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Managing hyperlipidemia: Strategies for preventing cardiovascular disease

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Abstract
The hyperlipidemias comprise a heterogeneous group of disorders of lipid metabolism having a damaging effect on the wellbeing of human population and causes greater morbidity and mortality, in both young and old people. Management of dyslipidemia forms an important part of strategies for preventing cardiovascular disease. "Statins" as HMG-CoA reductase inhibitors lowers cholesterol level in blood but long term use of these drugs have been reported for several adverse effects. Herbal products have been thought to be inherently safe, because of their natural origin and traditional use rather than on systemic studies designed to detect adverse effects. Dietary therapy together with hypolipidemic drugs is central to the management of hyperlipidemia. Two plants *Withania somnifera* Dunal (family: Solanaceae) and *Commiphora wightii* (Arnott.) Bhandari (family: Burseraceae) have been studied and documented most frequently, based on their frequent usage in folk medicine and acclaimed for health modulating properties.

Keywords: Hyperlipidemia, *Withania somnifera* Dunal, *Commiphora wightii* (Arnott.) Bhandari

Introduction
The hyperlipidemias comprise a heterogeneous group of disorders of lipid metabolism having a damaging effect on the wellbeing of human population and causes greater morbidity and mortality, in both young and old people. Its characteristic expression is an elevation in the plasma concentration of cholesterol and/or triglyceride and lipoproteins fractions [low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) as well as low levels of HDL. According to world health organization (WHO), hyperlipidemia is one of the major modifiable risk factors for atherosclerosis and coronary heart disease (CHD) contributing to the prevalence and severity of cardiovascular diseases. The CHD is the cause of 25-30% of deaths in most industrialized countries (Park, 2013) [10]. Atherosclerosis is the hardening and narrowing of the arteries which silently and slowly blocks arteries, putting blood flow at risk. The risk factors for CHD include hypercholesterolemia, smoking, hypertension, obesity, a strong family history of cardiovascular events and a sedentary lifestyle. The possible causes of hyperlipidemia are shown in Figure 1.

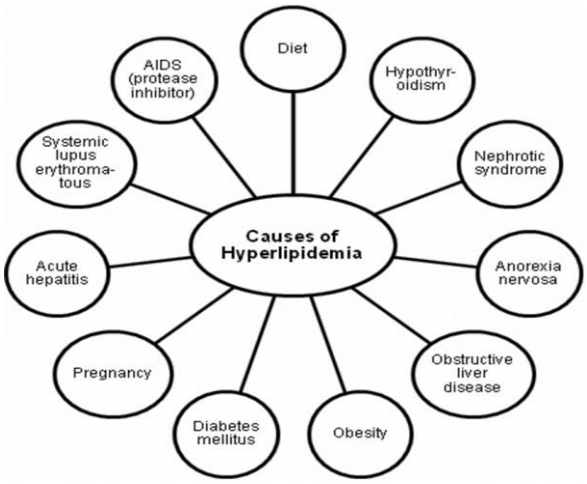

Fig 1.1: Possible causes of hyperlipidemia

Management of dyslipidemia

Management of dyslipidemia forms an important part of strategies for preventing cardiovascular disease. Lipid lowering is initially based on lifestyle advice, to which drugs should be added if treatment goals are not achieved within three months. No specific goals are set for triglycerides and HDL cholesterol but a triglyceride value of >1.7 mmol/l and HDL cholesterol <1.0 mmol/l (men) or <1.2 mmol/l (women) are regarded as markers of increased risk. Most of the current guidelines reflect the use of statin classes of drugs. Statins that are approved for use in the U.S. include: atorvastatin (Lipitor), fluvastatin (Lescol, Lescol XL), lovastatin (Mevacor, Altoprev), pravastatin (Pravachol), rosuvastatin (Crestor), simvastatin (Zocor), and pitavastatin (Livalo). "Statins" lowers cholesterol level in blood by reducing production of cholesterol by the liver by blocking the enzyme hydroxy-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) that is responsible for making cholesterol. Statins are referred to as HMG-CoA reductase inhibitors. Overall, statins reduced the risk of CHD by 31% and total mortality by 21%, benefit being equally evident in men and women below and above the age of 65. But long term use of these drugs have been reported for several adverse effects, such as statins have been reported to elevate amino-transferase three times greater than normal levels, hepatotoxicity and rhabdomyolysis (injury or death of muscle tissue), myopathy-diffuse muscle pain, renal insufficiency nausea, vomiting, headache, constipation, diarrhea, rash, and weakness etc. Nicotinic acid (niacin) has been reported to produce hepatic dysfunction, hyper-urecemia, acanthosis nigricans and gastritis (Katzung, 2012) [7]. Besides the adverse effects of the hypolipidemic drugs, the high cost of these drugs is also a main drawback especially for the developing countries.

A combination of side effects, contraindications and lack of response of synthetic drugs on disease progression highlight the need for newer therapies that minimize the frequency and severity of lipidemic excursions (Park, 2013) [10]. The plant kingdom historically had been the driving force for the development of novel drugs. Herbal products have been thought to be inherently safe, because of their natural origin and traditional use rather than on systemic studies designed to detect adverse effects. Approximately 80% of the world's populations rely on biomedicines for their health and wellbeing (Bharti *et al*., 2012 & 13) [2].

Currently, the use of complimentary/alternative medicine and especially the consumption of herbal medicines have been rapidly increasing worldwide. Dietary therapy together with hypolipidemic drugs is central to the management of hyperlipidemia (Katzung, 2012) [7]. Besides the well-known principles of dietary management involving restriction of total fat intake and substitution of poly- and mono-unsaturated fatty acids for saturated fatty acids, there has been much interest recently in the lipid lowering properties of so called phenolic compounds of plants origin. These compounds compete with cholesterol for incorporation into mixed micelles, thereby impairing its absorption from the intestine, but their limited lipid solubility makes it difficult to dissolve them in fat spreads in effective concentrations. This novel dietary approach is advocated as useful in the conventional management of dyslipidemia. Many Unani drugs have demonstrated favourable effects in modifying lipid risk factors for CHD. Various Ayurvedic herbs are utilized based on the stage and type of disease as well as the psychophysiologic constitution of the patient for antihyperlipidemic effect. Attempts have been made to quantitatively measure the effect of each phytomedicine alone and in combinations and also determine the type of effect of the combination of which some of them are unani drugs like Tukhme karafs (*Apium graveolens* Linn.) (Mansi *et al*., 2009) [9], Tukhme suddab (*Ruta graveolens* Linn.) (Parray, 2010) [11], lac (*Coccus lacca*) and filfile siyah (*Piper nigrum* Linn.) (Ghufran *et al*., 2011) [6] etc. Guggul is mentioned as early as from 3000 to 10,000 years ago in the Vedas, the holy scriptures of India for treating human illnesses. These medicines have emerged as unique, safe, effective, and relatively inexpensive remedies producing minimal or no side effects with tall claims of efficacy as add on therapy (Bharti *et al*., 2015) [3]. The isolation and formulation of active constituents from these plants along with their pharmacological and toxicological evaluation are the need of the modern therapeutics.

The efficacy of medicinal plants in management of hyperlipidemia is of great interest due to their favorable effects on metabolic profile. Two plants *Withania somnifera* Dunal (family: Solanaceae) and *Commiphora wightii* (Arnott.) Bhandari (family: Burseraceae) have been studied and documented most frequently, based on their frequent usage in folk medicine and acclaimed for health modulating properties.

Withania somnifera Dunal (family: Solanaceae), also known as Ashwagandha, Indian ginseng, or winter cherry is a rigid gray-whitish small 30-90 cm tall shrub with lanceolate oblong and very short stalked leaves. It is found in drier parts of Punjab, Gujarat, Simla and Kumaon in India. They are densely covered with minute, gray, stellated tomentum (filamentous hairlike growth). Flowers (7-12 mm across) are yellow, dioecious and polygamous. The seeds are dark brown, ear shaped, glabrous, having sharp fruity smell. The berry and fleshy fruit have carminative and depurative property and are also used for dyspepsia, and flatulence (Prasad *et al*., 2010) [12].

Commiphora wightii (Arnott.) Bhandari or Guggul or Gugglu belonging to family Burseraceae is a slow growing woody tree of paramount medicinal importance being over-exploited for medicinal purposes. The guggul plant is most common in northern India particularly in the states of Karnataka, Gujarat and Rajasthan. It is a shrub or small tree, reaching a maximum height of 4 m, with thin papery bark. The branches are thorny. The leaves are simple or trifoliate, the leaflets ovate, 1–5 cm long, 0.5–2.5 cm broad, irregularly toothed. It is gynodioecious, with some plants bearing bisexual and male flowers, and others with female flowers. The individual flowers are red to pink, with four small petals. The small round fruit are red when ripe (Sahni *et al*., 2005) [13].

In the middle 1990s, guggul was introduced into the Western medical and, soon thereafter, the interests in using guggul as a remedy for treating or preventing hypercholesterolemia and related cardiovascular diseases were widely spread in the *Western world*. Starting in the later 1990s, Guggul became one of those herbs holding huge promises for the development of hypolipidemic and antiatherogenic drugs. The hypolipidemic effect of these plants has been consistently demonstrated in various animal species, including rat, mouse, rabbit (Satyavati *et al*., 1969) [14], chicken (Baldwa *et al*. 1981) [1], domestic pig (Khanna *et al*. 1969) [8], dog and monkey (Dixit *et al*. 1980) [5]. These studies on the cardioprotective effects of Witahnia and guggul are fairly preliminary; however, the evidence for the beneficial effect of

these plants is encouraging. Till date, several activities such as antioxidant, anti-apoptotic, hypolipidemic, cardiotrophic, anticoagulant, antiplatelet, adaptogenic, hypoglycemic and anti-inflammatory of these plants have been reported and these mechanisms were believed to contribute the cardio-protective effect.

Considering its safety, efficacy and time tested utility in humans under different traditional systems of medicines, it is regarded as safe. Thus, these plants offer a natural alternative or as an adjunct with conventional agents with lesser side effects. However, for concrete evidence and its application as a drug in as per the stricter norms of drug development, more studies are required to evaluate those activities and the associated benefits in the prevention or treatment of cardiovascular diseases, especially dyslipidemia in humans. Although recent progress has been made in understanding the underlying mechanisms of Withania and guggul or guggulsterone-mediated diverse activities, further studies are required to firmly establish the mechanisms of actions.

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