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Herbal medications and target-based drug delivery strategies for hypertension

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CONTENTS

ABSTRACT

Heart failure, myocardial infarction, and stroke are among the major cardiovascular problems that can arise from high blood pressure, which is a common non-communicable condition. Beyond traditional medications, new herbal treatment techniques seek to treat hypertension by focusing on blood vessel smooth muscle function, inflammatory routes and pathways in the central nervous system. Novel approaches are intended to treat resistant hypertension, enhance blood pressure management, and accomplish further risk reduction beyond blood pressure reduction. Novel targets for antihypertensive treatment are also expected to be connected to RAAS. This review aimed to provide an in-depth mechanistic analysis of the intriguing new targets and the pharmacological action of phytochemicals associated with hypertension. These phytochemicals (Allicin, S-allyl cysteine) from *Allium sativum* L. (Garlic) and terpinen-4-ol from *Alpinia zerumbet* Pers. (Shell ginger), showed anti-hypertensive action, increasing NO activity. The other, crocin from *Crocus sativus* L. (Carl Linnaeus) (Saffron crocus), EGCG from *Camellia sinensis* (L.) (Tea plant), reduced oxidative stress by its antihypertensive action.

Keyword: Aminopeptidase inhibitors, AT2R, Compound 21, Herbal drugs, Hypertension, Phytochemicals

1. INTRODUCTION

Hypertension, defined as a continuous systolic arterial blood pressure (SBP) of at least 130 mmHg or a diastolic level of a minimum 80 mmHg, affects approximately 116 million adults and 1 billion people worldwide. Hypertension is associated with an increased risk of cardiovascular disorder (CVD) events and mortality, including cardiac arrest, stroke and coronary artery disease (11). The drugs used to treat hypertension include diuretics, β-receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, blockers of calcium channels and blockers of angiotensin II receptors. Yet, despite the accessibility to several anti-hypertensive medications, 1 in 5 persons (21 %) have uncontrolled hypertension due to adverse effects, intolerance and ineffectiveness. Considering the vast number of persons

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with uncontrolled blood pressure and the intricacy of the etiology, it is imperative to develop new targets and anti-hypertensive medications to additional options to those individuals (27). The angiotensin II receptor (AT2R) and aminopeptidase are the most intriguing novel targets. Angiotensin types 1 and 2 (AT1R, AT2R) are the two major receptors through which angiotensin II (Ang II), the RAS's principal effector, operates. It has been suggested that APA in the central RAS is a new target for antihypertensive drugs, because it cleaves angiotensin II to generate angiotensin III, which raises the pressure in the blood. This review contains novel herbs acting as antihypertensives, such as *Allium sativum* L. (Garlic), *Alpinia zerumbet* Pers. (Shell ginger) and *Crocus sativus* L. (Saffron crocus) shown in Fig. 1.

Allium sativum L. (Garlic) | *Alpinia zerumbet* Pers. (Shell ginger) | *Crocus sativus* L. (Saffron crocus)

Figure 1. Novel herbs associated with hypertension

2. NOVEL TARGETS IN HYPERTENSION

2.1. The Angiotensin II receptor

The primary RAAS hormone, Ang II, acts on AT1 and AT2 receptors to induce vasoconstriction and vasodilatory effects, respectively. Under healthy circumstances, the AT2 receptor's expression is kept low; nevertheless, under diseased situations such as myocardial infarction, vascular damage and renal failure, its expression is significantly raised for endogenous defence (8). Figure 2 illustrates how Ang II binds to and activates AT1R and AT2R, the two primary Ang II receptors in the classical renin-angiotensin system (RAS) pathway, which produce distinct responses.

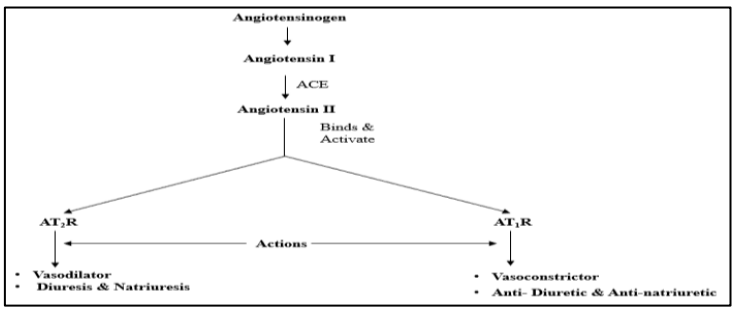

Figure 2. The RAS pathway, how ANG II binds to either one of the two receptors to activate and elicit the proposed functions.

2.1.1. Vascular and BP-lowering actions of AT2Rs: Nitric oxide/nitric oxide synthase (NO/NOs) pathways of signalling facilitate Ang II-induced blood vessel relaxation, which is mediated by the AT2 receptor (39,42). It was first suggested that AT2Rs reduce pressure-natriuresis; later, it was demonstrated that AT2R null mice had pressure and anti-natriuretic heightened sensitivity to exogenous Ang II (41). Later studies showed that the conventional pressure-natriuresis link is shifted to the right (less sensitive) in AT2R-null mice in conjunction with or without L-NAME-induced hypertension (32). The substantial reduction in the kidneys' nitric oxide (NO), bradykinin (BK) and guanosine cyclic 3′,5′-monophosphate (cGMP) in AT2R-null mice at baseline and in response to treatment with Ang II than wild-type animals was attributed to these animals' anti-natriuresis. Thus, AT2Rs counteract Ang II's effects through AT1Rs, which elevates sodium (Na+) reabsorption in the kidney tubes and causes anti-natriuresis (21,29). Ang II metabolite [des-aspartyl1]-Ang II (Ang III) is the main and perhaps unique endogenous AT2R agonist for the natriuretic response (23,35,36). Since aminopeptidase N breaks down Ang III to unproductive metabolites, very modest levels of systemic AT1R blockage or inhibition are necessary for the manifestation of Ang III-driven natriuresis through AT2Rs in healthy animals (23,34,35,36). However, concomitant AT1R blocking is not required for obese Zucker rats or diabetic rats treated with streptozotocin, even though AT2Rs exhibit increased renal proximal tubule AT2R expression in these scenarios (17,18,19). Surprisingly, AT2R antagonist PD-123319 (PD) inhibits the AT2R-dependent mechanism, via which selective intrarenal AT1R blockage causes natriuresis (34).

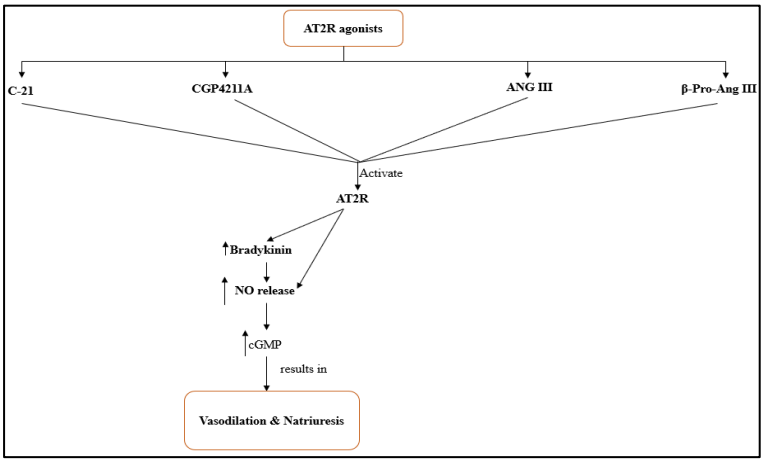

Figure 3. Present knowledge of how AT2R activation regulates blood pressure and natriuresis.

The quick reaction process is probably linked to elevated endogenous intrarenal Ang III levels, which in turn activate unblocked AT2Rs, even though this has not been explicitly investigated (23,34,35). The AT2R agonist Compound 21 (C-21), an extremely selective nonpeptide, has been used in recent investigations of AT2R-induced natriuresis (44). C-21 caused natriuresis by acting on the renal proximal tubule (RPT) when it was given to

healthy rats either systemically or internally (24). AT2R activation caused the C-21-induced natriuresis and was reliant on a BK-NO-cGMP signaling route (40). The migration of AT2Rs from within the cell to the apical membranes of plasma of renal proximal tubule (RPT) cells following acute C-21 administration may enhance and sustain the AT2R natriuretic response. Additionally, C-21 internalized and deactivated the key RPT Na+ transporters Na+-hydrogen exchanger-3 (NHE-3) and Na+/K+ATPase (NKA), suggesting that the process behind natriuresis is decreased RPT Na+ transport (24). Because there are currently no effective diuretic/natriuretic medications that act at the RPT, these data showed that AT2R activation would be additive to diuretics acting in the distal sections of the renal cell. When the extremely specific AT2R synthetic peptide agonist CGP42112A (CGP) is administered internally, it has natriuretic effects of acute AT2R activation. In this investigation, AT2R-induced natriuresis was linked to the inactivation of NKA in RPT cells and the recruitment of AT2R receptors to the apical membranes of the plasma (46). The overall mechanism of AT2R activation regulates blood pressure and natriuresis is described in Figure 3.

2.2. Aminopeptidase Inhibitors

Renin, also known as angiotensinogenase, converts the protein angiotensinogen into the peptide angiotensin I. There after the angiotensin-converting enzyme (ACE) breaks down angiotensin I to form angiotensin II. To create angiotensin III, angiotensin II is cleaved by aminopeptidase A (APA). Angiotensin III is broken down by aminopeptidase N (APN) to create angiotensin IV. It is important to note that angiotensin peptides have distinct functions in the central and systemic RASs. Angiotensin II is the main regulatory peptide that increases blood pressure in the former, whereas angiotensin III does the same in the latter (51,52). ACE and renin are two primary targets of antihypertensive medications in the systemic RAS (48). Antihypertensive medications target APA in the central RAS (9,28). Renin-angiotensin systems (RASs) both centrally and systemically control blood pressure (6,16). Some hypertensive individuals exhibit modest systemic RAS activity, but hyperactivity in the central RAS. As a result, therapies that target the systemic RAS are ineffective in these individuals (5). peptidases. For essential activities, the central and even systemic RASs depend on the same class of peptidases (33). We recently revealed the structure of APN, another zinc-dependent aminopeptidase in this family and its catalytic mechanism is comparable to APA (12). APA is distinct from other zinc metalloenzymes in the M1 family in that it preferentially cleaves acidic residues. Interestingly, calcium regulates the substrate selectivity of APA, which is distinct from all other zinc metalloenzyme families. More precisely, calcium decreases APA's enzymatic activity with basic residues, while increasing it with acidic residues (13,38). Since the calcium concentrations that regulate APA function fall between 1 and 2 mM, which is identical to the level found in brain fluid, the calcium-modulated substrate selectivity of APA is regarded as therapeutically relevant (22). An investigation by Yang *et al* (46) revealed that the S-1 domain of APA possesses a calcium-binding region and can only contain acidic remnants. This study also showed that APA has calcium-modulated substrate specificity, which helps in the creation of antihypertensive APA inhibitors. The Fig. 4 illustrates that the systemic and central RASs work cooperatively to control blood pressure.

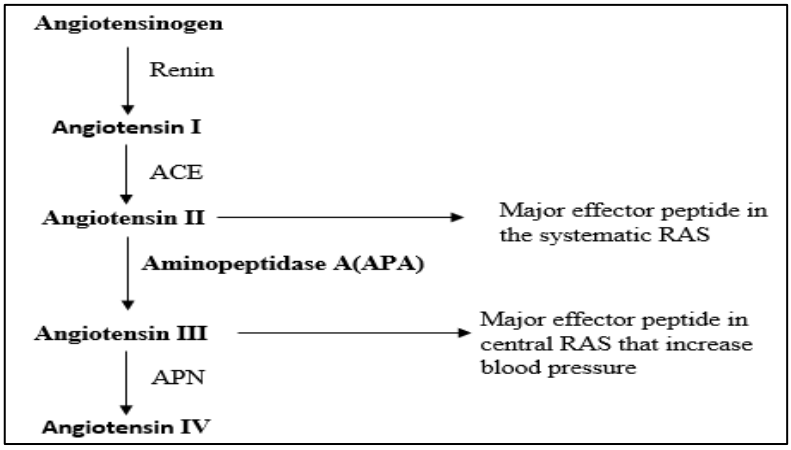

Figure 4. Systemic and central RASs work cooperatively to control blood pressure

Ang III is an RAAS brain peptide that is essential to regulate the expulsion of the hormone vasopressin and the level of blood pressure. An essential component of blood pressure control and vasopressin release, Ang III is a brain RAAS peptide (37). Therefore, targeted and selective Ang III inhibitors may lower blood pressure in cases of hypertension. A class of medications known as centrally acting APA inhibitors prevents the production of Ang III and is an effective treatment for hypertension (26). In a mouse model of myocardial infarction, APA inhibition prevents hypertrophy and fibrosis, restores cardiac function and normalizes cerebral RAAS (10).

3. NOVEL HERBAL PHYTOCHEMICALS TO TREAT HYPERTENSION

Very expensive synthetic drugs and hypertensive therapies prompted the search for herbs and the development of herbal medicine based on their active phytochemicals, which have significant potential in hypertension management. Because of their limited adverse effects and multi-targeted therapeutic potential, novel herbal phytochemicals have emerged as promising medicines to control hypertension. These bioactive substances, which come from plants like *Camellia sinensis* (L.), (Tea plant), *Curcuma longa* L. (turmeric) and *Allium sativum* L. (garlic) have antihypertensive properties through several mechanisms, such as vasodilation, renin-angiotensin system inhibition, antioxidant activity, calcium channel blocking and endothelial function modulation. By increasing nitric oxide bioavailability, decreasing oxidative stress and boosting vascular compliance, important phytochemicals such as curcumin, allicin and catechins have demonstrated effectiveness in lowering blood pressure. These natural substances are being researched more and more because they may be able to replace or supplement traditional antihypertensive medications, providing a more comprehensive and safe method of managing blood pressure over the long term. Table 1 summarizes the many herbs as well as the active phytoconstituents that help to manage hypertension.

Table 1. Herbs used to treat hypertension

Herb	Effects/ Mechanism	Concentration/ Dose	Experimental Model	Ref
Allium sativum L. (Garlic)	ROS scavenging	3 mg/ml	Neutrophils in humans	30, 49
	Raises the amount of antioxidants	From 125 to 2000 mg/kg	The hearts of Wistar albino rats	
	Raises NO	0.8 mg/ml	Rat isolated pulmonary arteries	
	NF-κB Prevents	250 mg/kg	Feeding rats high fructose	
Alpinia zerumbet Pers. (Shell ginger)	Blocks Ca2+ channels	1-20 mg/kg	Wistar rats	25
	Increases NO	100 and 300 µg/ml	DOCA-salt-induced hypertension in rats	
Andrographis paniculata (Burm.f.) (Green chiretta)	Scavenges ROS	0.7-2.8 g/kg	Spontaneous hypertensive rats (SHR)	4, 50
	Increases NO and Blocks Ca2+ channels	1 mg/ml	Isolated hearts from Sprague-Dawley rats	
	Inhibits NF-Kb	4 mg/kg	Npr1 gene-knockout mice	
Bidens pilosa L. (Black-jack)	Ca2+ antagonists	0.32 mg/ml	KCl-treated rat aorta	45
	Inhibits NF-κB and TNF-alpha activation	10-20 µg/ml	LPS-stimulated RAW 264.7	
Camellia sinensis (L.) (Tea plant)	Increases antioxidants	0.1%	Streptozotocin (STZ)-fed Sprague-Dawley rats	14, 47
	Blocks AT1 receptor	0.1%	STZ-fed Sprague-Dawley rats	
	Inhibits eNOS uncoupling	5 g/kg daily	Diabetic SHR	
	Inhibits NF-κB	5–30 µM (of EGCG)	Human endothelial cells	
Coptis chinensis Franch. (Huang lian)	Increases antioxidants, decreases NADPH oxidase and NF-κB	150 mg/kg	Atherosclerotic renovascular disease (ARD) Wistar rats	1
Crocus sativus L. (Saffron crocus)	Reduces oxidative stress and Increases antioxidants	200 mg/kg	BeCl2 -treated Wistar rats	15
	Activates eNOS	0.1-0.5 ml/kg	ischemia-reperfusion (IR) in rats	
	Inhibits NF-κB	0.1-0.5 mL/kg/day		
Cymbopogon citratus (DC.) (Lemon grass)	Increases NO bioavailability	30 mg/ml	Isolated aorta from SHR	7
Hibiscus sabdariffa L. (Roselle)	Scavenges ROS	2 mg/ml	CCl4 -induced hepatotoxicity in rat liver	3
	Increases NO	0.3 mg/ml	SHR isolated aorta	
	Lowers uric acid concentration	1500-2500 mg/kg	SHR	
Nigella sativa L. (Black cumin)	Blocks Ca2+ channels	2–14 mg/ml	Rat isolated aorta	2, 31
	Increases Na+, K+ and Cl− in urine	5 ml/kg/day	SHR	
Panax ginseng C.A.Mey. (Ginseng)	Increases eNOS	150 µg/m	SHR adrenal medulla	20
	Decreases TNF-α and IL-6	10 µM	Mouse macrophages	
Zingiber officinale Roscoe (Ginger)	Inhibits lipid peroxidation	0.05 mg/ml	Rat heart	43

4. CONCLUSIONS

The development of a new class of convenient and effective pharmaceuticals has become necessary due to the increasing incidence of higher blood pressure and its associated effects, as existing drugs, although beneficial in lowering blood pressure, have detrimental side effects with prolonged use. The novel peptide and non-peptide drugs have proved safer and more effective in clinical studies than existing drugs and the novel prospective targets we discussed in this study help to lessen the burden of high blood pressure. Tissue regeneration increases the expression of AT2R and stimulating it has positive effects on the brain, heart and kidneys. Regardless of blood pressure changes, AT2R activation promotes vasodilation and reduces inflammation. The primary RAS hormone that causes an increase in blood pressure, angiotensin III, is created when APA cleaves angiotensin II. Numerous herbs are useful to treat high blood pressure through various mechanisms. Among these herbs is *Allium sativum* L. (Garlic), which has the ability to scavenge reactive oxygen species, increase antioxidant and raise NO levels.

AUTHORS' CONTRIBUTIONS

RPM conceived of the present idea for the article. SHV performed the literature search, data analysis and wrote the manuscript. SWP and MS provided critical feedback and helped to shape the final draft.

DECLARATION

We declare that all authors of this Ms. have made substantial contributions. We did not exclude any author who substantially contributed to this Ms. We have followed our ethical norms established by our respective institutions.

CONFLICT OF INTEREST

The authors announce that they have no conflict of interest.

ETHICAL APPROVAL

The authors declare that the study was carried out following scientific ethics and conduct. However, this study did not involve any use of animals; hence, no ethical approval was obtained from the concerned committee.

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