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Hypolipidemic potential of plants used in Cuba

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Abstract

Dyslipidemia is a group of asymptomatic diseases due to abnormal concentrations of total cholesterol, low-density and high-density lipoproteins bound cholesterol (LDL-C and HDL-C respectively) and/or triglyceride in blood. It is a risk factor for thrombosis on atherosclerotic lesions, leading to atherothrombotic diseases (myocardial infarction, stroke or lower limb occlusive disease). Therefore, the therapeutic goal of hypolipidemic treatments is to reach a low cardiovascular risk status by the reduction of total cholesterol, triglyceride and LDL-C and the increase of HDL-C levels. New therapeutic options could be obtained from plants. Consequently, this review is focused on the pharmacological evidence available about the hypolipidemic potential of medicinal plants used in Cuba in order to provide a scientific basis for the development of plant-derived hypolipidemic products in this and other countries with environmental and/or cultural similarities. Plant profiles presented include information about the scientific and common names, botanical family, experimental conditions used, results obtained, mechanisms of action and active compounds. Data from fifteen plant species are described. The nine botanical families they belong to, mainly Liliaceae, Lamiaceae and Rutaceae, emerge as possible sources for hypolipidemic drug discovery. The information available about preparations from *Allium sativum* L. bulbs, *Citrus paradisi* L. fruits and *Hibiscus sabdariffa* L. flowers suggest that they are the most suitable for this purpose currently. Mechanisms of action and active agents should be elucidated for all plant products presented , manufacture methods (from plant collection to pharmaceutical technology) be standardized and its clinical efficacy and safety for patients confirmed.

Key words: Dyslipidemia, lipid, traditional medicine, pharmacology

Introduction

Dyslipidemia is a group of asymptomatic diseases due to abnormal concentrations of total cholesterol, low-density and high-density lipoproteins bound cholesterol (LDL-C and HDL-C respectively) and/or triglyceride in blood[1] that increase the risk for thrombosis on atherosclerotic lesions (atherothrombosis) at the artery wall that reduces the arterial lumen, the blood flow inside it and the oxygen supply to the affected organs. Leading to clinical events that are responsible for high number of deaths and disabilities worldwide (myocardial infarction, stroke or lower limb occlusive disease) [2]. Thus, the therapeutic goal of hypolipidemic treatments is to reach and maintain a low cardiovascular risk status by the reduction of total cholesterol, triglyceride and LDL-C and the increase of HDL-C levels.

Drugs with proved hypolipidemic efficacy include statins, compounds that inhibit the activity of acetyl-glut aryl coenzyme reeducates (HMG Co-A reductase), the cholesterol synthesis pathway limiting enzyme ; fibrates (fibric acid derivatives), by activating the hepatic lipoprotein lipase enzyme induce a reduction of triglyceride formation and increase of triglycerides breakdown and HDL synthesis in the liver; nicotinic acid derivatives (niacin) , inhibit lipoprotein lipase activity on adipose tissue leading to a decrease of triglycerides hydrolysis in adipocytes and the synthesis of triglyceride in the liver besides an increment of HDL-C level; cholesterol absorption inhibitors (ezetimibe), biliary acid sequestering agents and omega-3 fatty acids [1]. However, the side effects of some of these products [2,3] and the high cost of continued treatments with them may limit their use for many patients, therefore, discovering new efficacious, safe and economic hypolipidemic agents is a scientific challenge.

Many known drugs have been primary discovered from plants [4], suggesting that they could provide opportunities for developing new products. Thus, an analysis the information about plants with this therapeutic potential that are traditionally used in a given country is the first stage of the research strategy aimed to obtain efficacious and safe standardized herb preparations and/or purified drugs [4, 5] .

Atherothrombotic diseases are health problems worldwide. Cardio and cerebrovascular diseases are the second and third causes of death among adult Cuban population respectively [6] and the possibility to count with new therapeutic options against dyslipidemia is a matter of interest. However, there is a lack of information about the hypolipidemic potential of medicinal plants used in this country that would support drug development in Cuba and other countries with environmental and/or cultural similarities. Consequently, this review focused on the results of pharmacological evaluations performed with validated experimental models[7] and/or controlled clinical trials that suggest the possible therapeutic utility of preparations derived from plants used to treat different illnesses in Cuba[8-13].

Information was withdrawn from Google Scholar and PubMed data bases using the following search parameters or combinations: "the plant scientific name", "lipid", "cholesterol" and "dyslipidemia", "medicinal plant" "traditional medicine" without applying restrictions with respect to the publication date, the type of the study or the language.

The scientific and vernacular names, botanical families and uses in Cuba of plants with hypolipidemic potentials are summarized in the Table 1. Details of its pharmacological effects, proposed mechanisms of action and active principles are described as follows:

***Allium cepa* L.** (*A. cepa*)

A. cepa bulb aqueous extract induced the reductions of serum concentrations of total cholesterol, LDL-C and triglycerides when it was orally administered to rats under hypercholesterolemic diet [14]; however triglycerides but not cholesterol levels were affected when Streptozotocin-induced diabetic rats under a fat-rich diet were treated with this kind of extract [15]. S-methyl cysteine sulfoxide has been identified as its possible active principle that could provide bulb extracts with an inhibitory effect on HMG CoA reductase activity [16].

***Allium sativum* L.** (*A. sativum*)

Hypercholesterolemia was prevented in rats, rabbits, pigs and chicken, orally treated with oil,

aqueous or organic solvents *A. sativum* bulb extracts during atherosclerosis experimental induction [17-19] A hydro-alcohol extract showed total and LDL-cholesterol lowering effect without influence on triglycerides and HDL-C serum concentrations in hypercholesterolemic patients involved in a double-blind randomized- placebo-controlled clinical trials [17]. Inhibition of hepatic HMG-CoA reductase activity, as well as membrane and plasma lipoprotein remodeling, are the proposed mechanisms of action. S-allyl-cistein sulfóxide, allicin, dialyl, di and trisulphures are the identified *A. sativum* active principles [17-19].

***Aloe vera* (Linn.) Burm F.** (*A. vera*)
Orally administered *A. vera* leaf juice and gel inhibited Triton-induced increase of total cholesterol, LDL-C and triglyceride blood concentrations in mice [20]. *A. vera* leaf aqueous extract had similar effects in normal rabbits [21], diabetic rats [22] and mice [23].

***Bixa orellana* L.** (*B. orellana*)
Diet- , Triton-, fructose and ethanol – induced hyperlipidemia in rats and mice was prevented by oral treatments with *B. orellana* seed aqueous extracts [24, 25].

Citrus paradisi L. (*C. paradisi*)
C. paradisi fruit peel pepsin, orally administered, and showed ant atherosclerotic effect miniature swine [26]. Moreover, diet-induced hiperlipemia was prevented by *C. paradisi* fruit juice intake in rats [27]. A randomized - controlled clinical trial demonstrated a decrease of cholesterol LDL-C and LDL-C/HDL-C ratio in hypercholesterolemic patients after daily intake of *C. paradisi* peptin [28]. The flavonoid naringin has been identified as a probable principle active responsible of *C. paradisi* juice hypolipidemic effect [29].

***Citrus sinensis* L.** (*C. sinensis*)
Oral administration of fresh or lyophilized *C. sinensis* juices to rats and rabbits fed with hiperlipemic diets prevented the increment of total cholesterol, LDL-C and triglycerides in blood and induced the increase of HDL-C levels [30, 31]. A hypolipidemic effect was demonstrated also with hamsters treated with *C. sinensis* fruit fiber [32].

***Hibiscus sabdariffa* L.** (*H. sabdariffa*)
*H. sabdariff*a flower extract was effective to control blood lipid levels on hypercholesterolemic patients who participated in a randomized-double blind placebo- controlled clinical trial [33] . Furthermore, a triple blind randomized placebo-controlled clinical trial with obese adolescents with dyslipidemia, demonstrated that daily treatment with fine powdered calices of *H. sabdariff*a induced significant decrease of serum total cholesterol, LDL-C and triglyceride without change of HDL-C levels [34]. Anthocyanins have been identified as the possible contributors to the pharmacological effect of *H. sabdariffa* preparations [35].

***Morinda citrifolia* L.** (*M. citrifolia*)
M. citrifolia leaf, fruit and root hydro-alcohol extracts given orally to rats with experimentally induced hyperlipidemia was able to induce the reduction of serum lipid levels [36]. A similar effect was observed in hamsters under a high-fat/cholesterol diet that were treated with *M. citrifolia* fruit juice [37]. Decreases in LDL and increases in HDL, were observed in adult heavy smokers who participated in double blind, placebo-controlled clinical trial designed to investigate juice influence on hyperlipidemia [38].

***Ocimum basilicum* L.** (*O. basilicum*)
Prevention of Triton WR-1339- induced hyperlipidemia was demonstrated on rats and mice treated with *O. basilicum* leaf aqueous extract or its water, ethyl acetate and methanol sub-fractions concomitantly with the hiperlipemic stimulus [39, 40]. Similar results have been obtained with other experimental models like diet-induced hiperlipemia [41] and Streptozotocin-induced diabetes in rats [42]. An ethanol whole plant extract inhibited LDL-C oxidation, LDL-induced fat accumulation, as well as the esterification of de novo synthesized cholesterol and the number of scavenger receptors in macrophages *in vitro* [43].

***Ocinum sanctum* L.** (*O. santum*)
O. santum leaf extracts and essential oils showed lipid lowering effects in rats and rabbits fed hypercholesterolemic diets. Inhibition of lipid peroxidation has been demonstrated *in vivo* and *in vitro* [44- 46] .

***Persea americana* Mill.** (*P. Americana*)
Diet-induced hyperlipidemia was inhibited and plasma HDL-C concentration increased in rats treated with *P. americana* leaf water and methanol as well as fruit extracts [47, 48] . Additionally, the hypolipidemic effect of the treatment with fruit flour was demonstrated with mice on a hyperlipidemic diet [49].

***Salvia officinalis* L.** (*S. officinalis*)
Reduced serum total cholesterol and LDL/HDL-C ratio was demonstrated in rats after ad libitum intake of *S. officinalis* aqueous leaf extract [50]. A double-blinded placebo-controlled clinical trial with hyperlipidemic patients showed a decrease of total cholesterol and LDL-C and increase of HDL-C after treatment with aqueous extract from *S. officinalis* leaves[51].

***Tamarindus indica* L.** (*T. indica*)
Oral treatment with *T. indica* fruit pulp water extract was able to lower hyperlipidemia and increase serum HDL-C concentrations in hamsters fed with a high-cholesterol diet [52, 53]. More LDL receptor gene expression, decrease in the expression of HMG-CoA reductase gene, as well as prevention of hepatic lipid peroxidation were also induced [53]. On the other hand, lowering of total cholesterol and LDL-C and elevation of HDL-C, but a contradictory increment of triglyceride levels were demonstrated in healthy volunteers who participated in a randomized controlled clinical trial aimed to assess the effect of *T. indica* dry fruit pulp intake on blood lipids profile [54].

Tecoma stans Linn. (*T. stans*)
Rats with Triton WR 1339-induced hyperlipidemia exhibited significant reduction of blood lipid levels after *T. stans* flower hydro-alcohol extract oral administration. Furthermore, the elevated serum total cholesterol and triglycerides concentrations were attenuated and the HDL-C levels augmented in rats fed with a high-fat diet [55].

***Zingiber officinale* Roscoe** (*Z. officinale*)
Apo lipoprotein E deficient mice, rabbits and rats fed with hypercholesterolemic diets showed lower cholesterol levels in serum, heart and aorta, decreased blood lipid peroxidation and/or reduced number of atherosclerotic lesions in aorta after treatment with *Z. officinale* rhizome ethanol extracts [56-58]. On the other hand, a double-blind randomized placebo-controlled clinical trial with hyperlipidemic patients significant reductions of total cholesterol and triglyceride and increase of HDL-C plasma concentrations after daily intake of a *Z. officinale* rhizome dried ethanol extract [59]. Increment of the messenger RNAs pools for LDL and LDL receptors and reduction of hepatic HMG-CoA reductase activity, suggest that *Z. officinale* extract hypolipidemic effect is mediated by control of LDL receptor and cholesterol biosynthesis [60].

Discussion

This study has presented a list of 15 plant species with hypolipidemic potential that are used as folk remedies for different illnesses in Cuba. Pharmacological evidence have been obtained from the assessment with animals under experimental models of hyperlipidemia and/or normal or dyslipidemic human subjects
The nine botanical families that these plant species belong to, mainly Liliaceae, Lamiaceae and Rutaceae, emerge as possible sources to discover new therapeutic options for dyslipidemia. Statin-like activity has been shown by some plant products; however, the characterization of the mechanisms of action and chemical constituents responsible for the pharmacological effects of these natural preparations is still limited and more investigation must be carried out in this respect.
Though dyslipidemia is an asymptomatic disease that has been recognized as atherothrombotic risk factor in a relatively recent date, the popular use of *H. sabdariffa*, *B. orellana*, *O. basilicum* , *A. sativum* and *C. sinensis* to reduce blood lipid concentrations has been reported in Cuba[12], Brazil [24], Morocco [39] , India and Vietnam [61] and Brazil [62] respectively. Thus, the pharmacological evidence described here support the Ethnomedical findings and confirm the utility of these studies for drug discovery.
A research strategy for the development of hypolipidemic plant products could be proposed according to the information available as follows: First of all, plant preparations that have been assessed in randomized-controlled trials with patients suffering from hyperlipidemia, secondly those investigated in similar conditions but with normal subjects and thirdly those only studied in pre-clinical conditions.

A. sativum bulb hydro-alcohol extract could be considered in the first place since its possible mechanism of action and active principles have been identified, followed by *C. paradisi* fruit peptin , as well as *H. sabdariffa* flower extract and powder, because the knowledge about their possible active constituents would help standardizing manufacture conditions. Thus, they are the most suitable for this purpose currently.

Taking in account the influence of environmental conditions on plant metabolism and on the concentrations of metabolites responsible for the biological effects, the information summarized in this work could not be used in the clinical practice until methods for plant products manufacture (from plant collection to pharmaceutical technology) be standardized and its clinical efficacy and safety for patients confirmed.

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Scientific name (Family)	Common Name	Traditional uses in Cuba [8-13]
Allium cepa L. (Liliaceae)	Cebolla	Food, inflammation, pain, intestinal parasites, fever, bronchial asthma, gastric disorders, diuretic.
Allium sativum L. (*Liliaceae*)	Ajo	Spice, cold, pain and circulatory disorders.
Aloe vera (Linn.) Burm. f. (Liliaceae)	Sábila	Hepatitis, gastric ulcers, hemorrhoids, bronchial asthma, pneumonia.
Bixa orellana L. (Bixaceae)	Bija	Spice, bronchial asthma, diuretic.
Citrus paradisi L. (Rutaceae)	Toronja	Fruit, cold, hypertension.
Citrus sinensis L. (Rutaceae)	Naranja dulce	Fruit, cold, circulatory diseases.
Hibiascus sabdariffa L. (Malvaceae)	Flor de Jamaica, Serení	Diuretic, hypolipidemic.
Morinda citrifolia L (Rubiaceae)	Noni	Diabetes, hypertension.
Ocimum basilicum L. (Lamiaceae)	Albahaca blanca	Spice, spasmolytic, emetic, diuretic, cold, diarrhea, cancer, high blood pressure, Sedative, somniferous.
Ocinum sanctum L. (Lamiaceae)	Albahaca morada	Diabetes, fever, headache, cold, cough, stomachache.
Persea americana Mill (Lauraceae)	Aguacate	Food, antitussive, emmenagogue, abortive, diuretic.
Salvia officinalis L. (Lamiaceae)	Salvia	Headache, cold, inflammation, fever, dyspnea, tonic remedy.
Tamarindus indica L. (Cesalpinaceae)	Tamarindo	Fruit, hepatic disorders, stomach ulcer, hemorrhage, diuretic.
Tecoma stans Linn. (Bignoniaceae)	Saúco amarillo	Diabetes
Zingiber officinale Roscoe (Zingiberaceae)	Jengibre, Ajengibre	Spice, anti-vomiting, anti-rheumatic, aphrodisiac, immune-stimulant, tonic, anti-diarrheic, cough reliever.

Table 1. Plants with hypolipidemic potentials used in Cuba