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Study on the Natural Vasodilators

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MR. Hamadi maamar

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List of abbreviations

NO: Nitric Oxide
cGMP: Cyclic Guanosine Monophosphate
cAMP: Cyclic Adenosine Monophosphate
VSMCs: Vascular Smooth Muscle Cells
EC: Endothelial Cells
PGs: Prostaglandins
ACh: Acetylcholine
eNOS: Endothelial Nitric Oxide Synthase
ROS: Reactive Oxygen Species
BP: Blood pressure
WHO: World Health Organization
GBA: Gamma-Aminobutyric acid
EDHF: Endothelium-Derived Hyperpolarizing Factor
RAAS: Renin-Angiotensin-Aldosterone System
TCM: Traditional Chinese Medicine
IBMX: 3-Isobutyl-1-methylxanthine
sGC: Soluble Guanylate Cyclase
PKA: Protein Kinase A
BKCa: Big Potassium Calcium-Activated Channel
LTCC: L-Type Calcium Channel
PHE: Phenylephrine
THIQ: Tetrahydroisoquinoline
TMAO: Trimethylamine-N-oxide
PGI2: Prostacyclin
[Ca2+]i: Intracellular calcium ion concentration
A2AAR:A2A adenosine receptor
KATP: ATP-sensitive potassium channel
H_1 receptor: Histamine H1 receptor
Arg: L-Arginine
NOHA: Nω-hydroxy-L-arginine (an enzyme-bound intermediate in NO synthesis)
H_4O: 6-(R)-Tetrahydrobiopterin (cofactor for NOS)
NAD (P) H oxidase: Nicotinamide adenine dinucleotide (phosphate) hydrogen oxidase
XOR: Xanthine oxidoreductase
BH4: Tetrahydrobiopterin
$ONOO^-$: Peroxynitrite
IP_3: Inositol 1, 4, 5-triphosphate
PMB: Photobiomodulation
PPM: Low-level laser therapy (appears interchangeable with PMB)

AchM3R: M3 muscarinic acetylcholine receptor
PGI_2: Prostaglandin I2 (prostacyclin)
PGE_2 : Prostaglandin E2
TXA_2: Thromboxane A2
COX: Cyclooxygenase
EDHF: Endothelial-derived hyperpolarizing factor
CCBs: Calcium channel blockers
NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells
PI3K: Phosphoinositide 3-kinase
AMPK: AMP-activated protein kinase
DHA: Docosahexaenoic Acid
EPA: Eicosapentaenoic Acid
HAPE: High-Altitude Pulmonary Edema
HFrEF: Heart Failure with Reduced Ejection Fraction
HFpEF: Heart Failure with Preserved Ejection Fraction
LVEF: Left Ventricular Ejection Fraction
ADRs: Adverse Drug Reactions
CYP3A4: Cytochrome P450 3A4 (enzyme involved in drug metabolism)
INR: International Normalized Ratio
RAAS: Renin–Angiotensin–Aldosterone System

Introduction

Introduction

For several years, chronic diseases such as cardiovascular and cerebrovascular diseases (CCVDs) have posed significant global challenges. Concurrently, a strong correlation has been observed between CCVDs and vascular lesions such as hypertension ***(Tang et al., 2021).*** Cardiovascular disease (CVDs) continues to be the leading cause of morbidity and mortality globally, and hypertension has been identified as a significant modifiable risk factor. The dynamic equilibrium of vasodilation, a process by which blood vessels relax to facilitate increased blood flow, is crucial for blood pressure regulation. Although pharmacological vasodilators are employed in clinical settings, adverse reactions and the development of drug resistance have spurred considerable interest in exploring alternatives of natural origin ***(Tang et al., 2021).***

It is widely acknowledged that the lengthy and intricate pathophysiology of cardiovascular and cerebrovascular disease (CCVDs) mortality impedes human health. In 2016, cardiovascular diseases constituted 31% of global reported by the World Health Organization (WHO), some of which include peripheral arterial disease, atherosclerosis, cardiomyopathy, hypertensive heart disease, ischemic heart disease, hemorrhagic stroke, myocarditis, and endocarditis **(Kratz al., 2017; Roth et al., 2017)**. Crucially, hypertension is closely related to several common chronic CCVDs, such as heart failure, myocardial infarction, stroke, dementia of the vascular system, and chronic kidney diseases **(Sureda et al., 2017).** However, hypertension is usually a result of vascular lesions, including vessel wall thickening, stenosis, occlusion, and endothelial cell injury **(Mathieu et al., 2009; Farias et al., 2010; Howlett, 2014; Singh et al., 2017)**. For instance, high blood pressure increases mechanical strain on arterial walls, which can hasten the formation of atherosclerotic plaques and increase the risk of ischemic heart disease (IHD). Such vascular changes worsen disease outcomes over time by compromising blood flow and affecting the delivery of oxygen and nutrients to the essential organs. Therefore, it is crucial to understand the reciprocal relationship between hypertension and vascular pathology to develop more effective preventive and therapeutic approaches for the management of CCVDs. Natural products, which are tiny molecules formed from natural dietary compounds and Traditional medicine plants (TMPs), are known as natural vasodilators, most of which are alkaloids, flavonoids, or terpenoids, and can improve biological metabolism by regulating the activity of enzymes in the body **(Loai and Zohar, 2015).**

Vasodilation, the expansion of blood vessels, represents a crucial physiological process governed by a complex interaction of neural, hormonal, and local metabolic factors. These factors modulate vascular resistance, which subsequently affects blood pressure and tissue perfusion. Understanding the vasodilation mechanisms has become essential for developing treatments for various cardiovascular diseases. By exploring how these factors interact, researchers can identify. Potential therapeutic targets to improve vascular health and enhance overall circulation. This sophisticated mechanism entails the relaxation of smooth muscle cells within the vessel walls, resulting in an increased vessel diameter ***(Bulboacă et al., 2016).*** Vasodilation is not merely a passive relaxation but an active process meticulously regulated to maintain homeostasis and adapt to varying physiological demands ***(Xu et al., 2021)***. Prolonged constriction of the smooth muscle within arterioles can lead to hypertrophy and thickening of the vessel wall, underscoring the importance of maintaining a balanced vascular tone ***(Delong & Sharma, 2021)***. The extent of influence is contingent upon stimulus frequency, duration, and contraction frequency ***(Sarelius & Pohl, 2010)***. The initiation of vasodilation can arise from various stimuli, including metabolic signals such as hypoxia, hypercapnia, and the accumulation of adenosine, potassium ions, or hydrogen ions near blood vessels, indicating increased tissue activity and metabolic demand. Additionally, endothelial cells, which form the inner lining of blood vessels, play a vital role in mediating vasodilation by releasing vasoactive substances such as nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factors.

In light of the diseases associated with cardiovascular and cerebrovascular disorders (CCVDs), the question arises as to whether natural substances could provide safer and more sustainable alternatives for the treatment of hypertension and related conditions. This consideration is particularly pertinent given the adverse side effects, reduced efficacy, and potential for drug resistance associated with prolonged use of pharmaceutical vasodilators. What are the current limitations, therapeutic potential, and mechanisms of action of natural vasodilators in the clinical setting? Furthermore, to what extent does the existing literature substantiate their safety and efficacy?

This literature dissertation was conducted to evaluate existing research on natural vasodilators, with an emphasis on their mechanisms of action, potential efficacy in hypertension treatment, and their role in mitigating the risk or progression of cardiovascular and cerebrovascular diseases (CCVDs). This dissertation aims to discern these research gaps. Through a deep understanding of the phenomenon of vasodilation, understanding the classification by which

certain vasodilators react, involving the main subject of the study, which is the natural vasodilators, highlighting the mechanism of action of certain bioactive compounds. It also focuses on the most significant vascular disorders and their diagnosis via these natural dilators. As well as the risks, side effects, and drug interactions.

Chapter 1

Chapter I. The phenomenon of vasodilation

I.1. Definition of vasodilation

Vasodilation is the process by which blood vessels increase in diameter. An important physiological process that controls blood pressure, tissue perfusion, and blood flow distribution throughout the body. Numerous overlapping variables, including systemic hormones, neuronal signals, and local metabolic factors, interact highly to guarantee that tissues receive enough oxygen and nutrients while making it easier to eliminate metabolic waste products ***(Clegg and Gabhann 2015)***. The dynamic, reticulated, and hierarchically structured vascular system always adjusts to changes in gene expression, cell-cell communication, local oxygen gradients, and other chemical and mechanical stimuli ***(Clegg and Gabhann 2015).***

Vasodilation is essential in regulating cardiovascular homeostasis and physiological responses to various challenges. This mechanism involves the relaxation of vascular smooth muscle cells in the walls of blood vessels, causing the vessel to dilate and lower vascular resistance. The complex interplay between local and systemic factors controlling vasodilation acts to optimise blood flow for the particular tissue. Such metabolic needs may differ across individual tissues and organs. The complexity of vasodilation is also manifested by the involvement of vasodilation in various physiological responses, including thermoregulation, exercise training, and immune response. Furthermore, the ability of the vascular system to adapt to both acute and chronic complications is an animal's adaptation, and the rest of the system is important.

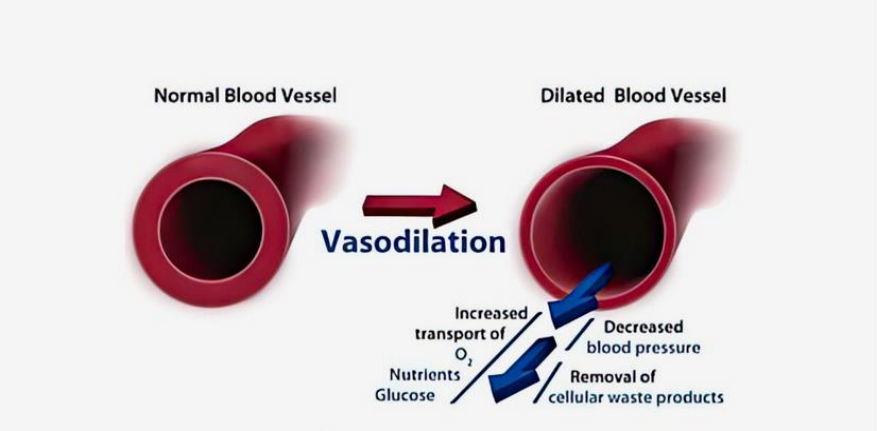


Figure 1 schematic summary showing the concise benefits after vasodilation of a blood vessel.

I 1.1 The different actors involved in the phenomenon of vasodilation

I 1.1.1 Endothelial cells

The endothelial cells are situated on a basal membrane formed by extracellular matrix proteins released by fibroblasts, which separates them from the underlying cells. They play a crucial role in vasodilation by producing nitric oxide (NO), a potent vasodilator.

Nitric oxide (NO) is thought to be the endothelium-dependent relaxing factor (EDRF) that mediates vascular relaxation in response to various stimuli ***(Huang et al., 1995).*** Endothelial cells are uniquely positioned to respond to rheological and humoral conditions and transduce these changes into vasoactive signals ***(Green et al., 1996).***

I 1.1.2Vascular smooth muscle cells

Vascular smooth muscle cells (VSMCs) constitute the cellular components of the normal blood vessel wall, providing structural integrity and regulating vessel diameter through dynamic contraction and relaxation in response to vasoactive stimuli. Their spindle-shaped architecture characterizes them and plays a crucial role in maintaining the structural integrity and function of blood vessels ***(Alford et al., 2011) (Metz et al., 2011)***. In their normal, differentiated state, VSMCs exhibit a contractile phenotype, expressing specific contractile proteins, ion channels, and cell surface receptors that regulate the contractile process ***(Metz et al., 2011).*** Interestingly, VSMCs demonstrate remarkable plasticity in their structure and function. In response to injury or stress, they can switch from a contractile to a synthetic phenotype, becoming less differentiated and acquiring proliferative, migratory, and synthetic capabilities ***(Tang et al., 2022)***. This phenotypic switching allows VSMCs to perform multiple tasks in both physiological and pathological conditions ***(Hu et al., 2019).***

I.1.1.3Nitric oxide (NO)

It is a key signaling molecule in vasodilation. It is produced by endothelial cells and can also be generated from nitrite reduction by deoxygenated myoglobin in vascular smooth muscle ***(Totzeck et al., 2012)***. NO activates soluble guanylate cyclase, leading to increased cGMP and subsequent vasodilation ***(Morgado et al., 2011).***

I.1.1.4 Cyclic nucleotides (cAMP and cGMP)

They are important second messengers that mediate vasodilation through multiple mechanisms, including decreasing cytosolic calcium concentration, hyperpolarizing smooth muscle cell membranes, and reducing the sensitivity of the contractile machinery ***(Morgado et al., 2011).***

Interestingly, some studies have identified additional actors in vasodilation. For example, the integrin αvβ3 expressed by smooth muscle cells can interact with RGD-containing peptides to cause vasodilation ***(Mogford et al., 1996).*** Additionally, myoglobin in vascular smooth muscle has been shown to contribute to nitrite-dependent hypoxic vasodilation ***(Totzeck et al., 2012).***

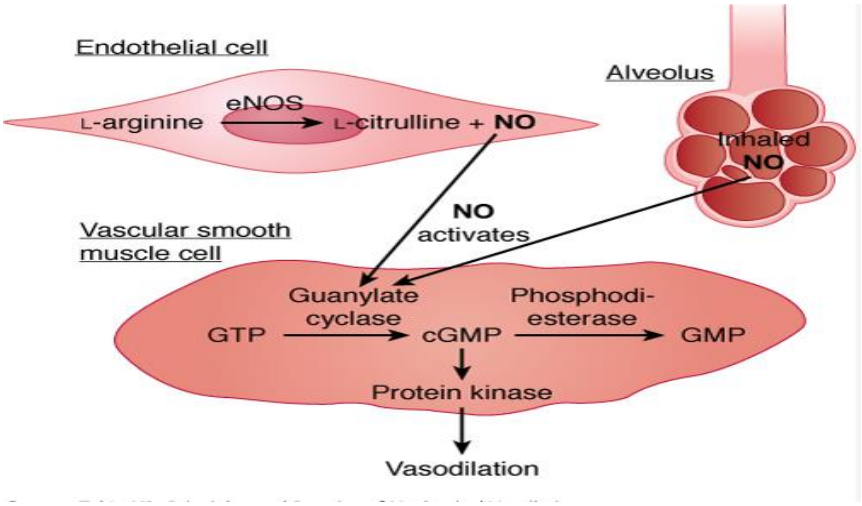


Figure 2 shows the schematic pathway of NO signal transduction in the two main compartments, which have a principal role in vasodilation.

I.2 Definition of vasodilators

Vasodilators are a class of a diverse group of pharmacological agents and endogenous substances that dilate blood vessels, improving blood flow and reducing blood pressure by acting on different components of the vascular smooth muscle and endothelial cells that line the inner walls of blood vessels. The balance between vasoconstrictors and vasodilators is essential for maintaining vascular tone and overall cardiovascular health, with disruptions in this equilibrium contributing to the pathogenesis of various cardiovascular diseases ***(Xu et al. 2021)***. They are commonly used to treat various cardiovascular conditions, including

hypertension, heart failure, and angina ***(Haghighat et al., 2024)(Sorkin & Clissold, 1987)***. These drugs work by relaxing the smooth muscles in blood vessel walls, leading to increased vessel diameter and reduced peripheral resistance ***(Sorkin & Clissold, 1987).***

At the forefront of vasodilation mechanisms is the endothelium, the single layer of cells lining the inner surface of blood vessels, which plays a pivotal role in regulating vascular tone and reactivity ***(Lüscher 2000).***

However, it is important to note that vasodilators can cause side effects such as orthostatic hypotension, headaches, and fluid retention, necessitating careful monitoring and personalized treatment approaches ***(Netala et al., 2024; Sorkin & Clissold, 1987).***

I.2.1 Classification

There are several categories of vasodilators, and many classifications by which we can classify them according to the differentiation criteria of these medications. The most commonly used is the one that classifies them based on their site of action. We will distinguish as follows: **1) Arterial predominant vasodilators**, most of which are: "Hydralazine, Minoxidine, Calcium Channel Blockers, Diazoxide, and Fenoldopam"

2) Venous predominance of vasodilators, we can cite only Nitrates derivatives

3) Mixed predominant vasodilators, most common are "Na nitroprusside, ACE inhibitors, Angiotensin receptor blockers, α-blockers"

They all have one common goal: reducing hypertension by decreasing blood pressure, which can have an adverse effect, "Reflex tachycardia." Meanwhile, they can cause "Na and fluid retention H2O," that is, in addition to the vasodilators; they are best used with "β-blockers and diuretics."

The main categories of vasodilators include:

1. Nitrovasodilators, Nitric Oxide (NO) Donors: - Organic nitrates (e.g., nitroglycerin, isosorbide dinitrate) - Sodium nitroprusside, these agents, such as nitroglycerin, generate nitric oxide (NO) which directly activates soluble guanylate cyclase, leading to increased intracellular cyclic GMP concentrations and smooth muscle relaxation ***(Waldman & Murad, 1988).***

2. Calcium Channel Blockers: - Dihydropyridines (e.g., nifedipine, amlodipine) - Non-dihydropyridines (e.g., verapamil, diltiazem)

3. Angiotensin-Converting Enzyme (ACE) Inhibitors: - Captopril, enalapril, lisinopril

4. Angiotensin Receptor Blockers (ARBs): - Losartan, valsartan, irbesartan

5. Endothelium-dependent vasodilators: Substances like acetylcholine require an intact endothelium to elicit vascular smooth muscle relaxation. They stimulate the release of endothelium-derived relaxing factor (EDRF), which activates guanylate cyclase and increases cyclic GMP production ***(Waldman & Murad, 1988).***

6. Endothelin Receptor Antagonists: - Bosentan, ambrisentan

7. Direct-acting Smooth Muscle Relaxants: - Hydralazine - Minoxidil

8. Atrial natriuretic peptides (ANPs): These peptides bind to specific receptors on vascular smooth muscle, activating particulate guanylate cyclase and elevating intracellular cyclic GMP concentrations ***(Waldman & Murad, 1988).***

9. ATP-sensitive K+ channel openers: Drugs such as cromakalim, diazoxide, and pinacidil act by opening ATP-sensitive K+ channels in arterial smooth muscle cells, causing hyperpolarization and vasodilation ***(Standen et al., 1989)***. - Nicorandil

11. Prostaglandin-based vasodilators: Compounds like prostaglandin I2 (prostacyclin) and its analogues activate delayed rectifier K+ channels in vascular smooth muscle cells, leading to hyperpolarization and relaxation ***(Li et al., 1997)***: - Alprostadil, epoprostenol

12. Phosphodiesterase Inhibitors: - Sildenafil, tadalafil (primarily used for erectile dysfunction)

13. Alpha-adrenergic Blockers: - Prazosin, doxazosin

This classification provides an overview of the main types of vasodilators based on their primary mechanisms of action. Each class works differently to achieve vasodilation, by either directly affecting vascular smooth muscle, modulating endothelial function, or interfering with vasoconstrictor pathways.

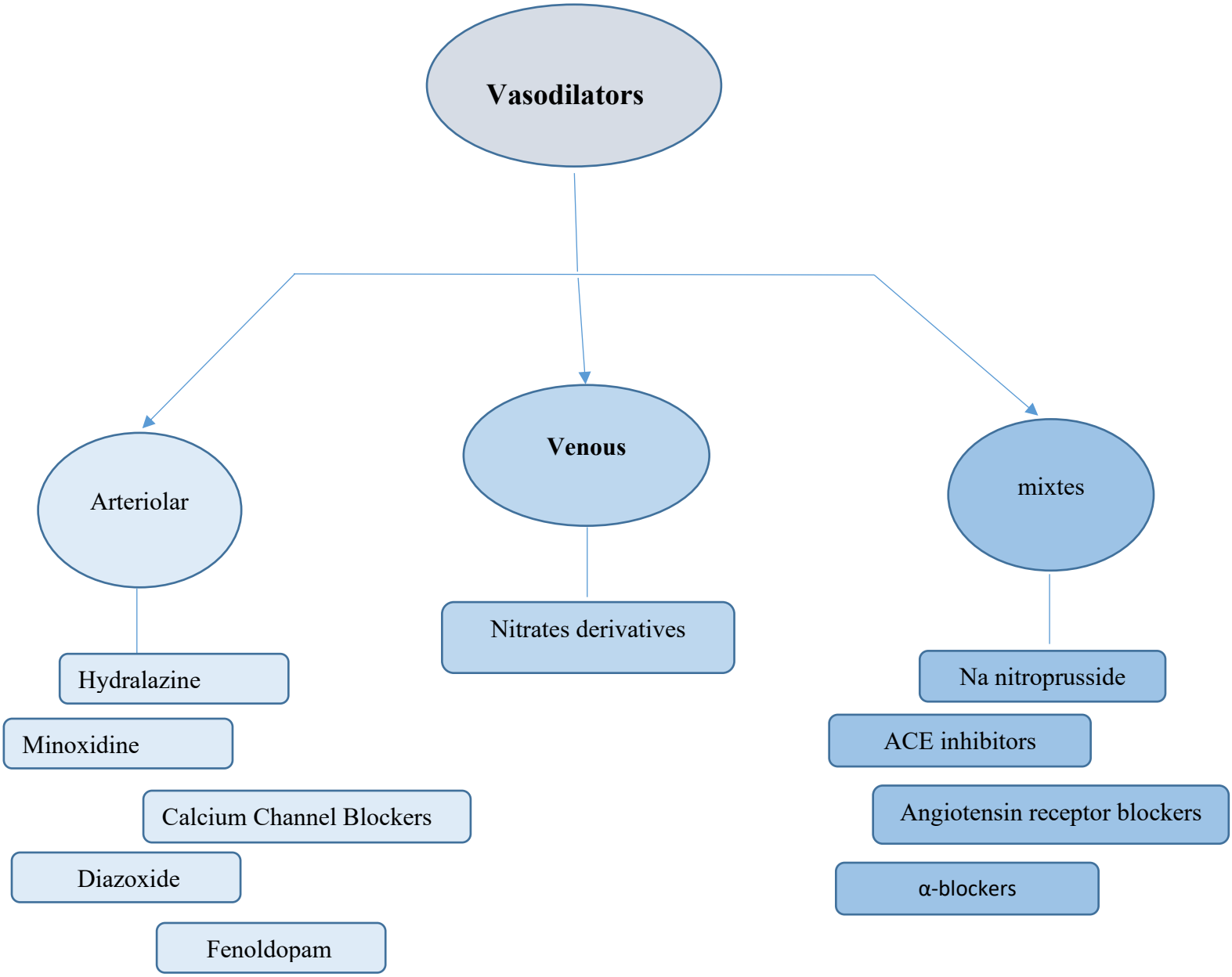


Figure 3 Plan showing the classification of some vasodilator drugs.

I.3 Blood vessels and arteries

I.3.1 Comparison between an arterial and venous wall

Blood vessels consist of three primary layers: the tunica intima, tunica media, and tunica externa. The innermost layer, the tunica intima, consists of endothelial cells that form the lining of all blood vessels, from the largest arteries and veins to the smallest capillaries **(Paz and D'Amore, 2008)**. These endothelial cells play a crucial role in vessel function and are subject to both genetic and environmental factors that determine their arterial or venous identity

(Adams, 2003; Paz & D'Amore, 2008). The primary difference between the arterial and venous walls lies in the thickness and composition of their layers, particularly the tunica media. Arterial walls are generally thicker and more muscular than venous walls, reflecting their need to withstand higher blood pressures. The tunica media of the arteries contains more smooth muscle cells and elastic fibers, allowing for better regulation of blood flow and pressure. In contrast, veins have thinner walls with a less developed tunica media, as they operate under lower pressure ***(Adams, 2003; Moyon et al., 2001).***

Interestingly, recent research has revealed that the differentiation of arteries and veins is not solely determined by hemodynamic forces but is also influenced by genetic programs ***(Adams, 2003; Chong et al., 2011).***

This genetic predisposition begins early in embryonic development, with arteries forming before veins in mammalian embryos ***(Chong et al., 2011)***. Additionally, specific molecular markers have been identified that distinguish between arterial and venous endothelial cells, such as EphrinB2 for arteries and EphB4 for veins ***(Herbert et al., 2009)***. These findings highlight the complex interplay between genetic factors and environmental influences in shaping blood vessel structure and function.

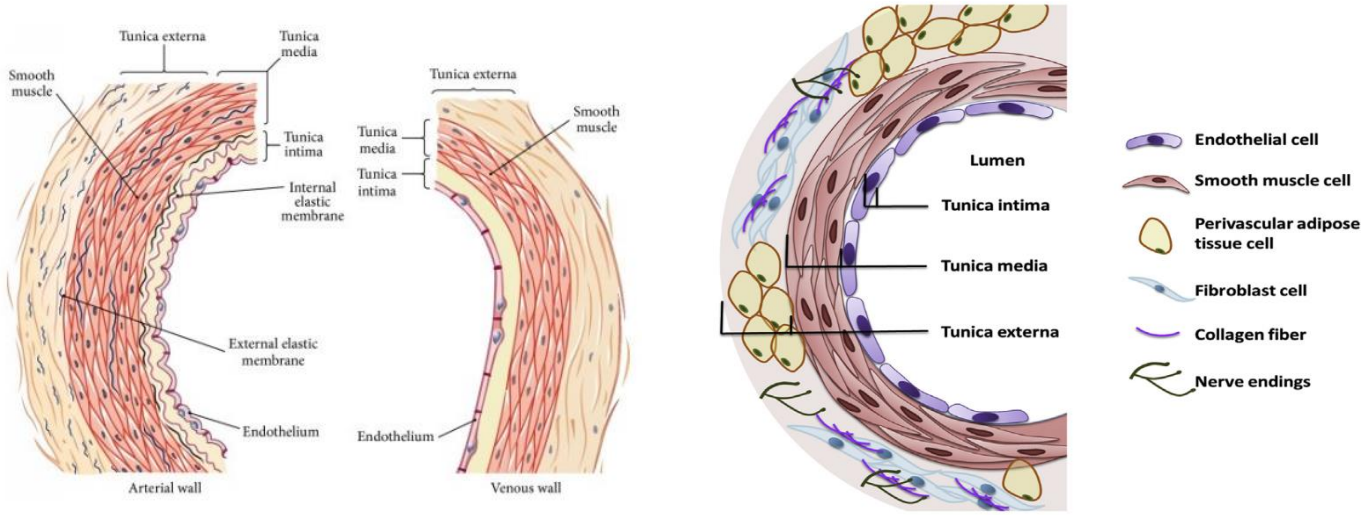


Figure 4 schematic summary of two figures showing the different structural parts of an arterial wall on the right and a comparison between the venous wall of a blood vessel and the arterial one.

I.3.2 Importance of blood vessels in the body

Blood vessels are essential for maintaining overall body function, adapting to physiological demands, and responding to pathological conditions. They play a crucial role in

it by serving multiple essential functions beyond simply conducting blood. They form a highly organized and complex closed circuit system that autonomously regulates blood flow, providing optimal oxygen and nutrient support to tissues while efficiently removing waste products ***(Eble & Niland, 2009)***. This vascular network is dynamic, capable of remodeling in response to various physiological and pathophysiological stimuli ***(Logsdon et al., 2013)***. Thus, their importance extends far beyond simple blood conduction, encompassing roles in nutrition, immunity, thermoregulation, and tissue repair.

-The importance of blood vessels extends to several key areas:

1. Nutrient and oxygen transport: Blood arteries, especially capillaries, facilitate the transfer of oxygen- and nutrient-laden blood to organs and tissues across the body. ***(Gornik & Beckman, 2005)***. This is essential for sustaining cellular activity and overall organ functioning.

2. Waste removal: The circulatory system facilitates the removal of metabolic waste products from tissues, helping to maintain homeostasis ***(Eble & Niland, 2009).***

3. Immune function: Blood vessels serve as a "highway" system for leukocytes, enabling immunological surveillance and rapid response to inflammation sites ***(Eble & Niland, 2009).***

4. Thermoregulation: Blood vessels play a role in regulating body temperature through heat transfer mechanisms, particularly in areas near the skin surface ***(Chato, 1980).***

5. Angiogenesis and tissue repair: Blood vessels can form new capillaries (angiogenesis) and collateral arteries, which are crucial for tissue repair and adaptation to ischemic stress ***(Maulik, 2006).***

6. Endocrine function: The endothelial cells lining blood vessels produce various substances, such as prostacyclin, that contribute to vascular health and function ***(Zetter, 1981).***

I.4 Mechanism of action of some vasodilator compounds

I.4.1 Potassium channel openers modulation

- Potassium channels play a central role in vasodilation by causing hyperpolarization of vascular smooth muscle cells, leading to muscle relaxation.

- Different potassium channels, such as calcium-activated, ATP-sensitive, and voltage-dependent, are involved in various vasodilatory responses ***(Gutterman et al., 2005).***

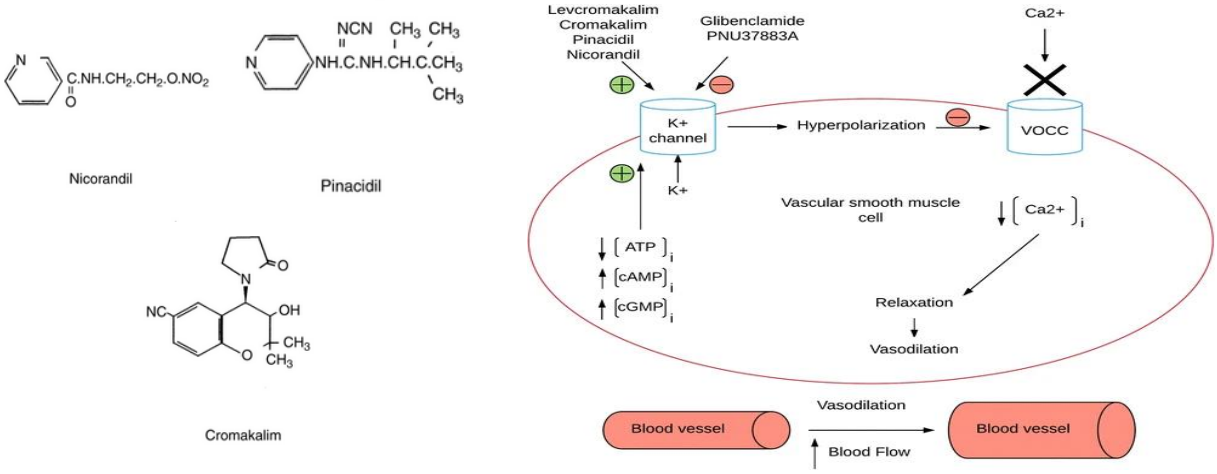


Figure 5 schematic summary showing how exogenous pharmacological agents (cromakalim and glibenclamide) regulate the activity of KATP channels by opening of vascular ATP-sensitive K channels. Endogenous molecules (ATP, cAMP, and cGMP) which help control the relaxation of the VSMCs

K+ Channel openers modulate vascular smooth muscle tone through multiple mechanisms, primarily by activating ATP-sensitive K+ (KATP) channels and large-conductance Ca^2-activated K+ (BKCa) channels ***(Edwards & Weston, 1995)***. This activation leads to membrane hyperpolarization and subsequent vasodilation ***(Dogan et al., 2019)***. The KATP channel is a complex composed of inwardly rectifying K+ channels and sulfonylurea receptor (SUR) subunits ***(Isomoto & Kurachi, 1997)***. K+ channel openers interact with specific residues in the last transmembrane helix of SUR, particularly SUR2 isoforms found in muscle tissues ***(Moreau, 2000)***. This interaction causes conformational changes that maintain the channel in an open state, increasing K+ efflux and hyperpolarizing the cell membrane ***(Bryan et al., 2005)***. Interestingly, some K+ channel openers like nicorandil have hybrid properties, activating both KATP channels and stimulating guanylyl cyclase to increase (cGMP) levels ***(Kukovetz et al., 1992)***. This dual mechanism contributes to their overall vasodilatory effect, with the relative contribution of each pathway varying depending on the drug concentration ***(Kukovetz et al., 1992)***. Additionally, K+ channel openers may have protective effects on mitochondria during oxidative stress, potentially through both K+ conductance-dependent and independent pathways ***(Ozcan et al., 2002)***.

I.4.2 Calcium channel blockers (CCBs)

Calcium channel blockers (CCBs) primarily work by inhibiting voltage-dependent L-type calcium channels in vascular smooth muscle cells and the myocardium ***(Scholz, 1997)***. This inhibition leads to a reduction in calcium influx, resulting in vasodilation and decreased myocardial contractility ***(Freshman, 2007; Godfraind, 2005)***. It can be used in hypertension and angina. The fundamental mechanism of action is shared across all CCBs; however, their pharmacological effects differ between subclasses ***(Frishman, 2007)***. Interestingly, although CCBs reduce calcium entry and produce vasodilatation, their effects on the heart can be more complex. The negative inotropic and chronotropic effects observed in vitro are often counteracted in vivo by a vasodilatation-triggered baroreceptor-mediated reflex increase in sympathetic tone, resulting in indirect cardiostimulation ***(Scholz, 1997)***. This compensatory mechanism helps to explain why some CCBs can be used in patients with certain cardiovascular conditions.

The development of second—and third-generation CCBs has revealed additional pleiotropic effects, such as regulating NO production and controlling smooth muscle cell proliferation, which may contribute to their therapeutic benefits beyond simple vasodilation ***(Mason et al., 2003).***

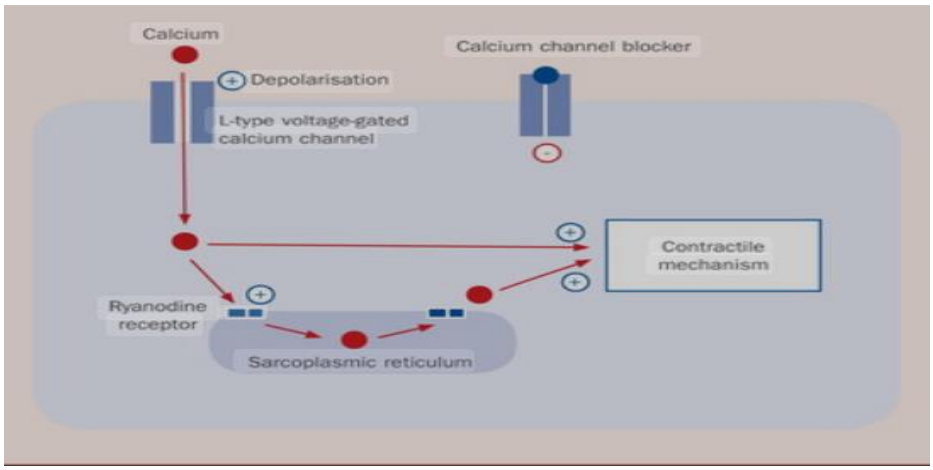


Figure 6 schematic summary showing how a normal process of depolarisation by the entry of Calcium makes a "Contractile mechanism" and how, by preventing access of (Ca^{2+}), using the "CCBs" through "L-type voltage-gated" would make a block in the Sarcoplasmic reticulum.

I.4.3 α_1-Adrenergic receptor blockers (α_1-blockers)

Alpha-blockers act as vasodilators primarily by antagonizing α1-adrenergic receptors in vascular smooth muscle, leading to relaxation and vasodilation ***(Traish et al., 2000; Vanhoutte & Rimele, 1982)***. This process happens when α_1-blockers inhibit Phospholipase C; thus, both

secondary messengers IP_3 and DAG, which are responsible for increasing intracellular Ca^{2+}, the responsible for the contraction, therefore resulting in a relaxation.

This mechanism involves inhibiting the vasoconstrictor effects of norepinephrine and other catecholamines on these receptors ***(Vanhoutte & Rimele, 1982)***. Interestingly, the sensitivity of different vascular beds to α-blockers can vary, possibly due to heterogeneity in α-adrenoceptor subtypes or functional differences in vascular smooth muscle cells rather than receptor pharmacology alone ***(Vanhoutte & Rimele, 1982)***. Additionally, some α-blockers may have additional mechanisms of action. For example, doxazosin has been shown to reduce peripheral resistance without causing reflex tachycardia, suggesting potential effects beyond simple α1-receptor blockade ***(Lund-Johansen & Omvik, 1991).***

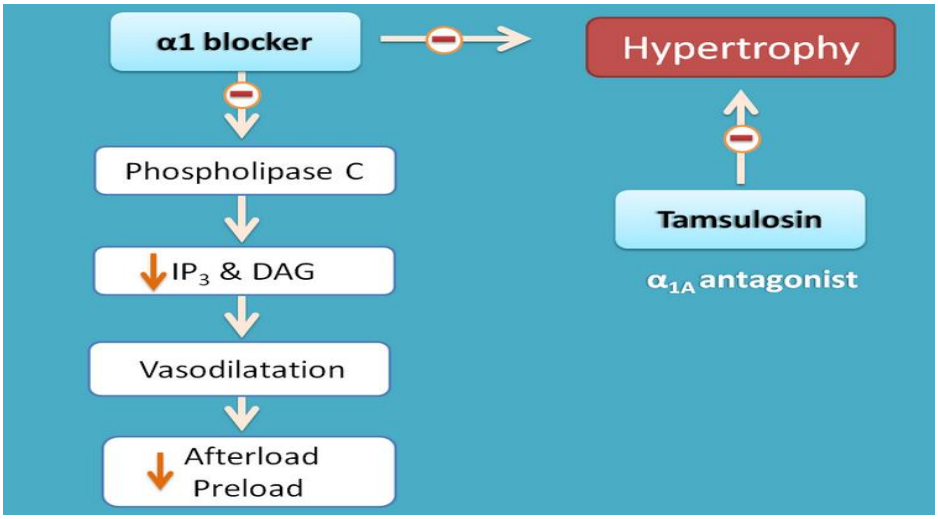


Figure 7 schematic summary showing how α1-Adrenergic Blockers blocks α_1 receptors thereby Inhibit α1 -mediated activation of phospholipase C and both secondary messages IP_3 and DAG responsible of increasing intracellular (Ca^{2+}) making the dilation of smooth muscle.

I.4.4 Mechanism of direct-acting vasodilator

In addition to the previous, some mechanisms we have a direct-acting vasodilator that has a direct influence on smooth muscle cells. Hydralazine, a synthetic direct-acting vasodilator, functions through mechanisms that have not been fully elucidated. It is recognized for inducing direct relaxation of arteriolar smooth muscle, potentially via redox-sensitive pathways that mitigate oxidative stress in vascular smooth muscle cells or by interfering with intracellular calcium handling. Unlike receptor-mediated agents, hydralazine does not operate through adrenergic or cholinergic receptors, resulting in a vasodilatory effect that is more pronounced in the arterioles than in the veins. Clinically, hydralazine is employed in the management of

moderate to severe hypertension, particularly in hypertensive emergencies and specific populations, such as pregnant women with preeclampsia.

I.5 Types of vasodilators according to the sources and origin

Vasodilators, which play a pivotal role in the management of conditions such as hypertensive emergencies and heart failure, can be classified into synthetic and natural categories based on their origin. Synthetic vasodilators are predominantly used in clinical settings, whereas natural vasodilators are derived from plant compounds. This distinction is essential for understanding the diverse mechanisms and applications of these compounds.

I.5.1 Synthetic vasodilators

- **Direct-acting Vasodilators**: These include drugs that act directly on vascular smooth muscles, such as nitrovasodilators, which release nitric oxide to induce vasodilation ***(Mallidi et al., 2015; Besada & Nguyen, 2024).***
- **Calcium Channel Blockers**: These inhibit calcium influx in vascular smooth muscle, leading to vasodilation ***(Mallidi et al., 2015; Besada & Nguyen, 2024).***
- **Adrenergic Antagonists**: These include beta and alpha-blockers that interfere with the sympathetic nervous system to reduce vascular resistance ***(Mallidi et al., 2015; Besada & Nguyen, 2024).***
- **Dopamine Agonists**: These act on dopamine receptors to induce vasodilation, particularly in the renal vasculature ***(Mallidi et al., 2015; Besada & Nguyen, 2024).***
- **Phosphodiesterase Inhibitors**: These increase intracellular cAMP or cGMP, leading to smooth muscle relaxation.

I.5.2 Classification table

Table 1: Shows the classification of vasodilators depending on their nature

Type	Subcategory	Examples	Source	Mechanism of Action
Synthetic Vasodilators	Nitrates	Nitroglycerin, Isosorbide dinitrate	Pharmaceutical	Donates nitric oxide → activates cGMP → smooth muscle relaxation
	Calcium Channel Blockers	Amlodipine, Verapamil	Pharmaceutical	Inhibits calcium influx → vascular smooth muscle relaxation
	ACE Inhibitors	Enalapril, Lisinopril	Pharmaceutical	Inhibits angiotensin-converting enzyme → ↓ angiotensin II → vasodilation
	ARBs	Losartan, Valsartan	Pharmaceutical	Blocks angiotensin II receptors → prevents vasoconstriction
	Direct Vasodilators	Hydralazine, Minoxidil	Pharmaceutical	Direct action on vascular smooth muscle → vasodilation
Natural Vasodilators	Endogenously Produced	Nitric oxide (NO), Prostacyclin	Body (endothelium)	Activates cGMP (NO) or increases cAMP (prostacyclin) → smooth muscle relaxation
	Dietary Compounds	L-arginine, Nitrates (beetroot), Omega-3s	Food (meat, fish, vegetables)	Enhances NO production, reduces inflammation, and modulates ion channels
	Phytochemicals	Flavonoids (green tea, cocoa), Allicin (garlic)	Plants, herbs	Antioxidant action, calcium channel modulation, and NO synthesis stimulation
	Minerals & Vitamins	Magnesium, Potassium, Vitamin C, Vitamin E	Diet, supplements	Modulates ion transport, antioxidant protection, and smooth muscle relaxation
	Traditional Medicinal Plants	Curcumin (turmeric), Gingerol (ginger), Ginseng	Herbal medicine	Anti-inflammatory effects, modulation of NO and prostaglandin pathways

I.5.3 Natural vasodilators

Vasodilators can be categorized into two primary groups based on their origin: natural (biological or dietary) and synthetic (pharmacological). Although synthetic vasodilators are extensively utilized in clinical practice, natural compounds are garnering increased attention due to their potential therapeutic advantages and minimal side effect profiles. The subsequent chapters delve into natural vasodilators, emphasizing their physiological importance and mechanisms of action.

Chapter 2

Chapter II. Natural vasodilators and their mechanism of action

II.1 Definition of natural vasodilators

Natural vasodilator compounds are molecules derived from natural sources that increase blood vessel dilation, enhance blood circulation, and lower blood pressure. These compounds, common in plants, are often produced endogenously or derived from natural sources and play a pivotal role in maintaining vascular homeostasis and regulating blood pressure ***(Tang et al., 2021)***. Their possible therapeutic advantages in supporting cardiovascular health have been investigated. The promise of natural vasodilators as safer substitutes for synthetic medications, with a reduced incidence of side effects, fuels their demand. Several of these substances have been recognized as potent vasodilatory agents. Common in plants, they have been explored for their potential therapeutic benefits in supporting cardiovascular health. Natural vasodilators, as possible safer substitutes for synthetic drugs with fewer side effects, generate interest in them.

These vasodilators often include natural compounds such as flavonoids, nitrates, and antioxidants, which significantly assist in relaxing blood vessels, thereby enhancing circulation. Some studies have also indicated that certain foods and herbs like beets, garlic, and dark chocolate may have significant and noticeable effects on vasodilation, especially when consumed regularly. Consequently, these natural alternatives may boost exercise performance, cognitive ability, and overall well-being, thereby extending their benefits to the heart and blood vessels.

II.1.1. Importance of natural vasodilators in medicine

Natural vasodilators serve an important function in medicine, especially in treating cardiovascular disease and hypertension. These chemicals, produced from traditional medicinal plants and natural products, have therapeutic properties that promote vascular relaxation and improve blood flow. Their importance is highlighted by their potential to serve as safer alternatives to synthetic medications, particularly in the treatment of preeclampsia and congestive heart failure. The following sections elucidate their significance and why they are important to consider in medicine ***(Tang & al., 2021).***

II.1.2. Role in emergency medicine

In emergency medicine, natural vasodilators play a crucial and effective role, especially in treating acute conditions that require rapid intervention to stabilize hemodynamics and improve patient outcomes. Critically, in cases such as pulmonary hypertension and hypertension, these agents help dilate blood vessels, reducing vascular resistance and increasing blood flow. Their uses and specific mechanisms are discussed in the following sections.

1. Applications in hypertensive emergencies

A crucial and effective role in managing hypertension is played by Vasodilators due to their ability to rapidly lower blood pressure, thereby protecting vital organs. Among the Vasodilators, such as nitric oxide donors and calcium channel blockers, are frequently prescribed medicines to reduce peripheral vascular resistance via diverse neurohormonal processes ***(Mallidi, Macias, & Lotfi, 2015).*** The impact of choosing a specific vasodilator on the systems of at-risk organs is frequently significant, emphasizing the necessity of personalized therapeutic strategies in this regard ***(Mallidi, Macias, & Lotfi, 2015).***

2. Role in Pulmonary conditions :

Vasodilators, including nebulized nitroglycerin, may reduce right ventricular strain in patients with acute pulmonary hypertension by decreasing pulmonary artery pressure ***(Ulloa & Tanzi, 2023).***

Pending the development of more definitive treatments, these drugs serve as a temporary measure to stabilize patients ***(Ulloa & Tanzi, 2023).***

Although natural vasodilators offer numerous benefits, the potential limitations and challenges associated with their use must be considered. The efficacy and safety of these compounds can vary based on their source and preparation; therefore, further research is required to fully understand their mechanisms and optimize their use in clinical settings. Additionally, the integration of natural vasodilators into mainstream medicine requires careful consideration of regulatory and quality control measures to ensure patient safety and treatment efficacy.

II.2 The differences between natural and synthetic vasodilators

The difference between natural and synthetic vasodilators primarily lies in their mechanisms of action. Natural vasodilators, which are often extracted from plant metabolites, mainly work through endothelial-dependent mechanisms by activating NO/cGMP signaling pathways that facilitate the relaxation of vascular smooth muscles ***(Luna-Vázquez et al., 2013)***. Additionally, they may inhibit voltage-dependent calcium channels, further contributing to vasodilation ***(Luna-Vázquez et al., 2013).*** In contrast, synthetic vasodilators, including calcium channel blockers, typically operate through endothelial-independent pathways by reducing the direct flow of calcium into vascular smooth muscle cells or the modulation of cyclic adenosine monophosphate (cAMP) levels. Which decreases contraction and promotes relaxation ***(Altura & Altura, 1984).***

Mechanisms of Action in Natural Vasodilators

- Nitric Oxide Pathway: Many natural compounds enhance vasodilation by stimulating NO production, which relaxes vascular smooth muscle ***(Luna-Vázquez et al., 2013).***
- Calcium Channel Blockade: Natural vasodilators can inhibit calcium influx, reducing vascular tone ***(Luna-Vázquez et al., 2013).***
- Diverse Chemical Structures: Secondary metabolites from plants exhibit a wide range of chemical structures, contributing to varied mechanisms ***(Luna-Vázquez et al., 2013).***

Mechanisms of Action in Synthetic Vasodilators

- Targeted NO Release: Synthetic vasodilators, such as nitroglycerin, primarily function by releasing NO, leading to vasodilation ***(Gagnon et al., 1980).***
- cAMP Modulation: Compounds like IBMX increase cAMP levels, promoting relaxation of vascular smooth muscle ***(Gagnon et al., 1980).***
- Specificity: Synthetic agents often have a more defined mechanism, allowing for targeted therapeutic applications ***(R et al., 2010).***

II.3 Classification of natural vasodilator compounds

II.3.1 Classification based on origin

Natural vasodilators encompass a diverse array of chemical compounds derived from plant sources, each characterized by unique chemical structures and mechanisms of action that facilitate the relaxation of blood vessels ***(Sezer & Uysal, 2021)***. Secondary metabolites play crucial roles in plant defense, pigmentation, and signaling, and have demonstrated therapeutic potential for cardiovascular disorders ***(Hussein & El-Anssary, 2018)***. The classification of these natural vasodilators can be approached from two fundamental perspectives: chemical structure and botanical origin, thereby enabling a more comprehensive understanding of their properties and applications. The primary chemical structures include flavonoids, phenolic acids, alkaloids, and terpenes, with botanical sources ranging from common herbs to specialized plant groups**. *(Adeosun & Loots, 2024; Bhatnagar, 2021; Zhang et al., 2013).***

II.3.2 Chemical structure

- **Flavonoids**: These are polyphenolic compounds found in various plants. Examples include apigenin and puerarin, which are known for their vasorelaxant properties through mechanisms such as calcium channel blockage and nitric oxide pathway activation ***(Tang et al., 2021; Ahmad et al., 2013).***

- **Phenolic Acids**: Compounds like curcumin are known for their vasodilatory effects, often linked to their antioxidant properties ***(Tang et al., 2021).***

- **Alkaloids**: This group includes compounds like berberine and sinomenine, which induce vasodilation through multiple pathways, including the activation of the eNOS/NO/sGC/cGMP pathway and modulation of calcium channels ***(Amssayef & Eddouks, 2023).***

- **Terpenes**: Compounds such as corosolic acid and meso-dihydroguaiaretic acid have shown significant vasodilatory effects, partly through the NO/cGMP pathway ***(Luna-Vázquez et al., 2018).***

From a structural point of view, natural vasodilators are divided into several main classes of "secondary metabolites" as mentioned above. Among these metabolites, we can then cite a few famous ones in each category.

❖ **Flavonoïdes**

Flavonoids are a class of polyphenolic chemical substances prevalent in plants, demonstrating several bioactivities; induce vasodilation often through endothelium-dependent mechanisms, including potential vasodilatory effects. These natural chemicals have been studied for their potential to treat chronic diseases and enhance cardiovascular health ***(Jasim et al., 2021; Laoué et al., 2022; Liu et al., 2022).***

- **Quercetin**

Quercetin, a naturally occurring dietary flavonoid, has shown pleiotropic effects, including potential cardiovascular benefits ***(Agrawal et al., 2020)***. It is a Flavanol class that belongs to the flavonoid family. Usually found in Onions, apples, berries, and broccoli has shown its ability to enhance endothelial NO synthase (eNOS) activity, inhibit endothelin-1, and reduce oxidative stress.

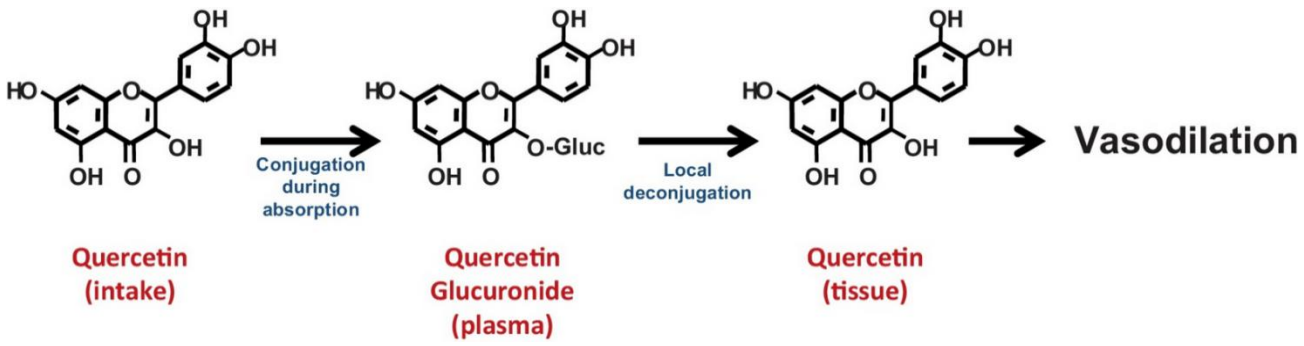


Figure 8 schematic summary showing how Quercetin is absorbed and converted into glucuronide in the plasma, then locally deconjugated in tissues to exert vasodilatory effects.

- **Epigallocatechin gallate (EGCG)**

The plant-derived catechin EGCG induces endothelium-dependent vasorelaxation and functions as a natural activator of eNOS in endothelial cells by enhancing its protein phosphorylation ***(Lorenz et al., 2004).*** It's a type of flavonol, "catechin," that has antioxidant action and can be found in green tea. It can lead to a vasodilation by generally promoting NO release.

- **Hesperidin**

Hesperetin has vasculoprotective properties that may elucidate the advantageous cardiovascular effects of citrus intake by enhancing flow-mediated dilation and diminishing levels of circulating inflammatory biomarkers ***(Rizza et al., 2011)***. Flavonone class belongs to the flavonoid family, which plays a role in inhibiting inflammatory mediators and improving vascular tone by acting on NO pathways. It is usually found in Citrus fruits (especially oranges and lemons).

- **Apigenin**

Apigenin (Ap), a flavonoid found in the Chinese herbal medicine "*Flos Chrysanthemi*", exhibits both anti-hypertensive and anti-inflammatory properties ***(Tang et al., 2021).*** Flavone class belongs to the flavonoid family, which leads to vasorelaxation by generally blocking the calcium channels in vascular smooth muscle. It is often found in Parsley, chamomile, and celery.

- **Naringenin**

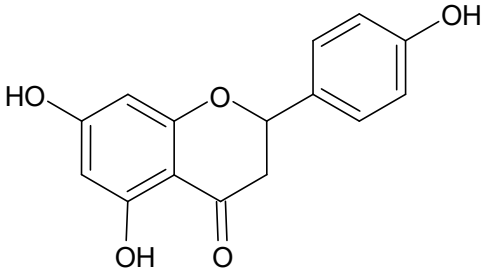
NGN and NAR influence cardiac endothelial cells and smooth muscle cells to promote vasodilation and permissive free blood flow ***(Adetunji et al., 2023).*** Naringenin (NGN) is a Flavonone class that belongs to the flavonoid family. Which usually enhances NO release, modulates potassium and calcium channels, has an antioxidant effect, and is generally found in grapefruit, tomatoes, and oranges.

- **Kaempferol**

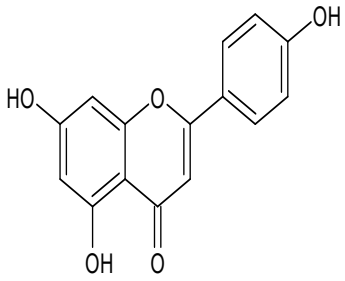
Kaempferol (Ka) induces vasodilation by inhibiting BKCa/LTCC channels or modulating the sGC/PKA pathway ***(Mahobiya et al., 2018),*** resulting in relaxation of pulmonary arterial rings pre-contracted with PHE ***(Tang et al., 2021)***. This flavonoid is prevalent in numerous edible plants, such as tea, cabbage, kale, broccoli, grapefruit, and beans. It has antioxidant and hypertensive effects by suppressing vasoconstrictive substances such as endothelin-1 while promoting endothelial-dependent relaxation ***(Mahobiya et al., 2018).***

- **Puerarin**

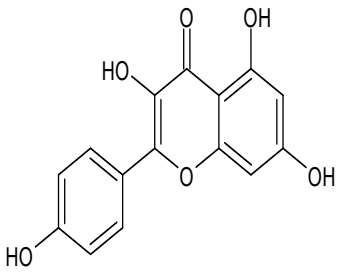
Puerarin (Pu) or "7-(β-D-Glucopyranosyloxy)-4′-hydroxyisoflavone" is the main isoflavone found in Pueraria lobata. The activities of (Pu) are concerned with endothelial cells or BKCa by enhancing nitric oxide (NO) production by up regulating endothelial nitric oxide synthase (eNOS) or inhibiting calcium influx in vascular smooth muscle cells, promoting relaxation **(Tang et al., 2021)**. It can also reduce oxidative stress and maintain endothelial function.



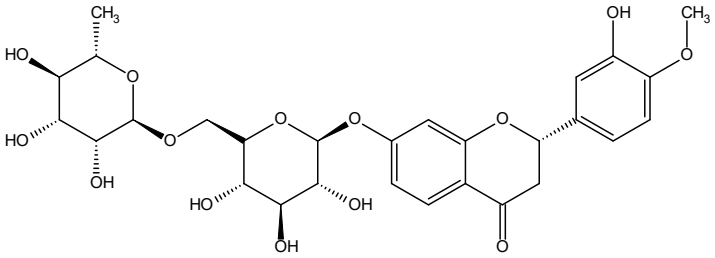
c) Naringenin



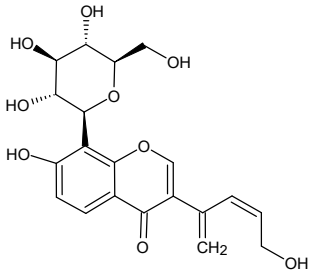
b) Apegenin



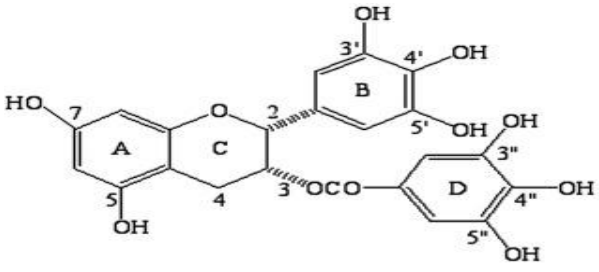
d) kaempferol



a) Hesperidin



e) Puerarin



Epigallocatechin gallate (EGCG)

Figure 9 Structures of some Flavonoïdes discussed.

❖ **Alkaloids**

Alkaloids, as natural chemical molecules, have shown promise as vasodilators, aiding in treating hypertension and cardiovascular disease. Tetrahydroisoquinoline (THIQ) alkaloids, a wide class of natural compounds, have a variety of structural characteristics and biological functions, including potential therapeutic applications **(Kim et al., 2023)**. Some alkaloids, such as those found in kratom (Mitragyna speciosa), have been examined for their effects on opioid receptors, which may indirectly affect vascular function **(Todd et al., 2020)**.

- **Reserpine**

Reserpine, an extract derived from the root of the naturally occurring plant "Rauwolfia serpentina," was historically employed as a primary treatment for hypertension **(Shamon & Perez, 2016)**. Reserpine reduces reflex vasomotor responses and directly affects peripheral vessels, independent of its influence on nervous activity ***(Gawade & Fegade, 2012).***

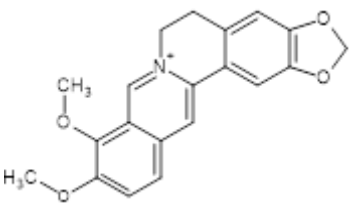
- **Berberine**

Berberine (BBR), a natural plant alkaloid extracted from Berberis vulgaris and Coptis chinensis (Huanglian) ***(Kong et al., 2020; Yang et al., 2021)***, has been demonstrated to confer cardiovascular protective effects. This is attributed to its ability to regulate gut microbiota **(Wang et al., 2022)** and inhibit the production of trimethylamine-N-oxide (TMAO) through its modulation. Empirical studies have indicated that BBR treatment improves vascular endothelial function and reduces blood pressure in hypertensive conditions ***(Wang et al., 2009; Cheng et al., 2013; Zhang et al., 2020a).***

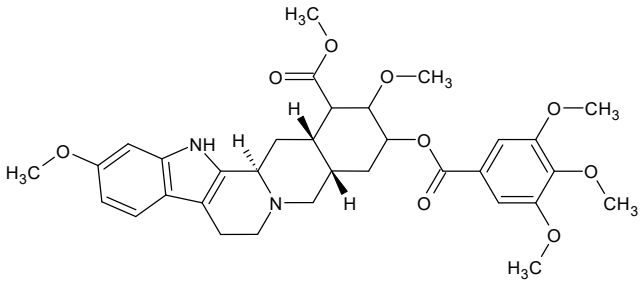
- **Sinomenine**

Sinomenine (*7, 8-didehydro-4-hydroxy-3, 7-dimethoxy-17-methyl-9α,13α,14α-morphinan-6-one*) is an alkaloid derived from the Chinese herb Sinomenium acutum Rehder et Wilson ***(Li et al. 2004)***. The mechanisms of action of sinomenine include vasorelaxation ***(Nishida & Satoh, 2007)***, which is mediated by the release of nitric oxide (NO) and prostacyclin (PGI2) from the endothelium. An increase in intracellular calcium ion

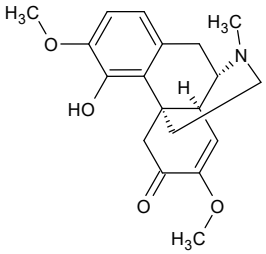
concentration ([Ca2+]i) within endothelial cells ***(Busse et al. 1998)*** leads to the activation of nitric oxide synthase (NOS) and the subsequent release of PGI2.



b) Berberine



a) Reserpine



c) Sinomenine

Figure 10 Structure of some alkaloids discussed**.**

❖ **Terpenes**

Terpenes, a variety of natural compounds, have received attention for their potential as vasodilators, particularly in terms of cardiovascular health. According to research, many terpenes have vasorelaxant properties, which can help lower blood pressure and treat hypertension. Among the terpenoids, we can mention the monoterpens class, which are the most famous ones dealing with vasodilation, along with Thymol, α-Terpineol, Carvacrol, eucalyptol (1,8-cineole), and many others. There are also some good ones like:

- **Limonene**

Limonene is the primary component that can be found in several citrus oils, including "orange, lemon, mandarin, lime, and grapefruit". It is among the most prevalent terpenes found in nature ***(Sun, 2007)***. The vasodilatory effect of it is significantly affected by the preservation of endothelium integrity, suggesting that it enhances endothelial function, crucial for vascular relaxation (Cardoso-Teixeira et al., 2018). It also stimulates A2A adenosine receptors

(A2AAR), increasing nitric oxide (NO) generation, which is required for vasodilation. This impact is most noticeable in asthmatic animals, where limonene improves A2AAR-mediated relaxation ***(Wyer et al., 2022).***

- **Borneol**

Borneol is a bicyclic monoterpene extracted from" Artemisia, Valeriana", and some other medicinal herbs. It causes vasorelaxation in aortic rings, which is affected by the presence of the endothelium. This action is mediated by the release of nitric oxide (NO) and prostanoids, which are essential for vascular relaxation ***(Santos et al., 2019).*** Also operates directly on vascular smooth muscle, largely by activating ATP-sensitive potassium (KATP) channels, resulting in muscular hyperpolarization and relaxation (Santos et al., 2019).

❖ **Phenolic Acids**

Phenolic acids are characterized by a hydroxyl group attached to an aromatic ring, enhancing their bioactivity ***(Tang et al., 2021)***. They have emerged as major natural vasodilators, largely by modulating nitric oxide (NO) levels and enhancing endothelial function. Among the famous ones, we can mention:

- **Curcumine**

Curcumin is a natural polyphenolic compound present in the Indian spice turmeric. Curcumin has been documented to diminish inflammation and oxidative stress by its anti-inflammatory, antioxidant, and antiaging effects, as well as the relaxation of the vascular smooth muscle cell by increasing nitric oxide production, improving vascular endothelial function. Source spécifiée non valide..

II.3.3 Botanical source

- **Compositae, Lamiaceae, and Orchidaceae**: These plant families are rich in traditional medicinal plants with vasodilatory properties, such as Vernonia amygdalina and Tridax procumbens ***(Tang et al., 2021).***
- **Camellia sinensis (Tea)**: Both black and green tea contain flavonoids that contribute to vasodilation through antioxidant mechanisms ***(Ahmad et al., 2013).***

- **Allium sativum (Garlic)**: Contains allicin, which has been shown to cause dose-dependent vasodilation ***(Ahmad et al., 2013).***
- **Nigella sativa (Black Seed)**: Known for thymoquinone, which improves endothelial function ***(Ahmad et al., 2013).***

Natural botanical vasodilators are sourced from various plants recognized for their therapeutic efficacy in the management of cardiovascular diseases. These plants contain bioactive compounds that facilitate vasodilation through diverse mechanisms, rendering them valuable in the treatment of conditions such as hypertension. We can highlight some specific plants like *"*Bidens pilosa, Alpinia purpurata, Allium sativum*"*.

- **Bidens pilosa**

Bidens pilosa, a perennial herb found in temperate and tropical climates, is one of about 230 to 240 recognized species. It is an extremely rich source of phytochemicals, particularly flavonoids and polyphenols. Plant flavonoids are commonly reported to have anticancer, anti-inflammatory, antioxidant, and other bioactivities, including antihypertensive and vasodilatory properties by acting as a calcium antagonist ***(Bartolome et al., 2013)***. It also contains important flavonoids such as quercetin, which is known to improve endothelial function by increasing nitric oxide (NO) production. This helps with vasodilation and blood pressure decrease.

- **Alpinia purpurata**

Alpinia purpurata, an ornamental plant native to the Pacific Islands, is commonly cultivated in Pernambuco, Brazil ***(Santos et al., 2012)***. A. purpurata hydroalcoholic extracts have been shown to exhibit vasodilating properties. It is acknowledged that it contains phenolic compounds, including flavonoids ***(Victório et al., 2009)***. These bioactive components are recognized for their ability to enhance endothelial function and vasodilation ***(Victório et al., 2009)***. Further research indicates that nitric oxide (NO) plays a role in A. purpurata-induced vasodilation.

b) *Alpinia purpurata* a) *Bidens pilosa*

Figure 11 Are both images of a) Bidens pilosa & b) Alpinia purpurata

- **Allium sativum**

Garlic, scientifically referred to as Allium sativum, is a bulbous plant that can grow up to 1.2 meters in height. The root bulb is used for medicinal purposes ***(Ali et al., 2023).*** Garlic serves as a natural vasodilator, significantly supporting cardiovascular health through various mechanisms. Allicin, the main bioactive compound, inhibits the angiotensin-converting enzyme (ACE), thus reducing levels of angiotensin II. This reduction leads to lower intracellular calcium levels and subsequent vasodilation by promoting vascular relaxation ***(Febyan et al., 2015)***. Moreover, garlic extracts display anti-inflammatory and antioxidant properties. ***(Ali et al., 2023).*** Allicin's antioxidant properties mitigate free radicals and oxidative stress in ventricular hypertrophy ***(Chan et al., 2013; Shi et al., 2018).***

Research indicates that enhancing endothelial function and inhibiting platelet aggregation can contribute to improved vascular health ***(Lu et al., 2023)***. Clinical studies have demonstrated that the daily consumption of garlic aids in reducing blood pressure and managing conditions such as hypertension and atherosclerosis ***(Qurbany, 2015; Adak & Silva, 2010).***

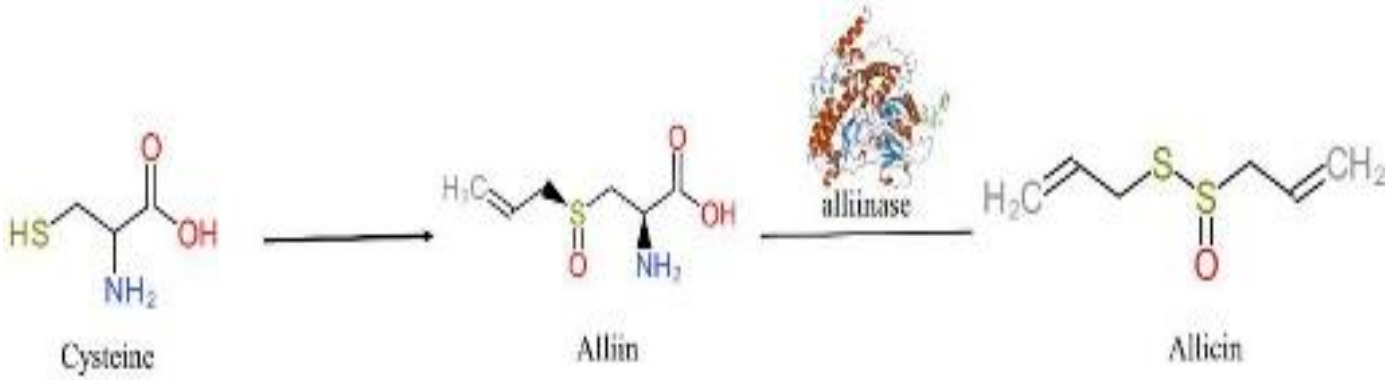


Figure 12 shows the allicin formation on the precursor alliin due to the action of alliinase enzyme.

II.3.4 Classification based on the mechanism of action

Natural vasodilators can be classified based on their mechanisms of action, which often involve the modulation of endothelial function, calcium channels, and potassium channels. The next sections go over these classes and their corresponding routes**.**

- **Endothelium-dependent mechanisms**

Many natural vasodilators, particularly those derived from plants, stimulate the eNOS pathway, producing enhanced nitric oxide (NO) generation. This results in vasodilation via the cGMP signaling pathway ***(Luna-Vázquez et al., 2013; Tang et al., 2021)***. Endothelium-dependent vasodilation is also demonstrated by alkaloids such as berberine and sinomenine, which increase eNOS activity and reduce oxidative stress ***(Amssayef & Eddouks, 2023).***

- **Calcium channel modulation**

A considerable variety of natural products have vasodilatory effects by blocking voltage-dependent calcium channels, which lowers intracellular calcium levels and increases vascular smooth muscle relaxation ***(McNeill & Jurgens, 2006; Tang et al., 2021)***. For example, flavonoids and phenolic acids have been found to block calcium influx, which contributes to their vasodilatory characteristics ***(Tang et al., 2021).***

- **Potassium channel activation**

Some natural vasodilators activate potassium channels, which causes vascular smooth muscle cells to hyperpolarize and then relax **(McNeill & Jurgens, 2006)**. This process is especially evident in alkaloids, which can open different types of potassium channels **(Amssayef & Eddouks, 2023).**

II.4 Natural vasodilators from dietary sources

Natural vasodilators are increasingly acknowledged for their potential in managing cardiovascular health and can be sourced from a variety of dietary origins. These natural compounds function by enhancing nitric oxide (NO) bioavailability, inhibiting calcium

channels, and providing antioxidant properties. The subsequent sections will explore key food sources and their bioactive components that facilitate vasodilation**.**

- **Garlic (Allium sativum):** contains allicin, which has been found to promote dose-dependent vasodilation in coronary arteries ***(Ahmad et al., 2013).***
- **Hawthorn (Crataegus spp.)** is known to improve endothelial-dependent relaxations, especially in aging-related vascular deficits ***(Ahmad et al., 2013)***.
- **Beetroot:** contains nitrates (NO_3^-), which improve NO bioavailability and promote vasodilation via the NO_3^-/NO_2^-/NO pathway ***(Silva et al., 2023).***
- **Black Green Tea (*Camellia sinensis*):**

Flavonoids in these teas contribute to vasodilation, likely through antioxidant properties ***(Ahmad et al., 2013).***

- **L-arginine and L-citrulline:** These amino acids increase NO production, improving endothelial function and reducing arterial stiffness ***(Silva et al., 2023).***
- **Potassium:** A daily intake of 1.5 g can restore endothelial function and promote muscle relaxation through NO release ***(Silva et al., 2023).***

Table 2*: Natural vasodilators from some common dietary sources*

Nutrient/Food Component	Function	Good Sources
Unsaturated Fats (Mono and Poly)	Improve blood cholesterol levels when replacing saturated or trans fats.	Fish (salmon, trout, herring), avocados, olives, walnuts, vegetable oils (soybean, corn, safflower, canola, olive, sunflower)
Omega-3 Fatty Acids	Reduce inflammation, decrease white blood cell adhesion to endothelium, may enhance vasodilation.	Fish, flaxseed, canola and soybean oils, wheat germ, Chinese broccoli
Antioxidants	Lower LDL oxidation, reduce inflammation, prevent plaque, may improve vasodilation.	Fruits, vegetables, beans, legumes, nuts, seeds, whole grains
Folic Acid	Breaks down endothelium-damaging homocysteine.	Citrus fruits, tomatoes, vegetables, grain products

L-Arginine	Promotes nitric oxide production, supports vasodilation and blood flow.	Plant & animal proteins, especially in nuts and legumes (e.g., lentils)
Fiber	Lowers cholesterol, aids weight loss, controls blood sugar.	Whole grains, fruits, vegetables, beans, legumes

II.5 The mechanism of action

II.5.1 Nitric oxide (NO)-dependent pathway

II.5.1.1 Nitric oxide (NO)

Nitric oxide is a heterodiatomic free radical that can participate in various biological functions ***(Loscalzo, 2000)***. It is a crucial signaling molecule in biochemistry and physiology. As a simple yet profound molecule, it consists of one nitrogen and one oxygen atom joined by eight bonds. The half-life of NO in whole blood is estimated to be under 2 milliseconds ***(DeMartino et al., 2018)***. NO plays a critical role in almost all of our bodily processes, making it vital for health and well-being. It is recognized for its diverse roles across various biological systems.

- It is critical in maintaining immune function and possesses antimicrobial properties.
- Facilitates cell-cell communication processes and regulates the response to injury and stress.
- Supports brain function and neurotransmission.
- Reduces inflammation and enhances exercise performance and stamina.
- Prevents the formation of arterial plaques, thereby reducing the risk of heart attacks and strokes.
- Prevents erectile dysfunction.
- Finally, and most importantly, it regulates blood flow and vasodilation, serving as the primary axis in this process.

II.5.1.2 The NO flow released causes

Nitric oxide is primarily produced by the endothelial cells; this is why it is called "Endothelial relaxing factor". It is released naturally by multiple factors:

1- When there is a shearing effect, which occurs when blood flow within a vessel increases and causes a stretch of the endothelial cells due to the viscosity of the blood, this shearing effect would mechanically trigger the vascular endothelial cells to release nitric oxide (NO).

2- The activation by visual amines may also cause the release of it.

3- The activation due to some receptors like Histamine "H_1 receptor" and prostacyclin.

II.5.1.3 The key enzymes involved in the production of nitric oxide in the human body

The human body synthesizes nitric oxide (NO) predominantly through two pathways: the L-arginine-NO-oxidative pathway and the nitrate-nitrite-NO reductive pathway ***(Lundberg, Weitzberg, & Gladwin, 2008)***. The main enzymes that produce nitric oxide (NO) are called nitric oxide synthases (NOS), and there are three types: **neuronal NOS** (**nNOS**), also called NOS (I), it is the one that is often found in the axon terminal of the neurons, **inducible NOS** (**iNOS**), also called NOS (II), involved in the inflammatory response that turned on in the activated macrophages, and **endothelial NOS** (**eNOS**) or NOS (III) which is the one constituent in the expressed inside endothelial cells ***(Förstermann & Sessa, 2012)***. It is also important to know that for both nNOS and eNOS, also (I) and (III), for them to work, they need Calcium to be elevated in the cytoplasm so they are called "Ca^{2+} Dependent ones" whereas for iNOS which doesn't need the Calcium "Ca^{2+} Independent one". Each of the Mammalian NOSs, also known as "flavoproteins", is homodimeric and contains heme. They also have a similar and identical structure and composition ***(Stuehr, 2004)***. Each isoform plays a distinct role in various physiological processes, including vascular regulation and immune response.

1-Regulation of NO Production

Factors: Calcium concentrations, protein interactions, and posttranslational modifications influence NOS activity, enabling meticulous regulation of NO levels for diverse physiological functions. ***(Childers & Garcin, 2017) (Bo & Chang, 2012).***

2-Nitric oxide synthases (NOS)

- **Isoforms:**
    - NOS (NOS1): Primarily found in neurons, involved in neurotransmission.

- iNOS (NOS2): Inducible form activated during immune responses, producing large amounts of NO.
- eNOS (NOS3): Located in endothelial cells, regulates vascular tone and blood flow ***(Król & Kepinska, 2020) (Wang et al., 2001).***

II.5.1.4 The L-arginine-NO-oxidative pathway production

1- Role of L-arginine in NO Production

L-Arginine (Arg) was subsequently identified as the precursor of nitric oxide and associated N-oxides (nitrite, nitrate). NO synthases, also known as NOSs (EC 1.14.13.39), facilitate the oxidation of arginine to nitric oxide and L-citrulline, employing NADPH and O_2 as cosubstrates ***(Alderton, Cooper, & Knowles, 2001)***. NOSs hydroxylate the terminal *guanidino nitrogen* of arginine to provide NOHA as an enzyme-bound intermediate. The enzyme then oxidizes NOHA further, generating NO and L-citrulline. 6-(R)-*Tetrahydrobiopterin* (H_4O) performs structural and redox functions in the NOS ***(Wei, Crane, & Stuehr, 2003)***. It is another essential cofactor that is strongly bound in NOS close to the heme ***(Wei, Crane, & Stuehr, 2003) (Alderton, Cooper, & Knowles, 2001).***

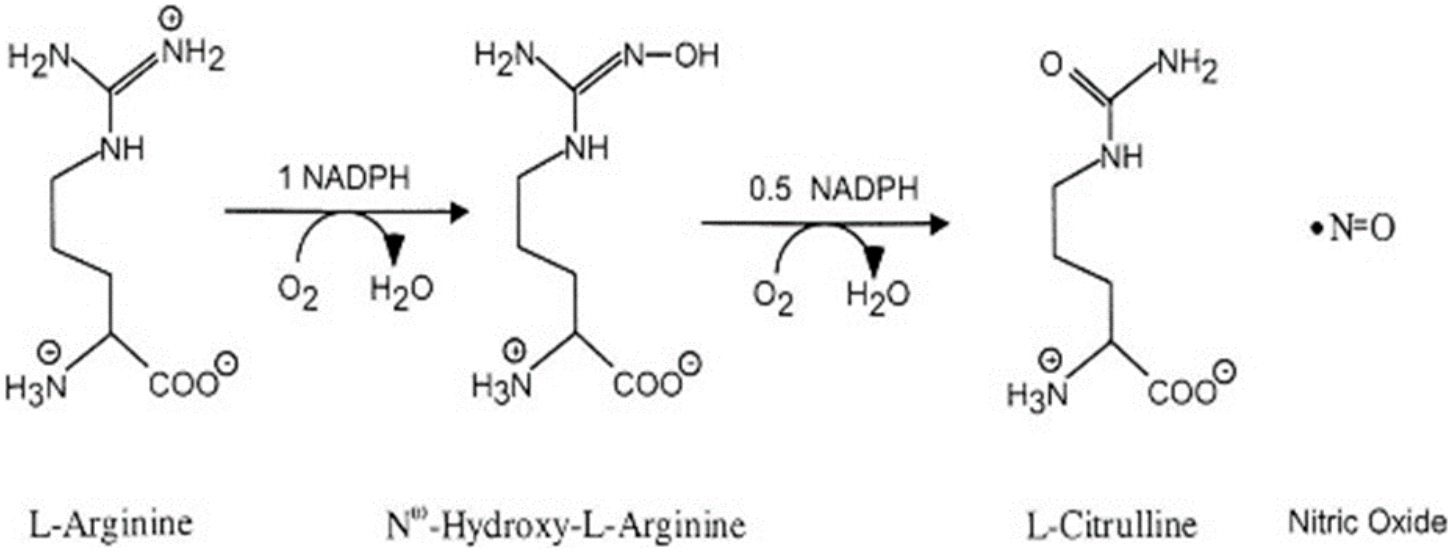


Figure 13 shows the two reactions of NO synthesis where NO catalyzes L-Arginine.

2-Influence of L-citrulline

L-citrulline can be recycled back into L-arginine, increasing NO production, particularly in settings where L-arginine is restricted ***(Baylis, 2006).***

Low urine citrulline levels are associated with blood pressure problems in pediatric CKD patients, suggesting a function in vascular health ***(Lin et al., 2016).***

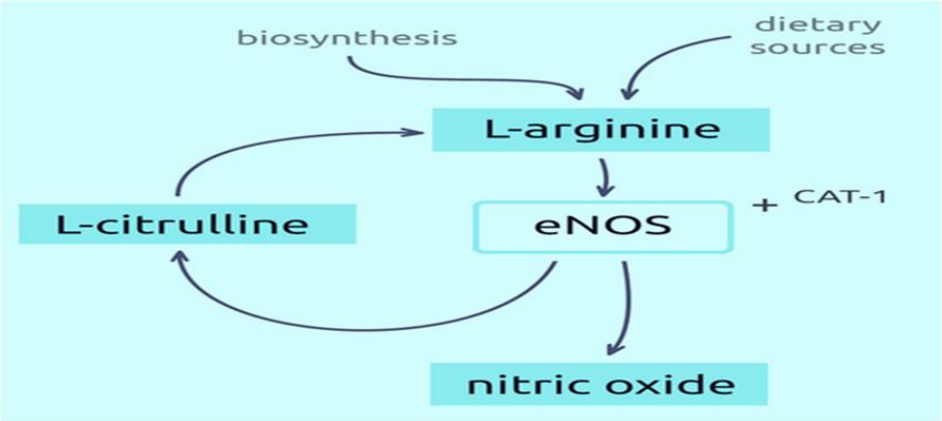
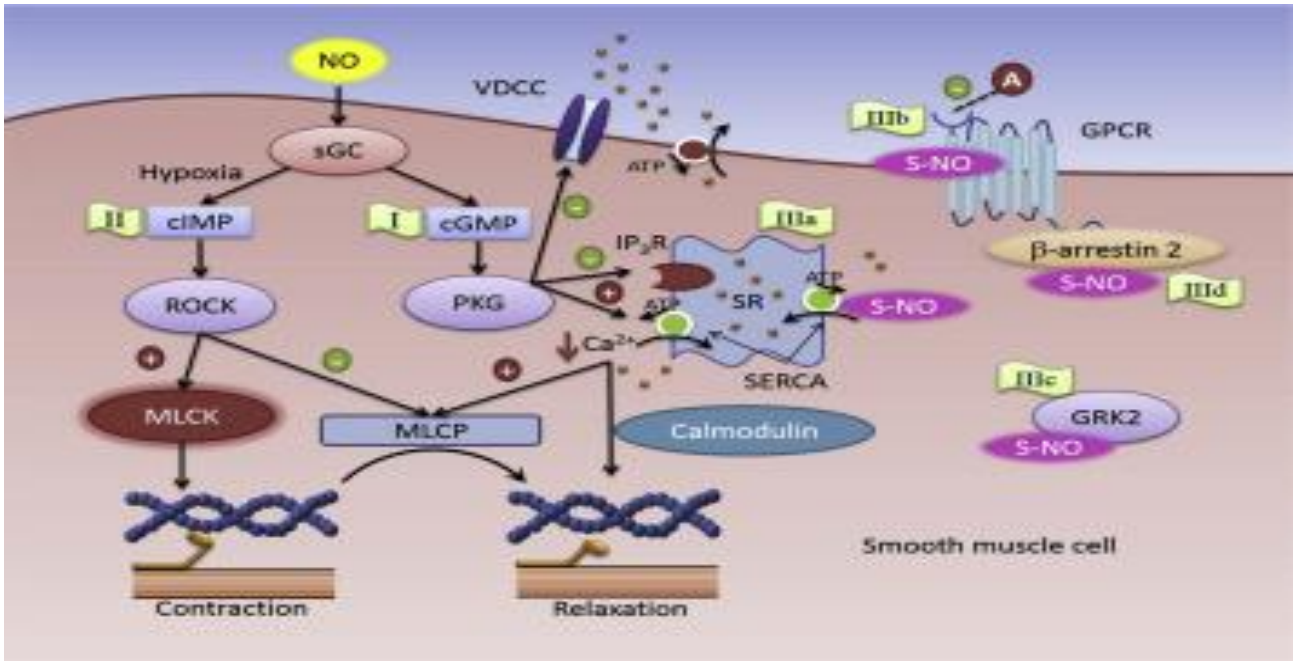


Figure 14 Synthesis of nitric oxide from L-arginine and recyclation of L-citrulline to L-Arginine.

3-Vascular actions of nitric oxide

Nitric oxide (NO) serves as a crucial regulator of vascular homeostasis, primarily by modulating vascular tone. It is synthesized within the cytosol of endothelial cells and swiftly diffuses into adjacent smooth muscle cells, where it exerts a paracrine effect. This effect happens when it activates soluble guanylyl cyclase (GTP), which increases the production of "3,5-cyclic guanosine monophosphate" (cGMP) ***(Jin & Loscalzo, 2010)***. Additionally, NO reduces cytosolic calcium (Ca^{2+}) concentration by inhibiting voltage-gated calcium



channels. It also activates protein kinase G (PKG), which phosphorylates proteins in the sarcoplasmic reticulum (SR) by blocking IP3 receptors and calcium-dependent potassium channels ***(Jin & Loscalzo, 2010)***. Consequently, the reduction in cytosolic Ca^{2+} concentration inhibits the formation of the "calcium-calmodulin-myosin light chain kinase" complex in vascular smooth muscle cells. This complex, influenced by calmodulin due to increased cytosolic calcium flux, plays a role in muscle contraction. The activation of "calcium-calmodulin-myosin phosphatase" by cGMP facilitates the dephosphorylation of myosin, leading to its detachment from actin. This process induces relaxation of the vascular muscle, thereby promoting vasodilation.

Figure 15 Regulation of vascular tone by nitric oxide (NO).

II.5.1.5 The nitrate-nitrite-NO reductive pathway

1-Definition of the nitrate nitrite- NO pathway

This pathway to NO formation is known to be reductive and NOS-independent, with enhanced activity during hypoxia or ischemia, or by aging. Both nitrite (NO2 −) and nitrate (NO3 −) denote their inorganic forms as anions of various salts with alkali cations ***(DeMartino et al., 2018)***. While nitrite is typically reduced to NO through proton and electron transfer events in mammalian vasculature by heme- and molybdenum-dependent enzymes, efficient nitrate reduction requires specialized enzymes in bacteria. Enteral symbiotic bacteria generate nitrite, which is further reduced to NO in the stomach or circulation ***(DeMartino et al., 2018)***.

2-Metabolism of nitrate/ nitrite-NO

The half-life of nitrite is approximately 42–52 min, thus (NO2 −) signals through various mechanisms, including the nitric oxide-soluble guanylate cyclase (NO-sGC) reductive pathway, which activates sGC via iron nitrosylation, subsequently converting guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) and promoting vasodilation ***(Jeffers et al., 2005)***. Additionally, nitrite participates in forming nitrosating agents through its dehydration to dinitrogen trioxide (N_2O_3), leading to the nitrosation of thiols, such as those present in complex I of the mitochondrial electron transport chain. This process is cytoprotective, as it inhibits the production of harmful reactive oxygen species (ROS) and the release of cytochrome c following reoxygenation **(*Chouchani et al., 2013)***. Furthermore, the oxidation of nitrite to radical nitrogen dioxide (NO2•) results in the nitration of various species,

including unsaturated fatty acids, thereby generating signaling nitro-fatty acids ***(Villacorta et al., 2016).***

Nitrite is commonly found in leafy green vegetables and beets, while nitrite is not typically present in natural foods. Humans can consume high levels of nitrate, particularly through vegetable-rich diets. While human nitrate reductase activity is a secondary function of xanthine oxidase for organic nitrates (R–ONO2) ***(Li et al., 2005),*** the reduction of inorganic nitrate is primarily attributed to the oral microbiome ***(Lundberg et al., 2008; DeMartino et al., 2018).***

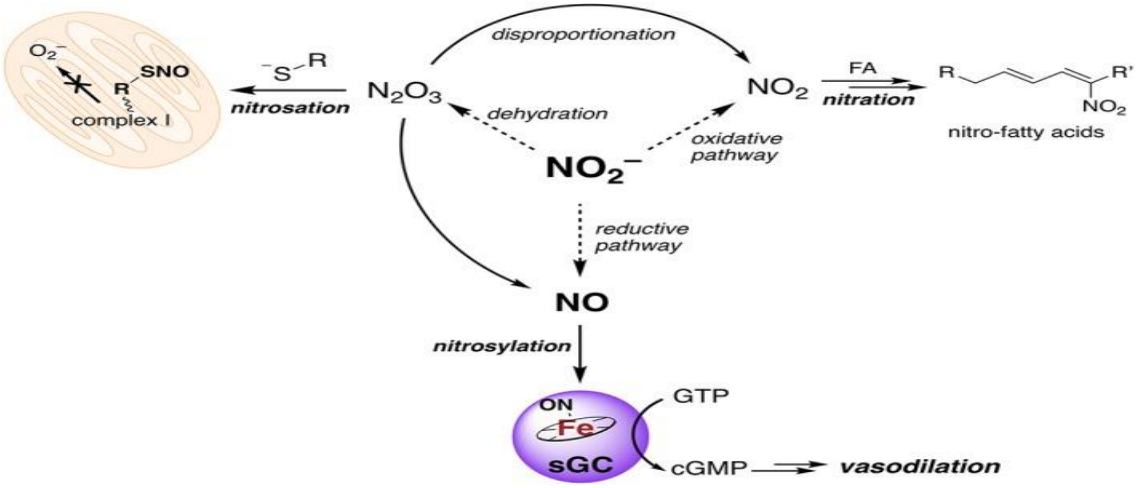


Figure 16 Schematic summary showing the protective and signaling effects of nitrite (NO2 −): where Nitrite can be reduced to NO, which nitrosylates ferrous haem in sGC, triggering cGMP production. Alternatively, it can be oxidized to yield NO2 •, which modifies redox-active thiols and activates transcription factors. Dehydration of nitrite can generate N2O3, which reacts with thiols, resulting in S-nitrosothiol formation, preventing damaging superoxide formation.

Upon ingestion, nitrate is reduced to nitrite by facultative anaerobes in the salivary glands using nitrate reductase enzymes to those found in soil bacteria (DeMartino et al., 2018) When swallowed, some nitrite is further reduced to nitric oxide (NO) in the stomach, modulating gastric fluid production and providing immunity against infections (Lundberg et al., 2011). The remainder is absorbed via the gastrointestinal tract and becomes part of the 'nitrate-nitrite-nitric oxide pathway' for vasodilatory control under hypoxic conditions.

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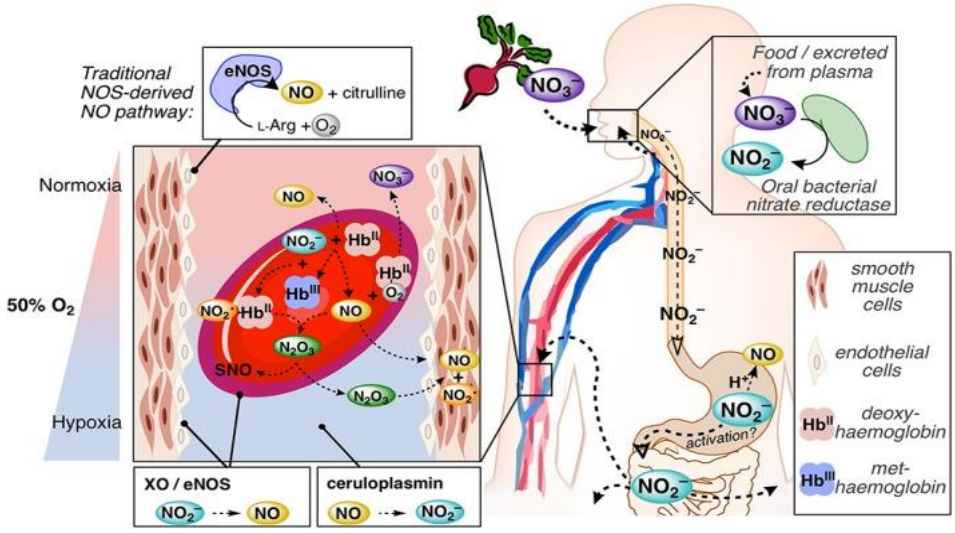

Figure 17 Schematic summary showing the nitrate-nitrite-NO pathway and the simplified chemical biology of nitrite within the vasculature.

II.5.1.6 Nitric oxide dysfunction in the context of oxidative stress

Nitric oxide failure is associated with oxidative stress, which is a primary cause of pathological conditions like cardiovascular disease and reproductive abnormalities ***(Madamanchi & Runge, 2008)***. The interaction between NO and reactive oxygen species (ROS), particularly the superoxide anion (O2−•), leads to the formation of peroxynitrite, a potent oxidant that exacerbates endothelial dysfunction by shifting from producing NO to generating more superoxide ***(Förstermann, 2010) (Dios et al., 2010)***. This contributes to disease progression. Oxidative stress deactivates NO, which causes oxidative damage, altered gene transcription, protein function, and enzyme activity. Peroxynitrite (ONOO−) has direct interactions with lipids, DNA, and proteins, as well as indirect interactions via radical-mediated mechanisms ***(Madamanchi & Runge, 2008).***

a) The Sources of superoxide (O2−•) production

- **The NAD(P)H oxidase enzyme complex**

The membrane-associated NAD(P)H oxidase enzyme complex in endothelial cells, vascular smooth muscle cells, adventitial cells, and fibroblasts reduces molecular oxygen by one electron, producing superoxide (O_2^{-}•) ***(Madamanchi & Runge, 2008).***

- **The xanthine oxidoreductase (XOR) enzyme system**

The xanthine oxidoreductase (XOR) enzyme system found on endothelial surfaces produces vascular (O^{2-}•). It catalyzes the oxidation of hypoxanthine to xanthine, which requires NAD+ as an electron acceptor. In hypercholesterolemic patients, reducing XOR activity with oxypurinol improved defective vasodilation, indicating that O2−• generation can limit bioavailable NO ***(Meneshian & Bulkley, 2002).***

- **The family of nitric oxide synthases (NOS)**

Endothelial cells may produce vascular oxygen (O2−•) via nitric oxide synthases (NOS) ***(Bouloumié et al., 1997)***. When L-arginine or BH4 levels are low, NOS uncouples and generates (O2−•) via one-electron reduction. Peroxynitrite (ONOO−) can also trigger NOS uncoupling**Source spécifiée non valide..** Hypercholesterolemia is associated with endothelial dysfunction ***(Verbeuren et al., 1986) (Khedara et al., 1998).***

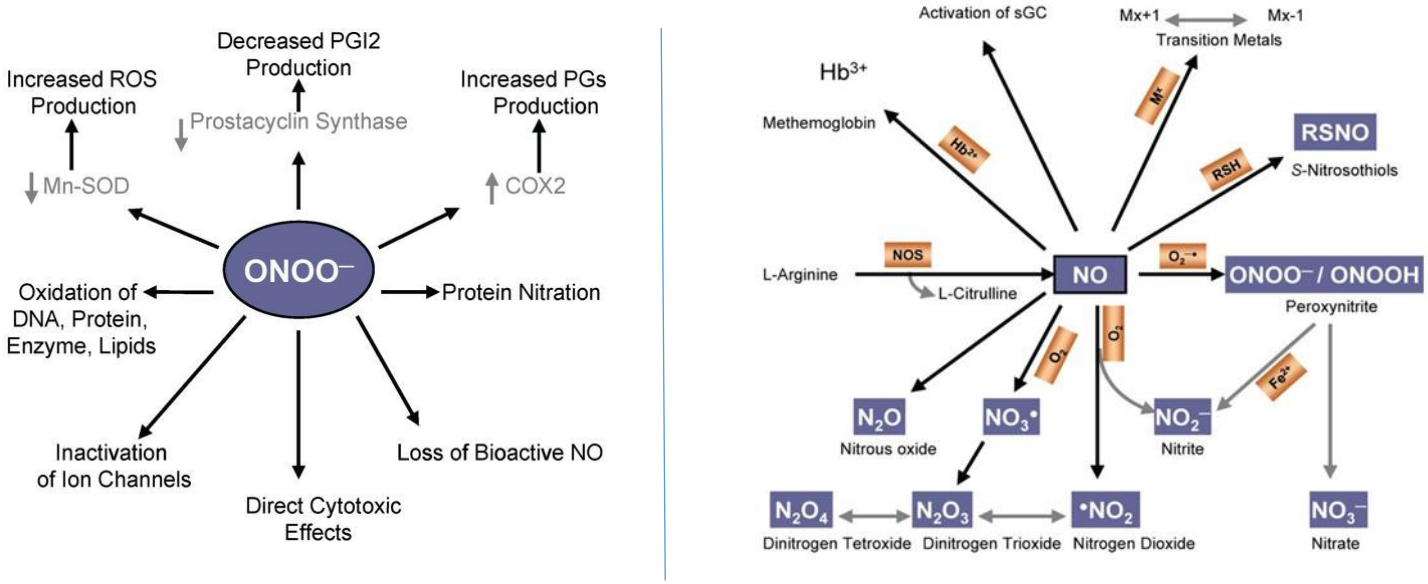

Figure 18 Shows on the right: The common Chemical Reactions of Nitric Oxide, whereas on the left.

b) The impact of oxidative stress on the vasculature

Oxidant species regulate various vascular signaling processes, including soluble "*guanylyl cyclases*" (sGC), prostaglandin synthesis, ceruloplasmin, myeloperoxidase, and tyrosine kinase-regulated systems. Increased O_2^-• generation leads to elevated cytoplasmic Ca^{2+}, which is subsequently constrained by the sarcoplasmic reticulum ***(Lounsbury et al., 2000)***. In smooth muscle cells, O_2^-• inhibits "inositol 1,4,5-triphosphate-sensitive responses" (IP_3) of the sarcoplasmic reticulum Ca^{2+}-ATPase, reducing Ca^{2+} uptake ***(Suzuki et al., 1993)***. This results in the contraction of smooth muscle cells, thereby raising their blood pressure.

II.5.1.7 Science-backed ways to boost the NO level in our body

1-Nasal breathing

Research suggests that specialized cells within the paranasal sinuses actively produce nitric oxide, facilitating its transport into the lungs through the process of respiration ***(Lundberg & Weitzberg, 1995).***

2-Humming

Humming enhances the production and release of nitric oxide (NO) by generating resonating sound waves. This vibration increases airflow oscillation in the sinuses, leading to a surge in NO release ***(Weitzberg & Lundberg, 2002).***

3-Exercies

Exercise stimulates the endothelium by enhancing oxygen (O2) levels and generating nitric oxide (NO) as a result of the mechanical forces induced by increased blood flow ***(Green, 2004).***

4- Diet

Natural dietary food compounds play a significant and crucial role in the vasodilatery effect, promoting blood flow and preventing hypertension, especially by their capacity to enhance nitric oxide (NO) ***(Siervo et al., 2013)***, which has an important role in that. Here are some of the famous foods that can help boost NO naturally in the body:

- Beets and beet juice

Beets and beet juice are known for stimulating nitric oxide production, as they are the richest natural source of nitrate compounds that the body can convert to NO. When consumed, nitrates are absorbed into the bloodstream, converted to nitrite by mouth bacteria, and further converted to NO in the stomach, facilitated by the body's acidic environment or specific enzymes ***(Siervo et al., 2013).***

- Garlic

Garlic, rich in compounds that activate NO synthesis, can increase NO production in the body. Allicin is a sulfur-containing compound in garlic that can release hydrogen sulfide (H_2S) and play a role in vasodilation by blocking Calcium channels. Allicin is also an antioxidant, protecting nitric oxide molecules from being degraded by ROS groups, in this case, superoxide (O_2^-), in oxidative stress. Garlic can also improve endothelial function ***(Chan et al., 2013).***

- Leafy greens

Leafy greens such as spinach, arugula (also known as rocket), and Romaine lettuce are rich in nitrates and, therefore, can play a significant role in enhancing nitric oxide (NO) levels.

- Celery

Celery, rich in antioxidants like vitamin C, flavonoids, and beta-carotene, can enhance the body's ability to protect NO molecules from oxidative stress. Its bioactives, including apigenin and luteolin, have anti-inflammatory properties, reducing inflammation and protecting the endothelium ***(Li et al., 2014).***

- Citrus fruits

Citrus fruits are rich in vitamin C, which serves as an excellent antioxidant. Vitamin C can enhance the activity of the nitric oxide synthase (NOS) enzyme, which is responsible for the production of nitric oxide (NO) through the oxidation pathway of L-arginine ***(Carr & Frei, 1999).***

- Watermelon

Watermelon can enhance nitric oxide (NO) production primarily due to its high content of L-citrulline, an amino acid that, once ingested, can be converted back into L-arginine in the kidneys and other bodily tissues, thereby further enhancing NO production ***(Hartman et al., 2019).***

Unlike L arginine supplements, L citrulline from watermelon is well-absorbed and may be more effective at increasing L arginine levels in the body than L arginine supplements, which may not be efficiently absorbed or cause GI distress for some people ***(Hartman et al., 2019).***

- Dark chocolate

Dark chocolate cacao is recognized for its high flavonoid content, especially epicatechin. It boosts nitric oxide (NO) levels by stimulating the endothelium, the inner lining of blood vessels, to produce nitric oxide. This effect is also achieved by increasing the activity of NO synthase ***(Heiss et al., 2003).***

- Pomegranates

Pomegranates' high concentration of antioxidants, particularly polyphenols like Punacollagen and alliin acid, stimulates the production of NO in the body and enhances its bioavailability by protecting it from oxidizing radicals ***(Aviram et al., 2002).***

- Nuts and seeds

Nuts and seeds, such as walnuts, almonds, pumpkin seeds, chia seeds, and flax seeds, can enhance the production of nitric oxide (NO) levels in the body primarily due to the presence of L-arginine. Additionally, some of these contain important antioxidants, such as vitamin E, flavonoids, and selenium, which have protective properties. Furthermore, certain nuts, like walnuts, contain “alpha-linolenic acid” (ALA), a type of omega-3 fatty acid that can improve endothelial function, which is beneficial for NO production ***(Ros, 2010).***

- Red grapes, peanuts, and berries

Grapes and berries contain a natural polyphenol, Resveratrol, which plays a crucial role by enhancing Nitric Oxide (NO) Production and has a significant antioxidant activity that can primarily protect the nitric oxide from being destroyed by oxidative stress and can improve the endothelial cell from any damage.

6- Photobiomodulation (PMB)

Low-level laser therapy (PPM) utilizes specific wavelengths of light to trigger biological reactions within cells, particularly via red and near-infrared light. ***(Selehpour et al., 2023).***

Cytochromes, especially cytochrome c oxidase, are essential for cellular energy production. Under certain conditions, NO can bind to these cytochromes, inhibiting their function and thereby reducing cellular energy production. PBM, in this context, especially at wavelengths around 650 nm and 840 nm, can displace NO from these cytochromes, restoring

mitochondrial function and increasing NO molecules in blood flow, which leads to vasodilation ***(Selehpour et al., 2023)***.

7-Optimizing the oral microbiome

Enhancing the oral microbiome in our mouth comprises a varied assemblage of bacteria, fungi, and viruses, collectively referred to as the oral microbiome. Beneficial bacteria in the oral cavity are essential for the conversion of dietary nitrates into nitrites, which serve as precursors to nitric oxide (NO**) *(MM Grant, 2019).***

II.5.1.8 Resveratrol and Dieckol, an example compound under the NO pathway

- **Resveratrol**

Resveratrol is a strong polyphenol compound found in grapes and berries. It is a molecule that plays an important role in the nitric oxide (NO) pathway, improving NO production and reducing oxidative stress by upregulating eNOS expression and activity, thus increasing NO availability and regulating blood pressure**Source spécifiée non valide.**. Resveratrol reduces NO-induced apoptosis in chondrocytes via the NF-κB pathway, therefore reducing inflammation**Source spécifiée non valide.**. It can also suppress endothelin-1 (ET-1), a potent vasoconstrictor, which may reduce vasoconstriction and enhance vasodilation balance. PI3K/Akt and AMPK resveratrol pathway play a significant role in improving endothelial function. This compound also helps to prevent age-related heart dysfunction by lowering oxidative damage and inflammation, which connects its actions to the NO pathway. Overall, its impact on cardiovascular health is remarkable.

- **Dieckol**

Dieckol, derived from the sea algae “Ecklonia cava”, has been found to increase vasodilation. It stimulates nitric oxide (NO) production via the PI3K/Akt/eNOS axis and calcium transients controlled by the M3 muscarinic acetylcholine receptor (AchM3R) ***(Lu et al., 2021)***. In zebrafish models, dieckol increased dorsal aorta diameter and controlled blood flow velocity ***(Lu et al., 2021).***

II.5.2 Prostaglandin pathway (PGI_2 / PGE_2)

II.5.2.1 Prostaglandin

Prostaglandins are natural vasodilators that play an important role in many physiological and pathological processes ***(Kim, 2008)***. They are produced from arachidonic acid and have a variety of effects on vascular tone, with certain kinds, such as PGE2, acting largely as vasodilators. This vasodilatory action is used in clinical settings, primarily to address disorders characterized by poor blood flow.

II.5.2.2 Biosynthesis and production of prostaglandin (PGs)

Prostanoids (PGs) and thromboxane A2 (TXA2) are produced when phospholipases release arachidonic acid (AA), a 20-carbon unsaturated fatty acid, from the plasma membrane and metabolize it via PGG/H synthase or COX. Bioactive PGs produced in vivo include prostaglandin E2 (PGE2), prostacyclin (PGI2), prostaglandin (PGD2), and prostaglandin (PGF2α). These lipid mediators help to maintain local homeostasis in the body. PG production levels and patterns shift substantially during an inflammatory response, with production peaking just before leukocyte recruitment and immune cell infiltration.

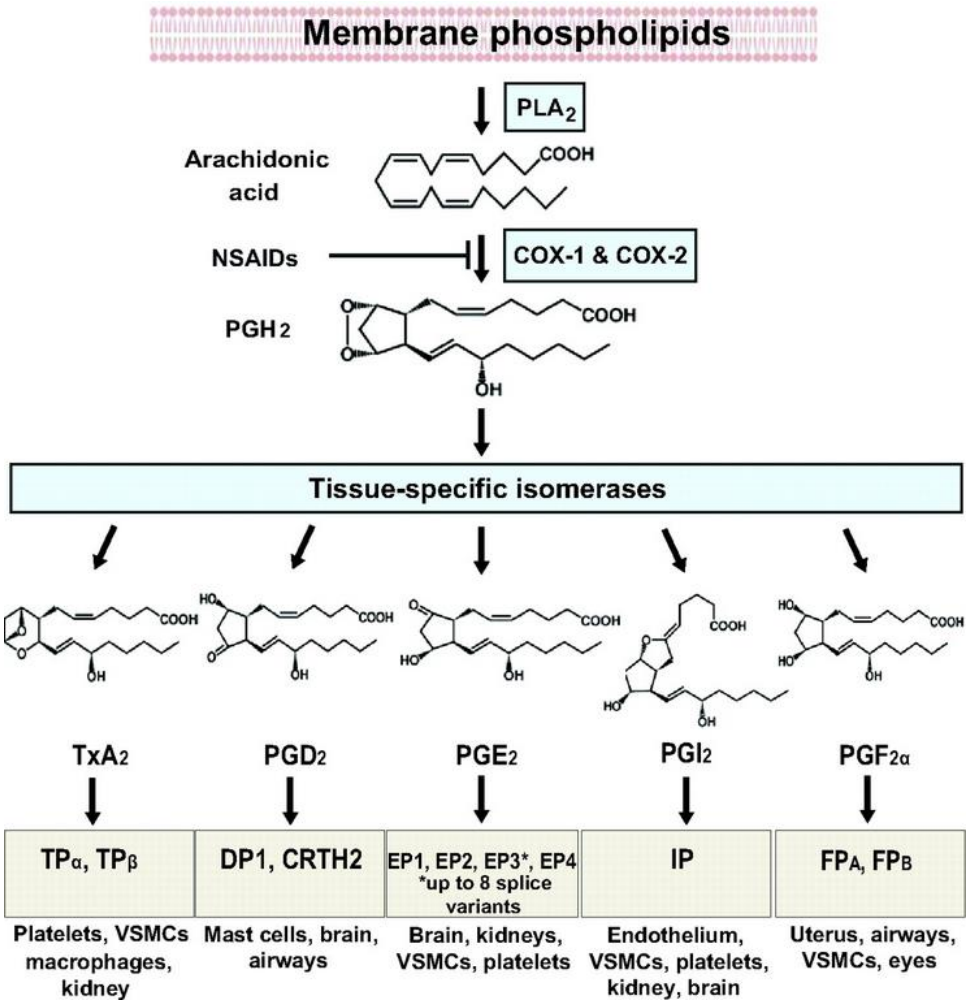

Figure 19 schematic summary shows the Overall Biosynthetic pathway of prostanoids.

II.5.2.3 Mechanism of action of PGs

Prostaglandins play an important part in vasodilation by serving as signaling molecules that relax vascular smooth muscle, resulting in enhanced blood flow. The mechanism of action is the creation and release of prostaglandins in response to diverse stimuli, which subsequently interact with specific receptors on vascular smooth muscle cells or endothelial cells to cause vasodilation. This process is frequently facilitated by the activation of certain signaling pathways, such as those involving nitric oxide (NO) and endothelial-derived hyperpolarizing factors (EDHF). The next sections go over the mechanisms and pathways involved in prostaglandin-induced vasodilation.

- **Prostaglandin Synthesis and Release**

Bradykinin, a powerful prostaglandin biosynthesis activator, causes coronary vasodilation by increasing the release of prostaglandin-E2-like molecules in the heart. Indomethacin, which inhibits prostaglandin synthesis, enhances this process while inhibiting bradykinin destruction ***(Needleman et al., 1975).***

Prostacyclin analogues activate particular potassium channels in pulmonary artery smooth muscle cells during vasodilation, which is mediated by the prostanoid I receptor and protein kinase A pathway ***(Li et al., 2009)***

- **Receptor-Mediated Pathways**

Prostaglandins promote vasodilation via engaging with P2Y receptors on endothelial cells, resulting in the production of NO, EDHF, and prostaglandins themselves. This interaction causes vascular smooth muscle to relax, followed by vasodilation ***(Wihlborg et al. 2003).***

- **Interaction With Other Mediators**

Prostaglandins frequently function in conjunction with other vasodilators, such as NO and EDHF. For example, in human arteries, the extracellular nucleotides' vasodilatory impact is mediated via a combination of NO, EDHF, and prostaglandins ***(Wihlborg et al., 2003).*** Prostaglandins play a role in vasodilation by modulating cardiovascular reflexes and pain during myocardial infarction and angina, where they work in conjunction with other mediators such as bradykinin ***(Needleman et al., 1975).***

Some sources of dietary food substances have a significant ability for enhancing the synthesis or activity of vasodilatory prostaglandins (especially prostacyclin, PGI_2). Like: **Omega-3 fatty acids** (fish oil), **Gingerol** (ginger), and **Turmeric** indirectly via COX modulation.

II.5.3 cAMP-mediated vasodilation: activation and mechanism

II.5.3.1 Cyclic adenosine monophosphate (cAMP)

The precise modulation of vascular tone is essential for maintaining adequate blood flow and pressure, with vasodilation playing a critical role ***(Mahdy et al., 2010)***. Cyclic adenosine

monophosphate (cAMP) is a common second messenger that regulates the effects of several hormones and neurotransmitters, including those that cause vasodilation. **(Bates, 2010).**

II.5.3.2 Molecular mechanism of (cAMP) activation

Adenylyl cyclases produce cyclic adenosine monophosphate from adenosine triphosphate, resulting in cell-type and stimulus-specific responses ***(Panjaitan et al., 2019; Sassone-Corsi, 2012)*.** The balance between cyclic adenosine monophosphate synthesis by adenylyl cyclases and breakdown by cyclic nucleotide phosphodiesterases carefully regulates its intracellular concentrations. Elevated cyclic adenosine monophosphate levels activate protein kinase A, a serine/threonine kinase that phosphorylates several intracellular target proteins, resulting in a cascade of downstream processes that eventually lead to vasodilation ***(Chang et al., 1998).***

II.5.3.3 Physiological Aspects of cAMP-Mediated Vasodilation

Protein kinase downstream targets that promote vasodilation are varied and function via various mechanisms, including the lowering of intracellular calcium concentrations in vascular smooth muscle cells, which is an important determinant of vascular tone ***(Touyz et al., 2018).***

Certain flavonoids act through β_2-adrenoceptor or direct cAMP elevation, such as **kaempferol** and **naringenin**, play a significant role in opening BKCa channels, leading to smooth muscle relaxation, potentially via cAMP-mediated pathways ***(Saponara, Sgaragli, & Fusi, 2006).*** In addition, **Forskolin** extract from "**Coleus forskohlii***"* is a potent activator of adenylate cyclase, leading to increased intracellular cAMP levels and subsequent smooth muscle relaxation ***(Laurenza, 1989)(Seamon, 1981).***

II.5.4 Calcium channel blockers mechanism

II.5.4.1 Calcium channel inhibition as a mechanism of natural vasodilator

Calcium ions (Ca^{2+}) play a significant role in controlling vascular smooth muscle contraction. Ca^{2+} influx through voltage-dependent calcium channels, especially L-type channels, causes muscular contraction and vasoconstriction. Inhibiting these channels reduces intracellular calcium levels, which promotes smooth muscle relaxation and vasodilation ***(Mironova, 2022)***. While synthetic calcium channel blockers (CCBs) are commonly utilized

in clinical settings to treat hypertension and other cardiovascular disorders, several natural substances have shown similar inhibitory effects on these channels. The most famous compounds that showed important effects are allicin, flavonoids, and ginger ***(Mironova, 2022).***

II.5.4.2 Allicin as a natural calcium channel modulator

Allicin, a sulfur-containing compound present in garlic, has been demonstrated to block L-type calcium channels in vascular smooth muscle cells by altering cysteine residues on channel proteins. According to certain research, it may affect L-type voltage-gated calcium channels in diabetic rats ***(Sánchez-Gloria, 2022)***. In addition, allicin is a provider of hydrogen sulfide (H_2S), a gaseous signaling molecule that causes membrane hyperpolarization and decreased calcium entry into cells by activating potassium channels and causing vasodilation. These modifications can disrupt channel function, contributing to its vasodilating effect. It also has antioxidant properties, which make it a perfect vasodilator compound ***(Sánchez-Gloria, 2022).***

II.5.5 Potassium channel modulation

II.5.5.1 Potassium channel modulation in natural vasodilation

Potassium (K^+) channel activation is a crucial method by which natural chemicals cause vasodilation after calcium channel suppression. Vascular smooth muscle cells' opening of these channels causes membrane hyperpolarization, which closes voltage-gated calcium channels, lowering intracellular calcium levels and relaxing the smooth muscle. Numerous natural substances, including sulfur-containing compounds, flavonoids, and polyphenols, have been demonstrated to target these pathways, demonstrating the variety of ways that nature promotes vascular health ***(Nelson, 1995).***

II.5.5.2 Curcumin as natural potassium channel modulators

Curcumin, a curcuminoid produced from "*Curcuma longa*" (turmeric), acts as a natural vasodilator by modulating potassium channels, particularly those that are ATP-sensitive (KATP) **(Xu, 2014)**. This causes hyperpolarization of vascular

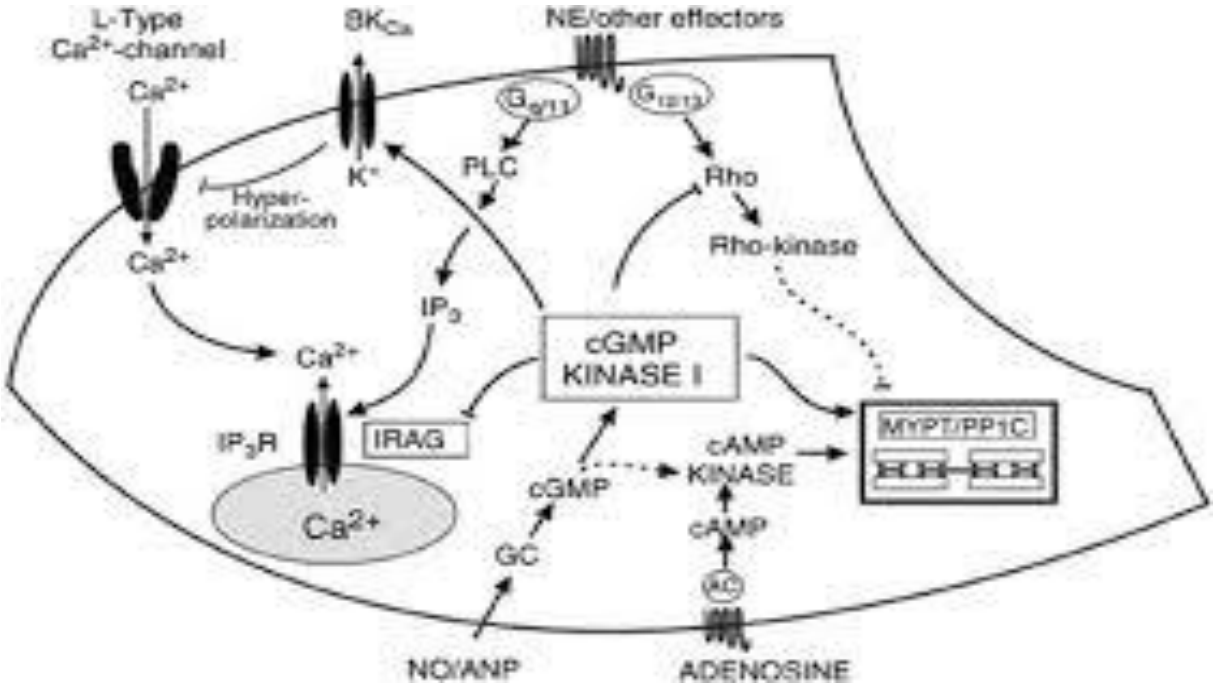

Figure 20 Shows Smooth Muscle Tone Regulation by (cGMP) kinase showing the effect of different modulators like L type calcium-channel and BKca potassium channel.

Smooth muscle cell membranes, which reduces calcium inflow and promotes relaxation of vascular tone. Curcumin's cardioprotective and antihypertensive benefits have been linked to better endothelial function and lower vascular resistance. When combined with other natural agents like allicin, they will modulate K^+ channels to maintain vascular homeostasis ***(Xu, 2014).***

II.5.6 Endogenous mediators of natural vasodilation

In addition to plant-derived compounds. The human body naturally produces vasodilators, including histamine and bradykinin, which regulate vascular tone, immune responses, and inflammation. Histamine, released from mast cells and basophils, binds to H_1 receptors on endothelial cells, causing nitric oxide release and smooth muscle relaxation. This

contributes to vasodilation in allergic and inflammatory reactions ***(Sandilands, 2013)***. Bradykinin, a peptide generated during the "kallikrein–kinin" cascade, promotes vasodilation by stimulating the release of NO, prostacyclin, and endothelium-derived hyperpolarizing factors. These vasodilatory effects are essential for blood pressure regulation and tissue perfusion. Although not acquired through diet, these molecules are considered "natural" vasodilators and complement dietary bioactives like resveratrol or allicin in supporting vascular health ***(Dachman et al., 1993).***

II.6 Comparison of efficacy

II.6.1 The efficacy of different natural vasodilators

Several research studies have investigated the efficacy of several natural vasodilators, revealing different methods and effects. Natural products frequently cause vasodilation via several routes, including nitric oxide release, potassium channel activation, and calcium channel inhibition ***(McNeill & Jurgens, 2006)***. In contrast, synthetic vasodilators, such as angiotensin-converting enzyme (ACE) inhibitors, have shown significant benefits in chronic heart failure, improving both functional status and death rates ***(Mulrow et al., 1988).***

II.6.2 Clinical efficacy

- Chronic Obstructive Pulmonary Disease (COPD)

Vasodilators such as PDE-5 inhibitors improved gas exchange but had minimal effects on pulmonary function ***(Han et al., 2024).***

- Heart Failure

ACE inhibitors were found to be highly beneficial in reducing mortality and increasing functional status in heart failure patients ***(Mulrow et al. 1988).***

- Cerebral Hemodynamics

Vasodilators increased cerebrovascular responsiveness without significantly affecting cerebral blood flow, indicating promise for stroke prevention ***(Webb, 2019).***While natural vasodilators have potential mechanisms, their clinical efficacy may not be comparable to proven synthetic medicines, especially in critical circumstances such as heart failure.

Chapter 3

Chapter III Medical and therapeutic application

III.1 Natural approaches to vasodilation: A therapeutic overview

III.1.1 Introduction to natural vasodilators and their clinical relevance

Natural vasodilators derived from plants offer promising therapeutic potential as treatment agents for managing cardiovascular disease, notably hypertension and heart failure. These bioactive substances, which include flavonoids, phenolic acids, and alkaloids, act through a variety of pathways ***(Luna-Vázquez et al., 2013)***. As we discussed in the previous chapter, these compounds primarily act by activating the nitric oxide/cGMP pathway, as many natural vasodilator compounds increase nitric oxide production, resulting in vasodilation ***(McNeill & Jurgens, 2006)*****,** highlighting the importance of this small molecule in this process, also by blocking voltage-dependent calcium channels, inhibiting calcium influx, and reducing vascular resistance ***(Tang et al., 2021)***. Some flavonoids and chemicals, such as allicin, have a particular effect on L-type calcium channels and increase the release of endothelium-derived relaxing factors. Furthermore, some of these compounds activate potassium channels, contributing to cytosolic hyperpolarization and vasorelaxation ***(McNeill & Jurgens, 2006).***

Traditional medicinal plants from families such as Compositae and Lamiaceae have shown vasodilatory and hypotensive activities ***(Tang et al., 2021)***. Natural therapies, including phytotherapy and herbal medicine, are gaining popularity for their unique advantages in preventing and treating cardiovascular diseases ***(Yang et al., 2016)***. All have been said, the clinical relevance of this substences still underscored by their potential as alternative therapies and nutritional supplementswhile many compounds demonstrate promising results in vitro and preclinical studies, although further research and more extensive clinical trials are needed to fully understand their efficacy and potential applications in cardiovascular disease management and validate their efficacy in clinical settings ***(Tang et al., 2021; Yang et al., 2016).***

III.1.2 The importance of understanding medical and therapeutic

Applications of natural vasodilators

Natural vasodilators derived from medicinal plants and bioactive substances provide alternative or complementary treatments for cardiovascular conditions such as hypertension,

angina, and heart failure ***(Gurney, 1994).*** These vasodilators enhance cardiovascular function by widening blood arteries, lowering peripheral resistance, and decreasing venous return ***(Gurney, 1994)***. Nitrovasodilators, such as organic nitrates and sympathomimetic drugs, produce nitric oxide (NO), which reduces smooth muscle tone and provides anti-ischemic effects ***(Kojda, 2000)***. Endothelial dysfunction is commonly induced by risk factors such as hypercholesterolemia, which reduces NO bioactivity and contributes to coronary artery disease **(Britten et al., 1999)**. Therapeutic therapies seek to enhance NO bioavailability through various mechanisms **(Britten et al., 1999).**

- Importance in Cardiovascular Health

Natural vasodilators can assist in controlling chronic conditions such as hypertension and other cardiovascular disorders, lowering the risk of consequences from vascular lesions ***(Tang et al., 2021)***. They work through a variety of mechanisms, including antioxidant actions that protect bioactive chemicals like NO, as well as vasodilation and lipid modification, all of which are necessary for cardiovascular protection ***(Sreedevi & Mavilavalappil, 2024)***. They are becoming recognized as important in the treatment of illnesses such as acute decompensated heart failure (ADHF), where they can improve patient prognosis and quality of life ***(Pan et al., 2024).***

Natural alkaloids have shown promise as vasodilators with endothelial-dependent and independent mechanisms, particularly via the eNOS/NO/sGC/cGMP pathway, potassium channel activation, and calcium channel modulation ***(Amssayef & Eddouks, 2023).*** These chemicals show promise for preventing and treating cardiovascular disorders, particularly hypertension ***(Amssayef & Eddouks, 2023).*** However, relying entirely on natural vasodilators without proper clinical validation may be risky, as evidence from clinical studies is required to confirm their safety and efficacy in diverse patient populations **(*Oxford University Press, 2022).***

III.2 Medicinal and clinical applications of natural vasodilators

III.2.1 Hypertension

Hypertension is a chronic illness characterized by persistently high blood pressure in the arteries. It is defined as a continuous blood pressure reading of 140/90 mm Hg or above, and is often asymptomatic, earning it the moniker "silent killer" ***(Khan et al., 2021)***. If left

untreated, it can lead to serious complications such as a heart attack, stroke, or kidney failure. Risk factors for hypertension include genetic predisposition, environmental variables, and lifestyle choices such as nutrition and physical inactivity ***(Mirza et al., 2024; Goorani et al., 2024)***. Additionally, obesity, excessive salt consumption, aging, and stress contribute to the risk ***(Goorani et al., 2024)***. Hypertension increases the likelihood of heart disease, chronic kidney disease, and stroke ***(Raj et al., 2024)***, as well as cognitive impairment. The underlying causes usually include vascular wall thickening, stenosis, occlusion, and endothelial cell damage.

III.2.1.1 The pathophysiology of hypertension

Hypertension's pathophysiology involves increased vascular resistance, which is caused primarily due arteriole constriction and an increase in blood volume. Natural vasodilators, such as those found in foods or herbal supplements, can significantly reduce vascular resistance by relaxing the vascular smooth muscle. This relaxation reduces peripheral vascular resistance and thereby lowers blood pressure.

III.2.1.2 Therapeutic role of natural vasodilators in hypertension Management

Natural vasodilators such as NO relax vascular smooth muscle, resulting in arteriole dilatation and lower peripheral resistance. These bioactive compounds reduce the workload on the heart by reducing arterial pressure, which helps to manage hypertension ***(Cohn et al., 2011).*** Studies indicate that natural vasodilators reduce systolic and diastolic blood pressure ***(Rysz et al., 2017).*** Long-term use of these bioactive medicines may lower the incidence of cardiovascular events linked with hypertension illness ***(Sica & Gehr, 2001).***

III.2.2 Atherosclerosis

Atherosclerosis is a complex illness characterized by chronic inflammation and the production of plaques within artery walls. A variety of genetic predispositions influence its growth. Over 160 genes are linked to atherosclerosis, influencing lipid metabolism and inflammatory responses ***(Marín-García, 2014)***. There are additional environmental considerations. Dyslipidemia, hypertension, diabetes, obesity, and smoking are major

contributors, which interact with genetic variables to cause and exacerbate the condition ***(Luca et al., 2023)***

The etiology is predominantly linked to pathophysiological mechanisms, such as endothelial injury. Damage to endothelial cells, also known as "endothelial dysfunction," elicits inflammatory responses, characterized by maladaptive inflammation, wherein macrophages contribute to the thickening of the arterial wall, thereby accelerating the progression of atherosclerosis ***(Monge, 2022)***. This process leads to the recruitment of monocytes, which differentiate into macrophages, facilitating plaque formation ***(Ross, 1996; Monge, 2022)***. Furthermore, plaque development involves the transformation of initial fatty streaks into complex atheromas, with fibrous plaques becoming susceptible to rupture, potentially resulting in acute cardiovascular events ***(Luca et al., 2023).***

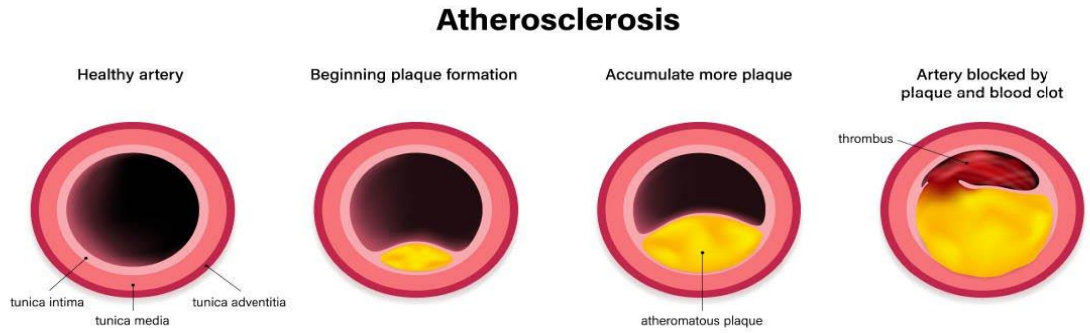

Figure 21 shows a healthy artery on the (left) and arteries exhibiting increasing disease characterized by atherosclerotic plaque.

III.2.2.1 The pathophysiology of atherosclerosis

The pathogenesis of atherosclerosis is defined by endothelial dysfunction, which occurs when oxidative stress lowers nitric oxide (NO) production, resulting in increased vascular resistance ***(Britten et al., 1999).*** Reactive oxygen species (ROS) further deactivate NO, worsening vasoconstriction and increasing ischemic conditions ***(Forte et al., 2016).***

III.2.2.2 Therapeutic role of natural vasodilators in atherosclerosis Management

Natural substances like resveratrol have been demonstrated to increase NO generation and improve endothelial function, hence mitigating the consequences of oxidative stress ***(Pereira et al., 2014).*** The decreased bioactivity of NO, which results in increased vascular resistance and paradoxical vasoconstriction, is a hallmark of this disease. Improvements in endothelial function, promoted by natural vasodilators, are associated with better clinical outcomes, including lower blood pressure and increased exercise tolerance ***(Britten et al., 1999.***

III.2.3 Pulmonary hypertension

Pulmonary hypertension (PH) is a complex illness defined by increased blood pressure in the pulmonary arteries, which can lead to a variety of consequences. It may be related to a variety of underlying diseases, including systemic sclerosis (SSc) and pulmonary arteriovenous malformations (PAVMs) ***(Majumdar & McWilliams, 2020; Pope et al., 2023).***

III.2.3.1 Therapeutic role of natural vasodilators in pulmonary Hypertension management

Natural vasodilators, such as nitric oxide (NO) and prostacyclin, are critical for lowering vascular resistance in pulmonary hypertension. NO relaxes vascular smooth muscle, lowering pulmonary vascular resistance and preserving vascular homeostasis ***(Maruhashi & Higashi, 2021)***, whereas prostaglandins, particularly prostacyclin, lower pulmonary arterial pressure and enhance blood flow in the lungs ***(Cohen et al., 2023)***. Natural vasodilators are essential for maintaining vascular homeostasis and lowering pulmonary arterial pressure.

The apelin system has been discovered as a possible therapeutic target for pulmonary hypertension because it operates as an endothelium-dependent vasodilator, which may have protective effects in the kidney injury models ***(Chapman et al., 2021)***. This discovery shows that the apelin system could be used to treat a broader range of vascular problems. Calcium-channel blockers such as nifedipine and phosphodiesterase-5 inhibitors, for example, have shown promise in the treatment of pulmonary hypertension, especially in high-risk patients

with recurrent high-altitude pulmonary edema (HAPE) ***(Sydykov et al., 2021)***. Prostacyclin analogues may also be used in combination therapy for pulmonary arterial hypertension if necessary**.**

III.2.4 Heart failure

Heart failure (HF) is a complex clinical illness defined by the heart's inability to pump enough blood to meet the body's metabolic needs. It can result from a variety of anatomical and functional problems and is frequently associated with illnesses such as myocardial infarction, hypertension, and valvular heart disease. The prevalence of HF is rising, with serious consequences for patient quality of life and healthcare systems ***(Heidenreich et al., 2022)***. HF is categorized based on left ventricular ejection fraction (LVEF) in:

- **HFrEF**: Reduced ejection fraction (LVEF ≤ 40%).
- **HFpEF**: Preserved ejection fraction (LVEF > 40%) ***(Malik et al., 2019).***

Common causes include coronary artery disease, hypertension, diabetes, and chronic inflammation ***(Katz, 2015).*** Patients typically used to experience dyspnea, fatigue, and fluid retention, leading to pulmonary and peripheral edema ***(Malik et al., 2019).***

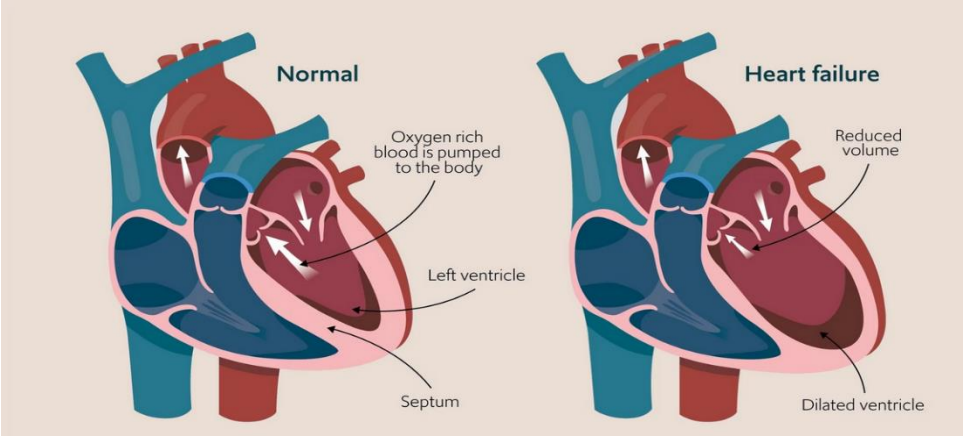

Figure 22 shows the differences between a heart failure on the left and a normal heart on the right.

While heart failure is commonly considered a progressive and debilitating condition, some individuals may experience periods of stability and recovery because of lifestyle changes and medical therapies. This emphasizes the necessity of tailored care in optimal lifestyle changes and medical therapies. This emphasizes the necessity of tailored care in optimal heart failure management**.**

III.2.4.1 Therapeutic role of natural vasodilators in heart failure Management

Natural vasodilators are important in controlling cardiac diseases by reducing preload and afterload, which improves cardiac output. These agents act by dilating blood arteries, lowering the resistance the heart must overcome to eject blood, and by reducing the volume of blood returning to the heart, lowering pressure in the heart's chambers. This dual action can greatly improve cardiac performance, especially in heart failure and post-surgical low cardiac output syndrome. The next sections go into the mechanisms and benefits of vasodilators in various settings**.**

In Preload Reduction, vasodilators like nitrates predominantly produce venodilation, which lowers left ventricular end-diastolic pressure by decreasing venous return to the heart. This reduction in preload can reduce heart failure symptoms and increase cardiac efficiency ***(Amsterdam et al., 1978).*** Agents such as hydralazine and nifedipine are used to reduce afterload by reducing systemic vascular resistance and permitting easier blood ejection from the heart, hence enhancing cardiac output ***(Amsterdam et al., 1978).***

Combining vasodilators and inotropic drugs has been found to improve cardiac function in CHF patients by lowering both preload and afterload, resulting in better ventricular function and cardiac output ***(Cantelli & Bracchetti, 1988).*** Vasodilators are utilized in pediatric patients after cardiac surgery to control low cardiac output syndrome by enhancing ventriculoarterial coupling and systemic oxygen supply**.**

III.2.5 Angina pectoris

Angina, or chest discomfort, is the most prevalent symptom of ischemic heart disease, which is a leading cause of morbidity and mortality globally ***(Hermiz & Sedhai, 2023).***

Chest pain may arise from both cardiac and non-cardiac origins, necessitating a thorough history and physical examination to differentiate these causes and identify patients with acute coronary syndrome (ACS). Angina, a symptom of ACS, can be categorized into stable and unstable forms ***(Hermiz & Sedhai, 2023).***

III.2.5.1 Pathophysiology of angina

In order to produce the energy needed for contractility, the heart requires an appropriate oxygen supply. At the cellular level, ischemia enhances anaerobic glycolysis. This increases the concentration of hydrogen, potassium, and lactate in the venous return of the ischemic or affected area of the myocardium ***(Hermiz & Sedhai, 2023).***

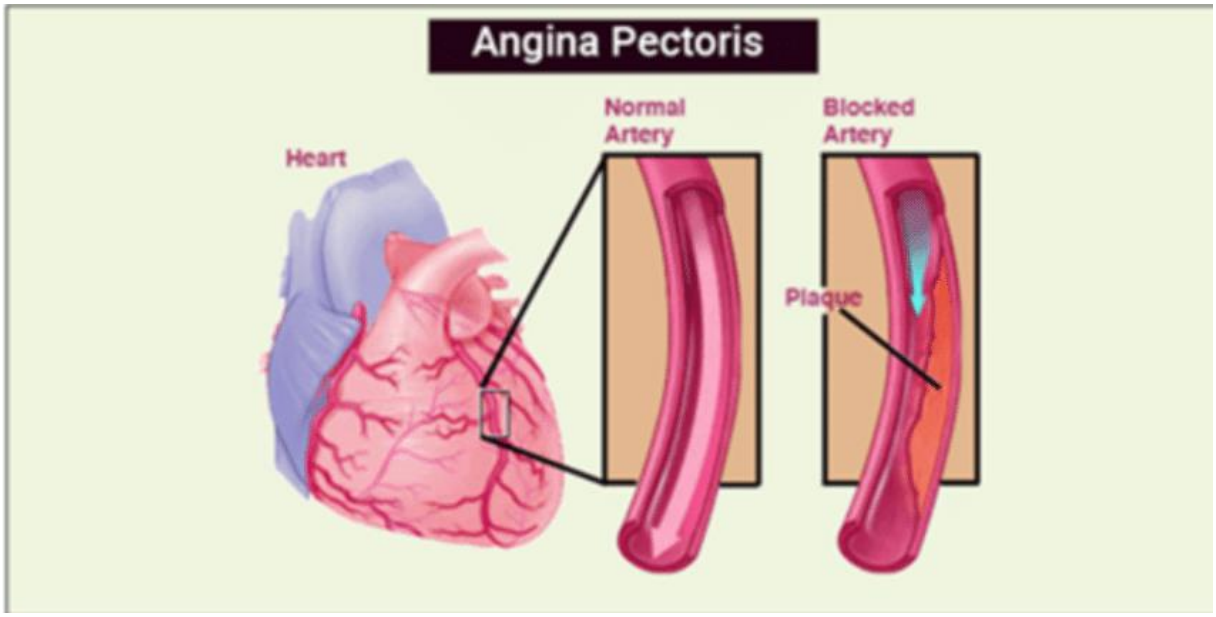

Figure 23 shows the causes that lead to Angina Pectoris, with a "chest pain" usually due to blocked arteries in the heart, which are plaques, thus, not enough blood flow in the heart muscle.

III.2.5.2 Therapeutic role of natural vasodilators in angina management

The therapeutic efficacy of natural vasodilators in managing angina is primarily attributed to their ability to enhance blood flow and alleviate ischemic symptoms. Nitrates, drugs or dietary supplements containing nitrates, and the pharmacological agent nicorandil are pivotal in this context, as they activate nitric oxide (NO) signaling pathways, leading to the relaxation of vascular smooth muscle. This physiological response results in a reduction of preload and myocardial oxygen demand, thereby mitigating angina symptoms ***(Tarkin & Kaski, 2015).***

Both nitrates and nicorandil are effective in preventing angina, with nitrates being a long-established treatment option ***(Tarkin & Kaski, 2015)***. However, chronic use of long-acting nitrates may lead to endothelial dysfunction and increased cardiovascular risk **(Tarkin &**

Kaski, 2015). Common side effects include headaches and orthostatic hypotension, necessitating careful management to avoid nitrate tolerance ***(Tarkin & Kaski, 2015).***

III.2.6 Peripheral vascular disorders

Peripheral vascular disorders (PVD) refer to a group of conditions affecting blood vessels outside the thoracic area, which are primarily caused by atherosclerosis **(Criqui & Aboyans, 2015)**. These problems have a substantial impact on patient health, causing issues such as intermittent claudication, critical limb ischemia, and elevated cardiovascular risk. The global prevalence of PVD is increasing due to causes such as aging populations, obesity, and diabetes.

III.2.6.1 Types of peripheral vascular disorders

-There is three types:

- **Peripheral Arterial Disease (PAD):** Characterized by reduced blood flow, leading to symptoms like claudication and critical ischemia
- **Carotid Artery Disease (CAD):** Involves narrowing of the carotid arteries, increasing stroke risk
- **Aortic Aneurysms:** Abnormal bulging in the aorta, which can lead to life-threatening complications

III.2.6.2 Therapeutic role of natural vasodilators in peripheral vascular management

Natural vasodilators, such as omega-3 polyunsaturated fatty acids (PUFAs) like DHA and EPA, are essential in peripheral vascular control. These PUFAs lower blood pressure and promote vasodilation by activating potassium channels, resulting in hyperpolarization and relaxation. Their structural properties are important for their vasodilatory effects, implying the possibility of targeted therapeutics ***(Bercea et al., 2021),*** whereas ketone bodies, such as beta-hydroxybutyrate and acetoacetate, are promising therapeutic agents for cardiovascular diseases, modulating myocardial utilization, reducing inflammation and fibrosis, and promoting angiogenesis and vasodilation. Ketone therapies are now being evaluated in clinical trials for the treatment of heart failure ***(Matsuura et al., 2023)***. On the other hand, the apelin

system, which includes the apelin receptor and its endogenous ligands, has the potential to be a therapeutic target for kidney and cardiovascular ***(Chapman et al., 2021).***

Chapter 4

Chapter IV Challenges and risks of natural vasodilators

IV.1 Introduction to natural vasodilator risks

Plant-based natural vasodilators pose numerous problems and dangers for the treatment of cardiovascular diseases like hypertension and angina. The application of these compounds is indeed daunting, as they face multiple challenges, despite their purported therapeutic value. Along with improved blood flow and reduction in hypertension, these compounds certainly possess some advantages especially in term of efficacy and clinical limitations. Natural vasodilators sometimes demonstrate inconsistent efficacy across different patient populations and conditions, with only 15% to 25% of patients experiencing useful hemodynamic changes ***(Packer, 1985).***

The clinical advantages of these medications in heart failure and pulmonary hypertension are often lacking strong support ***(Rubin & Swan, 1981) (Singh et al., 2017)***, also explaining how natural substances attain a vasodilating effect is multifactorial and not fully understood, involving nitric oxide and potassium channel pathways ***(McNeill & Jurgens, 2006)***, and even possible contraindications such as systemic hypotension and worsening pre-existing cardiovascular disease may complicate treatment results ***(Packer, 1985)*** Moreover, no comprehensive clinical trials are studying the long-term safety and effectiveness of natural vasodilators, especially within Western medicine ***(Silva et al., 2022).***

The search for natural products to help manage hypertension is underexplored, with much of the focus from places such as China and India, pointing to a disparity in global research focus ***(Silva et al., 2022)***. However, their safety and efficacy are not fully comprehended. In this chapter, we will discuss the major concerns regarding their clinical use with four fundamental focus points: clinical applicability issues of non-uniformity and standardization, inconsistent side effects and related toxicity, unforeseen interactions with other therapeutic agents, and government-created boundaries for safety from the consumer's perspective.

IV.2 Variability and lack of standardization

Natural vasodilators differ and lack standardization. Such variation makes it more challenging to use these natural products in a clinical setting, due to differences in mechanisms of action, the complexity of plant-derived compounds, and individual physiological responses as factors.

IV.2.1 Individual variability of natural vasodilators in medicinal plants

The greatest challenge when using natural vasodilators is their composition and potency variability. Mother Nature has endowed us with numerous resources, products of natural origin, especially phytotherapeutics, which change as their bioactive compounds are influenced by plant species or geographic region, cultivation conditions, harvest time, and storage. It has been demonstrated that people respond quite heterogeneously, and even homogeneously, to natural vasodilators such as cocoa flavanols, which can have some definite impact on clinical results ***(Bapir et al. 2022)***. Such responses may be attributed to baseline hemodynamic parameters, in this case blood pressure, along with population sample genetic differences in some pathways of drug metabolism ***(Bapir et al., 2022)***. Moreover, the method of extraction, whether it be aqueous, alcoholic, or otherwise, can greatly impact the active constituents' concentration, clinically relevant potency, and efficacy ***(Muyumba, 2021)***. This, together with the absence of clear guidelines for the pharmacologic and therapeutic dose, leads to unpredictable results in clinical effectiveness and side effects, anxiety that can be appeased only through systematic research and standardized treatment strategies ***(Wachtel-Galor & Benzie, 2011).***

The lack of supervision in the production and sale of herbal supplements poses a greater problem due to the risk of adulteration, contamination, or lower than needed concentration. As a result, the clinical reliability and safety of these natural agents remain uncertain without rigorous standardization and regulation.

IV.2.2 Standardization challenges of natural vasodilators

One of the most important barriers to the application of natural vasodilators into conventional therapeutics is the uniformity in their formulation and application. Unlike herbal medicines, resorted to by many people today, synthetic drugs undergo many studies, follow strict manufacturing processes, and have a Tested. This discrepancy in the quality assurance procedures stems from the lack of universal criteria for the identification of active compounds ***(Ekor, 2014).***

Compounding these challenges is the significant chemical diversity of compounds derived from plants, with extraction method and plant source affecting concentrations of active ingredients ***(Luna-Vázquez et al. 2013),*** and the absence of standardized dosing and preparation methods resulting in varied effects in studies ***(Webb 2019)***. As a result, inconsistency in the form of dose, quality, and bioavailability reduces the therapeutic value and safety of herbal remedies. Moreover, the lack of standardization coupled with an absence of regulatory standards makes it impossible to initiate reliable clinical trials or perform comparative assessments of efficacy. Numerous scientific reviews have stressed the daunting task of ensuring the quality of herbal preparations while also calling for the establishment of international consensus-based quality control systems and pharmacopoeia standards to be developed for herbal preparations.

IV.2.3 Adulteration and quality issues in herbal medicine use

Quality control in herbal supplements remains a major problem, especially when these supplements are advertised as natural vasodilators. According to Wachtel-Galor and Benzie.

Many herbal products do not adhere to certain manufacturing standards ***(Wachtel-Galor & Benzie, 2011),*** resulting in variance in the concentration of the active compounds in different batches.

This inconsistency not only qualifies as treatment, but it is also detrimental in terms of the possibility of underdosing or overdosing. Furthermore, research indicates that there is

recurrent adulteration of products, which is the contamination of a product with undeclared synthetic pharmaceuticals, heavy metals, or other substances not indicated on the label ***(Posadzki et al., 2013)***. Such practices pose health risks and erode the faith of the consumers, particularly in places that have little or no supervision of regulations ***(Ekor 2014).***

IV.3 Side effects and toxicity

The use of natural vasodilators may result in side effects like hypotension and dizziness, which become critical issues in therapeutic instances. These effects have cutting consequences due to some of the actions of the vasodilators concerning the regulation of blood pressure and vascular tone. Natural vasodilators cause the synthesis of natural vasodilators results in the lowering of arterial blood pressure due to blood vessel relaxation, which leads to hypotension, especially when standing**.**

On the other hand, Canning effects of the carotid sinus baroreceptor reflex activate compensatory responses that can, however, lead to inadequate counterbalance to the reduction in blood pressure, resulting in dizziness ***(Pettinger & Mitchell, 1988).***

IV.3.1 Incidence and patient impact

In a study of 37,670 patients, dizziness was reported as a common vasodilator adverse effect, along with flushing and headache ***(Kubota et al., 1995).*** Dizziness has been associated to poor neurological outcomes, including an increased risk of dementia and stroke ***(Juraschek et al., 2020)***. Certain vasodilators, like a liskiren, can sensitize the Bezold-Jarisch reflex, leading to bradycardia and hypotension, particularly when combined with other RAAS-blocking agents ***(Sever, 2013).***

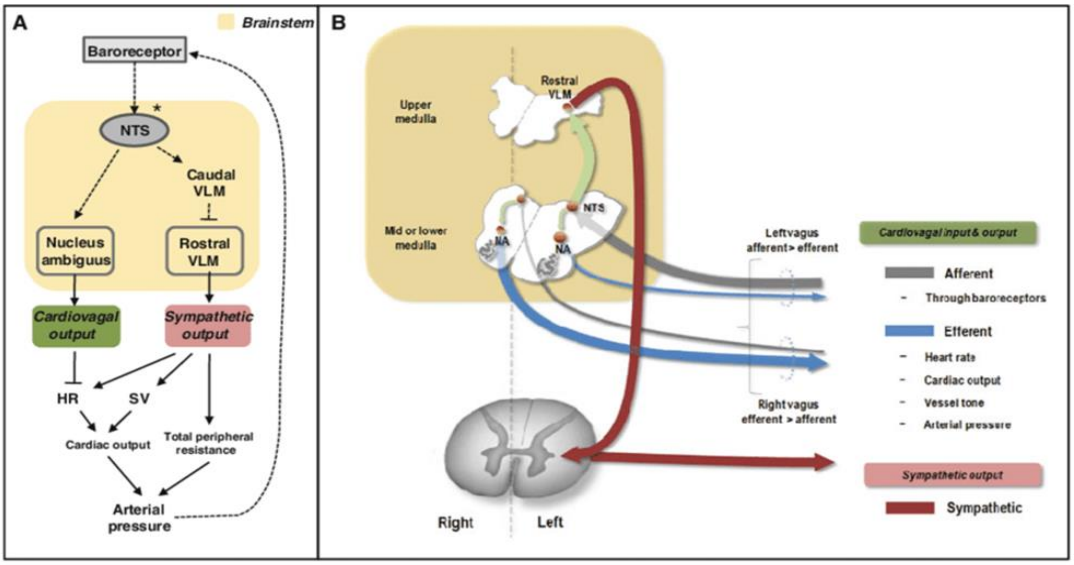

Figure 24 A schematic illustration of the baroreceptor reflex is presented. This reflex, which encompasses interactions between the nucleus tractus solitarius (NTS) and the ventral medulla, operates as a feedback mechanism to mitigate fluctuations in arterial blood pressure. Laterality-dependent variations between afferent and efferent vagal circuits are typically associated with the side effect of vasodilation. The transient alteration in blood pressure activates the baroreceptor neurons.

IV.3.2 Management strategies

To mitigate side effects, vasodilators are often combined with beta-blockers and diuretics, which can help stabilize blood pressure and reduce dizziness. also a regular monitoring of blood pressure and patient symptoms is crucial for adjusting dosages and ensuring safety ***(Pettinger & Mitchell, 1988).***

IV.3.3 Clinical observations

A case study highlighted that postural hypotension, characterized by a significant drop in blood pressure upon standing, can lead to dizziness and other symptoms. This condition affects about 6% of the population ***(Kim et al., 2023)***. Also there is a study of antihypertensive combinations, dizziness and hypotension were noted as common side effects, emphasizing the need for careful monitoring ***(Iyalomhe et al., 2014).***

IV.4 Drug interactions

Like other herbal solutions, natural vasodilators may react with synthetic drugs by either enhancing their effects or producing negative outcomes. Such interactions stem from shifts in pharmacokinetics and the regulation of drug transporters, which affects a drug's absorption,

metabolism, and excretion. Interactions of this nature can improve the expected outcomes of the administered medications or cause increased harmful side effects. The careful blending of natural and synthetic vascular agents demands consideration, lest they trigger undesired results.

IV.4.1 Potentiation of drug effects

Natural vasodilators can improve the efficacy of synthetic antihypertensive medications. For example, the combination of vasodilators and beta-blockers has been shown to produce a synergistic antihypertensive effect, as seen with hydralazine and propranolol ***(Zacest, 1976).*** Additionally, synthetic compounds such as SKF 525-A have been shown to potentiate the effects of hypotensive drugs, implying that natural vasodilators may similarly enhance drug efficacy by affecting drug metabolism or transport ***(Goldstein & Rossi, 1959).***

IV.4.2 Adverse effects and toxicity

Co-administration of natural compounds with synthetic drugs can lead to synergistic toxicity. This is often due to changes in drug metabolism and excretion, which can increase drug concentrations and lead to adverse effects ***(Khadka et al., 2021).***

IV.4.3 Pharmacokinetic interactions

The pharmacokinetics of synthetic drugs can be changed by natural vasodilators, which can impact how well they are absorbed and metabolized. Depending on the particular interaction, this may result in either increased efficacy or toxicity ***(Khadka et al., 2021).*** Although these substances lower systolic blood pressure, they have no discernible effect on cerebral blood flow, which suggests that their interaction with synthetic drugs may not have a negative impact on cerebral hemodynamics ***(Webb, 2019).***

Some example of pharmacokinetic interactions consists:

- ✓ **Cytochrome P450 Enzyme Interactions:** Herbal supplements have a major impact on medication metabolism by altering cytochrome P450 enzymes, particularly CYP3A4. Such interactions can change the pharmacokinetics of simultaneously delivered medicines, resulting in either potentiation or reduced efficacy ***(Wanwimolruk & Prachayasittikul, 2014).***

- ✓ **Garlic and Anticoagulants:** Garlic (*Allium sativum*), recognized for its antithrombotic qualities, can interact with anticoagulants such as warfarin. This combination has been shown to elevate the international normalized ratio (INR), raising the risk of bleeding problems ***(Prieto-Garcia et al., 2023).***

- ✓ **Ginkgo Biloba and Antiplatelet Agents:** Ginkgo biloba, which is commonly used to improve cognitive performance, has antiplatelet action. When taken with antiplatelet or anticoagulant medications, it may increase the risk of bleeding due to synergistic effects on platelet aggregation inhibition ***(Leonard, 2001).***

These interaction, a small groupe of many of which they have side effects especially when these natural compound found in a large section of herbal, in this case we are speaking about the cerebrovascular herbal, combine with other medication of the same targets.

The figure below shows some interactions between hypertensive druges and some cardiovascular herbal ***(Nyulas et al., 2024).***

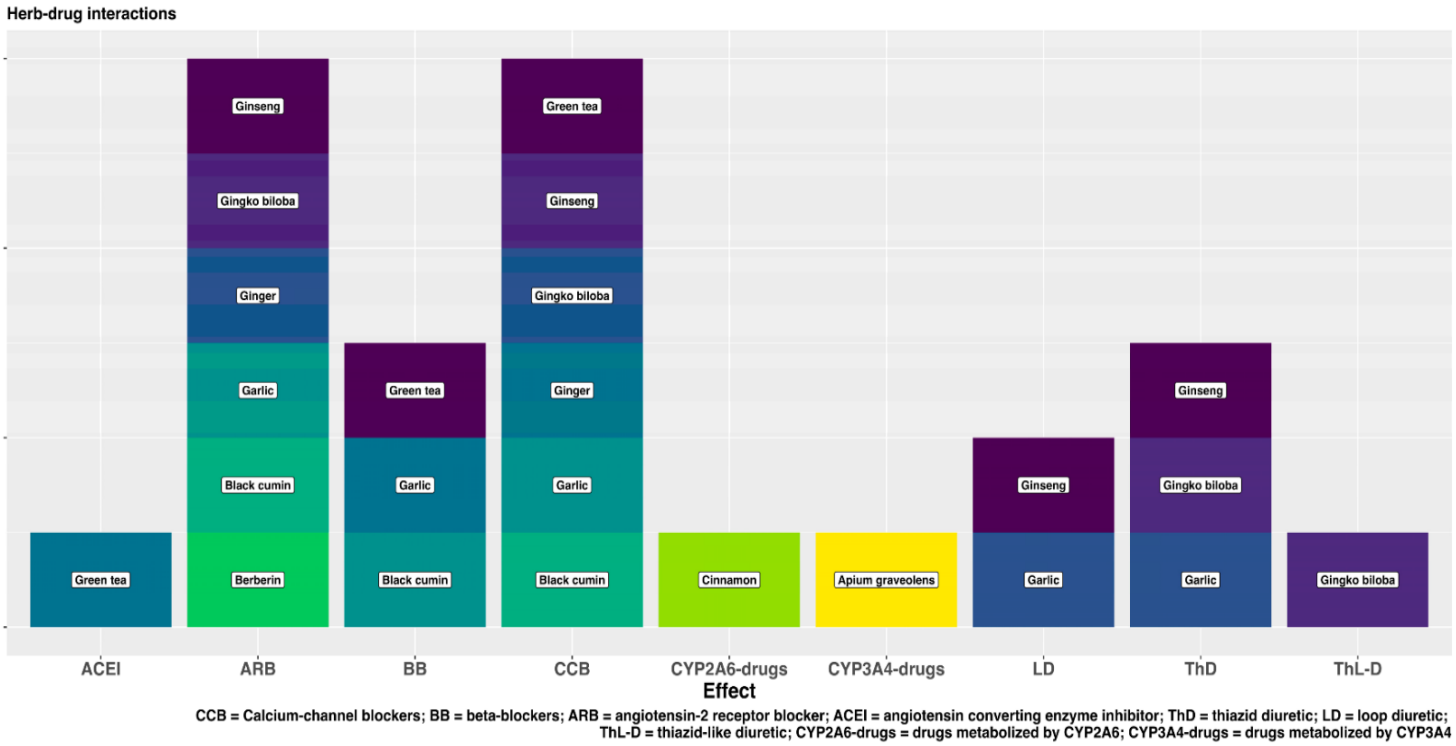

Figure 25 shows Drug-herb interactions

IV.5 Regulatory and consumer safety challenges

Natural vasodilators present a number of regulatory and consumer safety challenges, including concerns about product quality, regulatory supervision, and consumer awareness. Although natural vasodilators, which are frequently derived from plants, are well-liked for their alleged health advantages, their complicated mechanisms and lax regulatory frameworks present serious problems. The possibility of harmful interactions with other medications, as well as variations in product quality and labeling, exacerbate these difficulties.

IV.5.1 Regulatory challenges

These regulatory challenges are based on two main points:

- **Lack of Comprehensive Regulation**: In the United States, the FDA has limited authority to regulate herbal supplements, including natural vasodilators. This has resulted in contamination, misbranding, and dangerous dosages, all of which endanger consumer safety ***(Wright, 2019).***
- **Product Complexity**: Because botanicals are so diverse and have such complicated compositions, it is difficult to adequately standardize and control them. This intricacy can cause discrepancies in product quality and efficacy ***(Schieber, 2020).***

IV.5.2 Consumer safety concerns

Prescription drugs and natural vasodilators may interact, with potentially harmful health effects. The poor communication between patients and healthcare professionals about the use of these supplements increased the risk ***(Wright, 2019)***. Additionally, there is a widespread belief that natural products are safe, which can result in overuse and misuse of them without the right medical advice ***(Schieber, 2020).***

IV.5.3 Efforts and recommendations

The efforts to enhance the quality and authenticity of botanicals through advanced analytical techniques are ongoing. These measures aim to ensure that consumers receive safe and effective products ***(Schieber, 2020).***

Natural vasodilators pose health benefits, but the issues of regulation and safety need more supervision and consumer education. There needs to be collaboration from all levels of governance, such as the regulatory agency, the health practitioner, and the industry, in order for the consumer to benefit from the products without malfeasance.

Conclusion

Conclusion

The field of cardiovascular therapeutics is markedly richer in options with the addition of natural vasodilators because they can serve as alternatives or supplements to synthetic medicines. This dissertation has showcased the numerous methods via which these compounds achieve vasodilatory effects, such as the release of nitric oxide, prostaglandin activity, ion channel modulation, and phytochemical action.

While natural vasodilators are promising, they each possess their unique set of challenges. Their therapeutic application is predominantly restricted due to insufficient regulatory scrutiny, lack of standardization, compositional inconsistency, and possible side effects. Consideration of these issues raises the question of conducting scientific studies focusing on pharmacokinetics and toxicology to validate their efficacy and safety.

Natural vasodilators are indeed beneficial when it comes to the treatment and prevention of disorders pertaining to the vascular system, but the incorporation of these novel therapies into current medical practice calls for an interdisciplinary strategy that combines clinical and regulatory science along with pharmacology. They require more exploration and innovation in order to resolve the existing knowledge and practice gaps.

The future of natural therapy for vasodilation depends on finding new plant-derived compounds that are more potent, safer, and easier for the body to absorb. Recent studies are focusing more on the polyphenols, flavonoids, and alkaloids for their potential vasodilatory impacts through NO release, potassium channel opening, and calcium channel blockade ***(Forte et al., 2016)***. Researchers are also looking into the use of nanotechnology for the delivery systems involving these bioactive compounds to improve their therapeutic value by enhancing their stability and bioactive compounds targeted delivery. In addition, the fields of personalized medicine and genetic and metabolic profiling are beginning to have an impact on natural product research, allowing for bespoke natural vasodilator therapies tailored to specific individual needs ***(Martirosyan & Singh, 2015)***. All these advances can offer better approaches for the use of natural vasodilators in the management of cardiovascular diseases.

References of the bibliographic research

Adams, R. H. (2003). Molecular control of arterial–venous blood vessel identity. *Journal of Anatomy, 202*(2), 105–112. https://doi.org/10.1046/j.1469-7580.2003.00137.x

Adeosun, W. B. (2024). Medicinal plants against viral infections: A review of metabolomics evidence for the antiviral properties and potentials in plant sources. *Viruses, 16*(2), 218. https://doi.org/10.3390/v16020218

Adak, M. (2010). Garlic (Allium sativum) and its beneficial effect on cardiovascular disease: A review. *International Journal of Biomedical and Pharmaceutical Sciences, 4*(1), 1–20.

Adetunji, J. A. (2023). The protective roles of citrus flavonoids, naringenin, and naringin on endothelial cell dysfunction in diseases. *Heliyon, 9*(6), e17166. https://doi.org/10.1016/j.heliyon.2023.e17166

Agrawal, P. K. (2020). Quercetin: Antiviral significance and possible COVID-19 integrative considerations. *Natural Product Communications, 15*(12). https://doi.org/10.1177/1934578X20976293

Ahmad, A. K. (2013). Effects of selected bioactive natural products on the vascular endothelium. *Journal of Cardiovascular Pharmacology, 62*(2), 111–121. https://doi.org/10.1097/FJC.0B013E3182927E47

Alderton, R. K., Cooper, C. E., & Knowles, R. G. (2001). Nitric oxide synthases: Structure, function and inhibition. *Biochemical Journal, 357*(3), 593–615. https://doi.org/10.1042/bj3570593

Alford, P. W., Nesmith, A. P., Seywerd, J. N., Grosberg, A., & Parker, K. K. (2011). Vascular smooth muscle contractility depends on cell shape. *Integrative Biology, 3*(11), 1063–1070. https://doi.org/10.1039/c1ib00061f

Ali, A. A.-A. (2023). Potential of Allium sativum in blood pressure control involves signaling pathways: A narrative review. *Food Frontiers, 4*(1), 1–15. https://doi.org/10.1002/fft2.289

Altura, B. M. (1984). Microcirculatory actions and uses of naturally-occurring (magnesium) and novel synthetic calcium channel blockers. *Microcirculation, Endothelium, and Lymphatics, 1*(2), 185–220.

Amsterdam, E. A. (1978). Vasodilators in myocardial infarction: Rationale and current status. *Drugs, 16*(6), 506–521. https://doi.org/10.2165/00003495-197816060-00002

Amssayef, A., & Haouas, Z. (2023). Alkaloids as vasodilator agents: A review. *Current Pharmaceutical Design.* https://doi.org/10.2174/1381612829666230809094313

Aviram, M., Dornfeld, L., Rosenblat, M., Volkova, N., Kaplan, M., Coleman, R., Hayek, T., Presser, D., & Fuhrman, B. (2002). Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: Studies in humans and in atherosclerotic apolipoprotein E-deficient mice. *The American Journal of Clinical Nutrition, 71*(5), 1062–1076. https://doi.org/10.1093/ajcn/71.5.1062

Bapir, M. C.-M. (2022). Assessing variability in vascular response to cocoa with personal devices: A series of double-blind randomized crossover n-of-1 trials. *Frontiers in Nutrition, 9*, 886597. https://doi.org/10.3389/fnut.2022.886597

Bartolome, A. P., Villaseñor, I. M., & Yang, W.-C. (2013). Bidens pilosa L. (Asteraceae): Botanical properties, traditional uses, phytochemistry, and pharmacology. *Evidence-Based Complementary and Alternative Medicine, 2013*, 340215. https://doi.org/10.1155/2013/340215

Bates, D. O., Curry, F. R. E., & Vionnet, V. (2010). Vascular endothelial growth factors and vascular permeability. *Cardiovascular Research, 87*(2), 262–271. https://doi.org/10.1093/cvr/cvq105

Baylis, C. (2006). Arginine, arginine analogs and nitric oxide production in chronic kidney disease. *Nature Reviews Nephrology, 2*(4), 209–220. https://doi.org/10.1038/ncpneph0143

Bent, S. (2008).*Herbal medicine in the United States: Review of efficacy, safety, and regulation. Journal of General Internal Medicine*, 23(6), 854–859. https://doi.org/10.1007/s11606-008-0632-y

Bercea, C. M. (2021). Omega-3 polyunsaturated fatty acids and hypertension: A review of vasodilatory mechanisms of docosahexaenoic acid and eicosapentaenoic acid. *British Journal of Pharmacology, 178*(4), 860–877. https://doi.org/10.1111/bph.15336

Besada, S., & Abd-Elsayed, A. (2024). Vasodilators. In A. Abd-Elsayed (Ed.), *Basic anesthesia review* (pp. 698–699). Oxford University Press. https://doi.org/10.1093/med/9780197584569.003.0287

Bhatnagar, A., & Sharma, S. (2021). A review on chemical constituents and biological activities of the genus Picrorhiza (Scrophulariaceae). *International Journal of Current Pharmaceutical Research, 13*(5), 18–27. https://doi.org/10.22159/ijcpr.2021v13i5.1901

Bo, H., Chen, Y., & Chen, C.-Y. (2012). Function and mechanism of nitric oxide(I): Characteristics and function. *Acta Biophysica Sinica, 28*(3), 173–184. https://doi.org/10.3724/sp.j.1260.2012.20007

Bouloumié, A., Bauersachs, J., Linz, W., & Fleming, I. (1997). Endothelial dysfunction coincides with an enhanced nitric oxide synthase expression and superoxide anion production. *Hypertension, 30*(4), 934–941. https://doi.org/10.1161/01.hyp.30.4.934

Britten, M. B., & Britten, A. M. (1999). Clinical importance of coronary endothelial vasodilator dysfunction and therapeutic options. *Journal of Internal Medicine, 245*(4), 325–335. https://doi.org/10.1046/j.1365-2796.1999.00449.x

Bryan, J. C.-C.-B. (2005). Insulin secretagogues, sulfonylurea receptors and KATP channels: From structure to disease. *Current Pharmaceutical Design, 11*(21), 2699–2716. https://doi.org/10.2174/1381612054546879

Bulboacă, A., Bolboacă, S. D., Stănescu, I. C., Bolboacă, A. C., & Boarescu, P. M. (2016). Protective effects of curcumin and nano-curcumin against oxidative stress and liver damage in a rat model of hypertension. *Iranian Journal of Basic Medical Sciences, 19*(7), 747–755.

Busse, R., Fichtlscherer, B., & Hecker, M. (1988). Hyperpolarization and increased free calcium in acetylcholine-stimulated endothelial cells. *American Journal of Physiology, 255*(4 Pt 2), H965–H969. https://doi.org/10.1152/ajpheart.1988.255.4.H965

Cantelli, I., & Cantelli, I. (1988). Combination of positive inotropic and vasodilating substances in congestive heart failure. *Cardiovascular Drugs and Therapy, 2*(1), 83–91. https://doi.org/10.1007/BF00054257

Cardoso-Teixeira, A. C. d. S. N. A. G. d. S. C., Silva, M. A., Monteiro, A. B., & Freire, A. O. (2018). Hydroxyl group and vasorelaxant effects of perillyl alcohol, carveol, and limonene on aorta smooth muscle of rats. *Molecules, 23*(6), 1430. https://doi.org/10.3390/molecules23061430

Carr, A. C., & Frei, B. (1999). Does vitamin C act as a pro-oxidant under physiological conditions? *The FASEB Journal, 13*(9), 1007–1024. https://doi.org/10.1096/fasebj.13.9.1007

Chan, J. Y. Y., Tang, F. Y., & Yang, K. K. (2013). A review of the cardiovascular benefits and antioxidant properties of allicin. *Phytotherapy Research, 27*(5), 637–646. https://doi.org/10.1002/ptr.4796

Chapman, F. A. (2021). The therapeutic potential of apelin in kidney disease. *Nature Reviews Nephrology, 17*(12), 840–853. https://doi.org/10.1038/s41581-021-00461-z

Chato, J. C. (1980). Heat transfer to blood vessels. *Journal of Biomechanical Engineering, 102*(2), 110–118. https://doi.org/10.1115/1.3138205

Cheng, F., Wang, Y., Li, J., Su, Y., & Sun, J. (2013). Berberine improves endothelial function by reducing endothelial microparticles-mediated oxidative stress in humans. *International Journal of Cardiology, 167*(3), 936–942. https://doi.org/10.1016/j.ijcard.2012.03.090

Childers, K., & Roush, W. (2017). Nitric oxide: Synthesis and action. In *Encyclopedia of Life Sciences (eLS).* John Wiley & Sons. https://doi.org/10.1002/9780470015902.a0000634.pub2

Chong, D. C., & Stainier, D. Y. R. (2011). Stepwise arteriovenous fate acquisition during mammalian vasculogenesis. *Developmental Dynamics, 240*(9), 2153–2165. https://doi.org/10.1002/dvdy.22706

Chouchani, E. T., Methner, C., Nadtochiy, S. M., Logan, A., Pell, V. R., Ding, S., James, A. M., Cochemé, H. M., Reinhold, J., Lilley, K. S., Partridge, L., Fearnley, I. M., Robinson, A. J., Hartley, R. C., Smith, R. A. J., Krieg, T., & Murphy, M. P. (2013). Cardioprotection by S-nitrosation of a cysteine switch on mitochondrial complex I. *Nature Medicine, 19*(1), 753–759. https://doi.org/10.1038/nm.3212

Clegg, L. E., & Mac Gabhann, F. (2015). Systems biology of the microvasculature. *Integrative Biology, 7*(4), 498–512. https://doi.org/10.1039/C4IB00296B

Cohen, J. B.-A. (2023). Cancer therapy-related hypertension: A scientific statement from the American Heart Association. *Hypertension, 80*(3), 46–57. https://doi.org/10.1161/hyp.0000000000000224

Cohn, J. N. (2011). Direct-acting vasodilators. *Journal of Clinical Hypertension, 13*(9), 644–649. https://doi.org/10.1111/j.1751-7176.2011.00507.x

Criqui, M. H. (2015). Epidemiology of peripheral artery disease. *Circulation Research, 116*(9), 1509–1526. https://doi.org/10.1161/CIRCRESAHA.116.303849

Dachman, W. D., Ford, G. A., Blaschke, T. F., & Hoffman, B. B. (1993). Mechanism of bradykinin-induced venodilation in humans. *Journal of Cardiovascular Pharmacology, 21*(2), 241–248.

Dela Paz, N. G., & D'Amore, P. A. (2009). Arterial versus venous endothelial cells. *Cell and Tissue Research, 335*(1), 5–16. https://doi.org/10.1007/s00441-008-0714-2

Delong, C., & Sharma, S. (2021). Physiology, vasodilation. In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK538326/

DeMartino, A. W., Smith, L. A., & Gladwin, M. T. (2018). Nitrite and nitrate chemical biology and signalling. *British Journal of Pharmacology, 176*(2), 228–245. https://doi.org/10.1111/bph.14484

Deshpande, S. R., & More, D. H. (2010). Synthesis and biological evaluation of 2-(N-substituted)-3H-phthalazin-1, 4-diones and 1-(N-substituted)-2, 4, 5-trihydropyridazin-3, 6-diones as potent vasodilators. *Indian Journal of Pharmaceutical Education and Research, 44*(1), 1–7.

Dogan, M. F. (2019). Potassium channels in vascular smooth muscle: A pathophysiological and pharmacological perspective. *Fundamental & Clinical Pharmacology, 33*(3), 282–302. https://doi.org/10.1111/fcp.12461

Eble, J. A., & Niland, S. (2009). The extracellular matrix of blood vessels. *Current Pharmaceutical Design, 15*(12), 1385–1400. https://doi.org/10.2174/138161209787846757

Edwards, G. W., Weston, A. H., & Wilson, C. (1995). Pharmacology of the potassium channel openers. *Cardiovascular Drug Therapy, 9*(2), 185–193. https://doi.org/10.1007/BF00878465

Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Pharmacology, 4*, 177. https://doi.org/10.3389/fphar.2013.00177

Eo, S. H., Kim, H. M., Lee, H. G., Lee, J. Y., & Kim, H. A. (2013). Resveratrol inhibits nitric oxide-induced apoptosis via the NF-κB pathway in rabbit articular chondrocytes. *Biomolecules & Therapeutics, 21*(5), 364–370. https://doi.org/10.4062/biomolther.2013.029

Ernst, E. (2002).*Toxic heavy metals and undeclared drugs in Asian herbal medicines. Trends in Pharmacological Sciences*, 23(3), 136–139. https://doi.org/10.1016/S0165-6147(02)01988-4

Farias, D., Pereira, A. F., & Rosa, G. (2010). Metabolic syndrome in coronary artery and occlusive vascular diseases: A systematic review. *Arquivos Brasileiros de Cardiologia, 94*(2), 150–178. https://doi.org/10.1590/s0066-782x2010000600024

Febyan, F. W. (2015). Peranan allicin dari ekstrak bawang putih sebagai pengobatan komplemen alternatif hipertensi stadium I. *Analisis CDK, 42*(4), 303–308. http://www.cdkjournal.com/index.php/CDK/article/download/1025/746

Forte, M. C. (2016). Targeting nitric oxide with natural derived compounds as a therapeutic strategy in vascular diseases. *Oxidative Medicine and Cellular Longevity, 2016*, Article 7364138. https://doi.org/10.1155/2016/7364138

Frishman, W. H. (2007). Calcium channel blockers: Differences between subclasses. *American Journal of Cardiovascular Drugs, 7*(1), 14–23. https://doi.org/10.2165/00129784-200707001-00003

Gagnon, G. R. (1980). Studies on the mechanism of action of various vasodilators. *British Journal of Pharmacology, 70*(2), 219–227. https://doi.org/10.1111/j.1476-5381.1980.tb07927.x

Gawade, B. V. (2012). Rauwolfia (reserpine) as a potential antihypertensive agent: A review. *International Journal of Pharmaceutical and Phytopharmacological Research, 2*(1), 46–49.

Godfraind, T., Miller, R., & Vanhoutte, P. M. (2005). Antioxidant effects and the therapeutic mode of action of calcium channel blockers in hypertension and atherosclerosis. *Philosophical Transactions of the Royal Society B: Biological Sciences, 360*(1464), 2259–2272. https://doi.org/10.1098/rstb.2005.1774

Goldstein, S., & Goldstein, S. (1959). Potentiation of the activity of hypotensive drugs: Effect of several synthetic compounds on six hypotensive agents in hypertensive rats and normotensive dogs. *Journal of Pharmacology and Experimental Therapeutics, 126*(2), 168–173. https://www.ncbi.nlm.nih.gov/pubmed/13665525

Goorani, S. Z. (2024). Hypertension: A continuing public healthcare issue. *International Journal of Molecular Sciences, 26*(1), 123. https://doi.org/10.3390/ijms26010123

Gornik, H. L., & Creager, M. A. (2005). Peripheral arterial disease. *Circulation, 111*(13), e169–e172. https://doi.org/10.1161/01.CIR.0000160581.58633.8B

Grant, M. M., & Grant, D. J. (2019). Next generation sequencing discoveries of the nitrate-responsive oral microbiome and its effect on vascular responses. *Journal of Clinical Medicine, 8*(8), 1110. https://doi.org/10.3390/jcm8081110

Green, D. J., Maiorana, A., O'Driscoll, G., & Taylor, R. (2004). Effect of exercise training on endothelium-derived nitric oxide function in humans. *The Journal of Physiology, 561*(1), 1–25. https://doi.org/10.1113/jphysiol.2004.068197

Green, D. J., O'Driscoll, G., Blanksby, B. A., & Taylor, R. R. (1996). Control of skeletal muscle blood flow during dynamic exercise: Contribution of endothelium-derived nitric oxide. *Sports Medicine, 21*(2), 119–146. https://doi.org/10.2165/00007256-199621020-00004

Gutterman, D. D., Miura, H., Liu, L., Kadlec, A. O., & Nithipatikom, K. (2005). Redox modulation of vascular tone: Focus on potassium channel mechanisms of dilation. *Arteriosclerosis, Thrombosis, and Vascular Biology, 25*(4), 671–678. https://doi.org/10.1161/01.ATV.0000158497.09626.3b

Gurney, A. M. (1994). Mechanisms of drug-induced vasodilation. *Journal of Pharmacy and Pharmacology, 46*(4), 242–251. https://doi.org/10.1111/j.2042-7158.1994.tb03789.x

Haghighat, L., DeJong, C., & Teerlink, J. R. (2024). New and future heart failure drugs. *Nature Cardiovascular Research*, 1–19. https://doi.org/10.1038/s41571-024-00989-1

Hartman, J. L., & Van Wyk, B. E. (2019). Citrulline and arginine content of taxa of Cucurbitaceae. *Horticulturae, 5*(1), 22. https://doi.org/10.3390/horticulturae5010022

Howlett, J. G. (2014). Nebivolol: Vasodilator properties and evidence for relevance in treatment of cardiovascular disease. *Canadian Journal of Cardiology, 30*(Supplement), S29–S37. https://doi.org/10.1016/j.cjca.2014.03.003

Heidenreich, P. A. (2021). AHA/ACC/HFSA guideline for the management of heart failure. *Journal of the American College of Cardiology, 79*(17), 263–421. https://doi.org/10.1016/j.jacc.2021.12.012

Heiss, C., Keen, C. L., & Kelm, M. (2003). Flavanols and cardiovascular health: Effects on endothelial function. *The Journal of Cardiovascular Pharmacology, 38*(6), 1–11. https://doi.org/10.1097/00005344-200312000-00002

Herbert, S. P., Huisken, J., Kim, T. N., Feldman, M. E., Houseman, B. T., & Stainier, D. Y. R. (2009). Arterial-venous segregation by selective cell sprouting: An alternative mode of blood vessel formation. *Science, 326*(5950), 294–298. https://doi.org/10.1126/science.1178577

Hermiz, C., & Hermiz, C. (2023). Angina. In S. Publishing (Ed.), *StatPearls*. Treasure Island. https://www.ncbi.nlm.nih.gov/books/NBK538166/

Huang, P. L., Huang, Z., Mashimo, H., Bloch, K. D., Moskowitz, M. A., Bevan, J. A., & Fishman, M. C. (1995). Hypertension in mice lacking the gene for endothelial nitric oxide synthase. *Nature, 377*(6546), 239–242. https://doi.org/10.1038/377239a0

Hussein, R. A., & El-Anssary, A. A. (2018). Plant secondary metabolites: The key drivers of the pharmacological actions of medicinal plants. In A. E. Abdel-Azim (Ed.), *Herbal medicine*. IntechOpen. https://doi.org/10.5772/intechopen.76139

Isomoto, S., Kondo, C., Yamada, M., Matsumoto, S., Higashiguchi, O., Matsuzaki, M., ... Kurachi, Y. (1997). Inwardly rectifying potassium channels: Their molecular heterogeneity and function. *Japanese Journal of Physiology, 47*(1), 11–39. https://doi.org/10.2170/jjphysiol.47.11

Iyalomhe, G. B. S., Omogbai, E. K. I., Isah, A. O., & Iyalomhe, S. I. (2014). Adverse events profiles during initiation of treatment with amlodipine or hydrochlorothiazide in type 2 diabetic Nigerians with essential hypertension. *American Journal of Internal Medicine, 2*(6), 131–137. https://doi.org/10.11648/j.ajim.20140206.11

Izzo, A. A., & Ernst, E. (2009).*Interactions between herbal medicines and prescribed drugs: A systematic review.* Drugs, 69(13), 1777–1798. https://doi.org/10.2165/11317010-000000000-00000

Jasim, H. A. (2021). Chalcones: Synthetic chemistry follows where nature leads. *Biomolecules, 11*(8), 1203. https://doi.org/10.3390/biom11081203

Jeffers, A., & Jeffers, X. (2005). Hemoglobin mediated nitrite activation of soluble guanylyl cyclase. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology, 142*(2), 130–135. https://doi.org/10.1016/j.cbpb.2005.04.016

Jin, R. C., & Loscalzo, J. (2010). Vascular nitric oxide: Formation and function. *Journal of Blood Medicine, 1*, 147–162. https://doi.org/10.2147/JBM.S7000

Juraschek, S. P. (2020). Orthostatic hypotension, dizziness, neurology outcomes, and death in older adults. *Neurology, 95*(14). https://doi.org/10.1212/WNL.0000000000010456

Kratz, J. M., Grienke, U., Scheel, O., Mann, S. A., & Rollinger, J. M. (2017). Natural products modulating the hERG channel: Heartaches and hope. *Natural Product Reports, 34*(7), 957–980. https://doi.org/10.1039/c7np00014f

Khedara, T. G. A. (1998). Hypercholesterolemic effect in rats of a dietary addition of the nitric oxide synthase inhibitor, L-Nω-nitroarginine, by less synthesis of bile acids. *Bioscience, Biotechnology, and Biochemistry, 62*(4), 773–777. https://doi.org/10.1271/bbb.62.773

Khadka, B. L.-T.-S. (2021). Impacts of drug interactions on pharmacokinetics and the brain transporters: A recent review of natural compound-drug interactions in brain disorders. *International Journal of Molecular Sciences, 22*(4), 1809. https://doi.org/10.3390/ijms22041809

Khan, M. N., Oldroyd, J. C., Chowdhury, E. K., Hossain, M. B., Rana, J., Renzetti, S., & Islam, R. M. (2021). Prevalence, awareness, treatment, and control of hypertension in Bangladesh: Findings from National Demographic and Health Survey, 2017–2018. *The Journal of Clinical Hypertension, 23*(10), 1830–1842. https://doi.org/10.1111/jch.14361

Kim, A. N. (2023). Recent advances in the total synthesis of the tetrahydroisoquinoline alkaloids. *Chemical Reviews, 123*(15), 9447–9496. https://doi.org/10.1021/acs.chemrev.3c00054

Kim, G.-H. (2008). Renal effects of prostaglandins and cyclooxygenase-2 inhibitors. *Electrolyte & Blood Pressure, 6*(1), 35–41. https://doi.org/10.5049/EBP.2008.6.1.35

Kim, J. P.-C. (2023). A case report of dizziness with postural hypotension improved by Korean medicine treatment. *The Journal of Internal Korean Medicine, 44*(3), 544–554. https://doi.org/10.22246/jikm.2023.44.3.544

Kojda, G. (2000). Therapeutic importance of nitrovasodilators, nitric oxide. In B. Mayer (Ed.), *Nitric oxide* (Vol. 143). Springer. https://doi.org/10.1007/978-3-642-57077-3_16

Kubota, K. P. (1995). Vasodilation-related adverse events in diltiazem and dihydropyridine calcium antagonists studied by prescription-event monitoring. *European Journal of Clinical Pharmacology, 48*(1), 1–7. https://doi.org/10.1007/BF00202163

Kukovetz, W. R., & Frey, F. J. (1992). Pharmacological interaction experiments differentiate between glibenclamide-sensitive K^+ channels and cyclic GMP as components of vasodilation by nicorandil. *European Journal of Pharmacology, 215*(1), 1–7. https://doi.org/10.1016/0014-2999(92)90002-K

Laoué, J. O. (2022). Plant flavonoids in Mediterranean species: A focus on flavonols as protective metabolites under climate stress. *Plants, 11*(2), 172. https://doi.org/10.3390/plants11020172

Laurenza, A. S. (1989). Forskolin: A direct stimulator of adenylate cyclase in rat aorta smooth muscle cells. *Journal of Pharmacology and Experimental Therapeutics, 205*(1), 1–7.

Laursen, J. B., & Laursen, S. M. (n.d.). Endothelial regulation of vasomotion in apoE-deficient mice: Implications for interactions between peroxynitrite and tetrahydrobiopterin. *Circulation, 103*(9), 1282–1288. https://doi.org/10.1161/01.cir.103.9.1282

Leonard, M. C. (2001). Interactions between herbs and cardiac medications. *Natural Medicines Journal, 4*(2).

Li, H., & Li, C. (2005). Xanthine oxidase catalyzes anaerobic transformation of organic nitrates to nitric oxide and nitrosothiols: Characterization of this mechanism and the link between organic nitrate and guanylyl cyclase activation. *Journal of Biological Chemistry, 280*(17), 16594–16600. https://doi.org/10.1074/jbc.M411905200

Li, P. J. (2014). In vitro and in vivo antioxidant activities of a flavonoid isolated from celery (Apium graveolens L. var. dulce). *Food & Function, 5*(1), 50–56. https://doi.org/10.1039/c3fo60273g

Li, Y., & Chen, S. (2004). Application of nonaqueous capillary electrophoresis for quantitative analysis of quinolizidine alkaloids in Chinese herbs. *Analytica Chimica Acta, 508*(1), 17–22. https://doi.org/10.1016/j.aca.2003.11.043

Li, Y., Kang, J. X., & Leaf, A. (1997). Differential effects of various eicosanoids on the production or prevention of arrhythmias in cultured neonatal rat cardiac myocytes. *Prostaglandins, 54*(2), 511–530. https://doi.org/10.1016/S0090-6980(97)00122-6

Li, Y. C. (2009). Prostacyclin analogues activate calcium-dependent potassium (KCa) channels via PPAR β/δ in pulmonary artery. *Circulation, 120*(18), S1021–S1022. https://doi.org/10.1161/circ.120.suppl_18.S1021-d

Lin, I.-C., H.-N., H.-J., & L. (2016). Low urinary citrulline/arginine ratio associated with blood pressure abnormalities and arterial stiffness in childhood chronic kidney disease. *American Journal of Hypertension, 10*(2), 115–123. https://doi.org/10.1016/j.jash.2015.11.008

Liu, Y. S. (2022). Hydroxylation decoration patterns of flavonoids in horticultural crops: Chemistry, bioactivity and biosynthesis. *Horticulture Research, 9*, uhab068. https://doi.org/10.1093/hr/uhab068

Loai, B., & Zohar, K. (2015). Interactions between CYP3A4 and dietary polyphenols. *Oxidative Medicine and Cellular Longevity, 2015*, Article 854015. https://doi.org/10.1155/2015/854015

Logsdon, E. A., Luck, R., & Chang, E. I. (2013). A systems biology view of blood vessel growth and remodelling. *Journal of Cellular and Molecular Medicine, 18*(8), 1340–1350. https://doi.org/10.1111/jcmm.12164

Luca, A. C., David, S. G., David, A. G., Țarcă, V., Pădureț, I.-A., Mîndru, D. E., Roșu, S. T., Roșu, E. V., Adumitrăchioaiei, H., Bernic, J., Cojocaru, E., & Țarcă, E. (2023). Atherosclerosis from newborn to adult—Epidemiology, pathological aspects, and risk factors. *Life, 13*(10), 2056. https://doi.org/10.3390/life13102056

Lundberg, J. O., & C. M. (2011). Roles of dietary inorganic nitrate in cardiovascular health and disease. *Cardiovascular Research, 89*(3), 525–532. https://doi.org/10.1093/cvr/cvq325

Lundberg, J. O., & W. E. (2008). The nitrate–nitrite–nitric oxide pathway in physiology and therapeutics. *Nature Reviews Drug Discovery, 7*(2), 156–167. https://doi.org/10.1038/nrd2466

Lundberg, J. O.-S. (1995). High nitric oxide production in human paranasal sinuses. *Nature Medicine, 1*(4), 370–373. https://doi.org/10.1038/nm0495-370

Lu, M. P. (2024). Advances in the study of vascular-related protective effects of garlic (Allium sativum) extract and compounds. *Journal of Nutritional Biochemistry, 124*, 109531. https://doi.org/10.1016/j.jnutbio.2023.109531

Lu, Y.-A., J.-G., & J. (2021). Ecklonia cava extract and its derivative dieckol promote vasodilation by modulating calcium signaling and the PI3K/Akt/eNOS pathway in in vitro and in vivo models. *Biomedicines, 9*(4), 438. https://doi.org/10.3390/biomedicines9040438

Luna-Vázquez, F. J.-A.-C.-M.-M. (2018). Vasodilator activity of compounds isolated from plants used in Mexican traditional medicine. *Molecules, 23*(6), 1474. https://doi.org/10.3390/molecules23061474

Luna-Vázquez, F. J.-A.-M.-M.-S. (2013). Vasodilator compounds derived from plants and their mechanisms of action. *Molecules, 18*(5), 5814–5857. https://doi.org/10.3390/molecules18055814

Madamanchi, N. R. (2008). Role of oxidative stress and nitric oxide in atherothrombosis. *Frontiers in Bioscience, 13*(1), 3568–3580. https://doi.org/10.2741/3084

Mahdy, R. N. (2010). The role of vascular endothelial growth factor in the progression of diabetic vascular complications. *Eye, 24*(9), 1576–1584. https://doi.org/10.1038/eye.2010.86

Mahobiya, A. S. (2018). Kaempferol induces vasorelaxation via endothelium-independent mechanisms. *Pharmacological Reports, 70*(5), 863–874. https://doi.org/10.1016/j.pharep.2018.03.006

Malik, J., Valerianova, A., Pesickova, S. S., Michalickova, K., Hladinova, Z., Hruskova, Z., ... & Tesar, V. (2023). Heart failure with preserved ejection fraction is the most frequent but commonly

overlooked phenotype in patients on chronic hemodialysis. *Frontiers in Cardiovascular Medicine, 10*, Article 1130618. https://doi.org/10.3389/fcvm.2023.1130618

Mallidi, J. M. (2015). Vasodilators and management of hypertensive emergencies. In P. B.-U. G. Jagadeesh (Ed.), *Pathophysiology and pharmacotherapy of cardiovascular disease* (1st ed.). Springer. https://doi.org/10.1007/978-3-319-15961-4_40

Marín-García, J. (2024). Molecular determinants of atherosclerosis. In *Post-Genomic Cardiology* (pp. 183–215). Elsevier. https://doi.org/10.1016/B978-0-12-404599-6.00006-8

Maruhashi, T., & Maruhashi, T. (2021). Pathophysiological association between diabetes mellitus and endothelial dysfunction. *Antioxidants, 10*(8), 1306. https://doi.org/10.3390/antiox10081306

Martirosyan, D. M. (2015). A new definition of functional food by FFC: What makes a new definition unique? *Functional Foods in Health and Disease, 5*(6), 209–223. https://www.ffhdj.com/index.php/ffhd/article/view/183

Mason, R. P., Walter, M. F., & Day, C. (2012). Pleiotropic effects of calcium channel blockers. *Current Hypertension Reports, 14*.

Mathieu, P., Poirier, P., Pibarot, P., Lemieux, I., & Després, J. P. (2009). Visceral obesity: The link among inflammation, hypertension, and cardiovascular disease. *Hypertension, 53*(4), 577–584. https://doi.org/10.1161/hypertensionaha.108.110320

Matsuura, T. R. (2023). Ketones and the heart: Metabolic principles and therapeutic implications. *Circulation Research, 132*(7), 882–898. https://doi.org/10.1161/circresaha.123.321872

Mazzanti, G., Di Sotto, A., & Vitalone, A. (2009).*Herbal products in cardiovascular care: Efficacy and safety. Drugs*, 69(1), 1–10. https://doi.org/10.2165/00003495-200969010-00001

McNeill, J. R. (2006). A systematic review of mechanisms by which natural products of plant origin evoke vasodilatation. *Canadian Journal of Physiology and Pharmacology, 84*, 803–821. https://doi.org/10.1139/Y06-028

Meneshian, A., & Meneshian, A. (2002). The physiology of endothelial xanthine oxidase: From urate catabolism to reperfusion injury to inflammatory signal transduction. *Microcirculation, 9*(3), 161–175. https://doi.org/10.1038/sj.mn.7800136

Mirza, M. N. (2024). The silent storm: Understanding hypertension. *International Journal of Innovative Science and Research Technology, 9*(4), 3405–3415. https://doi.org/10.38124/ijisrt/ijisrt24apr1387

Mironova, G. Y., & Mironova, H. N. (2022, November 15). Functional tuning of vascular L-type Ca2+ channels. *Frontiers in Physiology, 13*, 1058744. https://doi.org/10.3389/fphys.2022.1058744

Monge, J. M. (2022). Fundamental pathogenesis of atherosclerosis. In B. P. International (Ed.). https://doi.org/10.9734/bpi/capr/v8/8612f

Mulrow, C. D. (1988). Relative efficacy of vasodilator therapy in chronic congestive heart failure: Implications of randomized trials. *JAMA, 259*(23), 3422–3426. https://doi.org/10.1001/jama.1988.03720230032026

Muyumba, N. W., & Muyumba, S. M. (2021). Quality control of herbal drugs and preparations: The methods of analysis, their relevance and applications. *Talanta Open, 4*, 100070. https://doi.org/10.1016/j.talo.2021.100070

Needleman, P., & Needleman, K. (1975). Mechanism and modification of bradykinin-induced coronary vasodilation. *Proceedings of the National Academy of Sciences, 72*(6), 2060–2063. https://doi.org/10.1073/pnas.72.6.2060

Nelson, H. J. (1995). Regulation of membrane potential and diameter by voltage-dependent K^+ channels in rabbit myogenic cerebral arteries. *American Journal of Physiology-Heart and Circulatory Physiology, 269*(1), H348–H355. https://doi.org/10.1152/ajpheart.1995.269.1.H348

Nyulas, K.-I. S.-S.-A.-H.-S.-N. (2024). Cardiovascular effects of herbal products and their interaction with antihypertensive drugs—Comprehensive review. *International Journal of Molecular Sciences, 25*(12), 6388. https://doi.org/10.3390/ijms25126388

Pal, D., & Mitra, A. K. (2006).*Mucosal absorption of some hydrophilic drugs: Role of chelating agents and other permeation enhancers. Advanced Drug Delivery Reviews*, 56(11), 1391–1408. https://doi.org/10.1016/j.addr.2006.09.007

Pan, Y. Y. (2024). A novel therapeutic strategy for acute decompensated heart failure with vasodilators. *Medical Hypotheses, 184*, 111287. https://doi.org/10.1016/j.mehy.2024.111287

Packer, M. (1985). Vasodilator therapy for primary pulmonary hypertension: Limitations and hazards. *Annals of Internal Medicine, 103*(2), 258–270. https://doi.org/10.7326/0003-4819-103-2-258

Pan, Y. Y. (2024). A novel therapeutic strategy for acute decompensated heart failure with vasodilators. *Medical Hypotheses, 184*, 111287. https://doi.org/10.1016/j.mehy.2024.111287

Pettinger, W. A. (1988). Side effects of vasodilator therapy. *Hypertension, 11*(3 Pt 2), II34. https://doi.org/10.1161/01.HYP.11.3_PT_2.II34

Pereira, B. F. (2014). Resveratrol reverses the impaired vasodilation observed in 2K-1C hypertension through endothelial function improvement. *Open Journal of Medicinal Chemistry, 4*(2), 61–69. https://doi.org/10.4236/ojmc.2014.42009

Posadzki, P. W. (2013). Contamination and adulteration of herbal medicinal products (HMPs): An overview of systematic reviews. *European Journal of Clinical Pharmacology, 69*(3), 295–307. https://doi.org/10.1007/s00228-012-1353-z

Prieto-Garcia, J. M., & Prieto-Garcia, G. L. (2023). Potential pharmacokinetic interactions of common cardiovascular drugs and selected European and Latin American herbal medicines: A scoping review. *Plants, 12*(3), 623. https://doi.org/10.3390/plants12030623

Qurbany, Z. T. (2015). The benefits of garlic (Allium sativum) as antihypertension. *J Majority, 4*(3), 116–121.

Raj, R. G. (2024). Targeting hypertension: A review on pathophysiological factors and treatment strategies. *Current Hypertension Reviews, 20*(2), 70–79. https://doi.org/10.2174/0115734021293403240309165336

Rizza, S., & Rizza, M.-A. (2011). Citrus polyphenol hesperidin stimulates production of nitric oxide in endothelial cells while improving endothelial function and reducing inflammatory markers in patients with metabolic syndrome. *The Journal of Clinical Endocrinology & Metabolism, 96*(5), E782–E792. https://doi.org/10.1210/jc.2010-2879

Ros, E. (2010). Health benefits of nut consumption. *Nutrients, 2*(7), 652–682. https://doi.org/10.3390/nu2070652

Ross, R. (1996). The pathogenesis of atherosclerosis. *The New England Journal of Medicine, 340*(2), 441–460. https://doi.org/10.1056/NEJM199901143400207

Rubin, S. A. (1981). Vasodilator therapy for heart failure: Concepts, applications, and challenges. *JAMA, 245*(7), 763–771. https://doi.org/10.1001/jama.1981.03310320071035

Roth, G. A., Johnson, C., Abajobir, A., Abd-Allah, F., Abera, S. F., Abyu, G., et al. (2017). Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *Journal of the American College of Cardiology, 70*(1), 1–25. https://doi.org/10.1016/j.jacc.2017.04.052

Rysz, J. F.-B. (2017). Hypertension – current natural strategies to lower blood pressure. *Current Pharmaceutical Design, 23*(17), 2453–2461. https://doi.org/10.2174/1381612823666170215144649

Salehpour, F., & Salehpour, M. (2018). Brain photobiomodulation therapy: A narrative review. *Molecular Neurobiology, 55*, 6601–6636. https://doi.org/10.1007/s12035-017-0852-4

Sánchez-Gloria, J. L.-B.-R.-A.-G.-M.-A. (2022). Cellular mechanisms underlying the cardioprotective role of allicin on cardiovascular diseases. *International Journal of Molecular Sciences, 23*(16), 9082. https://doi.org/10.3390/ijms23169082

Sandilands, E. A. (2013). Histamine-induced vasodilatation in the human forearm vasculature. *British Journal of Clinical Pharmacology, 76*(5), 699–707. https://doi.org/10.1111/bcp.12110

Santos, G. K. (2012). Essential oils from Alpinia purpurata (Zingiberaceae): Chemical composition, oviposition deterrence, larvicidal and antibacterial activity. *Industrial Crops and Products, 40*, 254–260. https://doi.org/10.1016/j.indcrop.2012.03.020

Santos, S. E.-F.-J. (2019). New insights on relaxant effects of (−)-borneol monoterpene in rat aortic rings. *Fundamental & Clinical Pharmacology, 33*(2), 148–158. https://doi.org/10.1111/fcp.12417

Santos-Parker, J. R., Strahler, T. R., Bassett, C. J., Bispham, N. Z., Chonchol, M. B., & Seals, D. R. (2017). Curcumin supplementation improves vascular endothelial function in healthy middle-aged and older adults by increasing nitric oxide bioavailability and reducing oxidative stress. *Aging (Albany NY), 9*(1), 187–208. https://doi.org/10.18632/aging.101149

Saponara, S., & Saponara, T. (2006). Naringenin as large conductance Ca2+-activated K+ (BKCa) channel opener in vascular smooth muscle cells. *British Journal of Pharmacology, 149*(8), 1013–1021. https://doi.org/10.1038/sj.bjp.0706951

Sarelius, I. H., & Pohl, U. (2010). Control of muscle blood flow during exercise: Local factors and integrative mechanisms. *Acta Physiologica, 199*(4), 349–365. https://doi.org/10.1111/j.1748-1716.2010.02130.x

Satoh, S., & Satoh, N. (2007). Cardiovascular pharmacology of sinomenine: The mechanical and electropharmacological actions. *Drug Target Insights, 2*, 97–104. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3155221/

Schieber, A. (2020). Botanicals – Challenges abound, solutions in sight? *Current Opinion in Food Science, 32*, 144–148. https://doi.org/10.1016/j.cofs.2020.04.010

Seamon, K. B. (1981). Forskolin: Unique diterpene activator of adenylate cyclase in membranes and in intact cells. *Proceedings of the National Academy of Sciences, 78*(6), 3363–3367. https://doi.org/10.1073/pnas.78.6.3363

Sever, P. S. (2013). Hypotension and ischaemic stroke associated with liskiren in the ALTITUDE trial: Sensitisation of the Bezold–Jarisch reflex? *Journal of the Renin-Angiotensin-Aldosterone System, 14*(1), 1–2. https://doi.org/10.1177/1470320312468832

Shamon, S. D., & Perez, M. I. (2016). Blood pressure-lowering efficacy of reserpine for primary hypertension. *Cochrane Database of Systematic Reviews, 2016*(12), CD007655. https://doi.org/10.1002/14651858.CD007655.pub3

Shi, P. C. (2018). Allicin improves the function of cardiac microvascular endothelial cells by increasing PECAM-1 in rats with cardiac hypertrophy. *Phytomedicine, 51*, 241–254. https://doi.org/10.1016/j.phymed.2018.10.021

Sica, D. A. (2001). Direct vasodilators and their role in hypertension management: Minoxidil. *The Journal of Clinical Hypertension, 3*(3), 201–205. https://doi.org/10.1111/j.1524-6175.2001.00678.x

Siervo, M., & Siervo, L. (2013). Inorganic nitrate and beetroot juice supplementation reduces blood pressure in adults: A systematic review and meta-analysis. *The Journal of Nutrition, 143*(6), 818–826. https://doi.org/10.3945/jn.112.170233

Silva, D. V. (2023). A critical review on vasoactive nutrients for the management of endothelial dysfunction and arterial stiffness in individuals under cardiovascular risk. *Nutrients, 15*(11), 2618. https://doi.org/10.3390/nu15112618

Silva, M. P.-J.-N.-S. (2022). Bioactive natural products against systemic arterial hypertension: A past 20-year systematic and prospective review. *Evidence-Based Complementary and Alternative Medicine, 2022*, Article 8499625. https://doi.org/10.1155/2022/8499625

Singh, A., Laribi, S., Teerlink, J. R., & Mebazaa, A. (2017). Agents with vasodilator properties in acute heart failure. *European Heart Journal, 38*(5), 317–325. https://doi.org/10.1093/eurheartj/ehv755

Stuehr, D. J. (2004, October). Enzymes of the L-arginine to nitric oxide pathway. *The Journal of Nutrition, 134*(10), 2748S–2751S. https://doi.org/10.1093/jn/134.10.2748S

Sun, J. (2007). D-limonene: Safety and clinical applications. *Alternative Medicine Review, 12*(3), 259–264. https://pubmed.ncbi.nlm.nih.gov/18072821

Sureda, A., Silva, A. S., Sánchez-Machado, D. I., López-Cervantes, J., Daglia, M., Nabavi, S. F., et al. (2017). Hypotensive effects of genistein: From chemistry to medicine. *Chemico-Biological Interactions, 268*, 37–46. https://doi.org/10.1016/j.cbi.2017.02.012

Suzuki, Y. J., & Suzuki, P. L. (1993). Relationships between the effects of superoxide anion and palmitoyl-L-carnitine on the Ca(2+)-ATPase of vascular smooth muscle sarcoplasmic reticulum. *Journal of Molecular and Cellular Cardiology, 25*(7), 823–827. https://doi.org/10.1006/jmcc.1993.1092

Sydykov, A., Mamazhakypov, A., Maripov, A., Kosanovic, D., Weissmann, N., Ghofrani, H. A., Sarybaev, A. S., & Schermuly, R. T. (2021). Pulmonary hypertension in acute and chronic high altitude maladaptation disorders. *International Journal of Environmental Research and Public Health, 18*(4), 1692. https://doi.org/10.3390/ijerph18041692

Tang, F. Y., & Tang, L.-X., & Tang, F.-Z. (2021). Review of natural resources with vasodilation: Traditional medicinal plants, natural products, and their mechanism and clinical efficacy. *Frontiers in Pharmacology, 12*, 627458. https://doi.org/10.3389/fphar.2021.627458

Tarkin, J. M., & Kaski, J. C. (2015). Nicorandil. In *Pharmacological Treatment of Chronic Stable Angina Pectoris* (pp. 115–134).

Todd, D. A., & Todd, B. (2020). Chemical composition and biological effects of kratom (Mitragyna speciosa): In vitro studies with implications for efficacy and drug interactions. *Scientific Reports, 10*(1), 19158. https://doi.org/10.1038/s41598-020-76119-w

Ulloa, N. A. (2023). Nebulized nitroglycerin in the emergency department. *Clinical and Experimental Emergency Medicine, 10*(1), 104–106. https://doi.org/10.15441/ceem.22.411

Verbeuren, T. J., & Verbeuren, J. F. (1986). Effect of hypercholesterolemia on vascular reactivity in the rabbit. I. Endothelium-dependent and endothelium-independent contractions and relaxations in isolated arteries of control and cholesterol-fed rabbits. *Circulation Research, 58*(4), 552–564. https://doi.org/10.1161/01.res.58.4.552

Victório, C. P. (2009). Vasodilator activity of extracts of field Alpinia purpurata (Vieill) K. Schum and A. zerumbet (Pers.) Burtt et Smith cultured in vitro. *Brazilian Journal of Pharmaceutical Sciences, 45*(3), 539–545. https://doi.org/10.1590/S1984-82502009000300017

Villacorta, L., & Villacorta, G. Z. (2016). Nitro-fatty acids in cardiovascular regulation and diseases: Characteristics and molecular mechanisms. *Frontiers in Bioscience Landmark, 21*(4), 873–889. https://doi.org/10.2741/4425

Wachtel-Galor, S., & Wachtel-Galor, S. (2011). Herbal medicine: An introduction to its history, usage, regulation, current trends, and research needs. In C. P. Francis (Ed.), *Herbal medicine: Biomolecular and clinical aspects* (Vol. 2). Boca Raton. https://www.ncbi.nlm.nih.gov/books/NBK92773/

Waldman, S. A., & Murad, F. (1988). Cyclic GMP synthesis and function. *Pharmacological Reviews, 40*(4), 607–617.

Wang, J. M., & Wang, Y. Z. (2009). Berberine-induced decline in circulating CD31+/CD42- microparticles is associated with improvement of endothelial function in humans. *European Journal of Pharmacology, 614*(1–3), 77–83. https://doi.org/10.1016/j.ejphar.2009.04.037

Wang, L.-F., & Wang, L.-Y. (2023). Resveratrol prevents age-related heart impairment through inhibiting the Notch/NF-κB pathway. *Food Science & Nutrition, 12*(2), 1035–1045. https://doi.org/10.1002/fsn3.3817

Wang, X., & Wang, I. (2001). Nitric oxide, nitric oxide synthases and cyclooxygenase-2 in experimental focal stroke. In *Birkhäuser, Basel* (Vol. 86, pp. 343–350). https://doi.org/10.1007/978-3-0348-8297-2_26

Wang, Z. W. (2022). Berberine improves vascular dysfunction by inhibiting trimethylamine-N-oxide via regulating the gut microbiota in angiotensin II-induced hypertensive mice. *Frontiers in Pharmacology, 13*, 827970. https://doi.org/10.3389/fphar.2022.827970

Wanwimolruk, S., & Prachayasittikul, V. (2014). Cytochrome P450 enzyme-mediated herbal drug interactions (Part 1). *EXCLI Journal, 13*, 347–391. https://www.excli.de/index.php/excli/article/view/460

Webb, A. J. (2019). Effects of vasodilating medications on cerebral haemodynamics in health and disease: Systematic review and meta-analysis. *Journal of Hypertension, 37*(6), 1119–1125. https://doi.org/10.1097/HJH.0000000000002033

Wei, C.-C., Crane, B. R., & Stuehr, D. J. (2003). Tetrahydrobiopterin radical enzymology. *Chemical Reviews, 103*(6), 2365–2383. https://doi.org/10.1021/cr0204350

Wenhan, C. (1998). Regulation of extracellular calcium-activated cation currents by cAMP in parathyroid cells. *American Journal of Physiology-Endocrinology and Metabolism, 275*(2), E213–E221. https://doi.org/10.1152/ajpendo

Wihlborg, A. K. (2003). Extracellular nucleotides induce vasodilatation in human arteries via prostaglandins, nitric oxide, and endothelium-derived hyperpolarising factor. *British Journal of Pharmacology, 138*(8), 1451–1458. https://doi.org/10.1038/sj.bjp.0705186

Wright, I. (2019). Regulation and market reform: The essential foundations for a renewable future. In B. K. Sovacool, M. A. Brown, & S. Valentine (Eds.), *The Palgrave handbook of managing fossil fuels and energy transitions* (pp. 453–482). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-319-98490-2_18

Wu, C.-C., L.-T., Y.-W., & C.-J. (2019). EtcABC, a putative EII complex, regulates type 3 fimbriae via CRP-cAMP signaling in Klebsiella pneumoniae. *Frontiers in Microbiology, 10*, 1558. https://doi.org/10.3389/fmicb.2019.01558

Xu, J., Zhang, X., Monestier, M., & Wang, H. (2021). Vasodilation and the regulation of vascular tone: Mechanistic insights and therapeutic perspectives. *Frontiers in Physiology, 12*, 678262. https://doi.org/10.3389/fphys.2021.678262

Zacest, R. (1975). The clinical pharmacology of hypotensive vasodilator drugs. *The Medical Journal of Australia, 1*, 4–8. https://doi.org/10.5694/j.1326-5377.1975.tb140358.x

Zacest, R. (1976). The vasodilator—Beta-blocker interaction—Some determinants of its clinical success. *Australian and New Zealand Journal of Medicine, 6*, 65–76. https://doi.org/10.1111/j.1445-5994.1976.tb03339.x

Figures References

Figure 1 https://neurocarepro.com/understanding-vasodilation-the-key-to-enhanced-healing-and-how-red-light-therapy-can-help/

Figure 2 https://aneskey.com/nitric-oxide-as-an-adjunct/

Figure 4 https://www.researchgate.net/figure/Structure-of-arterial-wall-The-arterial-wall-is-composed-of-three-layers-tunica-intima_fig5_283261056

Figure 5 https://thejournalofheadacheandpain.biomedcentral.com/articles/10.1186/s10194-017-0800-8

Figure 7 https://www.egpat.com/tutorials/adrenergic-antagonists/selective-alpha-blockers

Figure 8 https://doi.org/10.1016/j.phrs.2014.07.005

Figure 11 https://pmc.ncbi.nlm.nih.gov/articles/PMC3712223/

https://www.logees.com/dwarf-red-ginger-alpinia-purpurata.html

Figure 12 https://iadns.onlinelibrary.wiley.com/doi/10.1002/fft2.289

Figure 13 **https://www.sciencedirect.com/science/article/pii/S0022316623031218#bib11**

Figure 14 https://doi.org/10.3390/nu14050961

Figure 15 **https://doi.org/10.1016/j.jphs.2015.09.002**

Figure 16 **https:**//doi.10.1111/bph.14484

Figure 17 **https://doi.10.1111/bph.14484**

Figure 20 **doi.org/10.1007/3-540-29832-0_1503**

Figure 21: **healio.com – Atherosclerosis Topic Review**

Figure 22 **https://guysandstthomasspecialistcare.co.uk/news/4-stages-of-congestive-heart-failure/**

Figure 23 **https://byjus.com/biology/angina-pectoris/**

Figure 24 https://tinyurl.com/yc5frbk2

Figure 25 https://doi.org/10.3390/ijms25126388

Abstract

Vasodilators are pharmacological agents that induce vasodilation, which is particularly important for controlling blood flow, pressure, and overall cardiovascular functions. There is a category of vasodilators known as natural vasodilators. These are bioactive compounds derived from certain food sources and plants that promote the widening of blood vessels, thereby improving blood flow and reducing blood pressure. These substances, similar to artificial ones, have attracted attention for their potential therapeutic applications in the management of cardiovascular diseases and conditions such as hypertension. Various bioactive components, including nitric oxide donors, prostaglandins, potassium and calcium channel openers and blockers like certain plant constituents (allicin), engage various biochemical pathways "Mechanism of action" to exert vasodilatory effects, most of which involve the relaxation of the endothelium and vascular smooth muscle.

The clinical use of natural vasodilators is associated with numerous drawbacks, including the variability of active constituents, the lack of standardization, potential harm due to side effects and toxicity, conventional drug interactions, and the lack of regulatory oversight. The dissertation aims to examine the potential therapeutic applications of natural vasodilators by evaluating their mechanisms of action and reviewing the existing scientific literature. It aims to elucidate the promises and challenges associated with the use of natural vasodilators in cardiovascular therapies while highlighting the need to advance preliminary studies, improve safety assessments, and establish clearer legal guidelines to ensure their effective integration into contemporary medical practice.

Key words: Vasodilation, Natural vasodilators, cardiovascular diseases, Mechanisms of action, Therapeutic applications

Résumé

Les vasodilatateurs sont des agents pharmacologiques qui induisent la vasodilatation, ce qui est particulièrement important pour contrôler le flux sanguin, la pression et les fonctions cardiovasculaires générales. Il existe une catégorie de vasodilatateurs que l'on appelle vasodilatateurs naturels. Ces derniers sont des composés bioactifs dérivés de certaines sources alimentaires et de plantes qui favorisent l'élargissement des vaisseaux, améliorant ainsi le flux sanguin et réduisant la pression artérielle. Ces substances, similaires à celles des artificielle, ont attiré l'attention pour leurs applications thérapeutiques potentielles dans la gestion des maladies cardiovasculaires et des affections telles que l'hypertension. Divers composants bioactifs, y compris les donneurs de monoxyde d'azote, les prostaglandines, les ouvreurs et bloqueurs des canaux potassiques et calciques comme certains constituants végétaux (l'allicine), engagent diverses voies biochimiques « Mécanisme d'action » pour exercer des effets vasodilatateurs, dont la plupart impliquent la relaxation de l'endothélium et du muscle lisse vasculaire.

L'utilisation clinique des vasodilatateurs naturels est liée à de nombreux inconvénients, notamment la variabilité des constituants actifs, le manque de standardisation, les dommages potentiels dus aux effets secondaires et à la toxicité, les interactions médicamenteuses conventionnelles et le manque de surveillance réglementaire. La dissertation vise à examiner les applications thérapeutiques potentielles des vasodilatateurs naturels en évaluant leurs mécanismes d'action et en passant en revue la littérature scientifique existante. Elle vise à élucider les promesses et les défis associés à l'utilisation des vasodilatateurs naturels dans les thérapies cardiovasculaires tout en soulignant la nécessité de faire progresser les études préliminaires, d'améliorer les évaluations de sécurité et d'établir des lignes directrices juridiques plus claires pour garantir leur intégration efficace dans la pratique médicale contemporaine.

Mots clé : Vasodilatation, Vasodilatateurs Naturelle, Maladies Cardio-vasculaire, Mécanisme d'action, Application thérapeutique.

ملخص

موسعات الأوعية الدموية هي مركبات صيدلانية تحفز توسع الأوعية، التي تقوم بالمساهمة بشكل خاص في التحكم بضغط، وتدفق الدم، اضافة الى التحكم بالوظائف القلبية الوعائية بشكل عام. هناك فئة من موسعات الأوعية تعرف بموسعات الأوعية الطبيعية. هذه الأخيرة هي عبارة عن مركبات نشطة بيولوجيًا مستمدة من مصادر غذائية معينة ونباتات تعمل هي كذلك على توسيع الأوعية الدموية، مما يحسن كذلك التدفق ويخفض ضغط الدم. هذه المواد، على غرار المواد الاصطناعية، قد جذبت الانتباه لتطبيقاتها العلاجية المحتملة في إدارة الأمراض القلبية الوعائية والحالات مثل ارتفاع ضغط الدم، حيث تشمل على مكونات نشطة حيوياً، بما في ذلك مانحي أكسيد النيتريك، والبروستاجلاندينات، ومفتحي ومثبطي قنوات البوتاسيوم والكالسيوم مثل بعض المكونات النباتية (الأليسين)، والتي تعمل على تفعيل مسارات بيولوجية كيميائية مختلفة لإحداث تأثيرات موسعة للأوعية، معظمها يتضمن استرخاء البطانة والعضلات الملساء الوعائية.

الاستخدام السريري لموسعات الأوعية الطبيعية يرتبط بالعديد من العيوب، بما في ذلك تباين المكونات الفعالة، وعدم وجود معايير موحدة، والضرر المحتمل بسبب الآثار الجانبية والسمية، والتفاعلات مع الأدوية التقليدية، وغياب الإشراف التنظيمي. تهدف هذه الدراسة إلى استنباط التطبيقات العلاجية المحتملة لموسعات الأوعية الطبيعية من خلال تقييم آليات عملها ومراجعة الأدبيات العلمية الموجودة. يهدف إلى توضيح الوعود والتحديات المرتبطة باستخدام موسعات الأوعية الطبيعية في العلاجات القلبية الوعائية مع تسليط الضوء على الحاجة إلى تطوير الدراسات الأولية، وتحسين تقييمات السلامة، ووضع إرشادات قانونية أوضح لضمان دمجها الفعال في الممارسة الطبية المعاصرة.

الكلمات المفتاحية: موسعات الاوعية الدموية، موسعات الاوعية الطبيعية، الامراض القلبية الوعائية، آليات العمل، توسع الاوعية، تطبيقات العلاجية.

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Study on the Natural Vasodilators

Dissertation presented for the purpose of obtaining a Master's Degree

Abstract

Vasodilators are pharmacological agents that induce vasodilation, which is particularly important for controlling blood flow, pressure, and overall cardiovascular functions. There is a category of vasodilators known as natural vasodilators. These are bioactive compounds derived from certain food sources and plants that promote the widening of blood vessels, thereby improving blood flow and reducing blood pressure. These substances, similar to artificial ones, have attracted attention for their potential therapeutic applications in the management of cardiovascular diseases and conditions such as hypertension. Various bioactive components, including nitric oxide donors, prostaglandins, potassium and calcium channel openers and blockers like certain plant constituents (allicin), engage various biochemical pathways “Mechanism of action” to exert vasodilatory effects, most of which involve the relaxation of the endothelium and vascular smooth muscle.

The clinical use of natural vasodilators is associated with numerous drawbacks, including the variability of active constituents, the lack of standardization, potential harm due to side effects and toxicity, conventional drug interactions, and the lack of regulatory oversight. The dissertation aims to examine the potential therapeutic applications of natural vasodilators by evaluating their mechanisms of action and reviewing the existing scientific literature. It aims to elucidate the promises and challenges associated with the use of natural vasodilators in cardiovascular therapies while highlighting the need to advance preliminary studies, improve safety assessments, and establish clearer legal guidelines to ensure their effective integration into contemporary medical practice.

Key words: Vasodilation, Natural vasodilators, Cardiovascular diseases, Mechanisms of action Therapeutic applications

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