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A COMPREHENSIVE REVIEW ON MECHANISM OF ACTIVITY OF VARIOUS HERBAL PLANTS ON ATHEROSCLEROSIS.

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Abstract

A major contributor to cardiovascular disease, atherosclerosis is an inflammatory vascular condition marked by a gradual buildup of cholesterol in the walls of the arteries. In recent years, problems with synthetic drug adverse effects have contributed to drug abuse. A new understanding of medicinal plants has therefore lately evolved, and extensive study has been done on these herbs in an effort to create novel organically based medications. The objective of this review paper was to examine the molecular processes of therapeutic plants with potential against atherosclerosis. The regulation of inflammatory factor expression, stimulation of PPARs, inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase), promotion of ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G (ABCG), facilitation of adiponectin activity, reduction of LDL cholesterol, and stimulation of PPARs are just a few of the mechanisms by which an improved understanding of these herbal mechanistic linkages is a crucial step before designing new plant-based medications.. An important part of the aetiology of atherosclerosis is inflammation. Excessive intimal fibrosis, the development of fatty plaques, the growth of smooth muscle cells, and the migration of inflammatory-response cells including platelets, monocytes, and T cells are all symptoms of the condition. The early stage of atherosclerosis in cardiovascular illnesses is represented by low density lipoprotein (LDL) oxidation to Ox-LDL. Increased peroxynitrite concentrations in some clinical conditions, including severe hypercholesterolemia, worsen atherosclerosis and vascular damage. It has been proven that medicinal plants have the ability to interact with these or other pathogenic variables to inhibit atherosclerosis.

Introduction

The word "atherosclerosis," which means thickening of the inner lining of arteries and fat buildup, is Greek in origin. The plaque's central core contains fatty material that is surrounded by fibrous tissue. Atherosis, which is a deposit of fat accompanied by many macrophages, and sclerosis, make up the two elements of the name "atherosclerosis" (fibrosis layer comprising smooth muscle cells [SMC], leukocyte, and connective tissue).

Atheromatous plaques, which are fatty deposits, develop in the inner layers of arteries as a result of the prevalent illness atherosclerosis. Small cholesterol crystals that are deposited in the intima and its supporting smooth muscle are the first step in the formation of these plaques. Once inside the arteries, the plaques expand due to the growth of adjacent smooth muscle and fibrous tissues, decreasing blood flow. Sclerosis or hardening of the arteries is brought on by fibroblasts producing connective tissue and calcium being deposited in the lesion. Finally, thrombosis and clot formation due to the uneven surface of the arteries cause an abrupt restriction of blood flow.

Increased oxidative damage, which alters antioxidant status and lipoprotein levels, is linked to hyperlipidemia and hyperglycemia. Studies have demonstrated that cholesterol-lowering medicinal herbs, in addition to their antioxidant properties, can lower blood lipid levels, particularly after meals. As a result, they can stop atherosclerosis and harm to the vascular endothelium.

The development of atherosclerotic alterations in blood arteries is influenced by numerous contributing risk factors to varied degrees, either directly or indirectly. Cigarette smoking, high blood pressure, diabetes, obesity, hypercholesterolemia, and a history of heart disease in the family are some of these. Recent problems with the adverse effects of modern synthetic pharmaceuticals have resulted in drug abuse, a lack of patient consultations, and ultimately a breakdown in the careful management of sickness. As a result, recent years have brought about a new understanding of medicinal plants, and extensive research has been done on these herbs. Since ancient times, the utilisation of medicinal plants to treat illnesses has drawn interest. Communities throughout many nations have been turning more and more to alternative medicine in recent years, particularly phytotherapy and nutritional supplements to treat conditions like atherosclerosis. Medicinal plants have had some reassuring results in addition to lowering healthcare expenses, and it is practical to utilise such plants even as adjuncts, particularly when existing medicines fail to control the disease. Additionally, substantial research on medicinal plants is necessary due to the fact that their adverse effects are typically less severe than those of manufactured medications.

The use of medicinal plants with less side effects may possibly contribute to an improved treatment of atherosclerosis due to the health implications of atherosclerosis, the relative ineffectiveness, high cost, and side effects of some conventional medications. Some of the medicines that are currently prescribed across the globe were created using established compounds with established processes. Having knowledge of such medications can help researchers screen isolated natural molecules, then synthesise and create pharmaceuticals with comparable structures. The mechanisms of action of medicinal plants used to treat atherosclerosis have been studied. Such research is necessary to create new pharmaceutical formulations that are more effective while having fewer negative effects. The current review's goal was to present the most comprehensive.

Major targets for anti-atherosclerotic activity

a. Modification of lipoprotein level

Triacylglycerol, proteins, and phospholipids make up the lipids that make up lipoproteins. It is widely accepted that the main risk factor for atherosclerosis is elevated blood cholesterol levels. Dyslipidemia and coagulation issues are two of the most significant risk factors for the development of atherosclerotic diseases, according to epidemiological studies (1).Excess LDL infiltrates arteries in a hyperlipidemic state and is retained in the tunica intima. The sub-endothelial area of the retained LDL suffers oxidative changes controlling the invasion of LDL can be accomplished in one of two ways the blood, increasing HDL levels, or focusing on the HMG CoA reductase enzyme, an enzyme that lowers cholesterol.

b. LDL oxidation

Free radical oxidative damage has been implicated as the cause of many diseases. There is ample proof from the research that has been done that LDL oxidation plays a significant role in the development of atherosclerosis.(2) LDL is transformed into mmLDL, which is still recognised by the LDL receptors, after infiltration of LDL in the artery. A purpose of the study is to fortify against LDL oxidation in order to stop the

onset and development of atherosclerosis. Due to the early reduction of atherosclerotic development, antioxidants that effectively halt LDL oxidation may prevent atherosclerosis.

c. Failure of endothelial cells and molecule adhesion

The blood artery wall's other cells and the circulating blood is connected by endothelial cells, which serve as an edge and functional link. NO, prostacyclin, endothelin-1, and angiotensin II are all produced by the endothelium.(3)

Nitric oxide (NO), a key signalling chemical produced by the NOS enzyme family, is essential for maintaining the homeostasis of the vascular system. NO has a variety of effects on the artery wall, such as activation and inhibition of platelet aggregation, inhibition of cell adhesion and migration, relaxation and inhibition of vascular smooth muscle cell growth, etc. Endothelial cells' ability to produce homeostatic mediators of vascular health, such as NO, is compromised by any biochemical or physical damage, which accelerates the development of atherosclerosis.(4) Therefore, maintaining healthy NO levels and endothelial cell activity can aid in halting the onset and progression of atherosclerosis.

Table 1. Mechanism of action of medicinal plants on atherosclerosis

Sr. no	Medicinal plants	Phytochemical constituents	Study design	Mechanism of action	Reference
1	Sage (salvia officinalis)	Total phenolics, total flavonoids and quarcetin	6 healthy female volunteers	The extract reduced the levels of triglycerides, LDL-C, TC, FG, 2hPPG and HbA1c,	1
2	Elephant garlic (*Allium ampeloprasum)*	Allicin	Hyperlipidemic hamsters	Hamsters fed a high-fat diet with Persian leek showed lower liver triglycerides (TG), plasma Alanine aminotransferase levels, and tumour necrosis factor gene expression than hamsters on a high-fat diet alone.	2
3	Licorice (*Glycerhiza glabra*)	Glycyrrhizin , tannins, sitosterol and stigmasterol	Hypercholesterolemic patients	Mean CIMT, LDL levels, blood pressure, and total cholesterol all decreased. This implies that licorice may slow the progression of atherosclerosis and other cardiovascular disorders.	3
4	Mulberry (*Morus alba*)	resveratrol p-coumaric acid, chrysin, catechin	Hypercholesterolemic mice	Hepatic PPAR- expression was increased while genes related to cholesterol were expressed less strongly.	4

5	Green tea (*Camellia sinensis*)	Theanine, polyphenols, Myricetin, caempherol, quarcetine	ApoE-knockout mice, fed with a high-fat diet	Enhanced the mRNA and protein expressions of hepatic PPAR and autophagy markers (LC3, Beclin1, and p62) in the vessel wall of ApoE-knockout mice, and decreased the blood levels of oxLDL.	5
6	Oregano (*origanum vulgare*)	Apigenin, luteolin, apigenin-7-O-glucoside	Isoproterenol (ISO)-induced myocardial injury in rats	protective impact against ISO-induced elevations in CRP, IL-6, IL-13, and TNF-	6
7	Citrus fruits	Flavonoids: naringenis and nobiletin	*Ldlr*$^{-/-}$ mice fed a high-fat cholesterol-containing (HFHC) diet	Improvements in hepatic steatosis, insulin sensitivity, hyperlipidemia, and blood monocytes, as well as a small decrease	7
8	Mango (*Mangifera Indica Linn*)	Mangiferin	Hypercholesterolemic mice	Prevent mitochondrial oxidative stress in atherosclerosis	8
9	Red spinach(*Amaranthus dubius)*	β-carotene, lutein and zeaxanthin	High-fat, high-cholesterol induced rats	Significantly lower the LDL level	9
10	Pineapple (*Ananas comosus*)	Bromelain, coumaric acid, ellagic acid, ascorbic acid	High cholesterol diet fed rats.	Through an improvement in hepatic cholesterol metabolism, pineapple fruit consumption can treat fatty liver and safeguard the vascular endothelium in diet-induced hypercholesterolaemia.	10
11	Turmeric (*Curcuma longa*)	curcumin	Hypercholesterolemic rabbits	Inhibits LDL oxidation, hypocholesterolemic effects in animals	11
12	Hibiscus(*Hibiscus rosa-sinensis)*	polyphenols	High fat diet induced rabbits	Reduce the production of foam cells, oxidised low-density lipoprotein, and oxidative damage	12

				to endothelial cells.	
13	Black pepper *(piper nigrum*)	Piperine	rat fed with high-fat diet	Piperine has antihypertensive and antithrombotic properties, may reduce myocardial ischemia, cardiac damage, and cardiac fibrosis, and may prevent arterial stenosis by reducing the proliferation of vascular smooth muscle cells.	13
14	Cinnamon(*cinnamomum vrerum)*	cinnamaldehyde	Streptozotocin-induced diabetic rats	The control of ERK1/2 activity in macrophages, prevented the production of CD36 and scavenger receptor class A (SRA), as well as acetyl LDL absorption.	14
15	Chili pepper(*Capsicum annuum*)	Capsaicin	High fat diet induced mice	Diminish plaque development in ApoE/ animals fed an HFD through the PPAR/LXRa pathway.	15
16	Anise (*Pimpinella anisum)*	Flavonoids and polyphenols	aniseed-treated diabetes patients	Decreased blood glucose, lipid profile, lipid peroxidation and protein oxidation in aniseed-treated diabetes patients.	16
17	Clove *(*Syzygium aromaticum)	Eugenol	High fat diet induced diabetic rats	Lowered the production of IL-1, IL-6, and IL-10, three pro-inflammatory cytokines, Reduces lipid level.	17
18	Saffron (*crocus sativus)*	Crocine, carotenoid	High fat diet induced rat/mice	Prevented the development of glycation and oxidation products, plaque, and inflammation in diabetic atherosclerotic rats.	18

19	Star anise (*Illicium verum)*	Trans-anethole [1-methoxy-4-(1-propenyl) benzene]	High fat diet induced *ApoE*$^{-/-}$ mice	Impede the development of atherosclerotic plaque	19
20	Tarragon(*Artemisia dracunculus*)	Isothiocynates, monoterpenes	Coated microplate wells with a combination of Laminin and collagens as two important adhesion proteins.	Exhibit anticoagulant action that inhibits the adhesion, aggregation, and secretion of platelets.	20
21	Ginkgo *(ginkgo biloba)*	Flavonids , terpenoids	High fat diet induced rabbits	GBE-mediated prevention of atherosclerosis is indicated by the GBE treatment's suppression of Cx43 expression.	21
22	Cornifructus *(Cornus officinalis)*	Polysaccharide fructus corni-1 and polysaccharide fructus corni-2	Apolipoprotein E-deficient (*ApoE*$^{-/-}$) mice fed high-fat diet	In ApoE/ animals fed an HFD, PFC-2 enhanced superoxide dismutase activity, increased serum levels of low-density lipoprotein cholesterol, total cholesterol, triglycerides, and malondialdehyde, and decreased the amount of lipid and macrophages in the aortic sinus plaque.	22
23	Black chokeberry (*Aronia melanocarpa)*	polyphenols	Culture medium containing Caco-2 (Human colorectal adenocarcinoma cell)	Reduced expression of FAS, ABCA1, HMG-CoA reductase, and ACOX1	23

24	Berberine(*Berberis aristata*)	Isoquinoline alkaloid	ApoE$^{-/-}$ mice fed a western-type diet	The vascular injury is brought on by EC dysfunction, and abnormal VSMC proliferation, migration, and apoptosis result in media thickening. In addition, blood monocytes cross the endothelial barrier and migrate to the intima to bring about a number of inflammatory reactions that aid in vascular remodelling.	24
25	Black hawthorn (*Crataegus pentaegyna*)	polyphenols, oligomeric procyanidins, and flavonoids.	Hypercholesterolemic rats	higher expression PPAR, LXR, and ABCA1	25
26	Bitter melon*(Momordica charantia)*	Triterpenes,phenolic compounds	ApoeE-/- mice	Reduces atherosclerotic plaque area, decreases serum soluble vascular cell adhesion molecule(VCAM) -1, P-selectin levels,MCP-1,IL-6 in aorta	26
27	Bamboo*(Sasa borealis)*	Anthraquinones,tannins, phenolics, glycosides, flavonoids, and phenolics.	Healthy young women with diet containing 25g of cellulose.	Serum total cholesterol, low-density lipoprotein cholesterol, and the atherogenic index were decreased	27
28	Arjuna tree (*terminalia arjuna*)	Flavons and tannins	High fat diet induced rabbits	Reduces the levels of TC, LDL, and TG while increasing HDL and reducing atherosclerotic lesion in the aorta	28
29	Fenugreek(*Trigonella foenum-graecum*)	alkaloids, flavonoids, saponins, mucilages(Galactomannan)	High cholesterol diet induced rabbits	Galactomannan, a component of fenugreek mucilage, has a hypolipidemic impact.	29
30	Peas *(pisum sativum)*	b-sitosterol	Swiss albino mice fed with standard diet	Possess thrombolytic	30

				activity; Reduced plasma total and LDL cholesterol and hepatic esterified cholesterol	

ApoE−/−: Apolipoprotein E-deficient CIMT: carotid intima-media thickness; LDL: Low density lipoprotein; ABCA1: ATP-binding cassette transporter, LXRα: Liver X receptor α; PPARs: Peroxisome proliferator-activated receptor; VCAM: vascular cell adhesion molecule; MCP: monocyte chemoattractant protein; IL: interlukin; LDL-C: low-density lipoprotein cholesterol; FG: Fasting glucose; hbA1C: Glycosylated haemoglobin 2hPPG: 2 h postprandial glucose TC: Total cholesterol; EC: Endothelial cells; VSMC: Vascular smooth muscle cells.

Supplemental Dietary fibre for atherosclerosis

The gut bacteria in the colon can ferment dietary fibre to create a range of short chain fatty acids with anti-atherogenic effects. A crucial short chain fatty acid called butyrate is formed during the fermentation of fibre and has been demonstrated to reduce inflammation.(31) Lipopolysaccharide-stimulated murine macrophages treated with butyrate produced less pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-, and less nitric oxide. Additionally, butyrate treatment of HUVEC for 24 hours boosted ICAM-1 expression but had no effect on VCAM-1 expression.(32) However, preincubation with butyrate reduced the amount of VCAM-1 that was expressed when TNF- was present, and this reduced the adherence of monocytes to endothelial cells.

The advantages of butyrate in treating atherosclerosis have also been shown in in vivo experiments. Comparatively to control mice, ApoE-deficient animals fed a chow diet supplemented with 1% butyrate for 10 weeks developed smaller and more stable lesions.(33) Due to decreased monocyte and macrophage migration to the plaque site and decreased expression of VCAM-1 and MCP-1 in the lesion, lesions were reduced by around 50%. Additionally, compared to the control mice, the lesions in the butyrate-supplemented mice contained more ECM, which is a sign of improved plaque stability.

Effective factors on atherosclerosis

Vitamin C:

Ascorbic acid, often known as vitamin C, is a water-soluble antioxidant that, in addition to scavenging ROS free radicals, also triggers the cycle of additional antioxidants including vitamin E and urate. Therefore, it is possible that using these two antioxidants will avoid the side effects of atherosclerosis and vascular disease. (34)

Vitamin E:

Because it is fat-soluble, vitamin E, or alpha-tocopherol, has been shown in a study on seminiferous tubules to be able to stop ROS from damaging sperm parameters. Because the tocopherol molecule can prevent two lipid peroxyl radicals from initiating two possible peroxidation chain reactions as a volatile antioxidant of the chain. It can stop the progression of atherosclerosis and cardiovascular disease's side effects (35)

Acids:

By binding to food minerals like iron and zinc and obstructing gastrointestinal absorption, reducing acids can have adverse effects on food. These include the phytic acid found in barley, grains, corn, and vegetables; the oxalic acid found in cocoa; the tannins found in tea, beans, and cabbage.

It is important to use these foods, which are strong sources of antioxidants and have a number of health benefits, to treat and prevent cardiovascular disease. However, these acids should be consumed less frequently when meat and diets high in zinc and iron are present. Dietary deficiencies in calcium and iron are caused by consuming too much meat, while phytic acid is absorbed more readily when cereals are consumed.(36)

Uric acid:

One protective factor against oxidative stress is uric acid. The antioxidant effects of serum uric acid help to scavenge and trap free radicals in human serum. Vascular dilatation increases and peroxynitrite-induced oxidative stress reduces because uric acid works with peroxynitrite to produce stable nitric oxide.(37)

Bacteria:

Involvement in the cell membrane, oxidation of the host cell membrane, production of oxygen free radicals and damage to the cell membrane, occasionally induction of apoptosis and increase in oxidation of lipids and cholesterol in the atherosclerotic plaque are all ways that certain bacteria and viruses, including Chlamydia pneumonia and Helicobacter pylori, and atherosclerosis, contribute to the development of atherosclerosis. (38)

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