce the problem of dyslipidemia, atherosclerosis, and coronary heart disease. Nutraceuticals can act on several biochemical pathways able to influence lipid disorders in the human body. Apart from the lipid-lowering effect, many nutraceuticals have antioxidant, antiplatelet, and anti-inflammatory properties which further enhances their beneficial role (Prabu *et al.*, 2012). The cholesterol-lowering action of nutraceuticals like monacolin of fermented red rice, polycosanol and berberine are well studied (Cicero *et al.*, 2017). Table 4 summarizes the action of commonly using nutraceuticals in various studies.

Sl.No.	Nutraceutical	Action
1.	Fiber	- LDL-C reduction by 4-14% - Effect on other cardiovascular risk factors - Relatively low-cost
2.	Phytosterols	- LDL-C reduction by 8-10% - No interaction with lipid-lowering drugs
3.	Soy products	LDL - C reduction by 4-13%
4.	Red yeast rice	- LDL-C reduction by 16-25% - Good safety profile

		- Reduction of cardiovascular risk
5.	Berberine	- LDL-C reduction by 20% - Better safety profile in patients with intolerance to multiple statins - Favourable effect on TG, HDL-C and blood glucose
6.	Policosanol	LDL-C reduction

Table 4: Action of commonly using nutraceuticals

Conclusion

Herbs have been used in medical treatment since the beginning of civilization and have become a cradle of human pharmacotherapy. Based on this, numerous researches were carried out in enumerating the hypocholesterolemic effect of plants and from the reports on their potential effectiveness; it is assumed that the botanicals have an unavoidable and commendable role to play in the management of hypercholesterolemia. Indian medicinal plants exhibits great cholesterol reducing potential not only in normal but also in high fat/cholesterol treated animals. More concentration in evaluating the beneficial effects of medicinal plants certainly will help to utilize the Indian biodiversity and traditional knowledge for prospecting novel compounds as pharmacologically effective products to manage hypercholesterolemia and allied clinical manifestations.

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