NATURAL PRODUCTS TARGETING NITRIC OXIDE AS A THERAPEUTIC STRATEGY FOR TREATMENT OF HYPERTENSION: A REVIEW

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Abstract

Hypertension remains a significant global health challenge, necessitating the exploration of novel therapeutic strategies. Nitric oxide (NO) signaling plays a pivotal role in blood pressure regulation, making it an attractive target for hypertension management. Natural products have garnered considerable attention for their potential to modulate NO signaling pathways and mitigate hypertension. This review provides a comprehensive overview of natural products targeting NO as a therapeutic strategy for hypertension treatment. We systematically examine the mechanisms by which natural compounds enhance NO bioavailability, promote vasodilation, and exert antihypertensive effects. Key natural products are evaluated for their efficacy in preclinical studies. Furthermore, we discuss the challenges and limitations associated with translating preclinical findings to clinical practice. Overall, this review highlights the promising role of natural products in modulating NO signaling pathways and offers insights into their potential as adjunctive therapies for hypertension management. Further research is warranted to elucidate the optimal dosing regimens, long-term effects, and potential drug interactions of natural compounds in diverse patient populations.

Keywords: Natural Products, Hypertension, Antihypertensive, Nitric Oxide Signalling

Introduction

Almost 1.13 billion people worldwide have hypertension, contributing nearly 7.1 million to the total deaths per year (1). The prevalence of hypertension varies across regions; being highest in the African continent (27%) than that in the Americas, which has the lowest prevalence (18%). Almost two-thirds of hypertensives live in low- and middle-income countries (1). The prevalence of hypertension may even be higher if all those with "masked" hypertension are detected and included. The name "masked hypertension" was proposed for those individuals with normal clinical blood pressure but raised blood pressure on either home blood pressure monitoring or ambulatory blood pressure monitoring (2, 3). If not adequately treated, masked hypertension carries similar adverse prognosis, both in terms of increased target organ damage and cardiovascular events, to that of other types of hypertension.

Clinically, the WHO defines hypertension as a systolic blood pressure (SBP) of above 140 mm Hg, or a diastolic blood pressure (DBP) of 90 mm Hg or more, after three repeated measurements at least 6 hours apart. End organ damage starts to increase significantly when blood pressure exceeds 140/90mm Hg. Untreated or sub-optimally controlled hypertension usually results in serious complications to major organs like the heart, brain, eyes and kidneys (4). Hypertensive patientsare at a greater risk of developing left ventricular hypertrophy, heart failure, myocardial infarction, haemorrhagic stroke, blindness, and renal disease (4, 5).

The cause of hypertension in 95% of the cases remains unknown (idiopathic/essential/primary), while in less than 5% it is due to secondary causes that include endocrine diseases, renal diseases, and drugs (6). Essential hypertension is a heterogenic entity, involving multiple and highly complex mechanisms, including activation of the renin-angiotensin-aldosterone system, sympathetic overdrive, enhanced renal tubule sodium reabsorption, oxidative stress-mediated vasoconstriction, and endothelial activation or dysfunction (7). Raised blood pressure in the obese is related to the high leptin levels that are usually present in the obese. Leptin-induced increase in blood pressure is associated with raised levels of endothelin-1 (ET-1), intracellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM) (8-10).

Conventional management of hypertension currently includes the use of diuretics, aldosterone inhibitors, renin inhibitors, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, alpha blockers, alpha agonists, beta-blockers, calcium channel blockers (CCBs) and vasodilators. The majority of the patients usually require two or more antihypertensive medications to achieve the target blood pressure. Many of these antihypertensives are also associated with side effects (11-14). This could compromise the compliance to treatment by the patients.

The cost of management of hypertension and its complications has become an enormous economic burden, running into billions of dollars worldwide (15). There is, therefore,a need to find ways to not only reduce the prevalence of hypertension but also ways to reduce t h e economic burden of its management at the same time. Preventative measures and cheaper and safer alternatives in the treatment and management of hypertension would certainly help to reduce the costs of management of hypertension (16).

The role and use of alternative and complimentary therapies for the management of hypertension continue to increase. Herbal remedies for the treatment of hypertension are being widely used throughout the world (17). Several factors may account for this wide scale use, including the high cost and side-effects associated with the conventional antihypertensive drugs. Herbal medicines are cheaper with presumably fewer undesired side effects (17-19). Besides this, it is also well-known that many plant extracts have, over the years, provided the starting point for synthesis of a large number of currently used pharmacological drugs. Plants contain thousands of bioactive components known to have significant therapeutic value. Numerous herbs have been investigated for their antihypertensive actions and the mechanism/s of action for some of these has also been identified (19, 20). There however, remain many newly discovered herbs and plants whose actions await verification (21, 22). This review focusses on herbs that have been shown to modulate nitric oxide signalling in their antihypertensive action.

Nitric oxide (NO) signalling and its role in hypertension

Nitric oxide synthase (NOS) is the enzyme required to catalyse the formation of nitric oxide (NO) from L-arginine, oxygen, the reduced form of nicotinamide-adenine-dinucleotide phosphate (NADPH), and a cofactor, tetrahydro-L-biopterin (BH4) (23, 24). Thus far, four isoforms of NOS have been identified and endothelial Nitric Oxide Synthase (eNOS)is abundantly expressed in the endothelium and is the main enzyme responsible for vasculature NO production (25).

In the vascular system, NO modulates vessel tone, diameter, and blood flow and exerts a potent antihypertensive effect (26). vascular endothelial growth factor (VEGF), bradykinin, and acetylcholine, are known to activate eNOS and lead to the production of NO causing vasodilation and a reduction in vascular resistance and blood pressure (27). NO diffuses from the endothelial cells into the vascular smooth muscle cells (VSMCs) and stimulates soluble guanylyl cyclase (sGC), which converts guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). cGMP triggers the activation of protein kinase G (PKG) and subsequently, phosphorylation of vasodilator-stimulated phosphoprotein). PKG mainly acts on myosin light chain phosphatase, which leads to dephosphorylation of the myosin light chains resulting in smooth muscle relaxation and vasodilatation (28). Besides vasculature relaxation, NO-cGMP signalling could also reduce blood pressure through the inhibition of renin secretion, which results in reduced angiotensin II production (29).

The role of NO in modulating vascular tone through vasorelaxation is crucial, and impaired NO-cGMP signalling has been recognised to be involved in the pathogenesis of hypertension (30). Impaired NO signalling can be due to the decreased bioavailability of NO associated with its interaction with superoxide. Likewise, decreased NO production due to reduced eNOS levels or uncoupling, reduced cGMP production by sGC, decreased PKG activity, and increased cGMP metabolism by PDE can directly affect the NO signalling cascade. It is important to note that NOS is responsible for the transfer of electrons from NADPH to the haem in the oxygenase domain (which is also the binding site for BH_4, oxygen, and L-arginine) where the electrons are used to reduced O_2 and oxidize L-arginine to L-citrulline and NO. However, when there is increased

oxidative stress, NO reacts with the abundant superoxide (O_2^-) forming peroxynitrite ($ONOO^-$), which oxidises BH_4 to BH_3 resulting in "eNOS uncoupling" and L-arginine depletion (25, 31, 32). Instead of producing NO, the uncoupled-eNOS produces mainly O_2^-, further enhancing the pre-existing oxidative stress. Peroxynitrite is a very powerful oxidant and a toxicant that can cause damage to the mitochondria leading to cell death. It is reported that BH_4 oxidation is increased by NADPH oxidase in salt-induced hypertension rat model (33).

Furthermore, increased expression of NADPH oxidase has been shown in spontaneously hypertensive (SHR) rats (25) while oral administration of BH_4 was able to attenuate hypertension in SHR (34). Depletion of L-arginine can be due to the action of arginase, an enzyme that converts L-arginine to L-ornithine and urea. The expression of arginase has been found to increase in several models of hypertensive rats (35, 36) and administration of arginase inhibitor lowers the blood pressure in SHR (37, 38). Similarly, L-arginine reduces the blood pressure of hypertensive individuals via increased production of NO when administered intravenously (39). Several animal studies have shown that genetically modified mice developed hypertension and premature aging of the vascular system. It is proposed that this involves NO-cGMP signalling impairment due to decreased eNOS expression and phosphorylation at Ser1177, increased reactive oxygen species (ROS) and cGMP-hydrolysing enzymes, PDE 1 and 5 activities (40-43). Mice lacking the eNOS gene are known to develop hypertension (44). Impairment in the nitric oxide synthesis pathway in patients with essential hypertension and their offspring suggests a role for NO in hypertension (45).

From the available information in the literature, there is sufficient evidence to suggest that the NO system is most likely involved in the pathogenesis of essential hypertension and modulation of the endogenous production of NO could provide another alternative in the management of hypertension. Nitric oxide (NO) signalling and its role in hypertension are summarized in Figure 1.

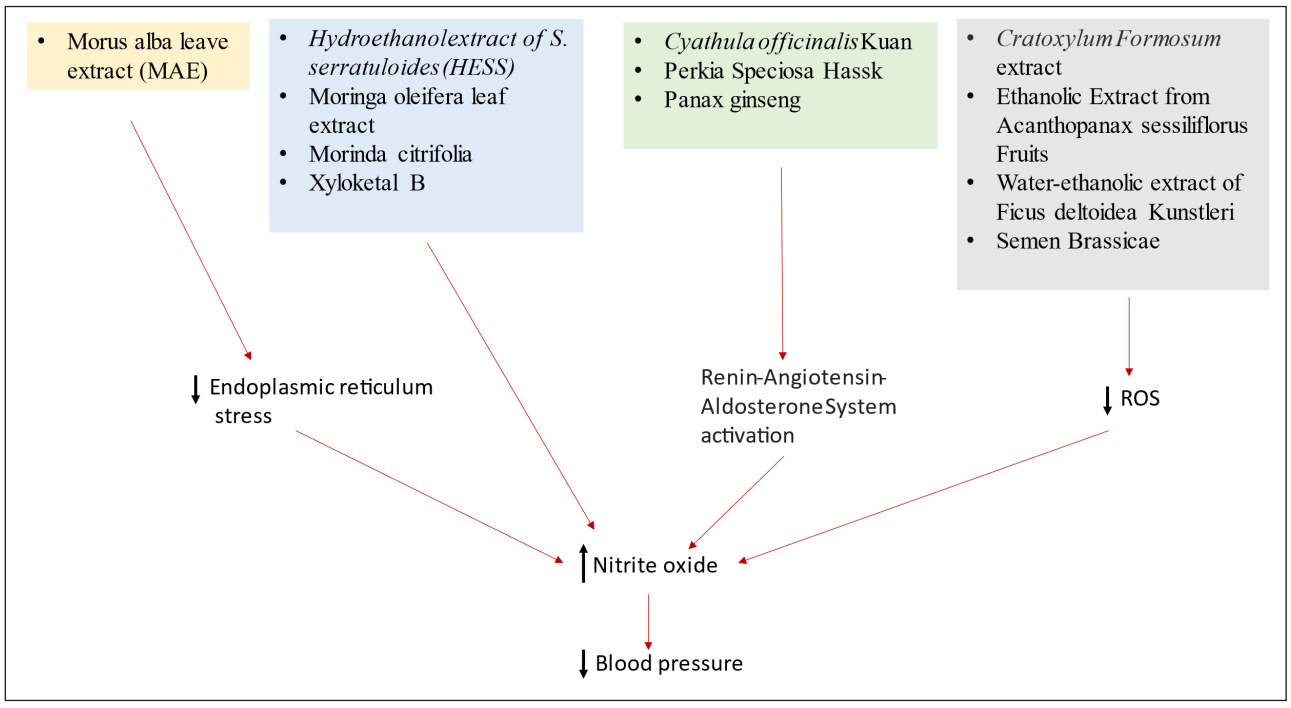

Figure 2: Graphical abstract showing the mechanism on how natural products modulating nitric oxide signalling for the treatment of Hypertension

Methodology

For this narrative review, a systematic search was conducted across multiple electronic databases including PubMed/MEDLINE, Embase, Scopus, Web of Science, and Google Scholar. The search strategy utilized a combination of keywords and MeSH terms related to hypertension, nitric oxide, natural products, and therapeutic strategies targeting blood pressure regulation. The keywords and MeSH terms included "hypertension," "blood pressure," "nitric oxide," "natural products," "phytochemicals," "herbal medicine," "plant extracts," "marine compounds," "therapeutic strategy," and "antihypertensive agents," among others.

The review encompassed articles published between January 2000 and January 2023 to capture the most recent advancements in the field of natural products targeting nitric oxide for hypertension treatment. Only articles written in the English language were included to ensure accessibility and comprehensiveness of the review.

Inclusion criteria for the review encompassed studies investigating the effects of natural products on nitric oxide signaling pathways specifically in the context of hypertension treatment. This included preclinical studies (both in vitro and in vivo) and clinical trials reporting outcomes related to blood pressure regulation, endothelial function, vascular health, and cardiovascular outcomes. Articles with available full-text articles and accessible abstracts were considered for inclusion.

Exclusion criteria were applied to studies not directly relevant to the topic of natural products targeting nitric oxide for hypertension treatment. This included studies focusing on synthetic drugs or interventions unrelated to natural products, articles published in languages other than English, and non-research articles such as case reports, letters, editorials, and conference abstracts.

The search strategy employed a systematic approach using Boolean operators and truncation to ensure comprehensive coverage of relevant literature. Duplicate articles were removed, and titles and abstracts were screened for relevance based on the inclusion and exclusion criteria. Full-text articles meeting the eligibility criteria were retrieved and assessed for data extraction and synthesis. Data were analyzed descriptively, and key findings were summarized to provide insights into the role of natural products in nitric oxide-mediated hypertension management.

The effects of natural products via modulation of NO signalling pathway in hypertension

a) *Senecio serratuloides*

Senecio serratuloides (S. serratuloides) is an Asteraceae with serrated leaves and tiny yellow flowers grown from a woody root or stem (46). *S. serratuloides* is a popular traditional medicine among people of Maputaland and Northern Kwazulu-Natal, South Africa used to treat a variety of illnesses (46, 47). Traditionally, this plant has been used extensively for respiratory infections (48) and for its wound-healing activities (49), which are believed to be related to its flavonoid and phenol contents (50). Antihypertensive effects of *S. serratuloides* was first reported by Tata et. al. (2019) in the N-Nitro-L-arginine methyl ester (L-NAME)-induced hypertension rat model. Chronic administration of L-NAME for 4 weeks reduced the NO bioavailability caused endothelial dysfunction, and increased blood pressure (51). Treatment with hydroethanol extract of *S. serratuloides (*HESS*)* at doses of 150 and 300 mg/kg significantly decreased systolic and diastolic blood pressures in a dose-dependant manner in these rats (51). Treatment with HESS at 300 mg/kg also significantly lowered low density lipoprotein cholesterol (LDL), very low-density lipoprotein (VLDL), and triglycerides (TG), while increasing the high-density lipoprotein cholesterol (HDL). HESS also prevented the L-NAME induced reduction in serum NO concentration, suggesting the involvement of NO. L-NAME treatment increased the concentration of LDL, which is known to interfere with eNOS activity. In normal conditions, eNOS is associated with cholesterol-enriched caveolae in the endothelial cells, where its activity can be carefully regulated. In hyperlipidaemia, LDL negatively affects the activity and sub-cellular distribution of eNOS, causing a decrease in NO bioavailability, while HDL causes activation of eNOS within the caveolae and, therefore, increasing NO generation.

HESS also prevented the deposition of collagen in cardiac tissue and lessened cardiomyocytes thickening induced by L-NAME, suggesting that HESS reduced cardiac fibrosis and hypertrophy of the heart respectively. Collectively, HESS showed antihypertensive, antihyperlipidemic, and cardioprotective effects in LNAME induced hypertensive rats, suggesting its potential as an antihypertensive drug that modulates the NO signalling pathway.

b) *Morus alba* Linn

Morus alba Linn or often refered as white mulberry or silk mulberry under the family of Moraceae (52). *Morus alba* Linn are mostly used to feed silkworms, but can be also eaten as a vegetable and utilised as cattle fodder (52). Numerous pharmacological studies demonstrated that *Morus alba* L. extracts (MAE) possesses antidiabetic (53), antimicrobial (54), anti-atherosclerosis (55), and anticancer activities (56). The most concentrated phenolic compound available in the extract is Rutin, followed by chlorogenic acid and flavonoid astragalin (52). Using spontaneously hypertensive rats (SHR), Carrizzo et al., showed for the first time that MAE reduced blood pressure and improved endothelial-dependent vasorelaxation of the resistance vessels in SHR rats in a dose dependant manner (57). However, MAE-induced vasorelaxation of the mesentery artery was absent in endothelium-stripped vessels or the presence of L-NAME.In addition, treatment with MAE up-regulated the PKR-like endoplasmic reticulum kinase (PERK) phosphorylation and heat shock protein 90 (HSP90), suggesting the site of these protein activation. Incubation with PERK inhibitor GSK2606414 and the HSP90 inhibitor SNX2112 with MAE abolished the HSP90 phosphorylation, resulting in the downregulation of eNOS phosphorylation. Similarly, MAE treatment also formed molecular complexes between eNOS and PERK/HSP90. These suggest that PERK and HSP90 as the most likely targets of MAE, revealing the beneficial action of two crucial proteins that act as stress sensors and chaperones thus leading to eNOS activation and endothelial-mediated vasorelaxation of resistant arteries (57).

c) *Moringa oleifera* Lam

Moringa oleifera Lam *(M.oleifera)* which under the family of Moringaceae family, is a tropical plant located at the south of the Himalayan Mountains, northern India (58). *Moringa oleifera* Lam extract has been reported to have pain-relieving (59), antioxidant, antihypertensive (60), anti-carcinogenic (61), anti-diabetic (62), hepatoprotective, and anti-microbial (58) activities. These have been attributed to the phytochemicals such as flavonoids or isothiocyanates found in the Moringa leaf (63). Intravenous administration

of aqueous extract of Moringa leaves (MOE) caused a significant rapid and dose-dependent reduction in mean arterial pressure (64). However, the protective effects of MOE on arterial blood pressure were absent in L-NAME-treated rats compared to the control, suggesting that the blood pressure-lowering effect of MOE was associated with NO-synthase function (64). Rats treated with MOE showed a dose-dependent relaxation in endothelium-intact mesenteric arterial beds that were pre-contracted with methoxamine, demonstrating that vasorelaxation induced by MOE was dependent on the endothelial function (64). Treatment with L-NAME significantly reduced MOE-induced relaxation in endothelium-intact arterial beds, but in contrast, indomethacin, which is an inhibitor of cyclooxygenase did not block the MOE-induced vasorelaxation (64). However, pre-incubation with sGC inhibitor, ODQ, attenuated the MOE-induced vasorelaxation. Human pulmonary artery endothelial cells (HPAECs) treated with MOE and ACh as positive control also showed up-regulation of NO synthesis, as measured by a tri-iodide based reductive ozone chemiluminescence. These results suggest the involvement of NOS-sGC dependent signalling in MOE-induced endothelium-dependent vasorelaxation in L-NAME-induced hypertensive rats (64).

d) *Morinda citrifolia* L. (Noni)

Morinda citrifolia L. (Noni), belonging to Rubiaceae family, is a medicinal tropical plant from Southeast Asia, Australasia, Pacific Islands, and Hawaii (65). Traditionally, its leaf is either consumed as a raw vegetable by various cultures globally or drinking the water in which its leaves have been boiled to improve postpartum health (66). In Malaysia, Noni is known as mengkudu and is mainly used in traditional medicine for the treatment of fever, cough, liver and kidney diseases, and internal bleeding in Malay population (67). The nutritional value of Noni is listed in the World Health Organization (WHO) and Food and Agriculture Organization (FAO) food composition table for East Asia and the Pacific Islands (65), as it contains a greater amount of *β*-carotene compared to other green leafy vegetables (68). Traditionally, Noni was believed to promote a wide range of medical health benefits, such as anticancer (69), anti-inflammatory (70), hypolipidemic (71), and hepatoprotective effects (65).

Two weeks of oral administration of Noni juice extract (NJE) to SHR/cp rats demonstrated a significant reduction in systolic and diastolic blood pressures (72). NO metabolite (nitrate and nitrite) excretion in the urine was threefold higher in (NJE) treated rats compared to that in the control rats. SHR/cp rats treated with (NJE) showed up-regulation of eNOS phosphorylation at Ser1177 and adenosine monophosphate-activated protein kinase (AMPK) phosphorylation in the aorta, compared to that in the controls. However, the vasorelaxation effect of Noni was abolished by the removal of the endothelium and by L-NAME. NJE treatment also significantly enhanced the NO level in human umbilical vein endothelial cells (HUVECs). In the same manner, as eNOS, NJE enhanced AMPK phosphorylation, but these effects were abolished by L-NAME and the AMPK inhibitor Compound C, suggesting that the NJE-induced vasodilatation involves AMPK pathway. In addition, NO production was suppressed by NJE when co-treated with CaMKKβ inhibitor, STO609, and Ca chelator BAPTA-AM, whereas the Sirt1 inhibitor EX527 did not inhibit the NJE-induced NO production in HUVECs. Ca2+ level in the cells was also elevated in NJE treated rats. These showed that NJE stimulates Calcium-Calmodulin signalling, which evokes the AMPK-eNOS pathway causing vasodilatation and reduction in blood pressure. LC–MS results and analysis from cellular effect of compounds on NO suggested that the biological property of NJE is contributed by deacetylasperulosidic acid, a major compound in NJE, which increases NO release. These findings provide evidence that NJE acts on the nitric oxide system and has the potential for use as a novel vascular endothelium-dependant therapy in hypertension (72).

e) *Xyloketal B (Xyl-B)*

Marine organisms are rich natural sources of novel bioactive materials with distinct structural features and biological activities (73). Xyloketal B (Xyl-B) is a novel marine compound isolated from a mangrove fungus, *Xylaria sp*. found around the South China Sea Coast (73). Extracts of Xyl-B have been shown to have a variety of biomedical activities including neuroprotection (74), antioxidant effects (75) and antioxidant (76), anti-glioma effects (77), and decreased atherosclerotic plaque formation in apolipoprotein E-deficient mice (78).

Xyl-B extract significantly attenuated the rises in systolic and diastolic blood pressures in 2-kidney-2-clip (2K2C) hypertensive rats (79). Xyl-B had greater vasorelaxant effect on KCl-induced vasoconstriction, endothelium-intact aortic rings than that in denuded rings. This effect was abolished in the presence of L-NAME suggesting that the vasorelaxant effects of Xyl-B are mediated via endothelium and possibly involving the nitric oxide system (80). Xyl-B also improved the vasorelaxant effect of acetylcholine (ACh) but not sodium nitroprusside (SNP). The inhibitory effect of Xyl-B on Phe-induced vasocontraction was reversed by methylene blue, a sGC inhibitor but not by indomethacin, PGI_2 inhibitor, suggesting that the anti-hypertensive effect of Xyl-B was mediating through the NO-sGC-cGMP pathway rather than PGI_2 (80). Xyl-B also elevates the bioactivity of endothelial eNOS in a dose- and time-dependent manner as well as increases the level of cGMP in co-cultured vascular smooth muscle cells (VSMC)-HUVECs, but not in mono-cultured VSMCs. Pre-incubation with Xyl-B significantly inhibited KCl-induced Ca^{2+} entry into smooth muscle cells *in vitro,* suggesting that Xyl-B's effects, also involve voltage-dependent Ca^{2+} channels (VDCCs), and ryanodine-induced vasoconstriction, implying its association with store-operated Ca^{2+} entry (SOCE). Collectively, these results show that Xyl-B has significant antihypertensive properties not only through the endothelial NO-sGC-cGMP pathway but also through smooth muscle calcium signalling, including VDCCs and SOCE (79, 80).

f) *Cratoxylum formosum* (CF)

Cratoxylum formosum (CF) is a commonly consumed traditional plant, usually eaten as a side dish or ingredient in food in Thailand (81). CF extract has been shown to have antioxidant and vessel-relaxing properties (82). It is also documented to have potent anticancer activity, particularly in cholangiocarcinoma (83), breast cancer (84) and liver cancer (85). Aqueous extract of CF has high levels of flavonoids, myricetin, and luteolin, as well as phenolic acids, syringic acid, protocatechuic acid, vanillic acid, and caffeic acid (83).

Potue et al. first reported the antihypertensive effects of CF extract (86). CF extract reversed L-NAME-induced increases in systolic blood pressure in rats (86). Compared to the normal group, CF extract also improved the endothelium-dependent vasorelaxation response to Ach. In addition, CF extract reduced the constrictor responses of the mesenteric vascular beds to sympathetic nerve stimulation in L-NAME-induced hypertensive rats (86). CF also attenuated aortic wall thickening in hypertensive rats (86). In addition, CF extract also significantly lowered reactive oxygen species production and plasma malondialdehyde (MDA) levels as well as raised plasma NOx compared to non-treated hypertensive rats. Moreover, CF extract supplementation reduced serum angiotensin-converting enzyme (ACE) activity and plasma Ang II levels in L-NAME hypertensive groups. Over-expressions of AT_1R protein, Akt, and STAT3 protein were downregulated by CF extract compared to L-NAME treated rats. In conclusion, extracts of CL have been shown to reduce blood pressure, endothelial dysfunction, decrease oxidative stress, enhance NO bioavailability, and inhibit the effects of ACE in L-NAME-induced hypertensive rats (86).

g) *Acanthopanax sessiliflorus*

Acanthopanax sessiliflorus (Rupr. & Maxim.) Seem., under the family of Araliaceae is found abundant in the Eastern region of Russia and Northeast Asian countries including Korea, Japan, and China (87). Traditionally, its root and stem are used for the management of rheumatoid arthritis (88), inflammation (89), and diabetes (90) while its fruits were reported to have antithrombotic and antiplatelet properties (91). Its fruits contain compounds such as chiisanoside, 22α-hydrochiisanoside, and aglycone (92, 93).

Jung et al. (90) demonstrated that ethanolic extract from *A. sessiliflorus* fruits (DHP1501) significantly facilitated endothelial NO production in a dose-dependent manner in HUVECs. In addition, DHP1501 exhibited electron passaging properties as demonstrated by 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2-azino-di-(3-ethylbenzthiazoline sulfonic acid) (ABTS), and oxygen radical absorption capacity (ORAC) assays. ROS accumulation induced by H_2O_2 in HUVECs was significantly attenuated by DHP1501 in CellROX and MitoSOX assays, suggesting its anti-oxidant activity. In porcine coronary artery rings, DHP1501 attenuated the contractile response to thromboxane mimetic U46619 in a dose-dependent manner. Oral administration of DHP1501 normalised SBP and DBP in SHR. DHP1501-administered rats also showed a reduction of serum renin and ACE concentration compared to the SHR group. DHP1501 was also found to enhance NO bioavailability via scavenging the free radical and inhibiting ACE activity, which subsequently led to relaxation of the blood vessels and reduction of blood pressure in SHR rats (90).

h) *Ficus deltoidea*

Ficus deltoidea (FD) belongs to the *Moraceae* family and is widely distributed throughout Malesia, a region that includes Malaysia, Thailand, and Indonesia (94). It is one of the many Malaysian herbal plants (95), consisting of 7 varieties including *var angustofolia, bilobate*, *intermedia, kunstleri, trengganuensis and montleyana* (96). Traditionally, the leaf is used to boost energy and as an herbal drink for beauty and health. Over the recent years, several researchers have attempted to investigate the medicinal or pharmacological properties of FD. *Ficus deltoidea* has been shown scientifically to possess anti-diabetic (97, 98), anti-oxidant (99, 100), wound healing (101) as well as anti-inflammatory properties (102).

The anti-hypertensive effect of FD *var kunstleri* (FDK) extract in SHR was reported recently (21). Oral administration of 1000 mg/kg of body weight of FDK leaf extract daily for 4 weeks, caused a significant reduction in blood pressure in SHR. This reduction in blood pressure was comparable to that in rats that received losartan. eNOS gene expression and its serum level were significantly higher in SHR receiving FDK extract, suggesting its potential role in enhancing the production of NO, a potent vasodilator by eNOS. Measurement of the total antioxidant capacity (TAC), of the FDK-treated SHR revealed higher antioxidant capacity compared to that in the control SHR. Examination of several other important genes in the antioxidant system revealed increased expression of mnSOD and FOXO3a in the kidneys of FDK-treated rats compared to the control. Additionally, rats treated with FDK had significantly lower angiotensin converting enzyme (ACE) activity and serum level of angiotensin I (Ang I), angiotensin II (ang II) and aldosterone when compared to the control hypertensive rats (21). Taken together, the anti-hypertensive effect of FDK extract involves upregulation of NO reduction of oxidative stress and a reduction in the renin-angiotensin-aldosterone system activity.

i) *Cyathula officinalis*

Cyathula officinalis Kuan (CO) is a species of Cyathula native belonging to the family of Amaranthaceae. It is native to China and Nepal and is also cultivated in Vietnam. It is often utilized as an emmenagogue, atonic, antiarthritic, anti-fertility, and diuretic agent. Additionally, it is also believed to fortify bones and muscles and improve circulation. Extract of CO has been shown to contain diverse compounds including palmitic acid, heterocyclic compounds, and phytoecdysteroids.

Zhao J et al. showed that CO when given to 12-week-old for 8 weeks deonstrated a significant reduction in their

blood pressure (103). The reduction in blood pressure was evident from as early as 2 weeks post-treatment. The serum level of NO was significantly higher in CO extract-treated SHR than in non-treated SHR. This corroborated with the increased gene transcription and protein level of eNOS in the aorta of and the carotids of CO-treated SHR; similar to that seen in enalapril-treated SHR. These findings appear to suggest that CO can increase not just the transcription of eNOS, but also enhance eNOS activity. In contrast, treatment with CO and enalapril resulted in reduced gene transcription of both ET-1 and AT1R in the aorta. ET-1 protein levels, but not the AT1R protein, in the aorta were significantly decreased following treatment with CO.

In the carotid, however, the transcription of both ET-1 and AT1R were significantly lower following treatment with CO. When investigating the effect of CO on arterial remodelling it was noticed that CO extract-treated SHR had a significantly lower thickness of the aorta's medial layer when compared to that in the controls. This suggested that *Cyathula officinalis* extract might also possess some anti-proliferative effects. Taken together, treatment of SHR with CO resulted in reduced blood pressure, inhibition of arterial remodelling, improvement in endothelial function as well as enhancement of the antioxidant system (104).

j) *Perkia Speciosa* Hassk

Parkia speciosa Hassk (PS) or stink bean from the family of Fabaceae is abundantly found in tropical regions such as Malaysia, Thailand, and Indonesia. In Malaysia, Singapore, and Indonesia, it is called "petai". The nutritional composition of the seed of PS includes protein, fats, carbohydrates, minerals, and fibers (105). PS is rich in phenolic compounds which can be found generally in all parts of the plant (106). Several other compounds can be found in the seeds of the PS such as terpenoids, alkaloids, and flavonoids (106). The bioactive potential of PS accounts for diverse health benefits such as anti-angiogenic and antioxidant properties (107) and antidiabetic properties (108).

Oral administration of 800 mg/kg of PS extract to SD rats has blunted the elevation of BP induced by L-NAME compared to the control group. Comparable effects in terms of BP reduction were seen in both PS extract group and the positive control group which received nicardipine. The serum level of the NO was higher in the PS extract group compared to those rats receiving L-NAME alone or L-NAME plus nicardipine, suggesting its role in enhancing the bioavailability of NO. Additionally, PS extract blunted the activity of the NADPH activity, preventing the formation of superoxide free radicals and promoting its antioxidant properties. In corroboration with that, cardiac lipid peroxidation content which was measured as thiobarbituric acid reactive sub-stance (TBARS) was found to be significantly lower in rats receiving PS extract in this study. This shows the role of PS in preventing the oxidative damage of lipids by ROS which will lead to cell damage or death. In addition to that, L-NAME-induced rats receiving PS extract had reduced ACE activity in the heart compared to the control. The same reduction was observed in rats receiving nicardipine. These findings suggested that the BP lowering effect of PS involved a few mechanisms which include restoration of plasma NO level, prevention of ROS production and activity as well as suppression of RAAS (109).

k) *Semen Brassicae*

Semen Brassicae, one of the popular Chinese Traditional Medicine is also known as the seed of *Brassica alba (L)* Boiss. It comes from the family of Brassicaceae. It is used traditionally for phlegm, pain, and swelling. Scientifically, this plant possesses an anti-hepatic fibrosis effect related to the TGF beta SMAD pathway and reduction of extracellular matrix deposition (110).

A recent study demonstrated the blood pressure lowering effect of water-decocted semen brassicae extract in SHR when given for 8 weeks. In this study, SHR receiving 3 doses of semen brassicae extract, ranging from 0.5 – 2.0 g/kg, via oral gavage daily, had significant reduction in their SBP and DBP starting from week 2 until week 8 of the study compared to the control SHR group. The same pattern of BP reduction was seen in the positive control group which received nifedipine 2.7 mg/kg (111).

In this study, the role of semen brassicae extract in preventing oxidative stress was examined. After 8 weeks of treatment of SHR with semen brassicae extract, the serum level of GSH-PX was significantly higher when compared to that in hypertensive group. This showed the ability of the extract to promote ROS scavenging activity in the hypertensive rats. Rats receiving semen brassicae extract also had significantly higher serum levels of NO and SOD compared to that in the hypertensive rats. In contrast, the level of MDA in the serum of rats receiving semen brassicae was significantly lower compared to that in the control, suggesting its role in preventing fatty acid peroxidation by the free radicals.

After 8 weeks of treatment, ET-1 and Ang II serum level were found to be lower in all the 3 groups that received different doses of water-decocted brassicae extract and the nifedipine-treated group, with the highest reduction seen in the high dose (2 g/kg) group of the extract. This promotes its promising role in reducing vascular tone as well as vascular constriction in hypertensive subjects. In the same study, semen brassicae extract of the highest dose group (2 g/kg) and nifedipine significantly prevented the thickening of the wall of the thoracic aorta based on H&E staining, suggesting their role in inhibiting the vascular remodelling effect which was observed in the hypertensive group. Furthermore, several anti-inflammatory markers were examined in the serum via ELISA assay and revealed significant reduction in some of the key mediators of inflammatory response namely IL-1b, IL-6, and TNF-α in the group of SHR treated with this extract and also in the nifedipine treated SHR group compared to that in the hypertensive control group. This suggests its potential role

in preventing inflammatory response which is one of the pathways leading to cell damage or disease progression (111).

Taken together, semen brassicea extract demonstrated an anti-hypertensive effect with various possible underlying mechanisms involving enhancement of NO level, suppression of oxidative stress and inflammation, and prevention of vascular remodelling.

I) *Panax ginseng*

Ginseng is one of the many medicinal plants used in many health-related conditions. It has been used in East Asian countries for years. The main bioactive component of ginseng is ginsenoside also called ginseng saponin. Some of the pharmacological benefits of ginseng include antidiabetic (112), anti-cancer (113), neuroprotective and antiangiogenic effects (114).

Lee et al. investigated the antihypertensive effect of Panax Ginseng herbs in hypertensive models (115). The compound was prepared as a fine root concentrate of red ginseng tail root (FR) as well as a hypotensive components-enriched fraction from red ginseng (HCEF-RG). Two groups of SHR received 500 mg/kg and 1000 mg/kg of FR, while another 2 groups of SHR received 500 mg/kg and 1000 mg/kg of HCEF-RG. Two control groups were Wistar Kyoto (WKY) and SHR control groups. SHR receiving FR1000 and HCEF-RG 1000 had significantly lower systolic blood pressure starting from week 2 till week 8. SHR fed with FR500, too had significant reduction in their blood pressure compared to control between weeks 4-6 period. SHR fed with HCEF-RG 500 had reduced in their blood pressure during week 6 before it increased again after that period. For diastolic BP, all 4 treatment groups had a reduction in blood pressure after week 4 of treatment. At 8 weeks, the HCEF-RG 1000 group had a significant reduction in diastolic BP compared to the control SHR. HCEF-RG 500 group had a significant reduction in their diastolic BP compared to control SHR only up to 6 weeks of treatment, suggesting a dose-response effect of this extract of the diastolic BP.

The effect of this extract on its ability to induce nitric oxide was examined by measuring the amount of nitrite in the plasma using a NO detection kit. Treatment of SHR with both FR and HCEF-RG induced higher production of NO in SHR. However, only FR 1000 and HCEF-RG 1000 had significantly higher NO levels in the plasma compared to non-treated SHR.

This study also investigated the effect of this extract on the renin-angiotensin aldosterone system (RAAS). Both doses of FR and HCEF-RG groups had significant renin activity inhibition, which was measured using Perkin Elmer 1470 WIZARD automatic gamma counter, compared to the control SHR. Plasma angiotensin II level was measured using ELISA assay and showed significantly low in SHR treated with FR 500 and HCEF-RG 1000, compared to control SHR. Significant ACE inhibitory activity was seen in SHR treated with FR 1000 and HCEF-RG 1000 compared to the control. This suggests the role of this extract in suppressing RAAS, hence preventing a rise in blood pressure. This concludes the potential of Panax ginseng herbs in reducing blood pressure via a few mechanisms namely suppression of RAAS and induction of NO production.

In a separate study, the effect of Korean Red Ginseng (KRG) was investigated on blood pressure conducted by Jeon et al. (116). Crude saponin 100 mg/kg (CS) and saponin-free fraction 100 mg/kg (SFF) which were purified from KRG were given intravenously to both hypertensive using one-kidney, one-clip Goldblatt method (IK1C) and Sprague Dawley (SD) treatment groups. In the control groups, CS treated hypertensive group showed a significant reduction in the systolic BP which was measured using right carotid artery catheterization, compared to the control SD group ($p < 0.01$). However, no significant different was observed in the systolic BP between the 2 groups receiving the SFF. The differences in the heart rate (HR) following intravenous administration of the extracts were measured from arterial BP pulses. The hypertensive group receiving SF extract had a significant increase in the HR compared to the control SD. SFF groups did not display significant changes in the HR between the 2 groups. These findings suggest the time-dependent effect of both CR and SFF, derived from the KRG, on the blood pressure and reflex tachycardia on the heart rate. This study also evaluated the effect of these 2 compounds on NO level in the rats and cultured endothelial cells (ECV304 cell line) after 72 hours of treatment.

CS when given to the hypertensive group augmented the production of NO (nitrite and nitrate) significantly ($p < 0.05$). Complementary to that finding, ECV304 cell lines treated with both CS and SFF resulted in increased production of NO compared to their baseline level. Following that, the activity of nitric oxide synthase (NOS) was measured in the homogenates of the rat aorta based on the conversion of *L*-[^{3}H] arginine to *L*-[^{3}H] citrulline. CS treatment to both SD and hypertensive rats augmented the increase of NOS in the aorta homogenates compared to their baseline NOS levels. Protein expression quantification of eNOS by western blot in the aorta of rats treated with SD revealed no significant changes with control group. Collectively, the mechanism of BP reduction of crude saponin in hypertensive rat might involve enhancement in the activity of NOS and subsequently increase in the production of NO from the endothelium.

The effects and mechanisms of action of natural products in hypertension are summarized in Table 1.

Common trend identified from the natural products

Based on the natural products that could modulating nitric oxide signaling for the treatment of hypertension, several common trends can be identified.

Many of the natural products listed are derived from plant sources, indicating a significant interest in botanical remedies for hypertension management. Examples include *Morus alba leaf extract, Moringa oleifera leaf extract,*

Table 1: The effects and mechanisms of action of natural products in hypertension.

	Species/ plant	Experimental Model	Biological effects and mechanism of action	References
a	Hydroethanol extract of *S. serratuloides (HESS)*	In vivo: L-NAME induced hypertension in rat	↓ BP ↓ LDL, VLDL, TG ↑ HDL ↑ NO ↓ deposition of collagen in cardiac tissue and lessened cardiomyocytes thickening	(117)
b	*Morus alba* leave extract *(MAE)*	In vivo: SHR rats	↓ BP ↑ PERK-HSP90 ↑ Endothelium dependant relaxation ↑ eNOS	(57)
c	*Moringa oleifera* leaf extract	In vivo: L-NAME induced hypertension in Wistar rats. Ex vivo: rat mesenteric arterial beds from Wistar rats. In vitro: HPAECs	↓ BP ↑ Endothelium dependant relaxation ↑ NO, NOS-sGC	(64)
d	Morinda citrifolia	In vivo: SHR/cp rats, In vitro: HUVECs	↓ BP ↑ Vasodilatation ↑ CaMKKβ-AMPK-eNOS pathway	(72)
e	Xyloketal B	In vivo: 2-kidney, 2-clip (2K2C) renovascular hypertensive rats In vitro: VSMC and HUVECs	↓ BP ↑ Endothelium dependant relaxation ↑ NO-sGC-cGMP pathway ↑ Voltage-dependent Ca^{2+} channels (VDCCs) ↑ Store-operated Ca^{2+} entry (SOCE)	(79, 80)
f	**Cratoxylum Formosum** extract	In vivo: LNAME-induced hypertension in rats	↓ BP ↓ vascular dysfunction and hypertrophy ↑ NO ↓ ROS ↓ renin angiotensin system and AT_1R/Akt/STAT3 pathway	(86)
g	Ethanolic extract from *Acanthopanax sessiliflorus* fruits	In vitro: HUVECs Ex vivo: Porcine Coronary Artery Rings In vivo: SHR rats	↓ BP ↓ ROS ↑ NO ↓ ACE activity ↑ Vascular relaxation	(90)
h	Water-ethanolic extract of *Ficus deltoidea Kunstleri*	In vivo: SHR rats	↑ TAC, eNOS, mRNA expression of catalase, mnSOD and FOXO3a.	(21)
i	Cyathula officinalis Kuan	In vivo: SHR rats	↑ NO ↑ eNOS transcription and protein level ↓ ET1 transcription and protein level ↓ AT1R transcription and protein level	(103)
j	*Perkia Speciosa Hassk*	In vivo: L-NAME induced SD rats	↑ NO ↓ BP ↓ NADPH oxidase activity ↓ ACE enzyme	(118)
k	Semen Brassicae	In vivo: SHR	↑ NO ↑ SOD activity ↑ GPX activity ↓ MDA	(111)
l	*Panax ginseng*	In vivo : SHR	↓ Renin activity, ACE activity, Ang II ↑ NO	(115)
		In vivo : 1K1C	↓ BP ↑ NO, NOS activity	(116)

Morinda citrifolia, Ficus deltoidea Kunstleri, Cyathula officinalis Kuan, Perkia Speciosa Hassk, and *Panax ginseng*. These plant extracts often contain bioactive compounds that can modulate nitric oxide signaling pathways and contribute to blood pressure regulation.

These natural products also known to modulate NO via reduction of antioxidant, ER stress or activation of RAAS. Several of the listed natural products are known for their antioxidant properties, which can help improve endothelial function and nitric oxide bioavailability. Compounds such as xyloketal B, found in marine organisms, and ethanolic extracts from Acanthopanax sessiliflorus fruits likely exert their effects through antioxidant mechanisms, ultimately enhancing nitric oxide signaling and vasodilation.

Some of the listed natural products have a history of use in traditional medicine and ethnopharmacology. For example, Semen Brassicae, derived from the seeds of Brassica plants, has been used in traditional Chinese medicine for various health conditions, including hypertension. Similarly, Panax ginseng, a well-known adaptogenic herb in traditional Chinese medicine, has been studied for its potential cardiovascular benefits, including modulation of nitric oxide signaling.

Overall, these common trend highlight the diverse array of natural products being investigated for their potential role in modulating nitric oxide signaling and treating hypertension. The focus on plant-derived extracts and their NO down-regulatory effects underscores the multidisciplinary approach to developing novel therapeutics for hypertension management.

Limitation

In the studies exploring natural compounds modulating nitric oxide signaling for hypertension treatment as listed in Table 1, there are limitations and challenges in the methodologies employed, particularly concerning the transition from in vitro and in vivo studies to clinical trials.

While in vitro experiments provide valuable insights into the mechanisms of action and potential efficacy of natural compounds, they often fail to fully recapitulate the complexity of human physiology. In vitro findings may not translate effectively to clinical settings due to differences in cellular responses, dosing requirements, and pharmacokinetics. Despite promising results observed in cell culture models and animal studies, the lack of clinical evidence hampers the validation and application of these findings in real-world patient populations. Thus, bridging the gap between preclinical research and clinical trials remains a significant challenge in the field.

Furthermore, the absence of pharmacodynamic and pharmacokinetic studies represents another notable limitation in the methodologies employed in these investigations. While in vitro and in vivo studies may demonstrate promising effects of natural compounds on nitric oxide signaling and hypertension-related pathways, understanding their pharmacological profiles is essential for safe and effective clinical translation. Pharmacodynamic studies elucidate the biochemical and physiological effects of compounds on the body, while pharmacokinetic studies assess their absorption, distribution, metabolism, and excretion. Without comprehensive pharmacodynamic and pharmacokinetic data, researchers lack crucial information necessary for determining appropriate dosing regimens, predicting potential adverse effects, and optimizing therapeutic outcomes in clinical settings. Therefore, the absence of pharmacodynamic and pharmacokinetic studies represents a significant limitation that hinders the progression of natural compound research from bench to bedside. Addressing these limitations through rigorous study design and comprehensive pharmacological profiling is essential for advancing the development and clinical application of natural compounds for hypertension management.

There are also heterogeneity of study designs. Studies examining the effects of natural compounds on nitric oxide signaling and hypertension may vary widely in their experimental designs, including differences in the choice of experimental models, methodologies, and outcome measures. This heterogeneity can make it challenging to compare findings across studies and draw definitive conclusions about the efficacy and safety of specific natural compounds.

Conclusion

We discussed the modulation of the nitric oxide signalling pathway on the mechanism of anti-hypertensive effects of various herbs or phytochemicals studied worldwide. Some of these herbs deserve further investigation on their explicit potential in the pharmacotherapy of cardiovascular disease mainly hypertension. These might offer further insight into the field of cardiovascular research with regard to the development of the new therapeutic potential of phytochemicals and aid in the development of adjuncts to the currently available anti-hypertensive drugs.

Competing interests

The authors declare that they have no competing interests.

Financial support

This research received no external funding.

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