A systematic review on safety and drug interaction of herbal therapy in hyperlipidemia: a guide for internist

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Summary. Because of reporting high side effects related to biosynthetic drugs, recent attention has been paid to the use of herbs instead of chemical drugs to balance serum lipids. The present systematic review aimed to evaluate the safety of herbal medicines and also to assess drug interaction in herbal therapy in treating hyperlipidemia. The international research databases including MEDLINE; Google scholar, Web of Science SciVerse Scopus (SCOPUS); EBSCO Academic Search; Cochrane Central Register of Controlled Trials (CENTRAL); and a Chinese database (China Network Knowledge Infrastructure [CNKI]) were searched from their respective inceptions up to September 2014 with the search terms of "hyperlipidemia", "herbal medicine", "medicine traditional", "extract plant", "Traditional Medicine" and "Chinese Herbal Medicine" without narrowing or limiting search elements. A total of 85 randomized clinical trials (RCTs) studies were finally assessed on human subjects. A notable number of herbal drugs that are commonly used as an anti-hyperlipidemia agent may be interacted with a variety of biosynthetic drugs. In this regard, the most common reported herb-drug reactions were related to anticoagulants, antidepressants, anti-epileptic, anti-inflammatory, and/or even anti-hypertension and anti-lipidemic drugs. Also, a considerable number of anti-lipidemic drugs of plants origin may be accompanied with metabolic disturbances and serious complications within pregnancy and breast feeding. The main fundamental principles for administration of these drugs include physicians' complete awareness of the effects and interactions of these drugs, educating people not taking these drugs arbitrarily, and closely monitoring the verification and distribution of the drugs in the society. (www.actabiomedica.it)

Key words: herbal therapy, hyperlipidemia, interactions

Introduction

Ischemic heart disease as the most common cause for mortality and disabilities around the world is certainly triggered from a collection of potential risk factors that among these factors, dyslipidemia has been identified as the main arm for coronary atherosclerosis. The increase in the level of cholesterol, triglycerides, low density lipoprotein (LDL) and oxidized LDL particles and adversely the decrease in high density lipoprotein (HDL) particles in the bloodstream are strongly associated with atheroma formation in the walls of arteries (atherosclerosis), which is the principal cause of coronary artery disease. Several experimental, animal and interventional studies have indicated lower morbidity and mortality in coronary heart diseases with reduction of serum total cholesterol and improvement in HDL cholesterol (Pickin et al., 1999). Prevention or treatment of such disorders can be achieved by targeting the causative factor for hyperlipidemia and hypercho-

lesterolemia through diet and/or drug administration (Grundy et al., 2004; LaRosa, 1990). In this regard, lowering serum levels of cholesterol, triglycerides, and LDL as well as elevating HDL level is a main target for inhibiting progression of coronary artery disease and also for preventing its-related adverse and life-threatening events. For this purpose, the principles of conventional treatment have been based on reducing cholesterol biosynthesis, which will lead to lower blood levels. A variety of biochemical drugs such as statins is available today which is involved in lowering cholesterol biosynthesis in the liver; however as the late or high-dose using these agents, the administration of statins may result in increased risk of chronic toxic effects including carcinogenic, teratogenic, and mutagenic changes over a lifetime of use (4-6). Because of reporting high side effects related to these biosynthesis drugs, recent attention has been paid to the use of herbs instead of biosynthetic drugs to balance serum lipids (7). For many years, plants had been used for medicinal aims. During 19th century, scientists tried to extract and amend the active ingredients from plants and started later making their own version of plant compounds (8). Nowadays, plants are considered as important sources of anti-hyperlipidemia treatment so that more than 80% of population of developing countries is dependent on traditional folk medicine therapies for treating their ailments (9). This fact has been recognized by international societies and its recommendations include evaluation of traditional medicines in primary health care of these countries (10). In this regards, a large number of medicinal plants have been evaluated for their hypolipidemic activity and thus a lot of herbal drugs have been experimented in this aspect (11, 12), but the safety and efficacy of these herbal drugs remains ambiguous. In addition, there has been no comprehensive evaluation of the clinical studies on the interaction between herbal and biosynthetic drugs. This systematic review of human source studies aimed to evaluate the safety of herbal medicines and also to assess drug interaction in herbal therapy in treating hyperlipidemia.

Methods

In the step of reviewing the literature, the following databases were searched from their respective inceptions up to September 2014: MEDLINE; Google scholar, Web of Science SciVerse Scopus (SCOPUS); EBSCO Academic Search; Cochrane Central Register of Controlled Trials (CENTRAL); and a Chinese database (China Network Knowledge Infrastructure [CNKI]). No language restrictions were imposed. Dissertations and abstracts were included. The search terms were "hyperlipidemia", "herbal medicine", "medicine traditional", "extract plant", " Traditional Medicine" and " Chinese Herbal Medicine" without narrowing or limiting search elements. All of the human studies on the effects of herbs with the key outcome of change in lipid profiles were included. All human studies of the use of herbal medicines for hyperlipidemia were included. Thus, we focused on the patients (both children and adults) with clinical diagnoses of hyperlipidemia who met the diagnostic criteria of the American Heart Association guideline for hyperlipidemia. All studies that used herbal medicines or combination therapy with conventional medicine versus placebo or other medications were included. Combinations of herbal medicines and non-medicinal therapy, such as acupuncture, and comparisons between different types of herbal medicines were excluded. We defined herbal medicines as product decoctions, concoctions, capsules, tablets, and powders that originated from botanical sources, such as whole plants or their adjuncts (13). The primary outcomes analyzed for the review included type of herbs, botanical sources, and common dosages of herbs used in trials. The secondary outcomes analyzed for the review were drug interactions with lipid-lowering herbs used. In final concluding, the safety of herbal drugs was discussed and appropriate instruction for using these drugs in combination with other drugs was presented.

Results

Terms of use

Of the publications identified from the initial database search, the results were identified and reviewed for inclusion or exclusion. A total of 85 randomized clinical trials (RCTs) studies were finally assessed on human subjects. The route of administration of herbs in almost all studies was oral intake. General and scientif-

ic names of plants, root of administration, human doses limits and some precautions and side effects are summarized in Table 1. Part of plants used as a therapeutic component was root of plant in *Burdock, Chicory, Orchis, and Ginger; fruit in Black cherry, Avocado, Grape, Brinjal, Milk thistle, Olive, Apple, American peooer, Bilberry, Common wheat, Tomato, Cherry, Haritali, Blackcurran, Coriander, Bitter orange christm lime, Orange,* and *Melon*; seed in *Pomegranate, Avocado, Blond plotitago, Grape, Milk thistle, Nutmeg, Oats, Soy, Fenugreek, Pumpkin, Bcack cumiv, Red yeast rice, Tamarind, Evening primrose, Dill, Corn, Comman bean,* and *Chickpea*; leaf in *Common Thyme, Aloe, Chamomile, Plantain, Chicory, Cabbage, Ginko, Thea, Olive, Purslane, Artichoke, Eugenol, Basil, Bulacy, Alfalfa, Dill,* and *Celery*; flower in *Yarrow,* and *Saf flowe*r; onion in *Onion* and *Garlic*; gum in *Guggul*; and rhizome in *Ginseng* and *Miswak*. The dose of administration varied Depending on the type of plant and root of administration from 100 mg to 200 grams.

Contraindications and precautions

Regarding precautions, the use of some of the plants are prohibited during pregnancy and breastfeeding including *Common, Aloe, Chamomile, Burdock, Plantain, Nutmeg, Oats, Ginseng, Thea, Soy, Fenugreek, American peooer, Pumpkin, Yarrow, Bcack cumiv, Eugenol, Guggul, Haritali, Evening primrose, Alfalfa, Dill, Saf flower, and Bitter orange christm lime*. The appearance of allergic reactions especially dermatitis has been reported following consumption of some types of plants including *Brinjal, Chicory*, and *Artichoke*. The precaution in the use of *Cabbage* in hypertensive patients or those with hypothyroidism has been emphasized. Also, the use of *Ginger* in patients with cardiac arrhythmia is also prohibited. The use of *Garlic* and *Bilberry* is not recommended in patients with gastrointestinal problems and the use of *Red yeast rice* in those with liver diseases is also prohibited. The precaution in the use of *Common wheat* in Gluten Sensitivity, *Comman bean* in gout disease, and *Celery* in asthma is also pointed.

Herb-drug interactions

As summarized in Table 2 and with respect to herb-drug interactions, some plants such as *Grep ransom* has interactions with some anti-epileptic, anti-hypertension, and anti-lipidemic drugs leading increased serum dosage of these drugs and create drug toxicity. *Avocado* can be interacted with warfarin, and MAO Inhibitors. *Pomegranate* is interacted with anti-hypertension, and anti-lipidemic drugs leading hypotension and increased the risk for rhabdomyolysis. *Bilberry* may be interacted with Aspirin, NSAIDS, Insulin, and anticoagulants led to increased risk for bleeding. The main interaction of *Ginger* with other drugs is generally related to antidepressants, anti-arrhythmic drugs, and anticoagulants. Also, *green tea* may be interacted with adenosine, anti-androgens, theophylline, and some anticoagulants. *Grape* is only interacted with methotrexate result in increasing side effects of this drug. *Psyllium* is frequently interacted with anticoagulants, antidepressants, digoxin, carbamazepine, lithium and some diuretics and thus simultaneous use of these two drugs is not recommended. The interaction between *Saf flowe*r and some synthetic drugs including aspirin, anticoagulants, and anti-hypertension drugs such as calcium-channel inhibitors has been also shown. *Evening primrose oil* may be interacted with a variety of drugs such as analgesics, anti-epileptic drugs, MAO inhibitors, antipsychotic drugs, and even statins. *Celery* is frequently interacted with ACE inhibitors, alcohol, and anticoagulants. The main interaction between *Yarrow* and other drugs is specified to the drugs used in the treatment of photo-dermatitis leading increase of photosensitivity. The use of *Dandelion* may be led to interaction with metronidazol. Also, the use of *Cabbage* may be interacted with acetaminophen, and vitamin K antagonists. *Ginko* is mainly interacted with anticoagulants, anti-epileptic drugs, MAO inhibitors, and antidepressants. *Ginseng* can be interacted with anti-hypertension drugs, digoxin, steroidal drugs, immunosuppressive drugs, and hypnotics. *Blueberry* is usually interacted with some antibiotics, insulin, metronidazole, anti-acids, and proton-pump inhibitors. Also, those studies which assessed interaction of *Thyme* with other drugs have suggested its interaction with 5-Fluorourasil, fluoroquinolones, amphotericin, leishmaniasis drugs, thyroid drugs, caffeine, hormonal drugs, hydrocortisone, hydrophilic drugs, and immunosuppressive drugs.

Table 1

General name	Scientific name	Part of plant	Dose limits	Precautions
Black cherry	Prunus cerasus	Fruit	20/d	--
Pomegranate	Punica gra natcm	Seed	8 g/d	--
Avocado	Persea ameri cana	Seed , Fruit	8 g/d	--
Common Thyme	Thymus volgaris	Leaf	2 g	Prohibited in pregnancy
Blond plotitago	Plantago ovate	Seed	7.5 g	--
Aloe	Aloe vera	Leaf	5	Prohibited in pregnancy
Grape	Vitis uinifera	Fruit , Seed	100 mg	--
Chamomile	Matricaria recutita	Leaf	2-8 g	Prohibited in pregnancy
Burdock	Arctium Loppa	Root	2-6 g	Prohibited in pregnancy
Brinjal	Solanum melongena	Fruit	3/d	Allergic effects
Milk thistle	Sipybum marinum	Fruit , Seed	12 g	--
Plantain	Plantago Lanceolata	Leaf , Seed	5 g	Prohibited in pregnancy
Chicory	Chicorium Lntybus	Root, Leaf	3-5 g	Dermatitis susceptibility
Onion	Allium cepa	Onion	20 g	--
Cabbage	Brassica oleracea	Leaf	10 g	In hypertension and hypothyroidism
Orchis	Orchis latifolia	Root	1 g	--
Nutmeg	Miristica fragrans	Seed	500 mg	Prohibited in pregnancy
Oats	Avena sativa	Seed	100 g	Prohibited in pregnancy
Ginseng	Eleuthero coccus	Rhizome	1 g	Prohibited in pregnancy
Ginko	Ginko biloba	Leaf	240 mg	--
Thea	Thea sinesis	Leaf	7 g	Prohibited in pregnancy
Ginger	Zingiber off icinalis	Root	2-4 g	Cardiac arrhythmia
Olive	Olea europea	Leaf , Fruit	7-8 g	--
Soy	Glycine soja	Seed	45 g	Prohibited in pregnancy
Apple	Malus orientalis	Fruit	1/d	--
Garlic	Allium sativum	Onion	1 g	GI problems
Fenugreek	Trigonella foenum	Seed	5 g	Prohibited in pregnancy
American peooer	Capsicum frutescens	Fruit	4/d	Prohibited in pregnancy
Bilberry	Vaccinium myrtillus	Fruit	5 g/d	GI problems
Purslane	Poryulaca oleracea	Leaf	100 g	--
Pumpkin	Cucurbita pepo	Seed	10-20 g	Prohibited in pregnancy
Yarrow	Achillea wilhelmsii	Flower	4 g	Prohibited in pregnancy
Common wheat	Triticum aestivum	Fruit	30-80 g	Gluten sensitivity
Tomato	Solanum lycopersicum	Fruit	100 g	--
Cherry	Prunus avium	Fruit	100 g	--
Artichoke	Cynara cardunculus	Leaf	1-9 g	Dermatitis susceptibility
Bcack cumiv	Nigella sativa	Seed	1.5 g	Prohibited in pregnancy
Eugenol	Eugenia jambolana	Leaf	2 g	Prohibited in pregnancy
Miswak	Musa paradisiaca	Rhizome	2 g	--
Guggul	Commiphora mukul	Gum	100 mg	Prohibited in pregnancy
Red yeast rice	Monascus purpureus	Seed	1.2-2.4 g	Liver disease
Tamarind	Tamarindus indica	Seed	10 g	Prohibited in pregnancy
Basil	Ocimum basilicom	Leaf	12 g	--
Bulacy	Osmium sanctum	Leaf	10 g	--
Haritali	Terminalia chebula	Fruit	1-3 g	Prohibited in pregnancy
Blackcurran	Vitis vinifera	Fruit	10 g	--
Evening primrose	Oenothera biennis	Seed	4 g/d	Prohibited in pregnancy
Alfalfa	Medicago sativa	Leaf	5-10 g	Prohibited in pregnancy
Dill	Anethum graveolens	Seed, Leaf	10 g	Prohibited in pregnancy
Walnut	Juglans regia	Core	80 g	--
Coriander	Coriandrum sativam	Fruit	1-10 g	-
Saf flower	Carthamus tinctorius	Flower	3-5 g	Prohibited in pregnancy
Corn	Zea mays	Seed	20 g	--
Comman bean	Pnaseolus unlgaris	Seed	100 g	Gout
Chickpea	Cicer arientinum	Seed	150 g	--
Bitter orange christm lime	Citrus aurantifolia	Fruit	20 g	Prohibited in pregnancy
Orange	Citrus aurantium	Fruit	4/d	--
Celery	*Apium graveolens*	Leaf	2 g/d	Asthma
Melon	Cucumis melo L	Fruit	20/d	--

Table 2.

Name of plant	Name of drug	Interaction	Result
Grep ransom	Amiodarone	Increase of plasma level	Toxicity, decrease of blood pressure
	Quinidine	Decrease of absorption	
	Carbamazepine	Increase of AUC	Toxicity symptoms of drug
	Sertraline	Increase of plasma level	Increase of drug side effects
	Trazodone		
	Nefazodone		
	Clomipramine		
	Caffeine	Decrease of clearance	Increase of insomnia and irritability
	Nitrates	Increase of plasma level	Increase of drug side effects
	Statins	Increase of plasma level	Increase of drug side effects (muscular pain)
	Cyclosporine	Increase of plasma level	Hepatic and renal toxicity
	Tacrolimus	Increase of plasma level	Renal toxicity
Avocado	Warfarin	Decrease of absorption	Decrease of drug effect
	MAO Inhibitors	Thiamine release	Hypertension crisis
Pomegranate	Statins	Increase of creatine kinase	Increased rhabdomyolysis
	ACE inhibitors	Inhibition of I to II converter	Hypotension
Bilberry	Aspirin, NSAIDS	Thromboxane inhibition	Risk of bleeding
	Insulin	Secretion stimulation	Hypoglycemia
	Supplementation with chromium	Increase of plasma level	Toxicity with chromium
	Plavix, ticlopidine	Anti-platelet aggregation	Anticoagulant reactions
Ginger	SSRIs	Serotonin antagonist	Changes in drug effect
	Anti-arrhythmic drugs	Increase of Ca2t ATPase	Changes in drug effect
	Anticoagulants	Inhibition of thromboxane B2	Increase of drug effects
	Benzodiazepines	Increase of GABA	Sleepiness
	Quinidine	Increase of Ca2t ATPase	Drug toxicity
Green tea	Adenosine	Caffeine antagonist	Changes in drug effect
	Anti-androgens	Inhibition of drug metabolism	Increase of drug effects
	Theophylline	Decrease of clearance	Increase of drug side effects
	Coumarin anticoagulants	Vit K antagonist effect	Decrease of warfarin effects
Grape	Methotrexate	Inhibition of xanthine oxidase	Increase of drug side effects
Psyllium	Anticoagulants	Decrease of absorption	Increase of drug side effects
	Tricyclic antidepressants	Decrease of absorption	Increase of drug side effects
	Anti-diarrheal	Fecal bulking	Increase of drug side effects
	Carbamazepine	Decrease of absorption	Increase of drug side effects
	Digoxin	Decrease of absorption	Decrease of daily dose of drug
	Diuretics	Decrease of absorption	Increase of drug side effects
	Lithium	Decrease of absorption	Increase of drug side effects
*Saf flowe*r	Anticoagulants	Anti-platelet aggregation	Anticoagulant reactions
	Aspirin	Increase of drug effects	Increase of drug side effects
	Ca-channel blockers	Microcirculation increasing	Increase of drug side effects
Evening primrose oil	Analgesics	Probability of seizure	Increase risk of seizure
	Anti-epileptics	Reduce the threshold neurons	High risk in patients with epilepsy
	Phenothiazines	Probability of seizure	Increase risk of seizure
	Statins	Inhibition of cholesterol production	Decrease of statin effects on lipids
Celery	ACE inhibitors	Allergic sensitivity	Allergic sensitivity and anaphylaxis shock
	Alcohol	Allergic sensitivity	Allergic sensitivity and anaphylaxis shock
	Sedatives	Increase the effects of N-butyl phthalide	Sleepiness
	Anticoagulants	Increase of drug effects	Increase of drug side effects

(continued)

Table 2.

Name of plant	Name of drug	Interaction	Result
Yarrow	Photodermatitis drugs	Increase of photosensitivity	Side effects of photosensitivity
Dandelion	Metronidazole	Disulfiram-like reaction	Nausea
Cabbage	Acetaminophen	Increase of metabolism	Decrease of drug effects
	Vitamin K antagonist	Increase of Vitamin K	Toxicity with Vitamin K
Ginko	Anticoagulants	Anti-platelet aggregation	Anticoagulant reactions
	Antiepileptic drugs	Probability of seizure	Increase risk of seizure
	MAO Inhibitors	Serotonin release	Serotonin syndrome
	SSRIs	Serotonin release	Serotonin syndrome
Ginseng	Anti-hypertensions	Increase of vascular resistance	Hypertension
	Digoxin	Increase of drug effects	Drug toxicity
	Estrogenic drugs	Estrogen- 3- sulfate inhibition	Estrogen inhibition
	Immunosuppressive	Stimulating the immune	Stimulating the immune reactions
	Hypnotics	Deeping sleep	Nervous sleepiness
Blueberries	Amoxicillin Omeprazole Clarithromycin	Increase of drug effects	Anti-H.pylori effects
	Insulin	Hypoglycemia	Hypoglycemia
	Metronidazole	Disulfiram-like reaction	Nausea
	Anti-acids Omeprazole	Decrease of gastric PH	GI complications
Thyme	5-Fluorourasil	Increase of skin absorption	Increase of skin absorption
	Fluoroquinolones	Decrease of drug effects	Susceptibility to infection
	Amphotericin B	Decrease of drug effects	Susceptibility to fungal infection
	Anti-Leishmaniasis and Entamoeba drugs	Increased drug effects due to the presence of thymol	Increase of drug effects
	Anti-thyroid drugs	Decrease of TSH	Hyperthyroidism
	Caffeine	Reduce the release of thymol	Decrease of the effect of caffeine
	Hormonal drugs	Increased estrogen and progesterone effects	Anti-testosterone effects
	Local hydrocortisone	Increased skin penetration of hydrocortisone	Increase of drug effects
	Hydrophilic Drugs	Increased skin penetration	Increase of drug effects
	Immunosuppressive	Stimulation of the increase of superoxide production	Immunosuppression

Discussion

As pointed in our study results, a notable number of herbal drugs that are commonly used as an anti-hyperlipidemia agent may be interact with a variety of biosynthetic drugs. In this regard, the most common reported herb-drug reactions were related to anticoagulants, antidepressants, anti-epileptic, anti-inflammatory, and/or even anti-hypertension and anti-lipidemic drugs. Therefore, most recommended precautions should be focused on concurrently use of these anti-lipidemic herbal agents and other drugs with high caution and with considering their synergetic effects. As an applied guideline for internists to administer herbal drugs for treating hyperlipidemia, the following recommendations can be pointed: First, a number of anti-lipidemic drugs of plants origin may be accompanied with metabolic disturbances and serious complications within pregnancy and breast feeding that thus their administration should be performed with full knowledge of their side effects in these periods. Second, some herbal drugs including *Avocado, Bilberry, Ginger, Green tea, Psyllium, Saf flower, Celery,* and *Cabbage* should be cautiously used in patients with coagulation disorders, as well as in those with the history of cardiovascular and or cerebrovascular disorders. Moreover, because of the direct interactions of some plants including *Grep ransom*, *Bilberry, Ginger*, *Psyllium* with cardiovascular medications such as digoxin, anti-arrhythmic drugs, or inotropes, the use of this agents in cardiovascular

disease states should be programmed with a deep and extensive study on their effects and drug interactions in these patients. In this regard, the use of some other herbal drugs such as *Bilberry* and *Blueberries* should be considered with high precaution.

This systematic review attempted to appraise the quality, efficacy/effectiveness, and safety of herbals used to treat hyperlipidemia. It indicated that there are herbals that have shown positive results via clinical trials for the treatment of hyperlipidemia that are available on the market today. However, most of these drugs may not be approved by scientific sources and thus may be administered traditionally that is very common in some societies such as our society. On the other hand, there are some traditional ideas and experiences in effectiveness of these herbs without considering their serious side effects. More and more studies are being dedicated to the effectiveness of herbs, and though some ailments are too severe or complicated to be treated without the consultation of a doctor or hospital, many people choose to try herbal remedies first in order to be economical and healthy. In addition, some types of herbal drugs may be commonly used without having a careful history of the patient records leading serious and even life-threatening consequences. Thus, the main fundamental principles for administration of these drugs include physicians' complete awareness of the effects and interactions of these drugs, educating people not taking these drugs arbitrarily, and closely monitoring the verification and distribution of the drugs in the society. Also, while it is recommended that doctors be consulted before integrating herbal remedies into a daily regimen or treating a condition, most herbs are self-explanatory, as they give dosage instructions and recommended length of ingestion on the labels.

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