Review

Exploring a New Natural Treating Agent for Primary Hypertension: Recent Findings and Forthcoming Perspectives

Shian-Ren Lin [1,2,†] **, Shiuan-Yea Lin** [3,†] **, Ching-Cheng Chen** [1,4] **, Yaw-Syan Fu** [5,6,*] **and Ching-Feng Weng** [5,7,*]

[1] Department of Life Science and Institute of Biotechnology, National Dong Hwa University, Hualien 97401, Taiwan; d9813003@gms.ndhu.edu.tw (S.-R.L.); abc57142001@yahoo.com.tw (C.-C.C.)
[2] Graduate Institute of Cancer Biology and Drug Discovery, Taipei Medical University, Taipei 110, Taiwan
[3] Department of Anatomy, Kaohsiung Medical University, Kaohsiung 80708, Taiwan; shiuanyea@yahoo.com.tw
[4] Camillian Saint Mary's Hospital Luodong,160 Zhongzheng S. Rd. Luodong, Yilan 26546, Taiwan
[5] Department of Biomedical Science and Environmental Biology, Kaohsiung Medical University, Kaohsiung 80708, Taiwan
[6] Center for Infectious Disease and Cancer Research, Kaohsiung Medical University, Kaohsiung 80708, Taiwan
[7] Department of Basic Medical Science, Center for Transitional Medicine, Xiamen Medical College, Xiamen 361023, China
[*] Correspondence: m805004@kmu.edu.tw (Y.-S.F.); cfweng-cfweng@hotmail.com (C.-F.W.); Tel.: +886-3-890-3609 (C.-F.W.); Fax: +886-3-890-0163 (C.-F.W.)
[†] These two authors contribute equally.

check for updates

Abstract: Primary hypertension describes abnormally-high systolic/diastolic blood pressure in a resting condition caused by various genetic or environmental risk factors. Remarkably, severe complications, such as ischemic cardiovascular disease, stroke, and chronic renal disease have led to primary hypertension becoming a huge burden for almost one-third of the total population. Medication is the major regimen for treating primary hypertension; however, recent medications may have adverse effects that attenuate energy levels. Hence, the search for new hypotensive agents from folk or traditional medicine may be fruitful in the discovery and development of new drugs. This review assembles recent findings for natural antihypertensive agents, extracts, or decoctions published in PubMed, and provides insights into the search for new hypotensive compounds based on blood-pressure regulating mechanisms, including the renin-angiotensin-aldosterone system and the sympathetic/adrenergic receptor/calcium channel system.

Keywords: Hypertension; herbal; natural compounds; RAAS; molecular docking

1. Introduction

Hypertension is a homeostatic blood pressure shift from normal (<120/80 mmHg) to abnormal levels (>140/90 mmHg) which is categorized into the following four stages: normal pressure (<120/80 mmHg), elevated pressure (120–139/80–89 mmHg), stage 1 hypertension (140–159/90–99 mmHg), and stage 2 hypertension (>160/100 mmHg) [1–3]. Only 5–10% of hypertensive patients can be diagnosed from certain causes e.g., aldosteronism, gestation, or renal artery stenosis (secondary hypertension); however, the other 90–95% of hypertensive patients have unknown or multiple reasons for their condition [4,5]. Despite uncertain causes, some predisposing factors for primary hypertension, such as

genetic variation, obesity, improper eating habits including excessive sodium and alcohol consumption, tobacco and marijuana use, and physical unfitness, are summarized [6–8].

About 31.1% of adults were hypertensive worldwide in 2010, with 28.5% of them living in high-income countries [9]. Notably, 32.5% of adults (17.3% of total citizens) are in various stages of hypertension in China [10]. Furthermore, the overall mortality of high systolic blood pressure is 20,526/100,000 people, and the age-standardized disability-adjusted life year rate (DALY) is 242.5/100,000 people [11,12]. These harsh statistics remind us that hypertension is highly prevalent, and is a burden on society in terms of the associated health expenditure. Generally, hypertensive patients endure various symptoms that are difficult to self-assess, such as headaches, dizziness, shortness of breath, chest pain, palpitations, and nosebleeds. However, common complications of hypertension are more severe, e.g., stroke, ischemic cardiovascular disease (ICD), and chronic kidney disease (CKD) (see Table 1) [13–15]. Therefore, the treatment and medical care of hypertension is a critical issue for elevating the well-being of mankind.

Table 1. Complications of hypertension.

Affect Organ	Complications
Cardiovascular system	Cardiac hypertrophy, heart failure, angina pectoris, coronary heart disease, myocardial infarction.
Artery	Atherosclerosis, aneurysms.
Brain	Stroke (ischemic or hemorrhagic), hypertensive encephalopathy, cognitive decline, dementia.
Eye	Retinopathy.
Kidney	Hypertensive nephropathy, chronic kidney disease.

The clinical foci of hypertension treatment comprise ameliorating blood pressure and preventing complications. Generally speaking, by using a blood pressure lowering approach, medication is the first choice, while the management life style gives constructive support in enhancing adherence [3,16]. Numerous agents, e.g., verapamil, amlodipine, and captopril, have been applied in the treatment of hypertension; the antihypertensive effects of these drugs have been well established [3,17]. Beyond medication, patients and clinicians propose a variety of supports from pharmaceuticals, society, family, and patient's personal pharmacogenomics for managing hypertension. Social isolation, low income, depression, or psychological distress have been ascertained as causes of withdrawal during treatment [3,16,18,19]. Statistical analyses from the investigation of African American women, Latino migrants, seasonal farmworkers, Chinese people, and people from south-west Nigeria have illustrated that social supports could promote patient adherence to treatment via sharing information and assisting in bringing about life style changes [20–23]. Surprisingly, about 10.3% of hypertension patients develop hypertensive resistance during the treatment regimen, which may be typified by a lower response to medications [24]. Nevertheless, several adverse effects—e.g., hyponatremia [25], hyperkalemia [26], and edema [27]—of recent medications do not facilitate the medical compliance of patients [28]. Accordingly, finding new blood pressure lowering agents with medical benefits for hypertensive patients, and to promoting the progress of new drug discovery, are increasingly important. Expectedly, cumulative research evidence has illustrated that natural compounds or herbal medicines are believed to be equipotent with fewer adverse effects compared to synthetic drugs [29]. In this review, we summarize recent findings pertaining to hypertension remedies from natural products and research approaches according the causes and shedding mechanism of hypertension that could provide new insights into perspective studies for the research and discovery of natural antihypertensive agents.

## 2. Physiological Regulation Mechanism in Blood-Pressure

Basically, the body undertakes the regulation of blood-pressure via two strategies: total blood volume and blood flow. Total blood volume is mainly mediated by renin-angiotensin-aldosterone systems (RAAS), while blood flow is predominantly regulated by neurogenic hypertensive system

and nitric oxide (NO) [30,31]. Consequently, current hypertensive medication also targets the aforementioned mechanisms (RAAS and neurogenic hypertensive system) to alleviate high blood pressure [1]. The following section will individually address each blood-pressure-controlling mechanism to summarize our present knowledge of the regulation of blood pressure, medications, and screening tools for natural compounds.

2.1. Renin-Angiotensin-Aldosterone System (RAAS)

2.1.1. Mechanical Action of RAAS in Blood-Pressure Controlling

RAAS is long-term regulator of blood pressure composed of renin (an aspartic protease produced by the juxtaglomerular apparatus of kidney), angiotensin converting enzyme (ACE, a zinc-dependent dicarboxyprotease secreted from the lungs), angiotensinogen (a hormone precursor), and aldosterone (mineralocorticoid hormone from adrenal cortex, the endpoint effector). Angiotensinogen is converted into angiotensin II (Ang II) because it is sequentially cleaved by renin and ACE; subsequently, Ang II stimulates the adrenal gland cortex to produce aldosterone [32]. Aldosterone raises blood-pressure via two phases: (i) potentiating Na^+/K^+-ATPase activity on sodium and water reabsorption of renal tubular cells; and (ii) consequently managing (i.e., increasing or decreasing) blood volume (see Figure 1A), as well as vascular smooth muscle cells for vasoconstriction [33,34]. To understand the cause of elevating blood pressure, the consequence of a decrease of sympathetic input and an increase in parasympathetic input to the heart is observed. Second, if the baroreceptors detect that blood pressure is too high, the cardio-regulatory center of the medulla will also decrease the sympathetic input to the blood vessels. This causes vasodilation instead of vasoconstriction, which decreases the total peripheral resistance and concurrently decreases blood pressure (see Figure 1B). In this section, we will not discuss the sympathetic nerve regulating system; rather, we will mainly focus on the regulation of the RAAS system in order to present a comprehensive review of potential targets for lowering blood pressure.
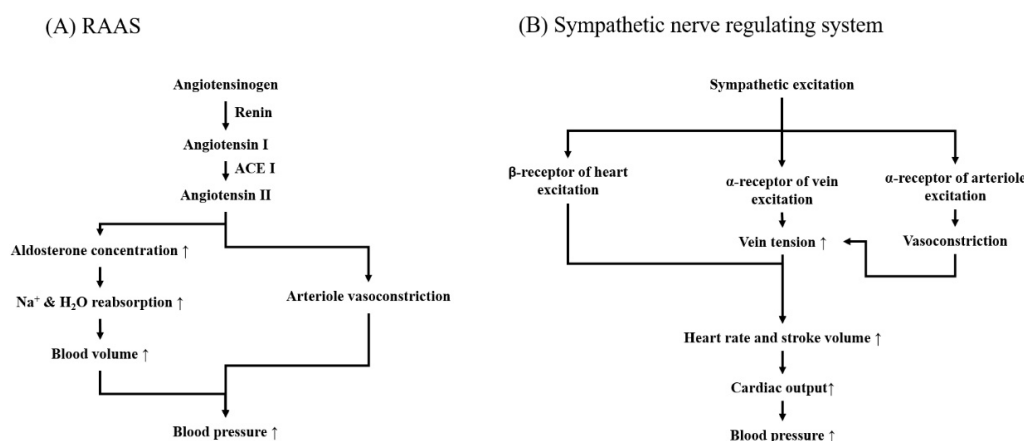
Figure 1. Regulating mechanism for blood pressure. (**A**) RASS; (**B**) Sympathetic nerve regulating system. RAAS: renin-angiotensin-aldosterone systems; ACE I: angiotensin converting enzyme inhibitor.

2.1.2. Conventional RAAS Modulators in Hypertensive Medication

According to the physiological mechanism of RAAS, several targets have been identified: ACE, the angiotensin II type-1 receptor (AGTR1), the aldosterone receptor, and Na^+/K^+-ATPase. ACE inhibitors (e.g., Captopril, Ramipril, and Fosinopril) and Ang II receptor blockers (e.g., Valsartan, Irbesartan, Candesartan, and Olmesartan) directly suppress Ang II and aldosterone production in the adrenal gland [35,36]. Aldosterone receptor inhibitors (also known as K^+-sparing diuretics, e.g., Spironolactone, Pironolactone, and Eplerenone) allosterically inhibit the interactions of aldosterone with its receptor. Additionally, Na^+/K^+-ATPase blockers (thiazides such as benzylhydrochlorothiazide and indapamide)

lead to reduced Na^+/K^+-ATPase activity and reduced water reabsorption [37]. Moreover, RAAS modulators can improve hypertension through directly diminishing the total blood volume. Hence, RAAS modulators play a major role in primary hypertension treatments [3]. However, RAAS modulators tend to preserve K^+ and eliminate Na^+, which would increase the risks of edema, hyperkalemia, and hyponatremia [25,26,37]. This adverse effect needs to be taken into account when using these modulators.

2.1.3. Methods for Screening RAAS Modulators

Numerous available models are used in the search for new RAAS modulators through in silico, in vitro, and in vivo approaches. Chemical induction, renal artery ligation, and genetic modification are common methods with which to generate the in vivo hypertensive model [38]. Of note, chemical induction is conducted by administrating 11-deoxycorticosterone acetate (DOCA) or Ang II, which results in transient hypertension [39,40]. Furthermore, transient hypertension transforms into persistent hypertension during chemical induction, which occurs when combined with a high-salt diet [40]. In general, the intravenous (i.v) or subcutaneous (s.c) administration of Ang II is a common model [41,42]. Ang II infusion could keep high levels of Ang II in serum; however, in experiments, animals needed to be anesthetized for more than 7 days [41,42]. Therefore, this technique is rarely used in drug screening but the risk of hypertensive complications, e.g., aneurysm, nephropathy, preeclampsia, and cognitive impairment [42–45]. Renal artery ligation is the most reported animal model for simulating reno-vascular hypertension, the most common cause of secondary hypertension [46]. Renal artery stenosis can be simulated by partial ligation on the left side or on both sides of the renal artery, leading to reno-vascular hypertension in animal models [47]. The genetic hypertension model is particular to spontaneous hypertension and includes over half of the hypertension population [38]. A well-known spontaneous hypertensive rodent model mainly used in the study of RAAS-induced hypertension is the spontaneous hypertensive rat (SHR) [48]. SHR is originally derived from inbreeding the Wistar–Kyoto (WKY) rats with hypertension, and is suitable for studying either hypertension or renal disease and left ventricular diastolic dysfunction [49,50]. Despite spontaneous hypertension, another primary cause of primary hypertension is obesity, which accounts for 60–75% of primary hypertension cases [51]. To study obesity-induced hypertension, the New Zealand Obese strain (NZO) is appropriate because of its spontaneously polygenic obesity and insulin resistance [52]. In diet-induced hypertension, a high-fat and high-salt diet could be alternatively applied to obtain the desired model [53]. A high-fat diet is another choice for obesity-induced hypertension mice model, and is usually coupled with type-2 diabetes [54]. When mice are fed with a high-salt diet for 4–8 weeks, glucocorticoid resistance could be found in animals, eventually resulting in hypercortisolemia, which is an appropriate model for the diuretic screening of hypernatremia, a cause of hypertension [55,56]. Currently, newly-bred, spontaneous Phase-1 hypertension (P1-HT) rats were successfully generated and used to confirm *Plantago asiatica* seed extract as a potentially antihypertensive herb when compared with SHR [57].

ACE inhibitors can also be tested by in silico to in vitro modeling. In in silico modeling, compound modules and ACE structural modules are employed to simulate ligand/receptor interactions. Higher molecular interaction strengths could demonstrate a greater possibility of being potent inhibitors [58]. By comparing interacting patterns, different ligand types might interact with different amino acid residues in ACE. For small molecules, Gln^{281}, Lys^{511}, and Tyr^{520} of ACE are essential for binding, forming a hydrogen bond with the ligand [59]. In the search of ACE peptide inhibitors, Val^{518}, His^{383}, His^{387}, and His^{51}, are the most important, forming electrostatic and hydrophobic interactions with peptide inhibitors and Zn^{2+} [60]. In the enzymatic approach, ACE activity could be determined by interacting with peptide derivatives that are composed of peptides and colorimetric indicators. The colorimetric assays for ACE are very sensitive, fast, and easy to use [61]. However, in vitro enzymatic conditions will not ever be equivalent to in vivo conditions, due to the highly complex composition of body fluids [62]. The foreseeable gap between enzymatic screening and in vivo or in vitro analyses needs more studies to shorten the distance.

Other RAAS targets, including AGTR1, aldosterone receptor, and Na^+/K^+-ATPase, could not be tested by colorimetric or chemical assay. Recently, cell membrane chromatography has used cell membranes as a stationary phase, allowing the molecules to interact with receptors on the cell membrane [63]. This technique could theoretically overcome the limitation of enzymatic assays for which this principle is not suitable for evaluations of ligand/receptor interactions [64]. Nonetheless, the interaction between cell membranes and ligand candidates could not distinguished whether they were activators or inhibitors. On the other hand, human kidney proximal tubule epithelial cells HK-2 have been identified as carriers of mineral corticoid receptor, angiotensin receptor type 2, and Na^+/K^+ ATPase expression [65–67]. Moreover, aldosterone is shown to be an apoptotic inducer in proximal tubule cells [68]. This evidence shows that HK-2 could be an ideal cellular platform for the screening of diuretics, be it Na^+/K^+ ATPase inhibitor or aldosterone receptor inhibitor. Hou et al. reported on the anti-hypertensive efficacy of malate and aspartate via NO and L-arginine generation in HK-2 cells [69]. Using HK-2 cells, they demonstrated that interleukin-17A raises blood pressure through upregulating Na^+/Cl^- cotransporter and Na^+/H^+ exchanger 3, which are also the main characters of sodium reabsorption in the proximal and distal convoluted tubules [70]. These studies have confirmed that HK-2 is a promising model for the screening of anti-hypertensive agents.

2.1.4. RAAS Modulators Identified from Nature

Numerous RAAS modulators have been identified in nature that can be classified as ACE and AGT1R inhibitors (Table 2). The identified ACE inhibitors include polyphenolics, alkaloids, and short-chain polypeptides (Table 2). Particularly in chalcones, these widespread flavonoids serve as calcium flux or ACE inhibitors [71,72]. Some Traditional Chinese medicines such as Dohaekseunggi-tang and Huatuo exhibit anti-hypertensive activity in benchside experiments, and are worthy of further investigation (Table 2). Some proteins digested and isolated from bonito, milk, sardines, seaweeds, or royal jelly show antihypertensive activity via inhibiting ACE activity. These bioactive peptides are currently available commercially [73,74].

Table 2. RAAS modulators from natural sources.

Source	Compound/Extractions	Evaluated Method	Reference
Crude extract/decoction for modulating ACE			
Dohaekseunggi-tang		in vivo	[75]
Huatuo reconstruction pill		in silico	[76]
Nigella sativa		enzymatic	[77]
Cymodocea Nodosa		+	[78]
Plantago major	Seeds extract	+	[79]
Mucuna pruriens		+	[80]
Syzygium cumini	Seeds extract	in vitro	[81]
Fucus spiralis		enzymatic	[82]
Eucalyptus camaldulensis *Litsea glaucescens*	Ferment	+	[83]
Lens culinaris	Sprouted extract	+	[84]
Pleurotus eryngii	polysaccharide	+	[85]
Phaseolus vulgaris	Ferment	+	[86]
Prunus amygdalus *Pistacia vera*	juice byproduct	+	[87]
Boza	protein extract	+	[88]
Nitraria sibirica	alkaloids	in vivo	[89]

Table 2. *Cont.*

Source	Compound/Extractions	Evaluated Method	Reference
Amaranthus dubius *Amaranthus hybridus* *Asystasia gangetica* *Galinsoga parviflora* *Justicia flava* *Oxygonum sinuatum* *Physalis viscosa*		enzymatic	[90]
Tulbaghia violacea		in vivo	[90]
Bulbus Fritillaria		in vivo	[91]
Crude extracts or decoction for AGT1R			
Apocynum venetum leaf extract		in vitro	[92]
DanHong injection		+	[93]
Liuwei Dihuang formula		+	[94]
Yiqi Huaju formula		in vivo	[95]
Songling xuemaikang capsule		+	[96]
ACE inhibitors			
Ampelopsis Brevipedunculata	(+)-Hopeaphenol; (+)-Vitisin A	enzymatic	[97]
Asparagus officinalis	Asparaptine	+	[98]
Avena sativa	WWK, WCY, FLLA	+	[99]
Bothrops jararaca	EWPRQIPP, EARPPHPPIPP, EWGRPPGPPIPP, EGGWPRPGP(Glu)IPP,	in vitro	[100]
Bothrops moojeni	(Pyro)EKWPPGGKVPP, (Pyro)EKPRPGPEIPP, (Pyro)ENWPWPGPEIPP	enzymatic	[101]
Cajanus cajan	VVSLSIPR	+	[102]
Camellia sinensis	Epigallocatechin gallate	+	[59]
Chinese Herb	Pentagalloylglucose, Isochlorogenic acid B, Methyl 3,4-di-O-caffeoylquinate, (−)-Epigallocatechin gallate, Epigallocatechin-3-O-Methylgallate	in vivo	[103]
Cleistanthus collinus	Cleistanthins A, B	in silico	[104]
Clerodendron trichotomum	Acteoside, Isomartynoside, Leucosceptoside A, Martynoside	enzymatic	[105]
Coptis chinensis	Berberine	in vitro	[91]
Coix larchryma-jobi	GAAGGAF, NPATY	in vivo	[60,106]
Delphinium sp.	Cyanin, Delphinidin	enzymatic	[107]
Desmodium styracifolium	Carlinoside, Schaftoside, Vicenin 1–3	+	[108]
Dioscorea opposita Thunb.	Diascorin	+	[109]
Egg York	Lapslpgkpkpd	+	[110]
Eucommia ulmoides	Megastigmane Enantiomers	in silico	[111]
Glycyrrhiza glabra	Licochalcone A	enzymatic	[59]
Glycyrrhiza uralensis	Echinatin	+	[59]
Limonium michelsonii	Isolates	+	[112]
Mucuna Pruriens	Genistein	+	[80]
Multisource	Caffeic Acid, Caffeoyl Acetate, Chlorogenic Acid, Ferulic Acid	+	[113]
Salvia hispanica L.	LIVSPLAGRL	+	[114]
Salvia miltiorrhizae	Salvianolic Acid B	+	[115,116]

Table 2. *Cont.*

Source	Compound/Extractions	Evaluated Method	Reference
	Lithospermic Acid B	+	[105]
Sargassum wightii	O-Heterocyclic Analogues	in silico	[117]
Tamarix hohenackeri	Chrysoeriol, Quercetin, Isoferulic acid, Methyl-4-O-methylgallate, Gallic acid, Methyl gallate	enzymatic	[118]
Toona sinensis	Quercetin, Resveratrol	+	[107]
Vigna radiata	KDYRL, VTPALR, KLPAGTLF	+	[119]
Xestospongia Cf. Vansoesti	Salsolinol	+	[115]
AGT1R inhibitors			
Alisma orientale	23-O-acetylalisol B, Alismol, Alisols A, Alisols B	enzymatic	[120]
Astragalus membranaceus	Astragaloside IV	in vitro	[121]
Cynodon dactylon	Linoleoylchloride, Diazoprogesteron, Didodecyl Phthalate	enzymatic	[122]
Eucommia ulmoides	Megastigmane Enantiomers	in silico	[111]
Salvia miltiorrhizae	Salvianolic acid B	in vivo	[123]
+	Tanshinone IIA	in vivo	[124]

+, as above; WWK, $(Trp)_2$-Lys; WCY, Trp-Cys-Tyr; FLLA, Phe-$(Leu)_2$-Ala EWPRQIPP, Glu-Trp-Pro-Arg-Pro-Gln-Ile-$(Pro)_2$; EARPPHPPIPP, Glu-Ala-Arg-$(Pro)_2$-His-$(Pro)_2$-Ile-$(Pro)_2$; EWGRPPGPPIPP, Glu-Trp-Gly-Arg-$(Pro)_2$-Gly-$(Pro)_2$-Ile-$(Pro)_2$; EGGWPRPGP(Glu)IPP, Glu-$(Gly)_2$-Trp-Pro-Arg-Pro-Gly-Pro-GluIle-$(Pro)_2$; (Pyro)EKWPPGGKVPP, PyroGlu-Lys-Trp-$(Pro)_2$-$(Gly)_2$-Lys-Val-$(Pro)_2$; (Pyro)EKPRPGPEIPP, PyroGlu-Lys-Pro-Arg-Pro-Gly-Pro-Glu-Ile-$(Pro)_2$; (Pyro)ENWPWPG PEIPP, PyroGlu-Asn-$(Trp-Pro)_2$-Gly-Pro-Glu-Ile-$(Pro)_2$; VVSLSIPR, $(Val)_2$-Ser-Leu-Ser-Ile-Pro-Arg; GAAGGAF, Gly-$(Ala)_2$-$(Gly)_2$-Ala-Phe; NPATY, Asn-Pro-Ala-Thr-Tyr; LIVSPLAGRL, Leu-Ile-Val-Ser-Pro-Leu-Ala-Gly-Arg-Leu; KDYRL, Lys-Asp-Tyr-Arg-Leu; VTPALR, Val-Thr-Pro-Ala-Leu-Arg; KLPAGTLF, Lys-Leu-Pro-Ala-Gly-Thr-Leu-Phe.

To screen AGT1R inhibitors, two parallel approaches, i.e., directly blocking receptor activity and reducing receptor expression, will be performed. Table 2 shows natural compounds that could block AGT1R activity. As far as we know, only five plants, i.e., *Alisma orientale* Juzepczuk, *Cynodon dactylon*, *Eucommia ulmoides* Oliver, *Astragalus membranaceus*, and *Salvia miltiorrhizae*, have traditionally been used as herbal medicines and contain identified natural AGT1R inhibitors (see Table 2). Two traditional Chinese medicines, i.e., the injection of DanHong and Liuwei Dihuang taken orally have also been proven to inhibit AGT1R activity in an in vitro assay (Table 2). On the other hand, Yiqi Huaju formula and Songling xuemaikang capsules have been found to attenuate hypertension in vivo through down-regulating AGT1R expression (Table 2). Tanshinone IIA, a flavonoid from *S. miltiorrhizae*, directly blocks AGT1R activity and reduces AGT1R expression via TGF-1β/Smads signaling *pathway* in vivo (Table 2). These reports provide the potential for insights into finding new RAAS modulators from natural sources.

Despite the data presented in Table 2, several common foods have also shown antihypertensive potency in multiple phases. Probiotics can diminish high blood pressure by mediating immunomodulation and adjusting sympathetic nerve activity [125]. Bioactive components of avocado (*Persea americana*) contain alkaloids, unsaturated fatty acids, and flavonoids that lessen either high arterial pressure or body weight [126]. Tomato (*Solanum lycopersicum*), a common vegetable, is another example of a natural ACE inhibitor. During the past two years, five clinical trials studying the health impact of tomato extracts on a high cardiovascular risk population pointed to a reduced risk of hypertension or other cardiovascular diseases [127–131]. By exploring the detailed mechanisms, the major bioactive component of tomato, lycopene, was identified as an ACE inhibitor and antioxidant that might be the main substance responsible for its antihypertensive efficacy [132]. Additionally, coffee and tea are well known as antihypertensive foods [133]. Tea and coffee have antihypertensive potential through diuresis [134,135] and changes in emotional states [136,137]. The main components of tea and coffee [138,139], caffeine, theophylline, chlorogenic acid, and

epigallocatechin, are known as antihypertensive compounds through their ability to modulate salt reabsorption and immunomodulation [137,139–142]. However, the antihypertensive efficacy of coffee and tea has been challenged by the latest epidemiological studies in different regions and on both genders. According to a statistical analysis of US adults and a meta-analysis from PubMed, coffee intake reduces the likelihood of hypertension [143,144]. In Singapore, antihypertensive potential versus daily coffee intake exhibits a U shape, and tea consumption slightly increases the risk of hypertension occurrence [145]. Through further investigation by gender, three epidemiological studies and meta-analyses reveal that only women could alleviate hypertensive risk through the consumption of coffee, except in the case of postmenopausal women [146–148]. These controversial results remind us of the discrepancy between recent knowledge and our common sense concerning coffee/tea consumption and lowering hypertensive risk.

2.2. Neurogenic Hypertensive System

2.2.1. Action Mechanism of Neurogenic Hypertensive System in Blood Pressure Managing

Unlike RAAS, which regulates blood pressure by controlling total blood volume, sympathetic nerves govern blood pressure by adjusting heart rate and vascular diameter. Sympathetic nerves send neurotransmitters (mainly epinephrine and norepinephrine) as signals to the sinus node and smooth muscle cells within blood vessels [149]. Once target cells receive signals via binding to adrenergic receptors (ARs), intracellular Ca^{2+} flow forms via the L-type Ca^{2+} channel, causing smooth muscle cell contraction [149]. ARs are divided into two types: α-type and β-type, for which α-AR mainly induces smooth muscle contraction and β-AR excites the sinus node and relaxes smooth muscle cells (see Figure 1B). This balancing pathway plays a critical role in mediating blood pressure.

2.2.2. Conventional Drugs for Modulating the Neurogenic Hypertensive System

The main actors for the neurogenic hypertensive system are ARs and the Ca^{2+} channel, so major modulators in this system are predominantly focused on ARs and Ca^{2+} channel. α-blockers (e.g., Doxazosin and Terazosin) block signals that are sympathetic toward α-AR, which induces vasocontraction [150]. β-blockers (e.g., Propranolol and Bisprolol) can hinder heart rates [151]. Critically, calcium blockers (e.g., Nifedipine and Diltiazem) act at the end of the neurogenic hypertensive system by inhibiting both heart rate and vasoconstriction [152]. Ordinarily, sympathetic hyperactivity is an important cause of primary hypertension in youth [153,154]. Hence, AR and calcium blockers are the first line of hypertension medication, especially primary hypertension in the young- or middle-aged population [155,156]. However, a rapid decrease of blood pressure might sometimes trigger ischemic heart disease [152]. Also, ARs are reported to induce sexual dysfunction like erectile dysfunction, ejaculatory disorder, and reduced sexual desire [157,158]. These adverse effects might diminish willingness to follow medical advice.

2.2.3. Approaches to Screening Controllers for Neurogenic Hypertensive System

The screening methods for controllers of neurogenic hypertensive systems are mainly in vitro, ex vivo, and in vivo models. In vitro assays are performed only at the cellular or tissue levels due to the absence of enzymes in the neurogenic hypertensive system. Chinese hamster ovary cells (CHO), vascular smooth muscle cells (VSMC, isolated from thoracic aorta or the commercial cell line, A7r5), and the cardiomyocyte cell line h9c2 are used to evaluate the overall inhibiting activity of AR or calcium. CHO cell derivatives like CHO-K1 and CHO-S are used as carriers for expressing α-AR or β-AR and for measuring the downstream cAMP change after the induction of the neurotransmitter [159,160]. These cell models exert a searching approach for a potential ligand. VSMC directly responds to signals from norepinephrine or external calcium supplements [121,161]. β-ARs and the Ca^{2+} channel have demonstrated their expression in the h9c2 cell line [162,163]. Hence, the h9c2 cell has been applied in the study of pathological or cardioprotective efficacy in ischemic heart disease or cardiac hypertrophy

for years [164,165]. However, the application of h9c2 is not widely used in screening β-blockers or calcium blockers in drug development; this weakness needs further exploration. An ex vivo model usually comprises 4 mm lengths of rat aortic rings isolated from the thoracic arteries and immersed in Krebs solution for treatment [166]. This explant model could directly observe the diameter changes of the aortic rings after treatment with a neurotransmitter or Ca^{2+} [167].

The two most frequently-used animals in in vivo models for screening neurogenic hypertensive systems are environmental stimulation and spontaneous hypertensive mice [168]. The principle of environmental induction involves using environmental stimulus to trigger psycho-emotional stress, and subsequently arterial hypertension, through sympathetic nerve hyperactivation [169]. Common environmental stimuli include flashing lights, loud noises, restraints, cages, and high/low temperatures [170]. Therefore, continuous stimulation is also useful for investigating neurogenic hypertensive systems. Inherited hypertensive mice, BPH/2J (Schlager), are derived from the hypertensive parental strain BPH/1J, whose hypertensive symptoms are milder than those of BPH/2J [171]. BPH/2J exhibits spontaneously-sympathetic hyperactivity and low RAAS activity that results in a high heart rate and high blood pressure [172,173]. Due to these different causes of hypertension, BPH/2J and SHR represent completely different approaches.

Despite the existence of the wet-lab model, one in silico model is also provided for neurogenic hypertensive systems, i.e., β$_2$-AR [174]. By evaluating ligand-binding properties, the essential ligand binding sites of β$_2$-AR are identified, i.e., Asp^{113} and Asn^{312} [175]. Also, polar amino acid residues in transmembrane domain 5 of β$_2$-AR, and especially Ser^{203} and Ser^{207}, play an important role in agonist-binding stabilization [175].

2.2.4. Natural ARs and Calcium Blockers

Compared with AGT1R, blocking the AR and L-type calcium channel is more common for maintaining normal-tension. The AR and calcium channel can directly control blood vessel diameter and vasoconstriction; this activation lessens the blood vessel diameter and causes an increase in blood pressure [152]. Comparing adrenergic blockers and calcium blockers, calcium blockers also affect the heart rate; thereby, calcium blockers are used in arrythmia more frequently than in hypertension [152]. For the treatment of hypertension, Table 3 shows known β-blockers and calcium blockers from natural sources. For α-blockers, tempol (a food in South-East Asia made from fermented soybean) and fermented *Lactobacillus rhamnosus* GR-1 could treat preeclampsia and ameliorate cardiac hypertrophy by inhibiting α-AR [176,177]. These two studies have demonstrated the anti-hypertensive potential of probiotics instead of RAAS. In a review about the pathogenetic characteristics of gut microbiota in hypertension published by Kang and Cai, a possible underlying mechanism affects hypertensive progress through three phases: inflammatory regulation, ACE inhibition, and sympathetic activity adjustment [178]; this area needs further investigation. Again, three coumarins (paeruptorin A, B, and C) isolated from *Peucedanum praeruptorum* Dunn and one alkaloid ((+)-nantenine) from *Nandina domestica* have also been shown to have α-AR blocker activities in vitro and in vivo [179]. These results further revealed that finding adrenergic blockers and calcium blockers from natural sources is a promising avenue of research in new drug discovery and development.

Table 3. Natural source β blockers and Ca^{2+} blockers.

Source	Compounds	Test Method	Reference
Crude extract/decoction			
β-adrenergic receptor inhibitor			
Banxia Baizhu Tianma Tang		in vitro	[180]
Paeoniae Rubra		in vitro	[181,182]
Rhubarbs		in silico	[183]
Suaeda asparagoides		in vivo	[184]
Ca^{2+} channel inhibitor			
Alternanthera sessilis		in vitro	[185]
Capparis aphylla		in vivo	[186]
Coreopsis tinctoria		in vitro	[187]
Gentiana floribunda		in vivo	[188]
Jasonia glutinosa		in vitro	[161]
Juniperus excelsa		in vitro	[189]
Perovskia abrotanoides essential oil		in vitro	[190]
Pumpkin seed oil		in vivo	[191]
Ranunculus japoniucus		in vivo	[192]
Tiangou Jiangya		in vitro	[193]
Viola odorata		in vivo	[194]
Pure compounds			
β-adrenergic receptor inhibitor			
Nelumbo nucifera	Higenamine 4′-O-β-ᴅ-glucoside	in vitro	[195]
Notopterygium incisum	Isoimperatorin	enzymatic	[159]
Pimpinella anisum	Trans-anethole	in silico	[196]
Ca^{2+} channel inhibitor			
Agelanthus dodoneifolius	Dodoneine	in vitro	[197]
Glycosmis petelotii	N-demethylglypetelotine, Glypetelotine	in vitro	[198]
Peucedanum praeruptorum	Praeruptorin C	in vivo	[199]
Polygonum multiflorum	Emodin	in vitro	[200]
Sargassum siliquastrum	Sargachromenol D	in vitro	[201]
Stephaniae tetrandrae	Tetrandrine, Fangchinoline	in vivo	[202]
Stevia rebaudiana	Stevioside	in vivo	[203]

3. Conclusions and Remarks

In this article, we have collected recent research and developments of antihypertensive agents from natural sources according to the two main blood-pressure-regulating mechanisms: RAAS and the neurogenic hypertensive system. The implementation of American Heart Association (AHA)/European Society of Cardiology (ESC) guidelines for the management of hypertensive patients, as well as the public health and cost implications, need to be reflected upon [17]. However, drug resistance and poor adherence are urgent issues associated with the treatment of hypertension; these could be a niche for drug development, especially from natural sources [204]. Additionally, folk medicines, medicinal plants, and herbs may be incorporated into the regimen of anti-hypertension treatments according to their experimental efficacy in preclinical trials. Figure 2 summarizes such substances. To accelerate the screening rates, molecular docking is a potential tool for use before any wet-lab validation, including enzymatic tests or cellular assays. However, the absence of target protein modules is an emergent application for molecular docking in antihypertensive compound discovery. Also, recently-developed

cellular or enzymatic analyzing methods are not particularly well-suited for the in vivo or in silico discovery, validation, or evaluation of the regulating mechanisms of blood pressure. Nevertheless, numerous compounds or decoctions have been found to have hypotensive efficacy. Moreover, some studies have found other enzymes that could also become antihypertensive targets, such as endothelial NO synthase (eNOS) [123,205–210], endothelin-1 receptor [211], and G-protein-coupled receptor kinase 4 (GRK4) [212].
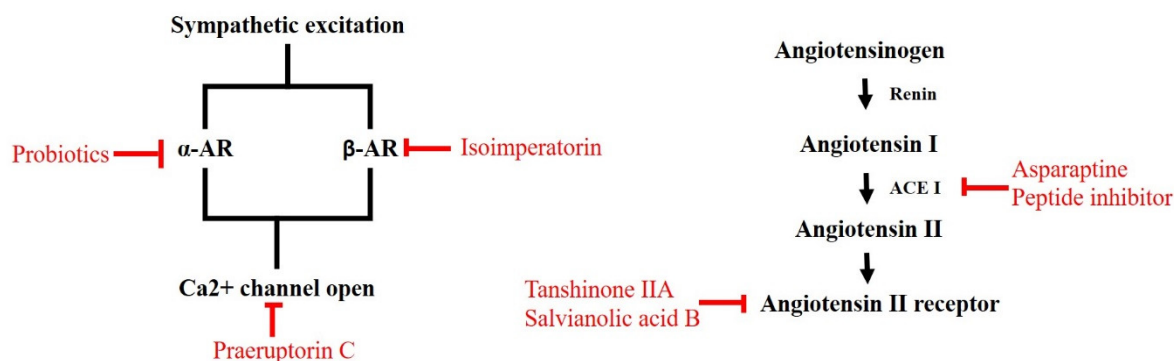
Figure 2. Natural compounds act on blood pressure control.

Additionally, the characteristics of the gut–brain axis in blood pressure regulation has received much attention in recent decades. To our knowledge, gut microbiota and the brain could cross talk through various routes, e.g., small microbial metabolites such as sodium butyrate and vitamin D, autonomic nerves system, and intestinal immunocytes [213–217]. A comparison of gut microbiota between healthy and hypertensive people reveals compositional differences, particularly in Firmicutes and Bacteroidetes; this difference might be attributed to the cause of hypertension, at least partially [218]. Accordingly, some studies have focused on the treatment of fluctuating gut microbiota. Probiotic products, such as kefir and lactulose, have been shown to negate hypertensive symptoms in a rat model [125,219,220]. This evidence also offers an insights into the potential of applying natural-source gut-microbiota modulators or traditional Chinese herbal medicine in hypertensive regimens [221]. The exploration of new targets for drug screening to accelerate anti-hypertension drug discovery and development can be more profitable and more effective than other recent methods.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. James, P.A.; Oparil, S.; Carter, B.L.; Cushman, W.C.; Dennison-Himmelfarb, C.; Handler, J.; Lackland, D.T.; LeFevre, M.L.; MacKenzie, T.D.; Ogedegbe, O.; et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth Joint National Committee (JNC 8). *JAMA* **2014**, *311*, 507–520. [CrossRef]
2. Zhang, W.; Li, N. Prevalence, risk factors, and management of prehypertension. *Int. J. Hypertens.* **2011**, *2011*, 605359. [CrossRef] [PubMed]
3. Whelton, P.K.; Carey, R.M.; Aronow, W.S.; Casey, D.E., Jr.; Collins, K.J.; Dennison Himmelfarb, C.; DePalma, S.M.; Gidding, S.; Jamerson, K.A.; Jones, D.W.; et al. 2017 ACC/AHA/AAPA/ABC/ACPM/ AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the american college of cardiology/american heart association task force on clinical practice guidelines. *J. Am. Coll. Cardiol.* **2018**, *71*, e127–e248. [CrossRef] [PubMed]

4. Bolivar, J.J. Essential hypertension: An approach to its etiology and neurogenic pathophysiology. *Int. J. Hypertens.* **2013**, *2013*, 547809. [CrossRef] [PubMed]

5. Puar, T.H.; Mok, Y.; Debajyoti, R.; Khoo, J.; How, C.H.; Ng, A.K. Secondary hypertension in adults. *Singap. Med. J.* **2016**, *57*, 228–232. [CrossRef] [PubMed]

6. Ji, L.D.; Li, J.Y.; Yao, B.B.; Cai, X.B.; Shen, Q.J.; Xu, J. Are genetic polymorphisms in the renin-angiotensin-aldosterone system associated with essential hypertension? Evidence from genome-wide association studies. *J. Hum. Hypertens.* **2017**, *31*, 695–698. [CrossRef] [PubMed]

7. Alshaarawy, O.; Elbaz, H.A. Cannabis use and blood pressure levels: United States national health and nutrition examination survey, 2005–2012. *J. Hypertens.* **2016**, *34*, 1507–1512. [CrossRef]

8. Andriolo, V.; Dietrich, S.; Knüppel, S.; Bernigau, W.; Boeing, H. Traditional risk factors for essential hypertension: Analysis of their specific combinations in the EPIC-Potsdam cohort. *Sci. Rep.* **2019**, *9*, 1501. [CrossRef]

9. Mills, K.T.; Bundy, J.D.; Kelly, T.N.; Reed, J.E.; Kearney, P.M.; Reynolds, K.; Chen, J.; He, J. Global disparities of hypertension prevalence and control: A systematic analysis of population-based studies from 90 countries. *Circulation* **2016**, *134*, 441–450. [CrossRef]

10. Lewington, S.; Lacey, B.; Clarke, R.; Guo, Y.; Kong, X.L.; Yang, L.; Chen, Y.; Bian, Z.; Chen, J.; Meng, J.; et al. The burden of hypertension and associated risk for cardiovascular mortality in China. *JAMA Intern. Med.* **2016**, *176*, 524–532. [CrossRef]

11. Forouzanfar, M.H.; Liu, P.; Roth, G.A.; Ng, M.; Biryukov, S.; Marczak, L.; Alexander, L.; Estep, K.; Hassen Abate, K.; Akinyemiju, T.F.; et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. *JAMA* **2017**, *317*, 165–182. [CrossRef] [PubMed]

12. Hay, S.I.; Abajobir, A.A.; Abate, K.H.; Abbafati, C.; Abbas, K.M.; Abd-Allah, F.; Abdulkader, R.S.; Abdulle, A.M.; Abebo, T.A.; Abera, S.F.; et al. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: A systematic analysis for the global burden of disease study 2016. *Lancet* **2017**, *390*, 1260–1344. [CrossRef]

13. Muxfeldt, E.S.; de Souza, F.; Margallo, V.S.; Salles, G.F. Cardiovascular and renal complications in patients with resistant hypertension. *Curr. Hypertens. Rep.* **2014**, *16*, 471. [CrossRef] [PubMed]

14. Walker, K.A.; Power, M.C.; Gottesman, R.F. Defining the relationship between hypertension, cognitive decline, and dementia: A review. *Curr. Hypertens. Rep.* **2017**, *19*, 24. [CrossRef] [PubMed]

15. Van den Born, B.H.; Lip, G.Y.H.; Brguljan-Hitij, J.; Cremer, A.; Segura, J.; Morales, E.; Mahfoud, F.; Amraoui, F.; Persu, A.; Kahan, T.; et al. ESC Council on hypertension position document on the management of hypertensive emergencies. *Eur. Heart J. Cardiovasc. Pharmacother.* **2019**, *5*, 37–46. [CrossRef] [PubMed]

16. Villalva, C.M.; Alvarez-Muino, X.L.L.; Mondelo, T.G.; Fachado, A.A.; Fernandez, J.C. Adherence to treatment in hypertension. *Adv. Exp. Med. Biol.* **2017**, *956*, 129–147. [CrossRef]

17. Williams, B.; Mancia, G.; Spiering, W.; Agabiti Rosei, E.; Azizi, M.; Burnier, M.; Clement, D.L.; Coca, A.; de Simone, G.; Dominiczak, A.; et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur. Heart J.* **2018**, *39*, 3021–3104. [CrossRef]

18. Cooper-DeHoff, R.M.; Johnson, J.A. Hypertension pharmacogenomics: In search of personalized treatment approaches. *Nat. Rev. Nephrol.* **2016**, *12*, 110–122. [CrossRef]

19. Nakaya, N.; Nakamura, T.; Tsuchiya, N.; Narita, A.; Tsuji, I.; Hozawa, A.; Tomita, H. Psychological distress and the risk of withdrawing from hypertension treatment after an earthquake disaster. *Disaster Med. Public Health Prep.* **2017**, *11*, 179–182. [CrossRef]

20. Hu, H.H.; Li, G.; Arao, T. The association of family social support, depression, anxiety and self-efficacy with specific hypertension self-care behaviours in Chinese local community. *J. Hum. Hypertens.* **2015**, *29*, 198–203. [CrossRef]

21. Osamor, P.E. Social support and management of hypertension in South-west Nigeria. *Cardiovasc. J. Afr.* **2015**, *26*, 29–33. [CrossRef] [PubMed]

22. Hall, E.; Lee, S.Y.; Clark, P.C.; Perilla, J. Social ecology of adherence to hypertension treatment in latino migrant and seasonal farmworkers. *J. Transcult. Nurs.* **2016**, *27*, 33–41. [CrossRef] [PubMed]

23. Fongwa, M.N.; Dela Cruz, F.A.; Hays, R.D. African American women's perceptions of the meaning of support groups for improving adherence to hypertension treatment: A conceptual model. *Nurs. Open* **2019**, *6*, 860–870. [CrossRef] [PubMed]

24. Noubiap, J.J.; Nansseu, J.R.; Nyaga, U.F.; Sime, P.S.; Francis, I.; Bigna, J.J. Global prevalence of resistant hypertension: A meta-analysis of data from 3.2 million patients. *Heart* **2019**, *105*, 98–105. [CrossRef] [PubMed]

25. Nadal, J.; Channavajjhala, S.K.; Jia, W.; Clayton, J.; Hall, I.P.; Glover, M. Clinical and molecular features of thiazide-induced hyponatremia. *Curr. Hypertens. Rep.* **2018**, *20*, 31. [CrossRef] [PubMed]

26. Bandak, G.; Sang, Y.; Gasparini, A.; Chang, A.R.; Ballew, S.H.; Evans, M.; Arnlov, J.; Lund, L.H.; Inker, L.A.; Coresh, J.; et al. Hyperkalemia after initiating renin-angiotensin system blockade: The Stockholm creatinine measurements (SCREAM) project. *J. Am. Heart Assoc.* **2017**, *6*, e005428. [CrossRef]

27. Hoover, T.; Lippmann, M.; Grouzmann, E.; Marceau, F.; Herscu, P. Angiotensin converting enzyme inhibitor induced angio-oedema: A review of the pathophysiology and risk factors. *Clin. Exp. Allergy* **2010**, *40*, 50–61. [CrossRef]

28. Tedla, Y.G.; Bautista, L.E. drug side effect symptoms and adherence to antihypertensive medication. *Am. J. Hypertens.* **2016**, *29*, 772–779. [CrossRef]

29. Lin, S.R.; Fu, Y.S.; Tsai, M.J.; Cheng, H.; Weng, C.F. Natural compounds from herbs that can potentially execute as autophagy inducers for cancer therapy. *Int. J. Mol. Sci.* **2017**, *18*, 1412. [CrossRef]

30. Rabkin, S.W. Considerations in understanding the coronary blood flow- left ventricular mass relationship in patients with hypertension. *Curr. Cardiol. Rev.* **2017**, *13*, 75–83. [CrossRef]

31. Hsu, C.N.; Tain, Y.L. Regulation of nitric oxide production in the developmental programming of hypertension and kidney disease. *Int. J. Mol. Sci.* **2019**, *20*, 681. [CrossRef] [PubMed]

32. Bernstein, K.E.; Khan, Z.; Giani, J.F.; Cao, D.Y.; Bernstein, E.A.; Shen, X.Z. Angiotensin-converting enzyme in innate and adaptive immunity. *Nat. Rev. Nephrol.* **2018**, *14*, 325–336. [CrossRef] [PubMed]

33. Feraille, E.; Dizin, E. Coordinated control of ENaC and Na$^+$,K$^+$-ATPase in renal Collecting DUCT. *J. Am. Soc. Nephrol.* **2016**, *27*, 2554–2563. [CrossRef] [PubMed]

34. Michel, M.C.; Brunner, H.R.; Foster, C.; Huo, Y. Angiotensin II type 1 receptor antagonists in animal models of vascular, cardiac, metabolic and renal disease. *Pharmacol. Ther.* **2016**, *164*, 1–81. [CrossRef] [PubMed]

35. Salvador, G.L.; Marmentini, V.M.; Cosmo, W.R.; Junior, E.L. Angiotensin-converting enzyme inhibitors reduce mortality compared to angiotensin receptor blockers: Systematic review and meta-analysis. *Eur. J. Prev. Cardiol.* **2017**, *24*, 1914–1924. [CrossRef] [PubMed]

36. Satoh, M.; Haga, T.; Hosaka, M.; Obara, T.; Metoki, H.; Murakami, T.; Kikuya, M.; Inoue, R.; Asayama, K.; Mano, N.; et al. The velocity of antihypertensive effects of seven angiotensin II receptor blockers determined by home blood pressure measurements. *J. Hypertens.* **2016**, *34*, 1218–1223. [CrossRef]

37. Roush, G.C.; Sica, D.A. Diuretics for Hypertension: A Review and Update. *Am. J. Hypertens.* **2016**, *29*, 1130–1137. [CrossRef]

38. Lin, H.Y.; Lee, Y.T.; Chan, Y.W.; Tse, G. Animal models for the study of primary and secondary hypertension in humans. *Biomed. Rep.* **2016**, *5*, 653–659. [CrossRef]

39. Sadegh Vishkaei, M.; Ebrahimpour, A.; Abdul-Hamid, A.; Ismail, A.; Saari, N. Angiotensin-I converting enzyme (ACE) inhibitory and anti-hypertensive effect of protein hydrolysate from Actinopyga lecanora (Sea Cucumber) in rats. *Mar. Drugs* **2016**, *14*, 176. [CrossRef]

40. Basting, T.; Lazartigues, E. DOCA-salt hypertension: An update. *Curr. Hypertens. Rep.* **2017**, *19*, 32. [CrossRef]

41. Bressan, A.F.; Fonseca, G.A.; Tostes, R.C.; Webb, R.C.; Lima, V.V.; Giachini, F.R. Interleukin-10 negatively modulates extracellular signal-regulated kinases 1 and 2 in aorta from hypertensive mouse induced by angiotensin II infusion. *Fundam. Clin. Pharmacol.* **2019**, *33*, 31–40. [CrossRef] [PubMed]

42. Lu, H.; Howatt, D.A.; Balakrishnan, A.; Moorleghen, J.J.; Rateri, D.L.; Cassis, L.A.; Daugherty, A. Subcutaneous angiotensin II infusion using osmotic pumps induces aortic aneurysms in mice. *J. Vis. Exp.* **2015**, *103*, e53191. [CrossRef] [PubMed]

43. Liu, Z.; Huang, X.R.; Chen, H.Y.; Fung, E.; Liu, J.; Lan, H.Y. Deletion of angiotensin-converting enzyme-2 promotes hypertensive nephropathy by targeting Smad7 for ubiquitin degradation. *Hypertension* **2017**, *70*, 822–830. [CrossRef] [PubMed]

44. Morgan, H.L.; Butler, E.; Ritchie, S.; Herse, F.; Dechend, R.; Beattie, E.; McBride, M.W.; Graham, D. Modeling superimposed preeclampsia using ang II (Angiotensin II) infusion in pregnant stroke-prone spontaneously hypertensive rats. *Hypertension* **2018**, *72*, 208–218. [CrossRef] [PubMed]

45. Foulquier, S.; Namsolleck, P.; Van Hagen, B.T.; Milanova, I.; Post, M.J.; Blankesteijn, W.M.; Rutten, B.P.; Prickaerts, J.; Van Oostenbrugge, R.J.; Unger, T. Hypertension-induced cognitive impairment: Insights from prolonged angiotensin II infusion in mice. *Hypertens. Res.* **2018**, *41*, 817–827. [CrossRef] [PubMed]

46. Herrmann, S.M.; Textor, S.C. Current concepts in the treatment of renovascular hypertension. *Am. J. Hypertens.* **2018**, *31*, 139–149. [CrossRef] [PubMed]

47. Grossman, R.C. Experimental models of renal disease and the cardiovascular system. *Open Cardiovasc. Med. J.* **2010**, *4*, 257–264. [CrossRef]

48. Carrive, P. Orexin, stress and central cardiovascular control. A link with hypertension? *Neurosci. Biobehav. Rev.* **2017**, *74*, 376–392. [CrossRef]

49. Mohammed-Ali, Z.; Carlisle, R.E.; Nademi, S.; Dickhout, J.G. Animal models of kidney disease. In *Animal Models for the Study of Human Disease*; Academic Press: Cambridge, MA, USA, 2017; pp. 379–417. [CrossRef]

50. Dupont, S.; Maizel, J.; Mentaverri, R.; Chillon, J.M.; Six, I.; Giummelly, P.; Brazier, M.; Choukroun, G.; Tribouilloy, C.; Massy, Z.A.; et al. The onset of left ventricular diastolic dysfunction in SHR rats is not related to hypertrophy or hypertension. *Am. J. Physiol. Heart Circ. Physiol.* **2012**, *302*, H1524–H1532. [CrossRef]

51. Hall, J.E.; do Carmo, J.M.; da Silva, A.A.; Wang, Z.; Hall, M.E. Obesity-induced hypertension: Interaction of neurohumoral and renal mechanisms. *Circ. Res.* **2015**, *116*, 991–1006. [CrossRef]

52. Lawson, H.A. Chapter 11—Animal models of metabolic syndrome. In *Animal Models for the Study of Human Disease*; Conn, P.M., Ed.; Academic Press: Boston, MA, USA, 2013; pp. 243–264. [CrossRef]

53. Bazzano, L.A.; Green, T.; Harrison, T.N.; Reynolds, K. Dietary approaches to prevent hypertension. *Curr. Hypertens. Rep.* **2013**, *15*, 694–702. [CrossRef] [PubMed]

54. Wang, C.Y.; Liao, J.K. A mouse model of diet-induced obesity and insulin resistance. *Methods Mol. Biol.* **2012**, *821*, 421–433. [CrossRef] [PubMed]

55. Drenjancevic-Peric, I.; Jelakovic, B.; Lombard, J.H.; Kunert, M.P.; Kibel, A.; Gros, M. High-salt diet and hypertension: Focus on the renin-angiotensin system. *Kidney Blood Press. Res.* **2011**, *34*, 1–11. [CrossRef] [PubMed]

56. Ivy, J.R.; Evans, L.C.; Moorhouse, R.; Richardson, R.V.; Al-Dujaili, E.A.S.; Flatman, P.W.; Kenyon, C.J.; Chapman, K.E.; Bailey, M.A. Renal and blood pressure response to a high-salt diet in mice with reduced global expression of the glucocorticoid receptor. *Front. Physiol.* **2018**, *9*, 848. [CrossRef] [PubMed]

57. Fu, Y.S.; Lue, S.I.; Lin, S.Y.; Luo, C.L.; Chou, C.C.; Weng, C.F. *Plantago asiatica* seed extracts alleviated blood pressure in phase I(-)Spontaneous hypertension rats. *Molecules* **2019**, *24*, 1734. [CrossRef] [PubMed]

58. Banegas-Luna, A.J.; Ceron-Carrasco, J.P.; Perez-Sanchez, H. A review of ligand-based virtual screening web tools and screening algorithms in large molecular databases in the age of big data. *Future Med. Chem.* **2018**, *10*, 2641–2658. [CrossRef]

59. Ke, Z.; Su, Z.; Zhang, X.; Cao, Z.; Ding, Y.; Cao, L.; Ding, G.; Wang, Z.; Liu, H.; Xiao, W. Discovery of a potent angiotensin converting enzyme inhibitor via virtual screening. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 3688–3692. [CrossRef]

60. Qiao, L.; Li, B.; Chen, Y.; Li, L.; Chen, X.; Wang, L.; Lu, F.; Luo, G.; Li, G.; Zhang, Y. Discovery of anti-hypertensive oligopeptides from adlay based on in silico proteolysis and virtual screening. *Int. J. Mol. Sci.* **2016**, *17*, 2099. [CrossRef]

61. Ahmad, I.; Yanuar, A.; Mulia, K.; Mun'im, A. Review of angiotensin-converting enzyme inhibitory assay: Rapid method in drug discovery of herbal plants. *Pharmacogn. Rev.* **2017**, *11*, 1–7. [CrossRef]

62. Garcia-Contreras, R.; Vos, P.; Westerhoff, H.V.; Boogerd, F.C. Why in vivo may not equal *in vitro*—New effectors revealed by measurement of enzymatic activities under the same *in vivo*-like assay conditions. *FEBS J.* **2012**, *279*, 4145–4159. [CrossRef]

63. Han, S.; Lv, Y.; Wei, F.; Fu, J.; Hu, Q.; Wang, S. Screening of bioactive components from traditional Chinese medicines using cell membrane chromatography coupled with mass spectrometry. *Phytochem. Anal.* **2018**, *29*, 341–350. [CrossRef] [PubMed]

64. Hou, X.; Wang, S.; Zhang, T.; Ma, J.; Zhang, J.; Zhang, Y.; Lu, W.; He, H.; He, L. Recent advances in cell membrane chromatography for traditional Chinese medicines analysis. *J. Pharm. Biomed. Anal.* **2014**, *101*, 141–150. [CrossRef] [PubMed]

65. Zhang, Y.R.; Yuan, Z.Y. Dopamine-mediated inhibition of renal Na+/K+-ATPase in HK-2 cells is reduced by ouabain. *Clin. Exp. Pharmacol. Physiol.* **2010**, *37*, 613–618. [CrossRef] [PubMed]

66. Wei, J.; Li, Z.; Ma, C.; Zhan, F.; Wu, W.; Han, H.; Huang, Y.; Li, W.; Chen, D.; Peng, Y. Rho kinase pathway is likely responsible for the profibrotic actions of aldosterone in renal epithelial cells via inducing epithelial-mesenchymal transition and extracellular matrix excretion. *Cell Biol. Int.* **2013**, *37*, 725–730. [CrossRef]

67. Saleem, M.; Pokkunuri, I.; Asghar, M. Superoxide increases angiotensin II AT1 receptor function in human kidney-2 cells. *FEBS Open Bio* **2016**, *6*, 1273–1284. [CrossRef]

68. Kitada, K.; Nakano, D.; Hitomi, H.; Kobori, H.; Deguchi, K.; Mori, H.; Masaki, T.; Nishiyama, A. Aldosterone induces p21-regulated apoptosis via increased synthesis and secretion of tumour necrosis factor-alpha in human proximal tubular cells. *Clin. Exp. Pharmacol. Physiol.* **2012**, *39*, 858–863. [CrossRef]

69. Hou, E.; Sun, N.; Zhang, F.; Zhao, C.; Usa, K.; Liang, M.; Tian, Z. Malate and aspartate increase l-arginine and nitric oxide and attenuate hypertension. *Cell Rep.* **2017**, *19*, 1631–1639. [CrossRef]

70. Norlander, A.E.; Saleh, M.A.; Kamat, N.V.; Ko, B.; Gnecco, J.; Zhu, L.; Dale, B.L.; Iwakura, Y.; Hoover, R.S.; McDonough, A.A.; et al. Interleukin-17A regulates renal sodium transporters and renal injury in angiotensin II-induced hypertension. *Hypertension* **2016**, *68*, 167–174. [CrossRef]

71. Mahapatra, D.K.; Bharti, S.K. Therapeutic potential of chalcones as cardiovascular agents. *Life Sci.* **2016**, *148*, 154–172. [CrossRef]

72. Zhuang, C.; Zhang, W.; Sheng, C.; Zhang, W.; Xing, C.; Miao, Z. Chalcone: A privileged structure in medicinal chemistry. *Chem. Rev.* **2017**, *117*, 7762–7810. [CrossRef]

73. Seca, A.M.L.; Pinto, D. Overview on the antihypertensive and anti-obesity effects of secondary metabolites from seaweeds. *Mar. Drugs* **2018**, *16*, 237. [CrossRef] [PubMed]

74. Bhat, Z.F.; Kumar, S.; Bhat, H.F. Antihypertensive peptides of animal origin: A review. *Crit. Rev. Food Sci. Nutr.* **2017**, *57*, 566–578. [CrossRef] [PubMed]

75. Sung, Y.Y.; Kim, D.S.; Choi, G.; Kim, S.H.; Kim, H.K. Dohaekseunggi-tang extract inhibits obesity, hyperlipidemia, and hypertension in high-fat diet-induced obese mice. *BMC Complement. Altern. Med.* **2014**, *14*, 372. [CrossRef] [PubMed]

76. Wu, K.Z.; Jiang, Y.G.; Zuo, Y.; Li, A.X. Establishment of the method for screening the potential targets and effective components of huatuo reconstruction pill. *Interdiscip. Sci.* **2014**, *6*, 125–132. [CrossRef] [PubMed]

77. Basi, Z.; Turkoglu, V. Purification of angiotensin-converting enzyme from human plasma and investigation of the effect of some active ingredients isolated from *Nigella sativa* L. extract on the enzyme activity. *Biomed. Chromatogr.* **2018**, *32*, e4175. [CrossRef] [PubMed]

78. Kolsi, R.B.A.; Salah, H.B.; Saidi, S.A.; Allouche, N.; Belghith, H.; Belghith, K. Evaluation of nutritional value, characteristics, functional properties of *Cymodocea nodosa* and its benefits on health diseases. *Lipids Health Dis.* **2017**, *16*, 238. [CrossRef] [PubMed]

79. Oboh, G.; Ademiluyi, A.O.; Oyeleye, S.I.; Olasehinde, T.A.; Boligon, A.A. Modulation of some markers of erectile dysfunction and malonaldehyde levels in isolated rat penile tissue with unripe and ripe plantain peels: Identification of the constituents of the plants using HPLC. *Pharm. Biol.* **2017**, *55*, 1920–1926. [CrossRef]

80. Khan, M.Y.; Kumar, V. Mechanism of antihypertensive effect of *Mucuna pruriens* L. seed extract and its isolated compounds. *J. Complement. Integr. Med.* **2017**, *14*. [CrossRef]

81. Syama, H.P.; Arya, A.D.; Dhanya, R.; Nisha, P.; Sundaresan, A.; Jacob, E.; Jayamurthy, P. Quantification of phenolics in *Syzygium cumini* seed and their modulatory role on tertiary butyl-hydrogen peroxide-induced oxidative stress in H9c2 cell lines and key enzymes in cardioprotection. *J. Food Sci. Technol.* **2017**, *54*, 2115–2125. [CrossRef]

82. Paiva, L.; Lima, E.; Neto, A.I.; Baptista, J. Angiotensin I-converting enzyme (ACE) inhibitory activity of *Fucus spiralis* macroalgae and influence of the extracts storage temperature—A short report. *J. Pharm. Biomed. Anal.* **2016**, *131*, 503–507. [CrossRef]

83. Gamboa-Gomez, C.I.; Gonzalez-Laredo, R.F.; Gallegos-Infante, J.A.; Perez, M.D.; Moreno-Jimenez, M.R.; Flores-Rueda, A.G.; Rocha-Guzman, N.E. Antioxidant and angiotensin-converting enzyme inhibitory activity of eucalyptus camaldulensis and *Litsea glaucescens* infusions fermented with kombucha consortium. *Food Technol. Biotechnol.* **2016**, *54*, 367–374. [CrossRef] [PubMed]

84. Penas, E.; Limon, R.I.; Martinez-Villaluenga, C.; Restani, P.; Pihlanto, A.; Frias, J. Impact of elicitation on antioxidant and potential antihypertensive properties of Lentil Sprouts. *Plant Foods Hum. Nutr.* **2015**, *70*, 401–407. [CrossRef] [PubMed]

85. Li, S.; Shah, N.P. Effects of *Pleurotus eryngii* polysaccharides on bacterial growth, texture properties, proteolytic capacity, and angiotensin-I-converting enzyme-inhibitory activities of fermented milk. *J. Dairy Sci.* **2015**, *98*, 2949–2961. [CrossRef] [PubMed]

86. Limon, R.I.; Penas, E.; Torino, M.I.; Martinez-Villaluenga, C.; Duenas, M.; Frias, J. Fermentation enhances the content of bioactive compounds in kidney bean extracts. *Food Chem.* **2015**, *172*, 343–352. [CrossRef] [PubMed]

87. Sila, A.; Bayar, N.; Ghazala, I.; Bougatef, A.; Ellouz-Ghorbel, R.; Ellouz-Chaabouni, S. Water-soluble polysaccharides from agro-industrial by-products: Functional and biological properties. *Int. J. Biol. Macromol.* **2014**, *69*, 236–243. [CrossRef]

88. Kancabas, A.; Karakaya, S. Angiotensin-converting enzyme (ACE)-inhibitory activity of boza, a traditional fermented beverage. *J. Sci. Food Agric.* **2013**, *93*, 641–645. [CrossRef]

89. Bakri, M.; Yi, Y.; Chen, L.D.; Aisa, H.A.; Wang, M.H. Alkaloids of *Nitraria sibirica* Pall. decrease hypertension and albuminuria in angiotensin II-salt hypertension. *Chin. J. Nat. Med.* **2014**, *12*, 266–272. [CrossRef]

90. Ramesar, S.; Baijnath, H.; Govender, T.; Mackraj, I. Angiotensin I-converting enzyme inhibitor activity of nutritive plants in KwaZulu-Natal. *J. Med. Food* **2008**, *11*, 331–336. [CrossRef]

91. Kang, D.G.; Oh, H.; Cho, D.K.; Kwon, E.K.; Han, J.H.; Lee, H.S. Effects of bulb of Fritillaria ussuriensis maxim. on angiotensin converting enzyme and vascular release of NO/cGMP in rats. *J. Ethnopharmacol.* **2002**, *81*, 49–55. [CrossRef]

92. Lau, Y.S.; Kwan, C.Y.; Ku, T.C.; Hsieh, W.T.; Wang, H.D.; Nishibe, S.; Dharmani, M.; Mustafa, M.R. Apocynum venetum leaf extract, an antihypertensive herb, inhibits rat aortic contraction induced by angiotensin II: A nitric oxide and superoxide connection. *J. Ethnopharmacol.* **2012**, *143*, 565–571. [CrossRef]

93. Zhang, M.Y.; Guo, F.F.; Wu, H.W.; Yu, Y.Y.; Wei, J.Y.; Wang, S.F.; Zhang, Y.X.; Xian, M.H.; Wu, Q.H.; Zhao, B.C.; et al. DanHong injection targets endothelin receptor type B and angiotensin II receptor type 1 in protection against cardiac hypertrophy. *Oncotarget* **2017**, *8*, 103393–103409. [CrossRef] [PubMed]

94. Zhang, Y.; Qian, X.; Sun, X.; Lin, C.; Jing, Y.; Yao, Y.; Ma, Z.; Kuai, M.; Lu, Y.; Kong, X.; et al. Liuwei Dihuang, a traditional Chinese medicinal formula, inhibits proliferation and migration of vascular smooth muscle cells via modulation of estrogen receptors. *Int. J. Mol. Med.* **2018**, *42*, 31–40. [CrossRef] [PubMed]

95. He, Y.M.; Yang, H.J.; Yang, Q.; Cui, J.G.; Wang, T.Z.; Chen, Y.; Wang, P.W.; Zhang, T.; Wang, W.J. Yiqi Huaju formula, a Chinese herbal medicine, reduces arterial pressure in saltsensitive hypertension by inhibiting reninangiotensin system activation. *Mol. Med. Rep.* **2015**, *12*, 5321–5327. [CrossRef] [PubMed]

96. Zhao, Y.Q.; Liu, W.; Cai, X.Y.; Xu, Q.; Shi, H.; Wang, W.; Wu, C.Y.; Li, J.; Wang, R.H.; Jiang, H.T. The regulatory mechanism of songling xuemaikang capsule on PPARgamma in spontaneously hypertensive rats: An experimental study. *Zhongguo Zhong Xi Yi Jie He Za Zhi* **2013**, *33*, 1236–1241.

97. Su, P.S.; Doerksen, R.J.; Chen, S.H.; Sung, W.C.; Juan, C.C.; Rawendra, R.D.; Chen, C.R.; Li, J.W.; Aisha; Huang, T.C.; et al. Screening and profiling stilbene-type natural products with angiotensin-converting enzyme inhibitory activity from *Ampelopsis brevipedunculata* var. hancei (Planch.) Rehder. *J. Pharm. Biomed. Anal.* **2015**, *108*, 70–77. [CrossRef]

98. Nakabayashi, R.; Yang, Z.; Nishizawa, T.; Mori, T.; Saito, K. Top-down targeted metabolomics reveals a sulfur-containing metabolite with inhibitory activity against angiotensin-converting enzyme in *Asparagus officinalis*. *J. Nat. Prod.* **2015**, *78*, 1179–1183. [CrossRef]

99. Bleakley, S.; Hayes, M.; O'Shea, N.; Gallagher, E.; Lafarga, T. Predicted release and analysis of novel ACE-I, renin, and DPP-IV inhibitory peptides from common oat (Avena sativa) protein hydrolysates using in silico analysis. *Foods* **2017**, *6*, 108. [CrossRef]

100. Morais, K.L.; Ianzer, D.; Miranda, J.R.; Melo, R.L.; Guerreiro, J.R.; Santos, R.A.; Ulrich, H.; Lameu, C. Proline rich-oligopeptides: Diverse mechanisms for antihypertensive action. *Peptides* **2013**, *48*, 124–133. [CrossRef]

101. Siemerink, M.; Schebb, N.H.; Liesener, A.; Perchuc, A.M.; Schoni, R.; Wilmer, M.; Hayen, H.; Karst, U.; Vogel, M. Development of a fast liquid chromatography/mass spectrometry screening method for angiotensin-converting enzyme (ACE) inhibitors in complex natural mixtures like snake venom. *Rapid Commun. Mass Spectrom.* **2010**, *24*, 687–697. [CrossRef]

102. Nawaz, K.A.A.; David, S.M.; Murugesh, E.; Thandeeswaran, M.; Kiran, K.G.; Mahendran, R.; Palaniswamy, M.; Angayarkanni, J. Identification and in silico characterization of a novel peptide inhibitor of angiotensin converting enzyme from pigeon pea (*Cajanus cajan*). *Phytomedicine* **2017**, *36*, 1–7. [CrossRef]

103. Liu, J.C.; Hsu, F.L.; Tsai, J.C.; Chan, P.; Liu, J.Y.; Thomas, G.N.; Tomlinson, B.; Lo, M.Y.; Lin, J.Y. Antihypertensive effects of tannins isolated from traditional Chinese herbs as non-specific inhibitors of angiontensin converting enzyme. *Life Sci.* **2003**, *73*, 1543–1555. [CrossRef]

104. Vijayakumar, B.; Parasuraman, S.; Raveendran, R.; Velmurugan, D. Identification of natural inhibitors against angiotensin I converting enzyme for cardiac safety using induced fit docking and MM-GBSA studies. *Pharmacogn. Mag.* **2014**, *10*, S639–S644. [CrossRef] [PubMed]

105. Kang, D.G.; Lee, Y.S.; Kim, H.J.; Lee, Y.M.; Lee, H.S. Angiotensin converting enzyme inhibitory phenylpropanoid glycosides from *Clerodendron trichotomum*. *J. Ethnopharmacol.* **2003**, *89*, 151–154. [CrossRef]

106. Li, B.; Qiao, L.; Li, L.; Zhang, Y.; Li, K.; Wang, L.; Qiao, Y. A novel antihypertensive derived from adlay (*Coix larchryma-jobi* L. var. ma-yuen Stapf) glutelin. *Molecules* **2017**, *22*, 123. [CrossRef]

107. Parichatikanond, W.; Pinthong, D.; Mangmool, S. Blockade of the renin-angiotensin system with delphinidin, cyanin, and quercetin. *Planta Med.* **2012**, *78*, 1626–1632. [CrossRef]

108. Zhang, Y.Q.; Luo, J.G.; Han, C.; Xu, J.F.; Kong, L.Y. Bioassay-guided preparative separation of angiotensin-converting enzyme inhibitory C-flavone glycosides from *Desmodium styracifolium* by recycling complexation high-speed counter-current chromatography. *J. Pharm. Biomed. Anal.* **2015**, *102*, 276–281. [CrossRef]

109. Nagai, T.; Nagashima, T. Functional properties of dioscorin, a soluble viscous protein from Japanese yam (*Dioscorea opposita* thunb.) tuber mucilage Tororo. *Z. Naturforsch. C. J. Biosci.* **2006**, *61*, 792–798. [CrossRef]

110. Eckert, E.; Zambrowicz, A.; Pokora, M.; Setner, B.; Dabrowska, A.; Szoltysik, M.; Szewczuk, Z.; Polanowski, A.; Trziszka, T.; Chrzanowska, J. Egg-yolk protein by-product as a source of ACE-inhibitory peptides obtained with using unconventional proteinase from Asian pumpkin (*Cucurbita ficifolia*). *J. Proteom.* **2014**, *110*, 107–116. [CrossRef]

111. Yan, J.; Shi, X.; Donkor, P.O.; Zhu, H.; Gao, X.; Ding, L.; Qiu, F. Nine pairs of megastigmane enantiomers from the leaves of *Eucommia ulmoides* oliver. *J. Nat. Med.* **2017**, *71*, 780–790. [CrossRef]

112. Jenis, J.; Kim, J.Y.; Uddin, Z.; Song, Y.H.; Lee, H.H.; Park, K.H. Phytochemical profile and angiotensin I converting enzyme (ACE) inhibitory activity of *Limonium michelsonii* Lincz. *J. Nat. Med.* **2017**, *71*, 650–658. [CrossRef]

113. Geng, F.; He, Y.; Yang, L.; Wang, Z. A rapid assay for angiotensin-converting enzyme activity using ultra-performance liquid chromatography-mass spectrometry. *Biomed. Chromatogr.* **2010**, *24*, 312–317. [CrossRef] [PubMed]

114. San Pablo-Osorio, B.; Mojica, L.; Urias-Silvas, J.E. Chia Seed (*Salvia hispanica* L.) pepsin hydrolysates inhibit angiotensin-converting enzyme by interacting with its catalytic site. *J. Food Sci.* **2019**, *84*, 1170–1179. [CrossRef] [PubMed]

115. Guo, S.; Li, P.; Fu, B.; Chuo, W.; Gao, K.; Zhang, W.; Wang, J.; Chen, J.; Wang, W. Systems-biology dissection of mechanisms and chemical basis of herbal formula in treating chronic myocardial ischemia. *Pharmacol. Res.* **2016**, *114*, 196–208. [CrossRef] [PubMed]

116. Gao, X.P.; Xu, D.Y.; Deng, Y.L.; Zhang, Y. Screening of angiotensin converting enzyme inhibitors from *Salvia miltiorrhizae*. *Zhongguo Zhong Yao Za Zhi* **2004**, *29*, 359–362.

117. Maneesh, A.; Chakraborty, K. Previously undescribed antioxidative O-heterocyclic angiotensin converting enzyme inhibitors from the intertidal seaweed *Sargassum wightii* as potential antihypertensives. *Food Res. Int.* **2018**, *113*, 474–486. [CrossRef]

118. Xing, Y.; Liao, J.; Tang, Y.; Zhang, P.; Tan, C.; Ni, H.; Wu, X.; Li, N.; Jia, X. ACE and platelet aggregation inhibitors from *Tamarix hohenackeri* Bunge (host plant of Herba Cistanches) growing in Xinjiang. *Pharmacogn. Mag.* **2014**, *10*, 111–117. [CrossRef]

119. Hou, D.; Yousaf, L.; Xue, Y.; Hu, J.; Wu, J.; Hu, X.; Feng, N.; Shen, Q. Mung bean (*Vigna radiata* L.): Bioactive polyphenols, polysaccharides, peptides, and health benefits. *Nutrients* **2019**, *11*, 1238. [CrossRef]

120. Makino, B.; Kobayashi, M.; Kimura, K.; Ishimatsu, M.; Sakakibara, I.; Higuchi, M.; Kubo, M.; Sasaki, H.; Okada, M. Local variation in the content of angiotensin II and arginine vasopressin receptor antagonistic terpenoids in the rhizomes of *Alisma orientale*. *Planta Med.* **2002**, *68*, 226–231. [CrossRef]

121. Lu, Y.; Li, S.; Wu, H.; Bian, Z.; Xu, J.; Gu, C.; Chen, X.; Yang, D. Beneficial effects of astragaloside IV against angiotensin II-induced mitochondrial dysfunction in rat vascular smooth muscle cells. *Int. J. Mol. Med.* **2015**, *36*, 1223–1232. [CrossRef]

122. Jananie, R.K.; Priya, V.; Vijayalakshmi, K. Secondary metabolites of Cynodon dactylon as an antagonist to angiotensin II type1 receptor: Novel in silico drug targeting approach for diabetic retinopathy. *J. Pharmacol. Pharmacother.* **2012**, *3*, 20–25. [CrossRef]

123. Ling, W.C.; Liu, J.; Lau, C.W.; Murugan, D.D.; Mustafa, M.R.; Huang, Y. Treatment with salvianolic acid B restores endothelial function in angiotensin II-induced hypertensive mice. *Biochem. Pharmacol.* **2017**, *136*, 76–85. [CrossRef] [PubMed]

124. Zhang, N.; Dong, M.; Luo, Y.; Zhao, F.; Li, Y. Danshensu prevents hypoxic pulmonary hypertension in rats by inhibiting the proliferation of pulmonary artery smooth muscle cells via TGF-beta-smad3-associated pathway. *Eur. J. Pharmacol.* **2018**, *820*, 1–7. [CrossRef] [PubMed]

125. Robles-Vera, I.; Toral, M.; Romero, M.; Jimenez, R.; Sanchez, M.; Perez-Vizcaino, F.; Duarte, J. Antihypertensive effects of probiotics. *Curr. Hypertens. Rep.* **2017**, *19*, 26. [CrossRef] [PubMed]

126. Tabeshpour, J.; Razavi, B.M.; Hosseinzadeh, H. Effects of Avocado (*Persea americana*) on metabolic syndrome: A comprehensive systematic review. *Phytother. Res.* **2017**, *31*, 819–837. [CrossRef]

127. Osinska, A.N.; Begier-Krasinska, B.; Rzymski, P.; Krasinska, A.; Tykarski, A.; Krasinski, Z. The influence of adding tomato extract and acetylsalicylic acid to hypotensive therapy on the daily blood pressure profiles of patients with arterial hypertension and high cardiovascular risk. *Kardiochir. Torakochirurgia Pol.* **2017**, *14*, 245–252. [CrossRef]

128. Krasinska, B.; Osinska, A.; Osinski, M.; Krasinska, A.; Rzymski, P.; Tykarski, A.; Krasinski, Z. Standardised tomato extract as an alternative to acetylsalicylic acid in patients with primary hypertension and high cardiovascular risk—A randomised, controlled trial. *Arch. Med. Sci.* **2018**, *14*, 773–780. [CrossRef]

129. Krasinska, B.; Osinska, A.; Krasinska, A.; Osinski, M.; Rzymski, P.; Tykarski, A.; Krasinski, Z. Favourable hypotensive effect after standardised tomato extract treatment in hypertensive subjects at high cardiovascular risk: A randomised controlled trial. *Kardiol. Pol.* **2018**, *76*, 388–395. [CrossRef]

130. Michalickova, D.; Belovic, M.; Ilic, N.; Kotur-Stevuljevic, J.; Slanar, O.; Sobajic, S. Comparison of polyphenol-enriched tomato juice and standard tomato juice for cardiovascular benefits in subjects with stage 1 hypertension: A randomized controlled study. *Plant Foods Hum. Nutr.* **2019**, *74*, 122–127. [CrossRef]

131. Wolak, T.; Sharoni, Y.; Levy, J.; Linnewiel-Hermoni, K.; Stepensky, D.; Paran, E. Effect of tomato nutrient complex on blood pressure: A double blind, randomized dose(-)response study. *Nutrients* **2019**, *11*, 950. [CrossRef]

132. Khan, N.I.; Noori, S.; Mahboob, T. Efficacy of lycopene on modulation of renal antioxidant enzymes, ACE and ACE gene expression in hyperlipidaemic rats. *J. Renin Angiotensin Aldosterone Syst.* **2016**, *17*, 1–7. [CrossRef]

133. Di Lorenzo, A.; Curti, V.; Tenore, G.C.; Nabavi, S.M.; Daglia, M. Effects of tea and coffee consumption on cardiovascular diseases and relative risk factors: An update. *Curr. Pharm. Des.* **2017**, *23*, 2474–2487. [CrossRef] [PubMed]

134. Zhang, Y.; Coca, A.; Casa, D.J.; Antonio, J.; Green, J.M.; Bishop, P.A. Caffeine and diuresis during rest and exercise: A meta-analysis. *J. Sci. Med. Sport* **2015**, *18*, 569–574. [CrossRef] [PubMed]

135. Abeywickrama, K.R.; Ratnasooriya, W.D.; Amarakoon, A.M. Oral diuretic activity of hot water infusion of Sri Lankan black tea (*Camellia sinensis* L.) in rats. *Pharmacogn. Mag.* **2010**, *6*, 271–277. [CrossRef] [PubMed]

136. Mancini, E.; Beglinger, C.; Drewe, J.; Zanchi, D.; Lang, U.E.; Borgwardt, S. Green tea effects on cognition, mood and human brain function: A systematic review. *Phytomedicine* **2017**, *34*, 26–37. [CrossRef]

137. Guessous, I.; Eap, C.B.; Bochud, M. Blood pressure in relation to coffee and caffeine consumption. *Curr. Hypertens. Rep.* **2014**, *16*, 468. [CrossRef]

138. Ye, N.S. A minireview of analytical methods for the geographical origin analysis of teas (*Camellia sinensis*). *Crit. Rev. Food Sci. Nutr.* **2012**, *52*, 775–780. [CrossRef]

139. Baspinar, B.; Eskici, G.; Ozcelik, A.O. How coffee affects metabolic syndrome and its components. *Food Funct.* **2017**, *8*, 2089–2101. [CrossRef]

140. Agunloye, O.M.; Oboh, G.; Ademiluyi, A.O.; Ademosun, A.O.; Akindahunsi, A.A.; Oyagbemi, A.A.; Omobowale, T.O.; Ajibade, T.O.; Adedapo, A.A. Cardio-protective and antioxidant properties of caffeic acid and chlorogenic acid: Mechanistic role of angiotensin converting enzyme, cholinesterase and arginase activities in cyclosporine induced hypertensive rats. *Biomed. Pharmacother.* **2019**, *109*, 450–458. [CrossRef]

141. Hussein, R.M.; Elsirafy, O.M.; Wahba, Y.S.; Kawy, H.S.; Hasanin, A.H.; Hamam, G.G. Theophylline, an old drug with multi-faceted effects: Its potential benefits in immunological liver injury in rats. *Life Sci.* **2015**, *136*, 100–107. [CrossRef]

142. Legeay, S.; Rodier, M.; Fillon, L.; Faure, S.; Clere, N. Epigallocatechin gallate: A review of its beneficial properties to prevent metabolic syndrome. *Nutrients* **2015**, *7*, 5443–5468. [CrossRef]

143. Ngueta, G. Caffeine and caffeine metabolites in relation to hypertension in U.S. adults. *Eur. J. Clin. Nutr.* **2019**, *1*. [CrossRef] [PubMed]

144. Xie, C.; Cui, L.; Zhu, J.; Wang, K.; Sun, N.; Sun, C. Coffee consumption and risk of hypertension: A systematic review and dose-response meta-analysis of cohort studies. *J. Hum. Hypertens.* **2018**, *32*, 83–93. [CrossRef] [PubMed]

145. Chei, C.L.; Loh, J.K.; Soh, A.; Yuan, J.M.; Koh, W.P. Coffee, tea, caffeine, and risk of hypertension: The Singapore Chinese health study. *Eur. J. Nutr.* **2018**, *57*, 1333–1342. [CrossRef] [PubMed]

146. Grosso, G.; Micek, A.; Godos, J.; Pajak, A.; Sciacca, S.; Bes-Rastrollo, M.; Galvano, F.; Martinez-Gonzalez, M.A. Long-term coffee consumption is associated with decreased incidence of new-onset hypertension: A dose-response meta-analysis. *Nutrients* **2017**, *9*, 890. [CrossRef] [PubMed]

147. Navarro, A.M.; Martinez-Gonzalez, M.A.; Gea, A.; Ramallal, R.; Ruiz-Canela, M.; Toledo, E. Coffee consumption and risk of hypertension in the SUN project. *Clin. Nutr.* **2019**, *38*, 389–397. [CrossRef]

148. Rhee, J.J.; Qin, F.; Hedlin, H.K.; Chang, T.I.; Bird, C.E.; Zaslavsky, O.; Manson, J.E.; Stefanick, M.L.; Winkelmayer, W.C. Coffee and caffeine consumption and the risk of hypertension in postmenopausal women. *Am. J. Clin. Nutr.* **2016**, *103*, 210–217. [CrossRef]

149. Tobe, S.W. beta-adrenergic receptor blockers in hypertension. *Can. J. Cardiol.* **2014**, *30*, S1–S2. [CrossRef]

150. Heran, B.S.; Galm, B.P.; Wright, J.M. Blood pressure lowering efficacy of alpha blockers for primary hypertension. *Cochrane Database Syst. Rev.* **2012**, CD004643. [CrossRef]

151. Wiysonge, C.S.; Bradley, H.A.; Volmink, J.; Mayosi, B.M.; Opie, L.H. Beta-blockers for hypertension. *Cochrane Database Syst. Rev.* **2017**, *1*, CD002003. [CrossRef]

152. Godfraind, T. Discovery and development of calcium channel blockers. *Front. Pharmacol.* **2017**, *8*, 286. [CrossRef]

153. Voora, R.; Hinderliter, A.L. Modulation of sympathetic overactivity to treat resistant hypertension. *Curr. Hypertens. Rep.* **2018**, *20*, 92. [CrossRef] [PubMed]

154. Saladini, F.; Palatini, P. Isolated systolic hypertension in young individuals: Pathophysiological mechanisms, prognostic significance, and clinical implications. *High Blood Press. Cardiovasc. Prev.* **2017**, *24*, 133–139. [CrossRef] [PubMed]

155. Cruickshank, J.M. The role of beta-blockers in the treatment of hypertension. *Adv. Exp. Med. Biol.* **2017**, *956*, 149–166. [CrossRef] [PubMed]

156. Wright, J.M.; Musini, V.M.; Gill, R. First-line drugs for hypertension. *Cochrane Database Syst. Rev.* **2018**, *4*, CD001841. [CrossRef] [PubMed]

157. La Torre, A.; Giupponi, G.; Duffy, D.; Conca, A.; Cai, T.; Scardigli, A. Sexual dysfunction related to drugs: A critical review. Part V: Alpha-blocker and 5-ARI drugs. *Pharmacopsychiatry* **2016**, *49*, 3–13. [CrossRef] [PubMed]

158. Sharp, R.P.; Gales, B.J. Nebivolol versus other beta blockers in patients with hypertension and erectile dysfunction. *Ther. Adv. Urol.* **2017**, *9*, 59–63. [CrossRef]

159. Yue, Y.; Xue, H.; Wang, X.; Yang, Q.; Song, Y.; Li, X. High-expression β(1) adrenergic receptor/cell membrane chromatography method based on a target receptor to screen active ingredients from traditional Chinese medicines. *J. Sep. Sci.* **2014**, *37*, 244–249. [CrossRef]

160. Tubio, M.R.; Fernandez, N.; Fitzsimons, C.P.; Copsel, S.; Santiago, S.; Shayo, C.; Davio, C.; Monczor, F. Expression of a G protein-coupled receptor (GPCR) leads to attenuation of signaling by other GPCRs: Experimental evidence for a spontaneous GPCR constitutive inactive form. *J. Biol. Chem.* **2010**, *285*, 14990–14998. [CrossRef]

161. Valero, M.S.; Olivan-Viguera, A.; Garrido, I.; Langa, E.; Berzosa, C.; Lopez, V.; Gomez-Rincon, C.; Murillo, M.D.; Kohler, R. Rock Tea extract (*Jasonia glutinosa*) relaxes rat aortic smooth muscle by inhibition of L-type Ca^{2+} channels. *J. Physiol. Biochem.* **2015**, *71*, 785–793. [CrossRef]

162. Parichatikanond, W.; Nishimura, A.; Nishida, M.; Mangmool, S. Prolonged stimulation of beta2-adrenergic receptor with beta2-agonists impairs insulin actions in H9c2 cells. *J. Pharmacol. Sci.* **2018**, *138*, 184–191. [CrossRef]

163. Ren, G.; Qiao, H.X.; Yang, J.; Zhou, C.X. Protective effects of steroids from Allium chinense against H_2O_2-induced oxidative stress in rat cardiac H9C2 cells. *Phytother. Res.* **2010**, *24*, 404–409. [CrossRef] [PubMed]

164. Kuo, S.C.; Li, Y.; Cheng, Y.Z.; Lee, W.J.; Cheng, J.T.; Cheng, K.C. Molecular mechanisms regarding potassium bromateinduced cardiac hypertrophy without apoptosis in H9c2 cells. *Mol. Med. Rep.* **2018**, *18*, 4700–4708. [CrossRef] [PubMed]

165. Tsai, F.J.; Ho, T.J.; Cheng, C.F.; Shiao, Y.T.; Chien, W.K.; Chen, J.H.; Liu, X.; Tsang, H.; Lin, T.H.; Liao, C.C.; et al. Characteristics of Chinese herbal medicine usage in ischemic heart disease patients among type 2 diabetes and their protection against hydrogen peroxide-mediated apoptosis in H9C2 cardiomyoblasts. *Oncotarget* **2017**, *8*, 15470–15489. [CrossRef] [PubMed]

166. Do, K.H.; Kim, M.S.; Kim, J.H.; Rhim, B.Y.; Lee, W.S.; Kim, C.D.; Bae, S.S. Angiotensin II-induced aortic ring constriction is mediated by phosphatidylinositol 3-kinase/L-type calcium channel signaling pathway. *Exp. Mol. Med.* **2009**, *41*, 569–576. [CrossRef]

167. Mao, L.M.; Qi, X.W.; Hao, J.H.; Liu, H.F.; Xu, Q.H.; Bu, P.L. *In vitro*, ex vivo and in vivo anti-hypertensive activity of *Chrysophyllum cainito* L. extract. *Int. J. Clin. Exp. Med.* **2015**, *8*, 17912–17921.

168. Sviglerova, J.; Kuncova, J.; Stengl, M. Chapter 9—Cardiovascular models: Heart secondarily affected by disease. In *Animal Models for the Study of Human Disease*; Conn, P.M., Ed.; Academic Press: Boston, MA, USA, 2013; pp. 195–220. [CrossRef]

169. Redina, O.E.; Markel, A.L. Stress, genes, and hypertension. Contribution of the ISIAH rat strain study. *Curr. Hypertens. Rep.* **2018**, *20*, 66. [CrossRef]

170. Leong, X.F.; Ng, C.Y.; Jaarin, K. Animal models in cardiovascular research: Hypertension and atherosclerosis. *Biomed. Res. Int.* **2015**, *2015*, 528757. [CrossRef]

171. Davern, P.J.; Jackson, K.L.; Nguyen-Huu, T.P.; La Greca, L.; Head, G.A. Cardiovascular responses to aversive and nonaversive stressors in Schlager genetically hypertensive mice. *Am. J. Hypertens.* **2010**, *23*, 838–844. [CrossRef]

172. Palma-Rigo, K.; Jackson, K.L.; Davern, P.J.; Nguyen-Huu, T.P.; Elghozi, J.L.; Head, G.A. Renin-angiotensin and sympathetic nervous system contribution to high blood pressure in Schlager mice. *J. Hypertens.* **2011**, *29*, 2156–2166. [CrossRef]

173. Jackson, K.L.; Dampney, B.W.; Moretti, J.L.; Stevenson, E.R.; Davern, P.J.; Carrive, P.; Head, G.A. Contribution of orexin to the neurogenic hypertension in BPH/2J mice. *Hypertension* **2016**, *67*, 959–969. [CrossRef]

174. The UniProt, C. UniProt: The universal protein knowledgebase. *Nucleic Acids Res.* **2017**, *45*, D158–D169. [CrossRef]

175. Chan, H.C.; Filipek, S.; Yuan, S. The Principles of Ligand Specificity on beta-2-adrenergic receptor. *Sci. Rep.* **2016**, *6*, 34736. [CrossRef] [PubMed]

176. Talebianpoor, M.S.; Mirkhani, H. The effect of tempol administration on the aortic contractile responses in rat preeclampsia model. *ISRN Pharmacol.* **2012**, *2012*, 187208. [CrossRef] [PubMed]

177. Ettinger, G.; Burton, J.P.; Gloor, G.B.; Reid, G. Lactobacillus rhamnosus GR-1 attenuates induction of hypertrophy in cardiomyocytes but not through secreted protein MSP-1 (p75). *PLoS ONE* **2017**, *12*, e0168622. [CrossRef] [PubMed]

178. Kang, Y.; Cai, Y. Gut microbiota and hypertension: From pathogenesis to new therapeutic strategies. *Clin. Res. Hepatol. Gastroenterol.* **2018**, *42*, 110–117. [CrossRef] [PubMed]

179. Han, S.; Li, C.; Huang, J.; Wei, F.; Zhang, Y.; Wang, S. Cell membrane chromatography coupled with UHPLC-ESI-MS/MS method to screen target components from Peucedanum praeruptorum Dunn acting on alpha1A adrenergic receptor. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* **2016**, *1011*, 158–162. [CrossRef] [PubMed]

180. Tan, C.S.; Loh, Y.C.; Ng, C.H.; Ch'ng, Y.S.; Asmawi, M.Z.; Ahmad, M.; Yam, M.F. Anti-hypertensive and vasodilatory effects of amended Banxia Baizhu Tianma Tang. *Biomed. Pharmacother.* **2018**, *97*, 985–994. [CrossRef]

181. Liu, C.; Zhang, X.; Jing, H.; Zhang, J.; Miao, Y.; Zhai, X.; Chen, S. Using open-tubular capillary electrochromatography with part-coating column for binding constants determination of beta2 -adrenergic receptor with seven drugs. *Electrophoresis* **2019**, *40*, 289–295. [CrossRef]

182. Liu, C.; Zhang, X.; Jing, H.; Miao, Y.; Zhao, L.; Han, Y.; Cui, C. Research on drug-receptor interactions and prediction of drug activity via oriented immobilized receptor capillary electrophoresis. *Electrophoresis* **2015**, *36*, 2433–2441. [CrossRef]

183. Feng, T.S.; Yuan, Z.Y.; Yang, R.Q.; Zhao, S.; Lei, F.; Xiao, X.Y.; Xing, D.M.; Wang, W.H.; Ding, Y.; Du, L.J. Purgative components in rhubarbs: Adrenergic receptor inhibitors linked with glucose carriers. *Fitoterapia* **2013**, *91*, 236–246. [CrossRef]

184. Endale, M.; Song, J.C.; Rhee, M.H.; Liu, K.H.; Kim, T.K.; Kwon, J.G.; Park, K.S.; Chung, K.M.; Kim, T.W. Inhibitory effect of *Suaeda asparagoides* (Miq.) extract on the motility of rat gastric antrum is mediated by beta-adrenoceptor. *Lab. Anim. Res.* **2011**, *27*, 317–325. [CrossRef] [PubMed]

185. Saqib, F.; Janbaz, K.H. Rationalizing ethnopharmacological uses of *Alternanthera sessilis*: A folk medicinal plant of Pakistan to manage diarrhea, asthma and hypertension. *J. Ethnopharmacol.* **2016**, *182*, 110–121. [CrossRef] [PubMed]

186. Shah, A.J.; Gilani, A.H. Blood pressure lowering effect of the extract of aerial parts of *Capparis aphylla* is mediated through endothelium-dependent and independent mechanisms. *Clin. Exp. Hypertens.* **2011**, *33*, 470–477. [CrossRef] [PubMed]

187. Sun, Y.H.; Zhao, J.; Jin, H.T.; Cao, Y.; Ming, T.; Zhang, L.L.; Hu, M.Y.; Hamlati, H.; Pang, S.B.; Ma, X.P. Vasorelaxant effects of the extracts and some flavonoids from the buds of *Coreopsis tinctoria*. *Pharm. Biol.* **2013**, *51*, 1158–1164. [CrossRef] [PubMed]

188. Khan, A.U.; Mustafa, M.R.; Khan, A.U.; Murugan, D.D. Hypotensive effect of *Gentiana floribunda* is mediated through Ca++ antagonism pathway. *BMC Complement. Altern. Med.* **2012**, *12*, 121. [CrossRef] [PubMed]

189. Khan, M.; Khan, A.U.; Najeeb ur, R.; Zafar, M.A.; Hazrat, A.; Gilani, A.H. Cardiovascular effects of *Juniperus excelsa* are mediated through multiple pathways. *Clin. Exp. Hypertens.* **2012**, *34*, 209–216. [CrossRef]

190. Shah, A.J.; Rasheed, M.; Jabeen, Q.; Ahmed, A.; Tareen, R.B.; Gilani, A.H.; Nadir, M.; Ahmad, V.U. Chemical analysis and calcium channel blocking activity of the essential oil of *Perovskia abrotanoides*. *Nat. Prod. Commun.* **2013**, *8*, 1633–1636. [CrossRef]

191. El-Mosallamy, A.E.; Sleem, A.A.; Abdel-Salam, O.M.; Shaffie, N.; Kenawy, S.A. Antihypertensive and cardioprotective effects of pumpkin seed oil. *J. Med. Food* **2012**, *15*, 180–189. [CrossRef]

192. Liu, S.J.; Liu, Y.; Zhang, X.; Yang, Z.C.; Liu, W.Z.; Tan, Y.Z. Effect of TGRJ on blood press, NO and Ang II in renal hypertensive rats. *Zhong Yao Cai* **2012**, *35*, 953–957.

193. Yang, Q.; Li, Y.; Weng, X.; Chen, Y.; Ruan, C.; Zhu, X. Effect of Tiangou Jiangya capsule on rabbit aortic strip contraction. *Zhongguo Zhong Yao Za Zhi* **2011**, *36*, 3349–3352.

194. Siddiqi, H.S.; Mehmood, M.H.; Rehman, N.U.; Gilani, A.H. Studies on the antihypertensive and antidyslipidemic activities of *Viola odorata* leaves extract. *Lipids Health Dis.* **2012**, *11*, 6. [CrossRef] [PubMed]

195. Kato, E.; Inagaki, Y.; Kawabata, J. Higenamine 4′-O-beta-d-glucoside in the lotus plumule induces glucose uptake of L6 cells through beta2-adrenergic receptor. *Bioorg. Med. Chem.* **2015**, *23*, 3317–3321. [CrossRef] [PubMed]

196. Kang, N.H.; Mukherjee, S.; Min, T.; Kang, S.C.; Yun, J.W. Trans-anethole ameliorates obesity via induction of browning in white adipocytes and activation of brown adipocytes. *Biochimie* **2018**, *151*, 1–13. [CrossRef] [PubMed]

197. Carreyre, H.; Carre, G.; Ouedraogo, M.; Vandebrouck, C.; Bescond, J.; Supuran, C.T.; Thibaudeau, S. Bioactive natural product and superacid chemistry for lead compound identification: A case study of selective hCA III and L-Type Ca^{2+} current inhibitors for hypotensive agent discovery. *Molecules* **2017**, *22*, 915. [CrossRef]

198. Cuong, N.M.; Khanh, P.N.; Huyen, P.T.; Duc, H.V.; Huong, T.T.; Ha, V.T.; Durante, M.; Sgaragli, G.; Fusi, F. Vascular L-type Ca^{2+} channel blocking activity of sulfur-containing indole alkaloids from *Glycosmis petelotii*. *J. Nat. Prod.* **2014**, *77*, 1586–1593. [CrossRef]

199. Wenjie, W.; Houqing, L.; Liming, S.; Ping, Z.; Gengyun, S. Effects of praeruptorin C on blood pressure and expression of phospholamban in spontaneously hypertensive rats. *Phytomedicine* **2014**, *21*, 195–198. [CrossRef]

200. Lim, K.M.; Kwon, J.H.; Kim, K.; Noh, J.Y.; Kang, S.; Park, J.M.; Lee, M.Y.; Bae, O.N.; Chung, J.H. Emodin inhibits tonic tension through suppressing PKCdelta-mediated inhibition of myosin phosphatase in rat isolated thoracic aorta. *Br. J. Pharmacol.* **2014**, *171*, 4300–4310. [CrossRef]

201. Park, B.G.; Shin, W.S.; Oh, S.; Park, G.M.; Kim, N.I.; Lee, S. A novel antihypertension agent, sargachromenol D from marine brown algae, *Sargassum siliquastrum*, exerts dual action as an L-type Ca^{2+} channel blocker and endothelin A/B2 receptor antagonist. *Bioorg. Med. Chem.* **2017**, *25*, 4649–4655. [CrossRef]

202. Huang, Y.L.; Cui, S.Y.; Cui, X.Y.; Cao, Q.; Ding, H.; Song, J.Z.; Hu, X.; Ye, H.; Yu, B.; Sheng, Z.F.; et al. Tetrandrine, an alkaloid from S. tetrandra exhibits anti-hypertensive and sleep-enhancing effects in SHR via different mechanisms. *Phytomedicine* **2016**, *23*, 1821–1829. [CrossRef]

203. Onakpoya, I.J.; Heneghan, C.J. Effect of the natural sweetener, steviol glycoside, on cardiovascular risk factors: A systematic review and meta-analysis of randomised clinical trials. *Eur. J. Prev. Cardiol.* **2015**, *22*, 1575–1587. [CrossRef]

204. Petit, G.; Berra, E.; Georges, C.M.G.; Capron, A.; Huang, Q.F.; Lopez-Sublet, M.; Rabbia, F.; Staessen, J.A.; Wallemacq, P.; de Timary, P.; et al. Impact of psychological profile on drug adherence and drug resistance in patients with apparently treatment-resistant hypertension. *Blood Press.* **2018**, *27*, 358–367. [CrossRef] [PubMed]

205. Lee, J.; Bae, E.H.; Ma, S.K.; Kim, S.W. Altered nitric oxide system in cardiovascular and renal diseases. *Chonnam Med. J.* **2016**, *52*, 81–90. [CrossRef] [PubMed]

206. Rattmann, Y.D.; Anselm, E.; Kim, J.H.; Dal-Ros, S.; Auger, C.; Miguel, O.G.; Santos, A.R.; Chataigneau, T.; Schini-Kerth, V.B. Natural product extract of *Dicksonia sellowiana* induces endothelium-dependent relaxations by a redox-sensitive Src- and Akt-dependent activation of eNOS in porcine coronary arteries. *J. Vasc. Res.* **2012**, *49*, 284–298. [CrossRef] [PubMed]

207. Ye, B.H.; Lee, S.J.; Choi, Y.W.; Park, S.Y.; Kim, C.D. Preventive effect of gomisin J from *Schisandra chinensis* on angiotensin II-induced hypertension via an increased nitric oxide bioavailability. *Hypertens. Res.* **2015**, *38*, 169–177. [CrossRef]

208. Abdallah, H.M.; El-Bassossy, H.M.; Mohamed, G.A.; El-Halawany, A.M.; Alshali, K.Z.; Banjar, Z.M. Phenolics from *Garcinia mangostana* alleviate exaggerated vasoconstriction in metabolic syndrome through direct vasodilatation and nitric oxide generation. *BMC Complement. Altern. Med.* **2016**, *16*, 359. [CrossRef]

209. Je, H.D.; Kim, H.D.; La, H.O. The inhibitory effect of apigenin on the agonist-induced regulation of vascular contractility via calcium desensitization-related pathways. *Biomol. Ther.* **2014**, *22*, 100–105. [CrossRef]

210. Xu, Z.; Wang, X.; Dai, Y.; Kong, L.; Wang, F.; Xu, H.; Lu, D.; Song, J.; Hou, Z. (+/−)-Praeruptorin A enantiomers exert distinct relaxant effects on isolated rat aorta rings dependent on endothelium and nitric oxide synthesis. *Chem. Biol. Interact.* **2010**, *186*, 239–246. [CrossRef]

211. Chen, C.Y.; Ho, L.T.; Yang, F.Y.; Juan, C.C.; Au, L.C. *Prunellae spica* extract contains antagonists for human endothelin receptors. *Am. J. Chin. Med.* **2013**, *41*, 85–98. [CrossRef]

212. Rayner, B.; Ramesar, R. The importance of G protein-coupled receptor kinase 4 (GRK4) in pathogenesis of salt sensitivity, salt sensitive hypertension and response to antihypertensive treatment. *Int. J. Mol. Sci.* **2015**, *16*, 5741–5749. [CrossRef]

213. Yang, T.; Zubcevic, J. Gut-brain axis in regulation of blood pressure. *Front. Physiol.* **2017**, *8*, 845. [CrossRef]

214. Vaidya, A.; Forman, J.P. Vitamin D and hypertension: Current evidence and future directions. *Hypertension* **2010**, *56*, 774–779. [CrossRef] [PubMed]

215. Yang, T.; Magee, K.L.; Colon-Perez, L.M.; Larkin, R.; Liao, Y.S.; Balazic, E.; Cowart, J.R.; Arocha, R.; Redler, T.; Febo, M.; et al. Impaired butyrate absorption in the proximal colon, low serum butyrate and diminished central effects of butyrate on blood pressure in spontaneously hypertensive rats. *Acta Physiol.* **2019**, *226*, e13256. [CrossRef] [PubMed]

216. Wang, L.; Zhu, Q.; Lu, A.; Liu, X.; Zhang, L.; Xu, C.; Liu, X.; Li, H.; Yang, T. Sodium butyrate suppresses angiotensin II-induced hypertension by inhibition of renal (pro)renin receptor and intrarenal renin-angiotensin system. *J. Hypertens.* **2017**, *35*, 1899–1908. [CrossRef] [PubMed]

217. Zuo, K.; Li, J.; Xu, Q.; Hu, C.; Gao, Y.; Chen, M.; Hu, R.; Liu, Y.; Chi, H.; Yin, Q.; et al. Dysbiotic gut microbes may contribute to hypertension by limiting vitamin D production. *Clin. Cardiol.* **2019**, *42*, 710–719. [CrossRef] [PubMed]

218. Mushtaq, N.; Hussain, S.; Zhang, S.; Yuan, L.; Li, H.; Ullah, S.; Wang, Y.; Xu, J. Molecular characterization of alterations in the intestinal microbiota of patients with grade 3 hypertension. *Int. J. Mol. Med.* **2019**, *44*, 513–522. [CrossRef]

219. Pimenta, F.S.; Luaces-Regueira, M.; Ton, A.M.; Campagnaro, B.P.; Campos-Toimil, M.; Pereira, T.M.; Vasquez, E.C. Mechanisms of action of kefir in chronic cardiovascular and metabolic diseases. *Cell. Physiol. Biochem.* **2018**, *48*, 1901–1914. [CrossRef]

220. Zhang, Z.; Zhao, J.; Tian, C.; Chen, X.; Li, H.; Wei, X.; Lin, W.; Zheng, N.; Jiang, A.; Feng, R.; et al. Targeting the gut microbiota to investigate the mechanism of lactulose in negating the effects of a high-salt diet on hypertension. *Mol. Nutr. Food Res.* **2019**, *63*, e1800941. [CrossRef]

221. Yang, M.; Lao, L. Emerging applications of metabolomics in traditional chinese medicine treating hypertension: Biomarkers, pathways and more. *Front. Pharmacol.* **2019**, *10*, 158. [CrossRef]