Herbs with anti-lipid effects and their interactions with statins as a chemical anti- hyperlipidemia group drugs: A systematic review

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Review Article

Abstract

BACKGROUND: The present systematic review aimed to express the clinical anti-lipid effects of different types of herbs, as well as described studied interactions between herbal remedies and prescribed drugs for hyperlipidemic patients which were based on in vitro experiments, animal studies, and empirical clinical experiences.

METHODS: For this systematic review, we explored 2183 published papers about herbal drugs interactions from November 1967 to August 2014, fulfilling eligibility criteria by searching in some databases such as Web of Science, Medline, Scopus, Embase, Cinahl, and the Cochrane database. The main keywords used for searching included: herbal medicine, herbs, statin, lipid, and herb-drug interaction.

RESULTS: Among published articles about herb-drug interactions, 185 papers met the initial search criteria and among them, 92 papers were potentially retrievable including a description of 17 herbs and medicinal plants. In first step and by reviewing all published manuscripts on beneficial effects of herbs on serum lipids level, 17 herbs were described to be effective on lipid profile as lowering serum triglyceride, total cholesterol, low-density lipoprotein cholesterol as well as increasing serum high-density lipoprotein level. Some herbs such as celery could even affect the hepatic triglyceride concentrations. The herbal reaction toward different types of statins is varied so that grapefruit or pomegranate was interacted with only some types of statins, but not with all statin types. In this context, administration of herbal materials can lead to decreased absorption of statins or decreased the plasma concentration of these drugs.

CONCLUSION: Various types of herbs can potentially reduce serum lipid profile with the different pathways; however, the herb-drug interactions may decrease pharmacological therapeutic effects of anti-hyperlipidemic drugs that should be considered when approved herbs are prescribed.

Keywords: Herbal Medicine, Herbs, Statin, Lipid, Herb-Drug Interaction

Date of submission: 1 Mar 2015, ***Date of acceptance:*** 27 Jun 2015

Introduction

Ischemic heart disease is one of the major causes of mortality and disabilities whole of the world, particularly in developing countries. Because of its rapid progression in order to inappropriate lifestyle and nutritional modification, it has been produced as the greatest vulnerable event.[1] The pattern of the spread of disease is highly associated with quality control of its major risk factors that among them, hyperlipidemia has the main staple role.[2,3] Nowadays, tend to use synthetic drugs to lower serum lipid in patients with hyperlipidemia is gradually decreased because of their related side effects, as well as a progression of drug resistance. In this regard, tend to use of medicinal plants has been doubled.[4] However, in some cases, the multi-drug prescription such as using synthetic drugs and herbs become a necessary, leading herb-drug

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interaction that is a major concern of specialists in pharmacology. These interactions may also increase pharmacological therapeutic effect that is more important in drugs with low safety and narrow therapeutic indices.[5] Unfortunately, the vast majority of these products are used unlicensed without the assessment of efficacy, safety, or quality. Furthermore, some herbal supplements are frequently associated with adverse events including all levels of severity, organ systems, and age groups that may worsen drug interactions when used in conjunction with chemical drugs.[6] In addition, recent statistics have evidenced that as many as 16% of prescription drug users consume herbal supplements,[7] fewer than 40% of patients disclose their herbal supplement usage to health care providers,[8] and many physicians are unaware of the potential for herb-drug interactions.[9] This knowledge deficiency evidently increases the likelihood of drug-herb interactions. The present systematic review aimed to express the clinical anti-lipid effects of different types of herbs as well as described studied interactions between herbal remedies and prescribed drugs for hyperlipidemic patients which were based on in vitro experiments, animal studies, and empirical clinical experiences.

Materials and Methods

For this systematic review, we explored 2183 published papers about herbal drugs interactions from November 1967 to August 2014, fulfilling eligibility criteria by searching in some databases such as Web of Science, Medline, Scopus, Embase, Cinahl and the Cochrane database. Our research was restricted to English language studies. The main keywords used for searching included: herbal medicine, herbs, statin, lipid, and herb-drug interaction.

Studies were included, and eligible if evaluated herb-drug interactions in therapeutic regimens for treatment of hyperlipidemia. In this review, case reports were excluded.

Papers matching inclusion criteria were reviewed in detail. Methodology of papers quality assessment was performed on the basis of some methodological elements that were previously described.[10] These criteria were including: prospective data collection, method of sampling, age range specification, inclusion and exclusion items specification, study setting specification, measurement tools validation, definition of disease status, sex and age specific prevalence report, data collection description, study limitations and possible correlates of disease and complications.

Among 2183 published articles about herb-drug interactions, 185 papers met the initial search criteria and among them, 92 papers were potentially retrievable including a description of 17 herbs and medicinal plants.

Results

Anti-lipid effects of herbs and related mechanisms

Among all studies evaluating effects of herbs on lipid profile and also those who assessed interactions between these herbs and lipid-lowering drugs, especially statins (Table 1), a minority of the studies focused on herb-drug interactions. Furthermore, with respect to the mechanisms of action as well as biological pathways involving drug interactions, these mechanisms have not been completely understood. In some experimental studies, the main mechanisms involved in reducing lipid levels or its effects increase of lipid-resistance to lipid oxidation induced by some co-factors such as Cu(2+) (Basil or Ocimum basilicum).[11,12] Some herbal extracts acts as induced inhibition of lipid accumulation during adipogenesis particularly via improvement of triglyceride-rich lipoprotein catabolism (blueberry or Vaccinium myrtillus).[13,14] In some herbs, the main factors for the relevant bioactivity is enriched 9(Z)-octadecenamide (oleamide) and ethanolic extracts responsible for inhibition of lipid production leading lowering serum triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL-C) or even hepatic triglyceride (celery or Apium graveolens).[15-17] Some herbs such as dandelion (Taraxacum officinale) acts via inhibition of adipocyte differentiation and lipogenesis in 3T3-L1 preadipocytes resulted in potentially decrease in different lipid profile including triglycerides, total cholesterol and LDL-C, as well as increase of high-density lipoprotein cholesterol (HDL-C) level both within a mid-term administration time.[18-20] The ethanolic extract of some herbs such as Eugenol or Eugenia jambolana can improve 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity that has a potential role in regulating serum lipid profile. It was also shown that hypolipidemic effect of this agent can be due to the presence of flavonoids, saponins, glycosides, and triterpenoids in its extract.[21-24] Modifying lipid peroxidation has been revealed as the main underlying mechanism of action in some herb extract (evening primrose oil) that is mediated by reduce of glutathione peroxidase activity and

increase of the activities of glutathione reductase and transferase.[25-30] In fenugreek (Trigonella foenum-graecum), the main mechanisms responsible for lowering serum triglyceride and total cholesterol include activating lecithin-cholesterol acyltransferase (47%), post heparin lipolytic activity (35%), triglyceride lipase (34%), lipoprotein lipase (20.8%), and increased excretion of fecal bile acids, as well as mediated through inhibition of fat accumulation and upregulation of LDL receptor (LDLR). In fact and at molecular level, thermostable extract of fenugreek seeds (TEFS) or TEFS can inhibit accumulation of fat in differentiating and differentiated 3T3-L1 cells through decreased expression of adipogenic factors such as peroxisome proliferators activated-receptor-gamma (PPAR-gamma), sterol regulatory element-binding protein-1, and CAAT element-binding proteins-alpha. Under sterol-enriched condition, TEFS up-regulated LDLR expression resulting in enhanced LDL uptake.[31-33] These underlying pathways are particularly revealed in diabetic states.[34-37] Ginger (Zingiber officinale) has been introduced as a lowering lipid peroxidation through its high acetylcholinesterase inhibitory activity. In fact, the inhibitory effect of ginger extracts on acetylcholinesterase activities and some prooxidants induced lipid peroxidation has been demonstrated that is usually mediated by effect on acetylcholinesterase activities, and sodium nitroprusside and quinolinic acid-induced lipid peroxidation.[38-42] Ginseng is a powerful herb affect via inhibition the increases of total cholesterol, LDL-C and triglyceride and also the decrease of HDL-C by down-regulating lipid accumulation and up-regulating adiponectin expression in the 3T3-L1 adipocyte cells. It seems that the main enzymatic pathways involved in this mechanisms include displaying 1,1-diphenyl-2-picrylhydrasyl and superoxide radical scavenging activities and inhibited hemolysis induced by 2,2'-azobis-2-amidinopropane dihydrochloride in a dose-dependent manner.[42-45] The anti-lipid effects of the grape are mostly mediated by resveratrol component that can significantly lower oxidized LDL and elevate HDL-C level that can be beneficial in atherosclerosis prevention. Moreover, administration of grape seed procyanidin extract (GSPE) can reverse the increase in plasma phospholipids. The alterations in the lipid metabolic pathways induced by GSPE were accompanied by lower free fatty acid levels in the plasma and decreased lipid and triglyceride accumulation. In this pathway, the effect of the oligomeric and polymeric procyanidin fractions in grape can also be trigger for lipolytic enzyme activities.[46-52] The strong effect of green tea polyphenols on reducing the body fat content and hepatic triacylglycerol and cholesterol accumulation has been also shown. It seems that green tea extract suppresses adiposity and affects the expression of lipid metabolism genes especially hepatic expression of the lipid catabolism genes acyl-coenzyme A oxidase 1, palmitoyl (ACOX1), acyl-coenzyme A dehydrogenase, c-4 to c-12 straight chain (ACADM), and peroxisome proliferator-activated receptor alpha (PPAR-α).[53-57] Analysis of methanolic extract and volatile oil extracted from Nigella sativa seed oil have shown reduction of the plasma triglycerides to near normal level and increase of HDL-C and its subfraction along with arylesterase activity levels caused by a significant decrease in hepatic hydroxymethylglutaryl (HMG)-CoA reductase activity.[58-63]

Table 1. Herbs with hypolipidemic effects

Name of herb	Biological effects
Basil	Lowering LDL and total cholesterol, increase of HDL
Blueberry	Lowering triglyceride and LDL levels
Celery	Decreasing serum triglyceride, total cholesterol, LDL-C and hepatic triglyceride
Dandelion	Decreasing serum triglyceride, total cholesterol, LDL-C and increasing HDL-C
Dill	Decreasing serum triglyceride
Eugenol	Decreasing serum triglyceride, total cholesterol, LDL-C and increasing HDL-C
Evening primrose oil	Decreasing serum triglyceride, total cholesterol
Fenugreek	Decreasing serum triglyceride, total cholesterol, HDL-C
Ginger	Decreasing serum LDL-C and increasing HDL-C
Ginseng	Decreasing serum triglyceride, total cholesterol, LDL-C and increasing HDL-C
Grape	Lowering oxidized LDL and elevate HDL-C level
Green tea	Suppresses adiposity and affects the expression of lipid metabolism genes
Nigella	Decrease in triglyceride and increase in HDL-C
Psyllium	Decrease in LDL

LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol

The beneficial effects of psyllium has been more focused on its regulatory effects on different components of metabolic syndrome such as improve glucose levels and insulin response, blood pressure, as well as lipid profile in both animals and humans, thereby reducing metabolic risk factors. According to recent reports, the use of psyllium could decrease insulin sensitivity, reduce android fat to gynoid fat ratio, as well as a reduce LDL-C. However, its physiological pathways have been already questioned.[64,65] Among different types of herbs, the position of dill as an anti-lipid agent is highlighted. Recent observations have been shown that the main hypolipidemic effect of this herb is order to activation of PPAR-α, an indispensable regulator for hepatic lipid metabolism by the extracts of dill caused by increased the mRNA expression levels of fatty acid oxidation-related genes in the liver and leading decrease of plasma triglyceride and glucose levels.[66] Its effect has been also shown in some recent clinical trials especially on lowering serum triglyceride level.[67]

Along with independent effects of the pointed herbs on lipid profile, some other herbal extracts such as red yeast rice or grapefruit indirectly influence serum lipid levels though their interactions with lipid-lowering drugs that are discussed in the next section.

Interaction between herbs and lipid lowering drugs

Regarding interaction between statin drugs and herbs which involved in lowering serum lipid profile, a few studies have been published. In a recent study by Rosenblat et al., although simvastatin with the dose 15 µg/ml could decrease macrophage cholesterol biosynthesis rate by 42% as compared to control cells, the combination of pomegranate and simvastatin resulted in an inhibitory effect up to 59% that was significant. Moreover, Simvastatin with the same dosage modestly decreased macrophage reactive oxygen species formation by 11% alone and by up to 63% concurrently with pomegranate.[68] In another experiment on interactive effects of grapefruit juice on chemical drugs, it has been revealed that the main mechanism for this interaction include inhibiting CYP3A4, the cytochrome P450 isoenzyme that most often involve in drug metabolism. With respect to interaction between grapefruit and statins, co-ingestion of this fruits can significantly elevated serum atorvastatin by 19-26% in one study and by 1.40 fold (95% confidence interval 1.02, 1.92) in another study compared with baseline and also elevated serum simvastatin by 3.6-fold (range 1.8-6.0 fold); however, no significant changes were detected in any pravastatin pharmacokinetic parameter examined when pravastatin was taken with grapefruit juice.[69-72]

Discussion

The growing use of herbal remedies has far exceeded the increase in available information on their benefits, adverse effects and drug interactions. Although compounds isolated from herbs have been shown to have important pharmacologic activities, but in some observations, actions of the herbs have been overestimated or underestimated. Moreover, both administrators and costumers have little-evidenced information on safety, effectiveness, and adverse effects of these herbs. In this regard, the increasing number of foods containing herbs has raised concerns at the food and drug administration (FDA).

Several herbs offer potential for cardiovascular conditions including hyperlipidemia, hypertension and congestive heart failure through a variety of mechanisms such as antioxidant, antiplatelet, fibrinolytic, anti-atherosclerotic, anti-hyperlipidemic, antiarrhythmic and vasodilatory actions.[73] The present study attempted to first review published evidence on the efficacy of herbs against hyperlipidemia as a potential coronary artery risk factor and after that it focused on some evidence on probable interactions between these herbs and anti-hyperlipidemic drugs, especially statins.[74,75] In first step and by reviewing all published manuscripts on beneficial effects of herbs on serum lipids level, 17 herbs were described to be effective on lipid profile as lowering serum triglyceride, total cholesterol, LDL-C as well as increasing serum HDL level. Some herbs such as celery could even affect the hepatic triglyceride concentrations. Although all shown herbs had similar target points on serum lipids, but the physiological affectivity mechanisms of drugs was widely different, including changes in lipid oxidation (basil, dill), induce of inhibiting lipid accumulation by lipid catabolism (blueberry), inhibition of lipid production (celery), Inhibition of adipocyte differentiation and lipogenesis (dandelion, grape, and green tea), reducing lipid peroxidation (evening primrose oil and ginger), activation of lipase enzymes (fenugreek), up-regulation of adiponectin expression in adipocyte cell (ginseng), and decrease in hepatic HMG-CoA reductase activity (nigella). In

fact, different parts of lipid metabolism pathways can be affected by various types of herbs. According to similar effects of chemical drugs on lipid metabolism process, interaction between these drugs and herbs is expectable. However, few studies were implemented to clear these interactions. Regarding drug-herb interaction, the interaction between some types of herbs and statins that are commonly used for improving hyperlipidemia has been considered. As previously shown, the herbal reaction towards different types of statins is varied so that grapefruit or pomegranate were interacted with only some types of statins, but not with all statin types. In this context, administration of herbal materials can lead to decreased absorption of statins or decreased the plasma concentration of these drugs. Simvastatin, pravastatin, and lovastatin are inhibitors of HMG-CoA reductase, the rate-limiting step in cholesterol synthesis.[9] Thus, any herbs involved in activation or inhibition of this enzymatic pathway can induce changes in drug absorption or catalysis.

Acknowledgments

This article has been derived from the Ph.D. thesis of the first author and financially supported by the research deputy of Shahrekord University of Medical Sciences, Iran.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Rouhi-Boroujeni H, Rouhi-Boroujeni H, Heidarian E, Mohammadizadeh F, Rafieian-Kopaei M. **Herbs with anti-lipid effects and their interactions with statins as a chemical anti-hyperlipidemia group drugs: A systematic review.** ARYA Atheroscler 2015; 11(4): 244-51.