ROLE OF VASCULAR INFLAMMATION IN INDUCTION OF HYPERTENSION AND THERAPEUTIC ROLE OF PLANT DERIVED TERPENES

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ABSTRACT

Hypertension is multifactorial and a serious chronic cardiovascular condition which affects the majority of population all over the world. Inflammation is a protective mechanism in response to infection or injury to the cells and maintains homeostasis within the body. However, sustained robust inflammation can cause vasoconstriction, provoking hypertension. The aetiology of high blood pressure is complex, and its exact mechanism is still yet to be discovered. However, we have tried to propose a general outlook of how inflammation induces hypertension. During injury, the innate immune system gets activated and releases pro-hypertensive cytokines and TNF-α. On further stimulation, it leads to the activation of adaptive immune response and releases pro-inflammatory mediators resulting into low-grade inflammation leading towards increased blood pressure and damage to end-organs. The immune mediated forms of hypertension can provide a hypothesis that may explain how an immune response that is triggered by the central nervous system would cause hypertension. Angiotensin-II, a modulator of blood pressure, can access CNS via circumventricular organs to activate circulating T-cells during vascular inflammation. ROS mediated generation of inflammatory response is also a major contributor to hypertension. Terpenes are plant derived secondary metabolites that have shown their role in many biological processes such as plant growth, development, reproduction and defence. They are considered as a potent therapeutic agent against hypertension due to their vasorelaxant and anti-inflammatory properties.

KEYWORDS: Hypertension, inflammation, terpenes, innate immune system, adaptive immune system.
INTRODUCTION
Hypertension is an important risk factor for a majority of diseases like cardiovascular morbidity and mortality, with 9.4 million deaths each year worldwide. Hypertension does not express any complaints, it often goes undiagnosed in many people, thus appropriately termed as ‘silent killer’. An estimated report says that 1.13 billion people worldwide, most (two-third) living in underdeveloped or developing countries, have hypertension. According to WHO, one of the global targets is to reduce the prevalence of high blood pressure and cardiovascular disease by at least 25% by the year 2025.¹

Hypertension
High blood pressure can be defined as a long-term medical condition in which the arterial pressure of blood is persistently elevated i.e., when the ratio of systolic to diastolic pressure is above 140mmHg over 90mmHg. The pathophysiology of disease is multifactorial and involves vascular smooth muscle dysfunction, endothelial dysregulation, angiogenesis, increased oxidative stress, alteration in renin-angiotensin-aldosterone regulatory activity.² Hypertensinogenic factors include obesity, high salt and alcohol intake, insulin resistance, population aging, stress, energy dense diet and sedentary lifestyle. The consistent increase in perfusion pressure within the arteries results in end-organ damage accompanied by increased risk of heart diseases and strokes.³ Hypertension is considered dangerous because besides contributing to chronic heart diseases and arterial aneurysm, it is also the leading cause of chronic kidney failure and decreases life expectancy of patients. Physical inactivity of an individual or genetic factors may contribute to its cause, or it might be due to certain diseases, endocrine disorders, narrowing of arteries etc.⁴

Hypertension is a complex condition which is further subdivided into two categories:
1. Primary, Idiopathic or essential hypertension: Essential hypertension accounts about 95% of hypertensive population.⁵ It is a heterogenous disorder in which patients suffer from high blood pressure, due to genetic variations, that are over or under-expressed,⁶ epigenetic modifications (like methylation, post-translational histone modifications, micro-RNA etc.) or environmental factors. Epigenetic modifications are an important hallmark in essential hypertension which appears to contribute to cardiovascular diseases and stroke.⁷ A recent report on exosomal miRNA suggests its use as a theragnostic tool for detecting essential hypertension and cardiac remodelling.⁷ Researchers suggest that single genetic traits may contribute to essential hypertension like GRA (Glucocorticoid
remediable aldosteronism) and AGT (Angiotensinogen). GRA is attributed to a well-defined mutation on chromosome 8q21 leading to aldosteronisms and stroke. Indeed, hypertension and diabetes often coexist; there is a bidirectional relationship between micro and macro-vasculature due to which buffer capacity between arteries decreases and peripheral resistance increases, resulting in arterial dysfunction and stiffness, further leading to impairment of insulin-mediated glucose disposal.\[8]\]

2. **Secondary hypertension:** This type of hypertension accounts for 5-15\% of hypertensive cases.\[5\] There are many causes of secondary hypertension, some being conditions like hyperparathyroidism, primary aldosteronism, sleep disorders like obstructive sleep apnea and also renovascular diseases.\[9,10\] Obstructive sleep apnea (OSA) is a condition in which person suffers from collapsed breathing during sleep and is awakened frequently from sleep. OSA episode produces surge in both, the diastolic and systolic pressure that keeps the average blood pressure levels raised during night or sometimes during daytime, when breathing is normal. This diurnal pattern of hypertension is due to over activity of the sympathetic nervous system and alterations in vascular structure and function, caused by oxidative stress and inflammation.\[11\] Certain drugs such as anti-inflammatory drugs, anti-infective drugs, steroids, sex hormones and certain herbal products elevate blood pressure and causes secondary hypertension.\[9\]

3. **Vascular inflammation inducing hypertension:** Inflammation is a biological reaction as well as main signifier of defence that is generally defined as non-specific reaction to malfunctioning of tissue. It is made use of by both innate and adaptive immune systems to contour infective infiltration in our body. Inflammation is broadly a process that destroys tissues, by involving and recruiting plasma proteins, leukocytes and fluids, at the site of the perturbed tissue.\[12\] It is a complex process containing many types of inflammatory cells that involves coordinated interaction between pro-inflammatory mediators, cellular surface and extracellular matrix.\[13\] The primary function of inflammation is to demolish or insulate the inherent source of the agitation, get rid of damaged tissues, and finally restore homeostasis at that site.\[14\]

Inflammation is reported to be involved in hypertension and major inflammatory cells that cause advancement in hypertension includes macrophages, B-cells, T-cells and few dendritic cells which accumulate in kidney, heart, vasculature and the brain.\[15\] Development of hypertension involves cells responsible for both innate as well adaptive immune
responses. A Caillon et al in their review have summarized role of innate and adaptive lines of defense in development of hypertension. Dysfunctional innate immune system by means of Toll like receptors 4 (TLR4) and TLR2 causes pathogenesis of high BP. There is increased expression of TLR-4 protein in the mesenteric arteries in the spontaneously hypertensive rats (SHR). Other studies have also reported that TLR2 and TLR 4 are upregulated in the kidneys, heart, brains and vessels of rats in many other forms of hypertension. Treatment of rats with TLR-4 antibodies decreased the blood pressure and serum levels of IL-6 in SHR. CD8 T cells, which are an important component of adaptive immune system play a significant part in the development of hypertension, as T cells have been found in the kidney of hypertensive rodents as well as in hypertensive human beings.

Norlander et al. (2018) recently demonstrated the presence of mineralocorticoid receptor (MR) on these cells; they also concluded that it is T cell receptor that has a significant role in systemic hypertension.

Investigators have also found that inflammation, hypertension and cardiovascular diseases are closely intermingled with one another. Sub-endothelial build-up of low-density lipoproteins (LDLs) in the vessel wall causes endothelial injury, which creates an imbalance between prostacyclin (PGI1) and nitric oxide (NO), and causes generation of reactive oxygen species (ROS). Activated endothelial cells secrete chemoattractant mediators such as Monocyte chemoattractant protein-1 (MCP-1), interleukin-8 (IL-8) and complement factors along with expression of ICAM-1, VACM-1 and selectins. This causes monocyte recruitment in the vascular wall and their differentiation into macrophages, perpetuating the release of pro-inflammatory cytokines, further elevating arterial pressure.

Talking of the brain, markers of inflammation (TNF-α and IL-1b) are too large to cross the blood -brain barrier. So, they can indirectly affect the brain by inducing (cyclooxygenase) COX-2 activity and releasing prostaglandins. Prostaglandin E2 activates neurohormonal system within the brain and invokes cytokine activation of hypothalamic-pituitary-adrenal-axis. Brain inflammatory response, thus, contributes to peripheral inflammation and development of hypertension.

During injury of vessels or skin, the epithelial and endothelial cells trigger the innate immune cells such as neutrophils, monocytes, macrophages and dendritic cells to release pro-hypertensive cytokines like interferon-ϒ (IFN-ϒ), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). This system further informs and directs the activation and
differentiation of adaptive immune system on injurious stimulation. The various APCs stimulate different T-cell subsets to release pro-inflammatory mediators. For example, CD8+ T-cells expresses IL-12, TNF-α and IFN-Υ; The CD4+ Th-1 cells releases TNF-α and IFN-Υ and Th-2 cells releases IL-13, IL-4 and IL-5.\[^{29}\] These mediators participate in low-grade inflammation leading towards increased pressure of blood and end-organ damage. T-reg cells, however, produce immunosuppressive cytokines such as TGF-β and IL-10, counteracting hypertensive effects. Investigators suggest that angiotensin-II, which is a modulator of blood pressure, can access CNS via circumventricular organs to activate circulating T-cells and cause vascular inflammation.\[^{30}\] Chronic Angiotensin-II infusion in blood vessels causes gathering of immune cells like B cells, T cells, macrophages and dendritic cells. These immune cells mostly collect in the adventitia and perivascular adipose tissues (PVAT) of small resistance vessels such as capillaries and arterioles and larger vessels. Immune cell accumulation in these places cause inflammation and it is reported that the degree is inflammation is greater in PVAT than other visceral fat.\[^{31,32}\] PVAT is reported to cause release of factors that affects the vascular tone and produce chemotactic molecules that further inflammation.\[^{33}\] The consumption of high fat diet leads to increased RANTES expression in adipose tissues. It is also reported that RANTES-dependent pathways promote accumulation of macrophages and IFNγ producing T cells into PVAT.\[^{34}\] Presence of circulating T cells in PVAT and in the kidney causes release of cytokines, particularly interleukin-17.\[^{35}\]

IL-17 is most widely studied cytokine and is linked with various diseases including psoriasis, rheumatoid arthritis, inflammatory bowel disease, and inflammation in the airways.\[^{36}\] IL-17 has also role in cardiovascular disease. Knockout studies on rodents showed that mice lacking IL-17 (IL-17\(^{-/}\)) do not develop hypertension.\[^{37}\] IL-17 activates NADPH oxidase\[^{38}\] and stimulates chemokine release therefore promoting hypertension\[^{39,40}\] IL-17 expression is under the regulation of IL-6; IL-6 causes transformation of growth factors and polarizes both CD4+ and CD8+ cells towards production of IL-17.\[^{41}\] Mice deficient in IL-6 are protected against angiotensin II-induced hypertension, kidney damage caused by high blood pressure and stress-induced hypertension.\[^{42,40,43}\] Hevia et al have reported that myeloid CD11c+ are part of both innate and adaptive immune system, and are essential for developing and maintaining hypertension in response to Ang-II infusion and high-salt diet. They also reported that CD11c+ APCs ablation has helped in lowering blood pressure in mice model. But on reconstruction of CD11c+ cells ablated mice with the wild-type CD11c+ hypertensive...
response was again established back to Ang-II pulse high salt infusion.[44] This CD11c is an integrin- X chain protein, and cells having this protein are are widely thought to be dendritic cells; but the protein CD11c is seen to be expressed by monocytes, macrophages, neutrophils even by B and T cells.[45]

Endothelial cells are single line cells that line the smooth muscle cells in the vascular system. These cells have diverse functions depending on the different vascular sites such as modulation of metabolic homeostasis, vascular hemodynamics, vascular permeability, coagulation and trafficking. In addition to these, endothelial cells also have important immunological functions and actively participate in both innate and adaptive immune response. Endothelial cells have an important function of presenting antigens, and their capacity to produce pro-inflammatory cytokines as well as anti-inflammatory cytokines is broadly reported in review by Mai et al.[46]

Endothelial microparticles (EMP) are complex vesicular structures with 0.1 -15 µM diameter, that are released from activated or apoptotic endothelial cells. EMP are made of phospholipid bilayers with transmembrane proteins and receptors on their surface and vesicles enclose some mRNA, enzymes and transcription factors.[47] EMP are novel biological marker that point to injury in the endothelium injury and also vasomotion disorders; these are involved in pathogenesis of diseases of metabolism, cardiovascular diseases, and inflammatory diseases. EMP levels are seen to increase in several cardiovascular diseases, such as coronary artery diseases, hypertension, arrhythmias, chronic heart failure, thromboembolism, asymptomatic atherosclerosis, and also when there is a failure of the ren system.[48-51] EMP contains endothelial proteins such as ICAM-1, PECAM-1, αβ3 integrin, and VE-Cadherin and nuclear materials in the endothelium such as microRNA, RNA and DNA. The EMPs through these nuclear materials and proteins can induce intracellular signalling in target cells.[52,53] EMPS promote coagulation and vascular inflammation because they have procoagulant and pro-adhesive properties.[54] In diabetic patients, level of circulating EMP is reported to increase with respect to control; these circulating EMPs are responsible for “vascular inflammation and endothelial dysfunction via activation of P38 by NADPH oxidase”.[55]

Angelot F et al have reported that EMPs secrete pro-inflammatory cytokines, IL-6 and IL-8, and induce proliferation of allogeneic naïve CD4+ T cells.[56] These dendritic cells then move towards spleen and lymph nodes (secondary lymphoid organs) so as to help the T-cells to recognize the antigenic peptide and promote coordinated interaction of MHC with T-cell
receptor at a specific site called “immunologic synapse”. An costimulation occurs at this site, that involves B7 ligand on the APCs (CD80 and CD86) with CD28 on the T cell. Other co-stimulatory molecules include members of tumour necrosis factor receptor superfamily (TNFRSF) and inducible co-stimulator (ICOS), which aids continued activation of T-cells. Other antigen presenting cells include activated macrophages, B-cells, and in addition, under certain circumstances, activated endothelial cells.[46] As a result of interaction and co-stimulation, T-cells proliferate, produce chemokines (e.g., CCL2 and CXCL8) and pro-inflammatory cytokines (IL-1β, IL-6, IL-12, IL-23,TNF-α) as well as prostaglandins and alter expression of surface receptors that emanates them from secondary lymphoid organs, homing towards the site of inflammation. T-helper cells also bind to B-cells and support the formation of antibodies. T-helper cells can be broadly categorised on the basis of specific cytokines they release e.g., Th-1 (IFN-γ), Th-2 (IL-4), and Th-17 (IL-17).[57] As compared with CD4+ cells (which recognise peptide presented by type-II MHCs), the CD8+ cells are activated by peptides presented by type-I MHC molecules, that are present on all nucleated cells. Activated CD8+ cells or cytotoxic T-cells, produce perforins and granzymes. Perforins create pores or channels in the membrane of the target cell; granzymes can enter the target cell through these pores and induce apoptosis, leading to increase in circulating apoptotic bodies, which is another mode of causing inflammation. Like CD4+ cells, CD8+ cells can also produce inflammatory cytokines that leads to hypertension.[58]

There has always been a substantial interest in A number of subtypes of T-cells contribute towards hypertension, which makes them a subject of interest. Norlander et al., (2018) found that mice lacking in CD8+ cells were protected from hypertension, whereas CD4+ lacking mice or MHC-II lacking mice were not. This shows that CD8+ T-cells play an important role in the genesis of hypertension. The naive CD8+ T-cells upon activation get subsequently matured into cytotoxic T-cells that expresses granzyme B, perforins, IFN-γ and TNF-α, following antigen stimulation by MHC-I. These T cells may become cytotoxic CD8+ T-cells and cytokines secreted by them contribute to apoptosis and inflammation. CD8+ cells that express mineralocorticoid receptor (MR) are key players in systemic hypertension. MR is a nuclear protein that binds with nuclear factor of activated T-cells-1 (NFAT1) and activator protein 1 (AP1) to promote generation of pro-hypertensive cytokines by CD8+ T-cells.[25] Further, these T-cells cause the distal convoluted tubule (DCT) in kidney of DOCA-salt mice to propagate hypertension in response to salt.[59] Thus, the CD8+ T cell is considered as an important contributor towards pathogenesis of hypertension.
The immune mediated forms of hypertension provide us with a concept of the way in which signals from the brain (CNS) cause an immune response that would cause hypertension. The hypothalamus and the brain stem are thought to be involved and it has been projected that they alter balance between the sympathetic and the parasympathetic outflow during hypertension.\(^{19}\)

ANRIL (antisense noncoding RNA in the INK4 locus) is a low expressed gene, consisting of 20 exons whose transcripts are seen in a variety of tissues and cell-type, including endothelial cells, smooth muscle cells, and cells of the immune system that are known to be involved in atherogenesis.\(^{60}\)

4. **Angiotensin-II induced hypertension:** Recent study supports the role of inflammation in the pathological process of hypertension induced by angiotensin-II.\(^{61}\) Angiotensin-II has pro-inflammatory actions which augments the release of inflammatory cytokines, reactive oxygen species (ROS) and adhesion molecules into the blood stream. Vascular action is primarily mediated with the help of Ang II-type 1 receptor present on the endothelial wall, which on activation promotes a cascade of cellular response including activation of phospholipase-C and release of intracellular calcium ions resulting in vascular smooth muscle contraction.\(^{62}\) The locally circulating inflamed cell into the blood stream also results in production and secretion of pro-inflammatory cytokines like interleukin-6, IL-1B and TNF-α. These pro-inflammatory mediators, later have effects on gene expression via NF-κB mediated transcription factors.

![Figure 1: Angiotensin-II induced inflammation and hypertension Abbreviations: Ang II, angiotensin II; ET-1, endothelin-1; (-), inhibition or reduction.\(^{63}\)](image-url)
Angiotensin-II is responsible for inflammatory response via ROS-mediated pathway of renal damage. Angiotensin-II activates NADPH oxidase and leads to manufacture of reactive oxygen species in cells of vascular smooth muscle (VSMCs), monocytes and endothelial cells which activates pro-inflammatory transcription factor activator protein and NF-κB. NF-κB act as a major contributor to intracellular inflammatory response. It is activated by numerous stimuli such as reactive oxygen species, protein kinase-C regulated proteins and inflammation-mediated cytokines. Activated NF-κB then translocate into the nucleus and regulates transcription of inflammatory genes. These further leads to production of chemokines such as monocyte chemotactic protein-1 (MCP-1), vascular cell adhesion molecule -1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1) leading to recruitment of monocytes and macrophages at the site of inflammation, thereby causing hypertension (figure 1). Chronic infusion of Angiotensin-II causes vascular accumulation of B-cells, T-cells and macrophages inside blood vessel’s perivascular adipose tissue (PVAT). This leads to release of paracrine factors like leptin, resistin and cytokines (IL-6 and TNF-a) which affects vascular tone and generation of chemotactic agents [such as MCP-1 (CCL2) and RANTES (CCL5)], promoting inflammation.

5. Oxidative Stress and Inflammation-induced hypertension: Inflammatory response leads to generation of ROS that contributes towards hypertension. The interest in unravelling the mechanism of activation of immune system via oxidative damage is increasing nowadays. The major forms of ROS species produced within the circulation are hydroxyl radical, peroxides and superoxides. Among the major ROS generators in VSMCs like mitochondrion are other cellular enzymes- xanthine oxidase, peroxidases, cyclooxygenases (COX), cytochrome P450 1B1, lipoxygenases; the membrane associated NADPH oxidases (NOX) has been of foremost importance. The level of superoxide is usually low within the blood stream due to the presence of superoxide dismutase (SOD). But during inflammation, it has been observed that the level of ROS increases within the blood via activation of NADPH oxidases. ROS oxidizes arachidonic acid to form isolevuglandins (IsoLG), a highly reactive lipid peroxidation product, which covalently modifies protein structure and function by cross linking with lysine residues. These altered proteins act as neoantigens within the antigen presenting dendritic cells, forming an autoimmune state. Activated dendritic cells releases pro-inflammatory cytokines such IL-6, IL-1B which drive T-cell proliferation and production of IFN-γ, IL-17A and TNF-α priming towards hypertension. (figure2).
Figure 2: Activation of immune cells and hypertension through formation of IsoLG-protein adduct. Hypertensive stimuli such as angiotensin-II, excess dietary salt and sympathetic outflow increases NADPH oxidase-dependent formation of ROS by dendritic cells. Arachidonic acid is oxidised as a result and IsoLG-protein adducts are formed. Activated dendritic cells produce pro-inflammatory cytokines such as IL-1β, IL-6 and IL-23 and induce proliferation of T-cells and also production of inflammatory mediators such as TNF-α, IFN-γ and IL-17 which contribute to hypertension and end-organ damage.\(^{[63]}\)

Other ROS mediators of inflammatory response involve the role of myeloid differentiation primary response protein 88 (MyD88). Extrinsic or intrinsic factors might cause release of oxidants within the cell that causes damage to nucleic acids, lipid and proteins. These oxidatively damaged cellular components act as endogenous ligand for PRRs. This in turn activates the TLR signalling which involves recruitment of TRIF (TIR-domain-containing adapter-inducing interferon-β) and MyD88 dependent pathways.\(^{[72]}\)

Earlier studies have shown that MyD88 act as a universal adaptor for immune related signalling and downstream activation of mammalian IL-1R and TLRs.\(^{[73]}\) This further activates IL-1R associated family kinases that gives a variety of functional outputs, such as...
activation of NF-κB, JNK (c-Jun N-terminal Kinase), mitogen activated protein kinases (MAPK) and activator protein-1 (AP-1) transcription factors. The activation of these downstream pathways leads to cascade of inflammatory response.

ROS also increases production of Cyclooxygenases- both constitutive (COX1) and inductive (COX2) leading to hypertension. In vascular endothelial and smooth muscle cells, angiotensin-II binds to angiotensin-II type1 (AT-1) receptors that induces NADPH oxidase and also activates COX-1/COX-2. Further, NADPH oxidase produces reactive oxygen species while COX-1/COX-2 produces prostaglandins and thromboxanes (collectively termed as prostanoids) which in turn can again activate NADPH oxidases; all this goes in a circuitous manner. It is well known from literature that prostanoids contribute significantly in sustaining vascular tone, salt water balance, release of renin and are also responsible for generating inflammatory responses. Moreover, cyclooxygenases stimulate smooth muscle contraction that results in causing hypertension. Further, any increase in ROS levels results in scavenging, procuring endothelial dysfunction and inflammatory changes within the blood vessels. ROS-mediated signalling via GPCR such as β-adrenergic receptor (β-AR) stimulates transcription of pro-inflammatory markers such as cytokines and chemokines, production and recruitment of various inflammatory cells in the myocardium, all leading towards cardiovascular diseases and hypertension.

6. Neutrophils and Vascular inflammation: Neutrophils are very short lived, terminally differentiated, bystander cells that can actively drive inflammatory processes within the body. Release of neutrophils into the blood stream is controlled by chemokines, adhesion molecules and certain growth factors. They have always been a large toolset ready to use at the inflammation site. Neutrophils function in three primary capacities; namely, release of granules, formation of neutrophil extracellular traps (NETs) and generation of ROS. During atherosclerosis, platelet-derived inflammatory mediators like chemokines, promotes the recruitment and activation of neutrophils. Activated neutrophils at the luminal side secrete granular proteins like cathepsin and cathelecidin that directly or indirectly promotes recruitment of myeloid cells. Neutrophil activation and the release of ROS at the luminal side result in dysregulation of underlying extracellular matrix and endothelial layer enabling infiltration of leukocytes and LDL extravasation. Cathepsin further stimulates activation of macrophages to release IL-1B and IL-18 towards inflammatory site within the intima. Thus, neutrophils accelerate
inflammation by fostering monocyte recruitment and further macrophage activation. Neutrophils also produce NET (neutrophil extracellular trap) to confine and eliminate pathogen. These are fibrous reticular structures are formed through a process called NETosis. NET formation was first reported in pulmonary arterial hypertension (PAH) patients in 2016 and have shown that NET triggers the activation of inflammatory response in pulmonary endothelial cells and promotes endothelial angiogenesis via myeloperoxidases, NFκB signalling and TLR4-dependent signalling.[88] Myeloperoxidase binds to CD11b/CD18 integrins and drives inflammatory reaction by promoting nuclear translocation and activation of NFκB via MAPK pathway.[89] Consequently, NETs augmented the release of ICAM-1 in leukocytes via NFκB dependent pathway. Literature demonstrates the secretion and activation of a variety of cytokines by neutrophils which influences aspects of not only inflammatory response but also of antiviral defence, angiogenesis, hemopoiesis and fibrogenesis. Chemokines produced by neutrophils act as chemotactic factor for dendritic cells, monocytes, macrophages and various T-helper cells which helps in orchestrating the recruitment and activation of leukocytes.[90]

7. **Pro-Inflammatory mediators: An insight towards hypertension**

Hypomethylation of pro-inflammatory genes increases the risk of inflammation induced hypertension. Inflammasomes act as signaling platforms for a variety of response whose primary function is to activate cysteine protease, caspase-1, which upon activation stimulates cytokines such as IL-1B and IL-18, that are known to be pro-inflammatory in nature. These are members of IL-1 pro-inflammatory cytokine superfamily and are found in monocytes and macrophages. Their actions are accomplished by the stimulation of explicit receptors, i.e. IL-1 type 1 receptor (IL-1RI) and IL-18 receptor α chain (IL-18Rα), for IL-1B and IL-18 respectively, which are found on several leukocyte subsets such as lymphocyte, monocyte and macrophages, endothelial cells and vascular smooth muscle cells.[91] IL-1B and IL-18 facilitates strong binding with their specific receptors and allows recruitment of adaptor molecules that activates a signal transduction pathway involving MAP kinases, JNK and also transcription factors such as activator protein-1 (AP-1) and NF-κB which are specifically renowned for inducing inflammatory gene expression and other hypertensive effects. IL-6 is another important pro-inflammatory cytokine which plays an important role in regulating CRP gene expression. CRP (C-Reactive Protein) is an acute phase protein that binds to a family of pentameric proteins (pentraxins) and approaches ligand in a calcium-dependent manner. It has important roles in activation of complement system and also
phagocytosis. CRP encourages monocytes to release pro-inflammatory cytokines such as IL-6, IL-1B and TNF-α; VCAM-1 and ICAM-1. IL-6 promotes vascular smooth muscle proliferation by regulating IL-1B and TNF-α. It has been found that in essential hypertension, there is hypomethylation of IL-6 genes. Similarly, DNA methylation at the promoter site can inhibit transcription of these genes. TLR-2 (Toll-like receptors) are important immune receptors which serves as a role in chronic inflammation associated with hypertension. Promoter gene hypermethylation of TLR-2 results in gene silencing while hypomethylation activates gene expression and enhances pro-inflammatory responses during hypertension. TLR-2 dimerizes with TLR-1 or TLR-6, for it to be activated. Ligand binding to these receptors facilitates recruitment of adaptor molecule, MyD88 that promotes association with IL-1 receptor–associated kinases and TNF-α associated factor. After dissociating from its receptor, this complex acts together with a different complex containing TGF-β activated kinase and its binding proteins. TGF-β activated kinase-binding protein itself gets activated in cytoplasm and causes activation of IκB kinase kinases (IKKs) that degrades IκB and subsequent release of NF-κB. Once NF-κB gets translocated into nucleus, there is activation of inflammatory cytokines and chemokines. TNF-α is another an important pro-inflammatory cytokine which is associated with renal injury and salt-sensitive hypertension (SSH). SSH is stimulated by chronic high salt intake. The exact mechanism of the production of TNF-α in SSH is still yet unclear while TNF-α antagonists have been shown to attenuate hypertensive response in many animal models.

8. Therapeutic role of plant-derived terpenes: Plants and some microorganisms produce terpenes or terpenoids that are secondary metabolites and have many medicinal properties. Terpenes being highly abundant and structurally diverse, have anti-microbial, anti-viral, anti-hypertensive and anti-inflammatory effects. They play an important role in many biological processes such as plant growth, development, reproduction and defence. They are made biosynthetically via mevalonate pathway from 5-carbon compounds, known as isoprenoids. The terpenes are classified on the basis of number of isoprenoid structures: hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), triterpenes (C30), and tetraterpenes (C40).

9. Monoterpenes: Carvacrol, a component of oregano is a monoterpenoid which induces vasorelaxation. Calcium is a well-known modulator of TRP channels activity and has shown inhibitory effects on TRPV3 (Transient receptor potential cation) channels.
Carvacrol causes influx of Ca\(^{2+}\) within the endothelial cells, resulting in increase in intracellular Ca\(^{2+}\), that leads to activation of K\(^{+}\)-channels. The activation of K\(^{+}\)-channels brings about hyperpolarization of plasma membrane of the endothelial cells and vascular smooth muscle cells, causing vasodilatation\(^{[101]}\) Isoegomaketone, a monoterpane and the main essential oil ingredient of *Perilla frutescens*, is known to suppress the production of IL-6, NO and MCP-1, which are significant intermediaries in inflammatory process; this evaluation was done by regulating the transcriptional activation of NF-κB and AP-1\(^{[102,103]}\) Linalool (LIN) is a monoterpane alcohol vasorelaxant effects.\(^{[104]}\) Furthermore, when complexed with B-cyclodextrin (B-CD), it shows improved pharmacological activity by increasing the level of anti-inflammatory cytokine (IL-10).\(^{[105]}\) α-Pinene, a bicyclic monoterpenoid inhibits the NF-κB protein translocation into the nucleus\(^{[106]}\) while α-Terpineol stimulates the release of NO from endothelium and activates the NO-cGMP pathway leading to vasodilation and hypotension.\(^{[107]}\)

10. **Sesquiterpenes:** Pseudoguaianolides, psilostachyin, parthenin and coronopilin are sesquiterpene lactones that have been studied in murine neutrophils. They exhibit anti-inflammatory potential through expression of IL-6, IL-1β and TNF-α. In these terpenes are present α-methylene-Y-lactone (αMYL), which is an oxygen containing ring with carbonyl function, and it is this group that is responsible for lowering blood pressure in humans.\(^{[108]}\) The insertion of azaspiro and butanolide within αMYL improved the anti-inflammatory activity of these terpenes. Parthenolide have shown to improve IL-8 chemotaxis and had a differential effect on vascular reactivity and relaxation. It inhibits nuclear translocation of p65 subunit and also inhibit DNA binding of NF-κB complex. Parthenolide alone has negligible effect on blood pressure; however when administered together with DHT (dihydrotestosterone), it prevented hypertension.\(^{[109]}\) Bolinaquinone, sesquiterpene hydroquinone/quinone, belongs to a class of marine sponge metabolites, inhibits the production of prostaglandinE2, thereby controlling hypertension. Avarol’s derivative avarol-3′- thiosalicylate (5A) showed anti-inflammatory properties by acting as an antioxidant and by inhibiting release of PGE2.\(^{[110]}\) Valerenic acid is also an effective natural sesquiterpene, used against cancer and inflammation. It is obtained from *Valeriana officinalis*. It inhibits NF-κB activation and cytokine activation. It is also effective during sleep disorders.
11. Diterpenes: A number of diterpenes like forskolin and stevioside occur in nature, and are seen to inhibit vascular contractility within experimental animals. Forskolin reduces intraocular pressure. Marrubium vulgare (Lamiaceae) is one diterpene that is extensively used as traditional medicine against hypertensive treatment and is proven to prompt vascular relaxation and decrease systolic blood pressure. Croton zambesicus induces vascular relaxation via blockage of extracellular Ca2+ influx and Orthosiphon aristatus reduces contractile activities in smooth muscles stimulated with potassium ions.\[^{111}\] The extracts made from the bark of Croton cajucara Benth (Euphorbiaceae) are used in folk medicine for the management of high blood pressure as it possesses anti-inflammatory properties.\[^{112}\]

![Figure 3: Inhibition by plant-derived terpenoids in NF-kB mediated signalling during hypertension.](image)

12. Triterpenes: *Olea Europea* in African and European Mediterranean countries, has the capacity to decrease blood pressure, exert an anti-arrhythmic activity, and preserve coronary blood flow. These activities are seen probably because of different mechanisms like blocking of beta receptors, Ca2+ antagonism, angiotensin-converting enzyme (ACE) inhibition as well as vasodilatory NO pathways.\[^{113}\] Maslinic acid, Erythrodiol and Uvaol possess NO-mediated vasodilative properties. The effect of oleic acid on blood pressure reduction is mediated by an enhance production of vasodilatory stimuli (e.g., cAMP and PKA) and decrease in vasoconstriction pathways (InsP3, Ca2+, diacylglycerols, and Rho kinase). This conclusion is supported by earlier studies demonstrating that ingestion of
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virgin olive oil reduces blood pressure as well as need for antihypertensive medication in humans.[114]

13. Tetraterpenes: Crocin (CRO), a carotenoid from the tetraterpenes family, prevents extracellular Ca2+ influx, thereby relaxing blood vessels as well as have protective effects against angiotensin II-hypertension.[115] Lutein, a cyclic tetraterpenoid present in fruits, vegetables and egg yolk, has strong oxidative scavenging capacity. It blocks the activation of ubiquitous nuclear transcription factor (NF-κB) playing a key role in many pathophysiological reactions and degradation of the inhibitor kB (I-κB). After the dissociation of complex by lutein, NF-κB can translocate into the nucleus, decreasing transcription of inducible gene x and synthesis of inflammatory markers such as cytokines, chemokines, and iNOS. The final effects of lutein involves not only the decreasing concentrations of TNF-α, interleukin 6 (IL-6), prostaglandin 2 (PGE-2), monocyte chemotactic protein 1 (MCP-1), and macrophage inflammatory protein 2 (MIP-2), but also reducing oxidative stress.[116] However, its antioxidant and anti-inflammatory capacity have been shown to have a positive influence not only in eyes but also in preventing the risk of CVD (cardiovascular diseases) and reducing blood pressure.

CONCLUSION
The purpose of this review was to discuss recent advancement in the knowledge of controlling blood pressure by immune mechanisms from basic and clinical studies in hypertension and therapeutic role of plant-derived terpenes as secondary metabolite. Mild increases in pro-hypertensive factors like Angiotensin-II or high-salt diet activates both the innate and adaptive immune systems as well as NADPH oxidases within the VSMCs. Activated inflammatory monocytes and macrophages releases reactive oxygen species that promotes activation of pro-inflammatory mediators and chemokines. The major inflammatory mediators include- increase in CRP, IFN-Υ, TNF-α, IL-1β IL-2, IL-6 and IL-17, each of which has roles in augmenting blood pressure. Angiotensin-II stimulates the release of ROS via NADPH oxidase that causes upregulation of NF-κB and other inflammatory mediators. Breakdown of NO and uncoupling of NO synthase in the smooth muscle cells, endothelium and blood vasculature provokes inflammation and endothelial dysfunction, contributing towards vascular diseases, atherosclerosis and hypertension. Genetic predisposition, or environmental influences such as high salt intake, could modify gene expression epigenetically or could have direct action on the brain that might increase sympathetic
activity or decrease parasympathetic activity, thus producing mild BP elevations. Terpenes help in relaxation effects through mechanisms that involve inhibition of Ca\textsuperscript{2+} influx in vascular smooth muscle or via quenching of reactive oxygen species (ROS), stimulation of nitric oxide (NO) synthesis and blocking NF-κB mediated pathway, thereby decreasing synthesis and release of pro-inflammatory mediators of hypertension. This review provides compelling evidence regarding how terpenes could act as therapeutics against hypertension. However, further work needs to be done for a better initiative in health and disease.

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