Review Article

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Natural bioactive components to inhibit endothelial dysfunction in atherosclerosis

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To recapitulate the reports on antioxidants from herbal sources that can battle oxidative stress and help combat the damage that takes place due to reactive oxygen species. This study strives to connect the finding and examination done for the management of endothelial dysfunction using antioxidants as a modern therapy. Endothelial dysfunction was ascertained to be the underlying cause of cardiovascular diseases like stroke, and hypertension. Since endothelial cells serve a crucial role in the maintenance of patent, functional capillaries, changes to endothelial cells and the vasculature are crucial to the pathogenesis of a wide range of the most terrible human diseases. Antioxidants found in herbal plants have been proven effective in the long run. Antioxidants have demonstrated to surge the effect of superoxide dismutase that helps destroy the superoxide anions. Further, pigments present in herbal plants such as anthocyanins, lycopene, and naringin help scavenge the free radicals. This report is a critical analysis of the role of oxidative stress in the dysfunction of the endothelium and outlines ongoing studies and examinations done on the management of endothelial dysfunction by utilizing herbal agents.

Introduction

Endothelial dysfunction is the most predominant and critical type of non-obstructive coronary artery disease (CAD) that causes the myocardium to constrict (narrow) instead of dilating (opening). There are no heart artery blockages in the case of endothelial dysfunction, but the large blood vessels on heart valves constrict instead.[1] The leading cause of death and disability in most developed countries is cardiovascular disease; alongside endothelial dysfunction is the first sign of its development. This condition is more prominent in women than in men.[1]

The endothelium plays a substantial role in maintaining vascular tone, hemostasis, thrombosis, and redox balance within the arterial wall. Also, it act as and also acts as a vasodilators, vasoconstrictors, pro-coagulants, and anticoagulants, inflammatory and anti-inflammatory, fibrinolytic and antifibrinolytics, oxidizing, and anti-oxidizing agents. It works by synthesizing and releasing various factor that relaxes endothelium, including vasodilator prostaglandins, NO, endothelium-dependent hyperpolarization factors, and endothelium-derived contracting factors. Endothelial dysfunction caused by irregular production or action of these relaxing mediators is essential for maintaining cardiovascular control and function.[2]

The endothelium plays a crucial role in the pathogenesis of many diseases and cardiovascular problems, such as atherosclerosis, cardiomyopathies, and systemic and pulmonary hypertension.[3] Endothelial dysfunction can be due to a non-adaptive functional phenotype. Epidemiological investigations have shown the relationship between specific elements and endothelial dysfunction.[4,5]

At the time of any cellular function, the human body is under constant stress that produces reactive oxygen species (ROS) (e.g., hydroxyl radicals, hydrogen peroxide and, superoxide radicals) due to uncoupled nitric oxide syntheses, NADPH oxidases and xanthine oxidase, etc. If this overburden is not combated on time, it will prompt to damage the endothelial cells. Oxidative damages are triggered

Keywords: Endothelial Dysfunction, Vascular Homeostasis, ROS, NADPH oxidase, Superoxide dismutase, Oxidative stress.

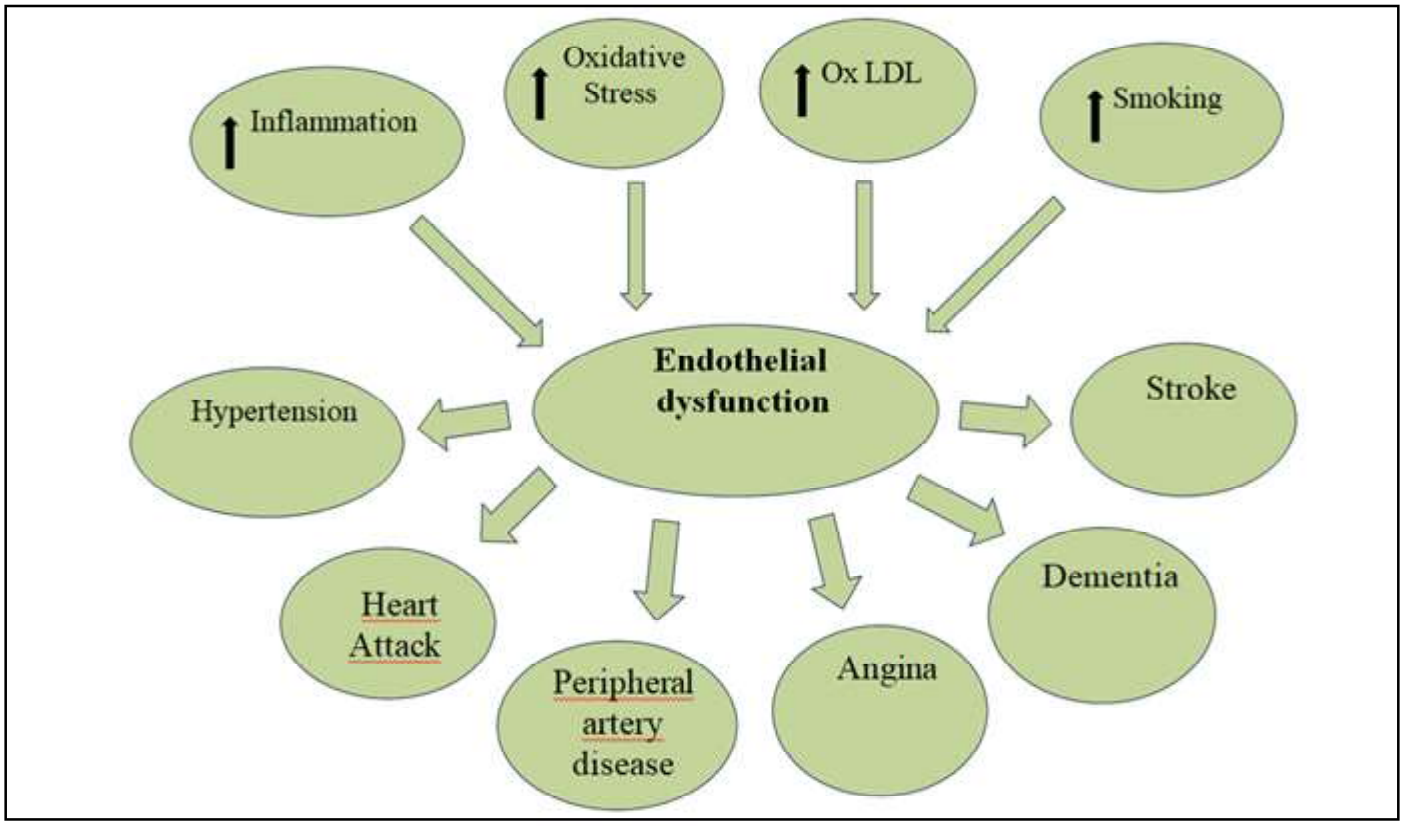

Figure 1. Underline representation of Endothelial Dysfunction. Increased Inflammation, Oxidative stress, Ox LDL, Smoking are the major causes that could commence to Endothelial dysfunction. Any damage to the endothelium cellline will lead to conditions such as Hypertension, Heart attack, Peripheral artery disease, Angina, Dementia, and Stroke.

by ROS that could further attack biomolecules such as lipids, proteins, and DNA.[6] ROS such as superoxide anion, singlet oxygen, hydroxyl, and hydrogen peroxide (H_2O_2) are frequently formed in biological reactions in the cellular system. They are crucial second messengers within the cells. ROS can directly impact vascular function and change the vascular tone by altering the availability of NO, and its signaling. Often the ROS generation and the antioxidant defense system are the primary cause of endothelial dysfunction, which further leads to vascular damage in both metabolic and atherosclerotic diseases.[7] The antioxidant mechanism present in our cellular system keeps a check on excessive ROS. It also helps maintain the free radicals and lipid peroxides, which could lead to endothelial dysfunction if not taken care of.[8] Various agents like E- selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) cause cellular adhesion, while interleukin-1, tumor necrosis factor-α and interferon-γ are major risk factors for endothelial damage. Antioxidant agents are substances that neutralizes ROS, prevent oxidation, and protect any cellular damage. Several plants species are found to have antioxidant chemical or molecules for example, curcumin, carotenoids, gingerols.[9,10] They are also widely present in edible microfungi, cereal, grains, microalgae.[11]

Several studies have evaluated that natural medication is essential for health care and are rich in antioxidant property. They have this protective action against many chronic diseases.[12] Bioactive components present in curcumin, garlic, naringin and ginger have been shown to have an antioxidant activity that is more convenient to use than modern medicines. These agents have no side effects improving the quality of life (Figure 1).

This article focuses on explaining the role of antioxidants in reducing ROS in a relationship with healthy endothelium and how it can help improve the health of the cardiovascular system. This article combines all the natural antioxidants and herbal sources chosen for an ongoing investigation to improve endothelial dysfunction.

The mechanism for endothelial dysfunction

Possible link between Oxidative stress and ROS

Oxidative stress happens due to the imbalance between the production and accumulation of reactive oxygen species that are thought to damage the cell endothelium. Superoxide radicals ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($^{\cdot}OH$),

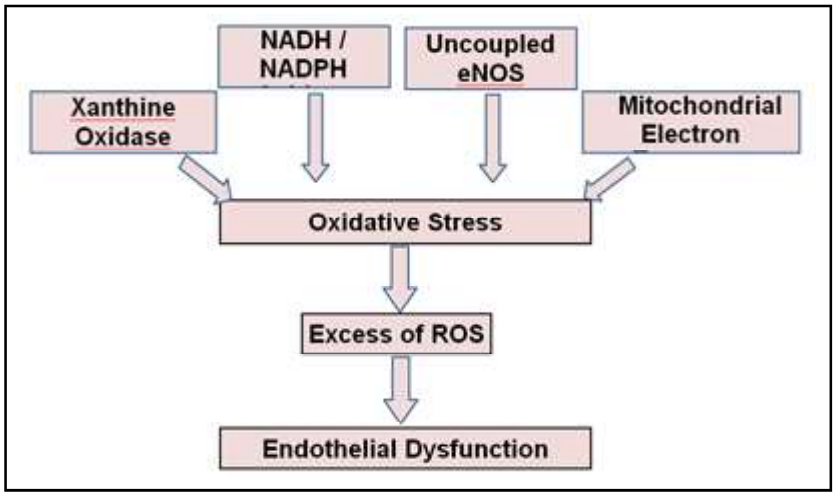

Figure 2. Represents the Factors playing a major part in Endothelial Dysfunction as Xanthine Oxidase, NADPH Oxidase, uncoupled eNOS, and Mitochondrial electron transport that follows to the Oxidative stress further could all kick start the production of Reactive oxygen species that could damage the Endothelium and commence the Endothelial Damage.

and singlet oxygen ($^1O_2$) are the reactive oxygen species that result due to oxidative stress. Oxidative stress damages the endothelium by disrupting the balance between vasoconstrictors and vasodilators. Endothelial dysfunction is a risk factor for cardiovascular disease, hypercholesterolemia, hypertension, etc.[13,14] Formation of Oxidative stress involves: (1). Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases–NADPH oxidase is a major source of ROS in the vessel wall and it also increases the production of $O_2^{\bullet-}$ by enzyme complex.[15-17] (2). Xanthine oxidase produces superoxide in endothelial cells and plays a crucial role in oxidative stress-induced regulation. (3). Mitochondrial electron transport generates the superoxides during oxidative phosphorylation that happens to be the primary source in the production of ROS and reactive nitrogen species (RNS). The disturbed mitochondrial function includes cellular dysfunction and impacts mitochondrial function, resulting in the excess generation of ROS (Figure 2).[19,20] Laboratory markers that can identify endothelial dysfunction are E- selectin, ICAM-1(intercellular adhesion molecule-1), VCAM-1(vascular cell adhesion molecule- 1) are activated by TNF-α which further causes NF-κB activation and plays a significant role in cell adhesion to the vascular endothelium that could further cause the endothelial dysfunction whereas interleukin-1, tumor necrosis factor-α, interferon-κ, monocyte chemoattractant protein- 1, tissue plasminogen activator, plasminogen activator inhibitor-1 and micro-albuminuria are involved in the inflammatory process and up-regulates the inflammatory cytokines.[21]

Role of ROS and SOD in endothelial dysfunction and its potential of medicinal plants

Endothelial dysfunction is the cause of the cardiac disorder, hypertension, and arterial disorder. Excess of ROS can lead to the activation of endothelial dysfunction. Reactive oxygen species have been shown to activate genes that control the formation of adhesion molecules and antioxidant enzymes which can further tip the balance toward vasoconstriction and oxidative stress. Studies have shown that a 50% increase in ROS production via NADPH oxidase can induce endothelial dysfunction. Animal studies have shown that NADPH oxidase is involved in O_2^- production.[22,23] Inactivation of endothelial nitric oxide synthase (eNOS) via decoupling of eNOS can reduce the amount of nitric oxide (NO) levels is thought to be the reason for the same.[24,25] In ordinary conditions, eNOS help oxidise L-arginine to L- citrulline to produce NO in endothelial cell. eNOS can produce O_2^- rather than NO when there is a deficiency of substrate l-arginine by uncoupling of eNOS.[26] Further micro-vesicles of endothelial origin have been shown to decrease nitric oxide (NO) production in vitro.[27,28]

ROS signaling plays a vital role in the mitigation of vascular diseases. Reactive oxygen species superoxide anion ($O_2^{\cdot-}$) are generated due to oxidative stress.[29] Endothelial cell lining of blood vessels produces ROS using membrane-bound NADPH oxidases[30] and xanthine oxidase.[31] Further, these agents interact with cell DNA, lipids, and protein, which leads to cell apoptosis and deregulation. Most of the time, excessive ROS is countered by the presence of superoxide dismutase (SOD) through dismutation, which, if not done, it can reduce NO and cause contraction of vascular smooth muscle [32,33] oxLDL when acted on endothelial cells to release IL-1 and TNF-α can also reduce the amount of nitric oxide that causes endothelial dysfunction. Superoxide dismutase is an enzyme in the body that helps to catalyze the dismutation of superoxide. It is thought to have an essential defense against oxidative stress in the body, it helps break down harmful oxygen molecules and prevents tissue damage. SOD is important in the modulation of oxidative stress. With the growing field of medicine and treatment, the definition of both has changed to make the quality of life better and improve the side effects caused by allopathic medicines. Herbs are plants with aromatic as well as medicinal

Table 1. List of examined bioacive herbal plants/compounds as mentioned.

Bioactive compounds	Source	Mechanism	Study Done on	Reference
Anthocyanin	Ribesnigrum	reduces the oxidative stress	Human	[94]
Anthocyanin/ delphinidins	Aristotelia chilensis	↓ ox LDL, ↓ expression of VCAM, ? endothelin-1	human umbilical vein endothelium	[39]
Anthocyanins	Fragaria vesca	↓ P-selectin and IL- 1β	Mice	[61]
Anthocyanins	Vaccinium corymbosum	Reduce oxidative stress	Human	[89]
Carotenoids	Diospyros kaki	↓ eNOS, Inhibit NFkB signaling	human umbilical vein endothelial cells	[95]
Catechin	Punica granatum	↓ macrophage oxidative stress	mice	[96]
Crocetin	Crocus sativus	↓ NFkB	Rabbit	[97]
Curcumin	Curcuma longa	↓ TNF-α, INF-γ, IL-1β	mice	[98]
DPPH/ Cymbopogoncitratus extract	Cymbopogon citratus	Inhibition of LPS-induced NF-κB activation.	human macrophageS	[58]
Epicatechin/ cocoa flavanol	Theobroma cacao	↓ ET-1 (endothelin-1),	Human	[99]
Ergothioneine	Agaricus bisporus	Inhibit adhesion molecule binding	Aortic endothelial cells	[100]
Flavonoid	Ginkgo biloba	↓ ROS level and eNOS expression	human umbilical vein endothelial cells (HUVECs)	[66]
Flavonoid	Spina ciaoleracea	↑NO Bioavailability	Human	[90]
Genipin	Gardenia jasminoides	Inhibit TNF-α	Human	[101]
Inorganic Nitrates	Beta vulgaris	Increases inorganic Nitrates (NO3?).	Healthy human	[45]
Lycopene	Solanum lycopersicum	Inhibit leukocyte adhesion, inhibition of NF-kB	Human	[80]
Naringenin / Flavanoid	Vitis vinifera	↓ oxidative stress	Human	[92]
Naringenin/Flavanone	Citrus sinensis	↑ NO bioavailability ↓ROS	Healthy human	[48]
Naringin	Citrus x paradisi	Inhibit NFkB signaling	Rat	[49]
Piceatannol	Passiflora edulis	↓ hsCRP, IL-6	Human	[67]
Polyphenols	Pistacia vera	↓TNF-α and IL-1β	Macrophage cell-line J774-A1	[70]

Quercetin	Allium cepa	↓ TNF-Alfa , ↓ NF-κB	Healthy Men	[38]
Rutin (RT) and Quercetin (QC)	Aristotelia chilensis	↑NO Bioavailability	Male Wistar rats	[40]
Terpenoids	Siegesbeckia pubescens	↓ NO in macrophage	RAW 264.7 macrophage	[102]

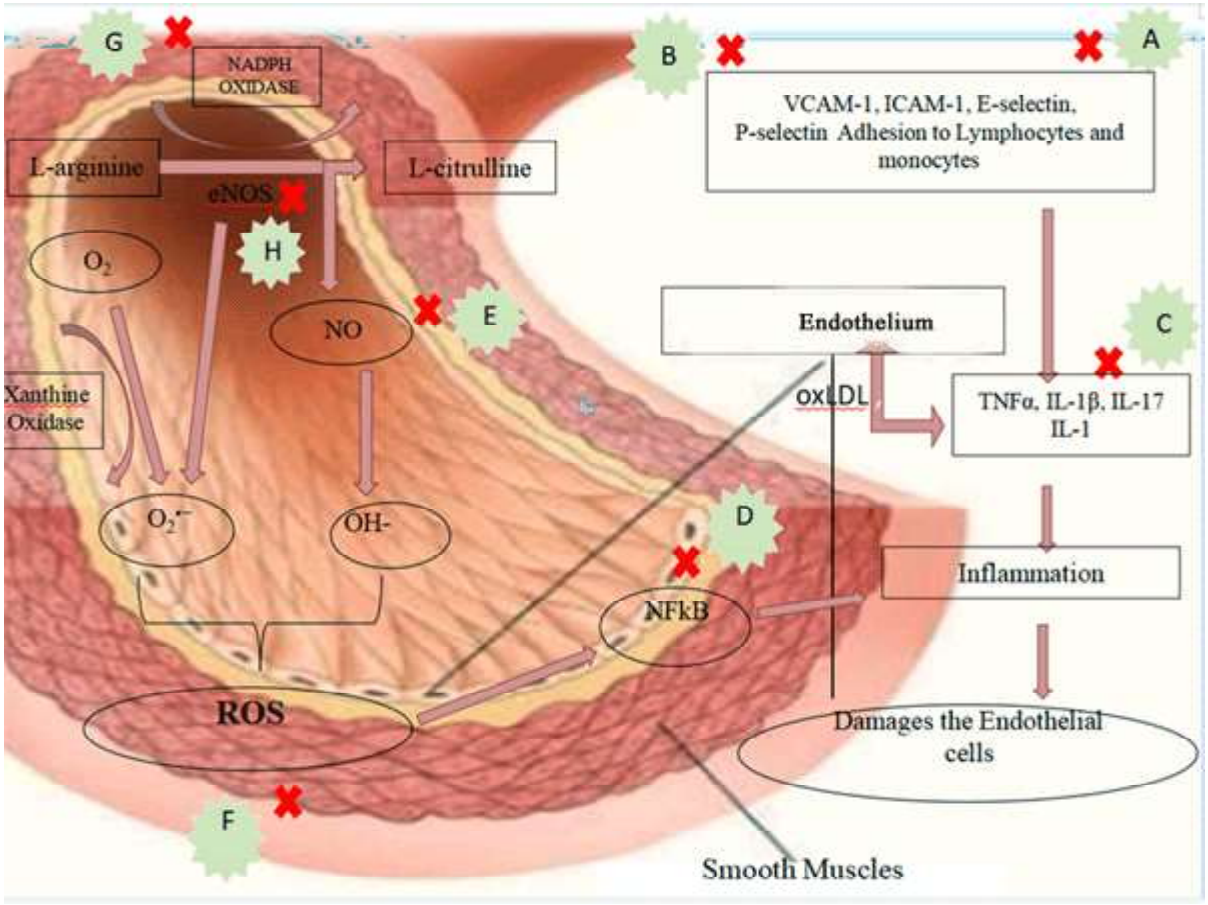

Figure 3. Represents the damage to the Endothelial cells, L-arginine is converted to L citrulline via the enzymatic action of endothelial NO synthase to produce NO. Decoupling to eNOS has shown to produce $O_2^{\cdot-}$ instead of NO. Also, O_2 present inside the Endothelium can be acted upon by Xanthine oxidase to potentiate $O_2^{\cdot-}$ through proteolysis. Decreased production of NO can manifest to impaired vasodilation/ or interrupt vasorelaxation. Oxidation of NO causes decreased Bioavailability of NO tips the balance to towards the increase in ROS. VCAM-1, ICAM-1, E-selectin, P- selectin are the adhesion molecules that prompt the attachment monocytes to the endothelium, which generates Cytokines. Peroxidation of LDL to OxLDL causes the oxidation of endothelium to generate TNFα, IL-1β, IL-17, IL-1 that cause Inflammation leading to Endothelial Dysfunction. Reactive oxygen species active NFkB that causes inflammation which further leads to Endothelial Dysfunction.

A. Inhibiting adhesion Molecules VCAM-1, ICAM-1, E-selectin and P-selectin using Anthocyanins, Adenosine and Ergothioneine.

B. Inhibit leukocyte adhesion to endothelium using Lycopene and Ergothioneine.

C. Inhibit pro-inflammatory molecules using Epicatechin, Catechin, Chlorogenic acid, Naringin, Anthocyanins and Piceatannol.

D. Inhibit NFkB signaling pathways and preventing inflammation, angiogenesis using Quercetin, Chlorogenic acid, Naringenin and Lycopene.

E. Reducing the levels of nitric (NO) bioavailability using Epicatechin, Catechin

F. Decrease reactive oxygen species (ROS) using Chlorogenic acid, Naringenin, Adenosine and Curcumin

G. Inhibit NADPH oxidase using Epicatechin.

H. Activate endothelial nitric oxide synthase (eNOS) using Triterpenic acid, Epigallocatechin gallate.

properties and many of those are rich in antioxidant properties as well.[34] Spices/ dried herbs have added flavor to our food for generations and help us fight several ailments. Studies have shown that several fruits, berries, vegetables, cereals, nuts, and pulses are good sources of antioxidants[34,35] (Figure 3). Brief about the natural plant and their bioactive constitutes which have been assessed for the suppression of endothelial dysfunction in atherosclerosis is given in Table 1. The table also enumerates the mechanism of action of compound with their pattern of examination.

Bioactive components from herbal plants effective in endothelial dysfunction

Allium Cepa

The main flavonoid antioxidant in *Allium cepa Linn* (Onion) is rutin and quercetin which are given chronically as quercetin-3-glucoside (51 mg). It has been shown to improve endothelial inflammation. [36,37] It acts as a free radical scavenger. Quercetin in vitro studies using different cell lines shows the inhibition of lipopolysaccharide (LPS)-induced tumor necrosis factor-α production by the prevention of TNF-α from directly activating nuclear factor-κB(NF-κB), it also reduces systolic blood pressure via reducing oxidized LDL(oxLDL). Other activities of quercetin are that it acts via affecting immunity and inflammation through its activity on leukocytes and by targeting intracellular signaling kinases.[37,38] The oxidant markers—nitrate (NO_3^-), nitrogen dioxide (NO_2), immunological markers interleukin (IL)-4, and immunoglobulin E (IgE) are much higher in *Allium cepa*.

Aristotelia Chilensis

Maqui (*Aristotelia chilensis*) is a bioactive compound-Anthocyanins. Anthocyanin/ Delphinidin (50 µM) shows potent antioxidant activity, and it works by reducing the oxidative stress through the Nrf2 pathway that reduces the expression of Endothelin-1 that further causes molecule adhesion and vasoconstriction via ICAM & VCAM.[39,40] Studies also show that anthocyanins can cause an increase in endothelial nitric oxide (NO) levels via the modulation of eNOS (endothelial NO synthase). It also acts by preventing nitric oxide oxidative damage and radical-induced NO conversion, which is caused NADPH oxidase. Rutin and Quercetin are other flavonoids present in *Aristotelia chilensis* that reduce NO availability and oxidative stress.[41]

Agaricus Bisporus

The bioactive compound in *Agaricus bisporus* is ergothioneine. Increased expression of adhesion molecules leads to further binding of monocyte to endothelial cells which further ignite the production of cytokines and inflammatory components. Ergothioneine interferes with the adhesion molecules' expression; it reduces the expression of E-selectin, VCAM -1, and ICAM-1. Ergothioneine has shown to be observed by endothelium *via* the Type 1 organic cation transporter, it protects the vessels from endothelial dysfunction.[42]

Beta Vulgaris

Beetroot (*Beta vulgaris*), also known as sugar beet is a rich source of inorganic Nitrates (NO_3^-). Beta vulgaris act by conversion of nitrate to nitrite (NO_3^- to NO_2^-) and further to NO by either enzymatic or non-enzymatic mechanisms of nitrate reductases (i.e., xanthine oxidase) which further reduces the deterioration of endothelial function by its feature of vascular homeostasis, potent dilator effect.[43,44] A randomized control trial was done on 15 adults, finding presented beetroot juice elevated the level of (NO_3^-) in plasma and a significant improvement in endothelial function.[45]

Citrus Sinensis

Oranges (*Citrus sinensis*) have flavanone compound Naringenin that shows its activity via regulating oxidative stress and by reducing the level of ROS via the pathways like MAPK and NF-κB.[46] Administration of NAR (100 mg/kg/day) for 6 months to mice leads to a marked reduction of reactive oxygen species. They are rich sources of Vitamin C, fiber, and many nutrients, including phenolic, and flavonoids which are also good antioxidant agents.[47,48] Several studies show that seed oil from oranges is used as a special diet since they contain relatively high amounts of antioxidants and bioactive compounds.[46]

Citrus Paradise

Grapefruit (*Citrus x paradisi*) is the most exotic fruit of all they have high antioxidants presence as naringin and naringenin(100 mg/kg) enhance NO bioavailability via increased eNOS activity and decreased NO inactivated to peroxynitrite.[49] Naringin is a flavonoid and has pharmacological activities, including free-radical scavenging and antioxidant properties; it reduces oxidative stress by decreasing ROS via pathway regulation MAPK/NF-κB. Naringenin helps reduce the infiltration of the inflammatory cells and oxidative stress and minimizes the plasma lipid concentration.[50]

Crocus Sativus

Crocus flower (*Crocus sativus*) is rich in natural

dicarboxylic acid carotenoid. Saffron (*Crocus sativus L.*) and its main constituents, i.e., crocin and crocetin, are natural carotenoid compounds, it has been reported for a wide spectrum of properties including anti-inflammatory, and anti-oxidative.[51] Crocetin was studied for 14 days on the induced vascular endothelial growth factor (VEGF) of fibroblast. Crocetin shows its effects by increasing NO bioavailability by up-regulating eNOS. Crocin and Crocetin may also suppress the activation of pro-inflammatory pathways via the nuclear factor kappa-B pathway.[52,53]

Curcuma Longa L.

Turmeric (*Curcuma longa L*) is a ginger family herb with the bioactive compound curcumin, curcuminoids and terpenoids. The antioxidant properties of curcumin have been known for ages it prevents endothelial dysfunction by inhibition of superoxides. Some studies have shown immunomodulatory action of curcumin happens due to— IL- 1β, and IL - 4. Curcumin (150 mg/kg/day for 8 weeks in mice) has shown its action via the action of extracellular signal regulated kinases (ERK), mitogen-activated protein kinase (MAPK) pathways to reduce TNF-α and Nrf2.[54,55] Curcumin has shown a marked decrease in TNF-α, INF-γ, IL-1β, and IL-6 due to inhibition of NF-κB.[56]

Cymbopogon Citratus

Lemongrass (*Cymbopogon citratus*) is one of the traditional essential oils that has been widely used. The antioxidant potential of *C. citratus* leaves is due to DPPH (1,1-diphenyl-2- picrylhydrazyl) acting as a radical scavenger. Nitric oxide demonstrates its scavenging abilities through the scavenging of superoxide anions and the inhibition of xanthine oxidase. Additionally, citral emerges as a prominent compound in this context.[57] Cymbopogon citratus extract is also found to have anti-inflammatory action via action on the NF-κB pathway which helps reduce the production of NO.[58]

Diospyros Kaki

Persimmon extract (*Diospyros kaki*), also known as Shi Ye (in Chinese) has a long history as Chinese traditional medicine. Diospyros kaki is rich in antioxidants such as ascorbic acid, carotenoids, and various polyphenols, including tannins. Carotenoids can stimulate the proliferation of B- and T-lymphocytes, the activity of macrophages and cytotoxic T-cells, effector T-cell function, and the production of cytokines. It shows its action by the inhibition of NO production in macrophages. It also decreases the expression of eNOS and has an anti-inflammatory effect. It prevents the damage of human endothelial cells via activation of eNOS and reduction in ET-1 secretion.[59,60]

Fragaria Vesca

Strawberries (*Fragaria vesca*) contain anthocyanins as an active compound. It has been shown to reduce the P-selectin expression and decrease IL- 1β. Studies with Fragaria vesca (0.1–1mg/ml) fed mice have shown a significant decrease in inflammatory molecules in the endothelial cells. Phenolic compounds in strawberries are famously known for their anti-inflammatory action which is achieved by inhibiting the NF-κB pathway and by stimulating Nrf2. Other studies show that biological activities are very well extended to other pathways that help in cell survival and metabolism.[61,62]

Gardenia Jasminoides

Fruits of gardenia (*Gardenia jasminoides*) are grown in multiple regions in China. It is used worldwide as an essential herbal medicine. It contains almost 16 bioactive components; the main bioactive compound is genipin (aglycone of iridoid glycoside), geniposide. Genipin affects vascular endothelial growth factor (VEGF) and increases NO bioavailability via eNOS phosphorylation. The novel anti-inflammatory and pharmacological action of genipin are by inhibiting inducible nitric oxide synthase (iNOS).[63] Studies have shown that genipin inhibits the expression of induced VCAM-1 (vascular cell adhesion molecule-1) protein in TNF-α.[64]

Ginkgo Biloba

Ginkgo biloba is a medicinal plant with excellent antioxidant properties. It is rich in flavonoids and terpenoids. Ginkgo biloba inhibits P-selectin, NADPH oxidase enzyme, and a potent xanthine oxidase (XO) inhibitor also has a bioactive protective effect. The flavonoid in *Ginkgo biloba* has been shown to improve vascular health and reduce inflammation and oxidative stress in the endothelial.[65,66] *Ginkgo biloba* GBE50 (25 micron/ml) has decreased ROS and eNOS expression in human umbilical vein endothelial cells (HUVECs) when interfered with by hypoxia.

Passiflora Edulis

Passion fruit (*Passiflora edulis*) seeds contain significant amounts of polyphenolic compounds, namely piceatannol and scirpusin B. These compounds exhibit antioxidant activity and exert a vasodilator effect. The increase in NO explains the effect of passion fruit that further reduces CVD risk. Piceatannol (20 mg/day)/8 weeks has shown a decrease—C-reactive protein (hsCRP), biological

antioxidant potential (BAP), interleukin-6 (IL-6), diacron reactive oxygen metabolite (dROM), with increased eNOS expression. A similar study with passion fruit skin shows positive results as a potential source of antioxidants. Several studies have reported that pectin reduces the infiltration of neutrophils and TNF-α.[67,68]

Pistacia Vera

Pistacia vera L. is the only species of pistacia genus producing edible nuts that contain a higher amount of polyphenols—catechin, cyanidin-3-O-galactoside, eriodictiol-7-O-glucoside, epicatechin, and gallic acid that explains its antioxidant effect.[69] The use of *Pistacia vera* decreased the levels of TNF-α and IL-1β in a concentration-dependent manner and also decreased ROS production.[70] Pistacia polyphenols exhibit their action via decreasing the regulation of iNOS expression, COX-2, and TNF-α.[71]

Punica Granatum

The pomegranate, *Punica granatum* L., is an ancient, mystical, unique fruit. Catechin is present in a rich amount of pomegranate (*Punica granatum*). It works by reducing macrophage oxidative stress, free radicals, and lipid peroxidation, and also prevents cell growth and induces apoptosis. Ellagitannins present in *Punica granatum* reduce macrophage oxidative stress.[72] Other compounds, such as oleanolic, ursolic, and gallic acid, increase NO production. Studies have shown pomegranate as a rich source of various phytochemicals responsible for its antioxidative and anti-inflammatory potential.[73,74]

Ribes Nigrum

Blackcurrant *Ribes nigrum* contains high polyphenols and flavonoids, specifically anthocyanins. Nitric oxide helps the vasodilatation of the epithelium via the expression of eNOS. Anthocyanins are studied to unregulate the eNOS activity.[75] Clinical trials on young smokers have shown that 50 mg of blackcurrant anthocyanin can attenuate acute endothelial dysfunction. It also reduces oxidative stress through the activation of the Nrf2 signaling pathway. The randomized controlled trial also shows endothelial function to improve via the reduction of oxidative stress.[76,77]

Solanum Lycopersicum

Tomato's scientific name is *Solanum lycopersicum*, a herbaceous plant which was probed against various life-sight-related disorders owing to various phytochemicals. It is an essential source of vitamin C, potassium, folic acid, and carotenoids, such as lycopene.[78] Lycopene is the main constituent of tomato, which has pro-inflammatory factors and reduces oxidative stress. The oleoresin in tomatoes interferes with the inflammatory signals in the endothelial cells by imitating inflammatory processes through a reduction in the endothelium.[79] Carotenoids help prevent the adhesion of molecules and act by inhibiting signalling through NF-κB, which helps reduce leukocyte adhesion to endothelium. An animal study on tomato extracts shows significant and dose-dependent anti-inflammatory; also, clinical trials have shown tomato extract intake a decrease in VCAM-1 and IL-13 levels.[80]

Siegesbeckia Pubescens

The roots of *Siegesbeckia pubescens* have been proven to show medicinal properties. Siegeskaurolic acid was found to significantly inhibit the production of nitric oxide (NO), prostaglandin E, and tumor necrosis factor-α (TNF-α). Active terpenoids act as anti-inflammatory agent. Siegeskaurolic acid (20 or 30 mg/kg/day, p.o.) decreases the NO level, has an anti-inflammatory effect, and is also found to inhibit iNOS, COX-2, and TNF-α via the downregulation of the nuclear factor-κ B (NF-κB) activation.[81,82]

Spinacia Oleracea

Spinach (*Spinacia oleracea L.*) is a widely functional food with a composition of flavonoids and nitrates; shown to enhance nitric oxide through different pathways, which can further enhance endothelial function and blood pressure. Furthermore, (i) It scavenges reactive oxygen species and prevents macromolecular oxidative damage, (ii) modulates expression and activity of genes involved in metabolism, proliferation, inflammation, and antioxidant defence, (iii) curbs food intake by inducing secretion of satiety hormones.[83,84]

Theobroma Cacao

The antioxidants effect of polyphenols and flavonols present in cocoa exert show their benefit in endothelium vasodilation and modulate inflammatory markers.[86,87] The Bioactive compound present in *Theobroma cacao* is epicatechin; it helps improve endothelial function by stimulating NO synthesis and also helps with reducing the effect of— arterial hypertension, proteinuria, and endothelial dysfunction. Epicatechin plays a significant role in reducing ET-1 (endothelin-1), systemic oxidative stress and inhibiting the activity of NADPH oxidase. Epicatechin cell membrane receptors act by eNOS activation.[85] The antioxidant effect of polyphenols and flavonols present in cocoa shows their benefit

in endothelium vasodilation and modulating inflammatory markers.[86,87]

Vaccinium Corymbosum

Blueberries (*Vaccinium corymbosum*) constitute a significant source of Anthocyanins and show a protective effect against reducing—oxidative stress and enhancing the endothelial functioning that is induced by a diet rich in cholesterol.[87] The bioactive compounds in berries contain mainly phenolic compounds, phenolic acids, flavonoids—anthocyanins and flavonols, tannins, and ascorbic acid. Blueberries also contain anthocyanins, flavonoids, and phenolic acids that help prevent oxidation. Studies have shown that consumption of blueberries has improved endothelial function by ↓ ox LDL, ↓ expression of VCAM, ↓ and endothelin-1via NO-cGMP activation in 8-12 weeks.[88,89]

Vitis Vinifera

Grape (*Vitis vinifera*) contains phenolic compounds, flavonoids and naringenin. In grape seeds, proanthocyanidins are the vast part of the polyphenolic extract that shows the vasodilatory effect, antioxidant activity and free radical scavenging effect.[90] The anti-inflammatory activity of proanthocyanidins includes modulation of the arachidonic acid via nuclear factor-κB that can help regulate oxidative stress by reducing ROS and NF-κB pathway.[91-93]

Conclusion

This article reviewed the herbal and bioactive components as a therapeutic and reliable source for treating endothelial dysfunction. This segment has tried to relate the effect of reactive oxygen species and oxidative stress on endothelial dysfunction in vivo or in vitro. A healthy diet with antioxidants-rich plants and vegetables could give robust disease management. ROS, including $O_2^{\cdot-}$, OH•, NO•, and $ONOO^-$ is generated due to modernized living conditions more often, and not enough antioxidants are present that can scavenge them, which might lead to preliminary damage of endothelium which can lead to additional ailments as we age. Free radicals in endothelium cells— NADPH oxidases, XO, and the eNOS that helps create ROS, which can prompt damage to the endothelial cells. Antioxidants in the herbal compounds help from the beginning of the damage and keep the reactive oxygen species in check. Several clinical studies have proven with time that antioxidants present in plants and vegetables help scavenge ROS and prevent damage. We have gone through several bioactive/phytochemicals that have helped fight the cause. The vast majority of research experiments or *in vitro* perception has proven the same and shown us the hope that phytochemicals and antioxidants present in fruits/vegetables/edible fungi might change the outcome of health in the long run. Much research has combined to show the potential impact of phytochemicals as a new treatment.

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