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REVIEW

Chinese herbal formulas for treating hypertension in traditional Chinese medicine: perspective of modern science

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Hypertension, which directly threatens quality of life, is a major contributor to cardiovascular and cerebrovascular events. Over the past two decades, domestic and foreign scholars have agreed upon various standards in the treatment of hypertension, and considerable progress has been made in the field of antihypertensive drugs. Oral antihypertensive drugs represent a milestone in hypertension therapy. However, the blood pressure standard for patients with hypertension is far from satisfactory. The study of Chinese herbal formulas for treating hypertension has received much research attention. These studies seek to integrate traditional and Western medicine in China. Currently, Chinese herbal formulas are known to have an outstanding advantage with regard to bodily regulation. Research shows that Chinese medicine has many protective mechanisms. This paper addresses the process of the antihypertensive mechanisms in Chinese herbal formulas for treating hypertension. These mechanisms are to be discussed in future research.
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INTRODUCTION

Cardiovascular and cerebrovascular events are the major causes of mortality worldwide.[1] Hypertension, a chronic disease in which the blood pressure (BP) in the arteries is elevated, is a major contributor to vascular morbidity and mortality. Patients with hypertension are more likely to have heart, brain, kidney and peripheral vascular diseases than those with normal BP. Over the past two decades, domestic and foreign scholars have agreed upon various standards in the treatment of hypertension. Robust evidence from randomized trials shows that the treatment of hypertension is remarkably effective, and a small reduction in BP might cause a large reduction in the risk of cerebrovascular event and myocardial infarction.[2] Oral antihypertensive drugs represent a milestone in therapy for hypertension and other cardiovascular diseases (CVDs); furthermore, they provide the primary and secondary prevention strategies to combat these diseases.[3] In addition, maintaining an active lifestyle, improving diet, monitoring total caloric intake and practicing adequate exercise have pivotal roles in hypertension treatment. Therapeutic strategies are based on the following principles. (a) Early intervention includes the prevention and treatment of pre-hypertension. In addition, the goal of therapy has changed from 'the lower, the better' to 'the earlier, the better', which coincides with ancient preventive medicine (that is, 'treat what is not yet ill'; the 'Huangdineijing' and 'Nanjing' classics in traditional Chinese medicine (TCM) theory).[4] This proverb promotes interventions to the internal organs that are not affected by the ongoing morbidity process and can be compared with avoiding target-organ damage (TOD) due to sustained high BP. (b) In a comprehensive intervention, the treatment focuses on risk factors and includes optimal antihypertensive strategies, such as antihypertensive therapy combined with lipid-lowering therapy or antihypertensive therapy combined with homocysteine-lowering therapy. (c) The therapeutic target changes from the simple goal of lowering BP to improving the complications associated with TOD to reduce the long-term risk of CVD, thereby achieving an ideal BP. (d) Furthermore, the treatment emphasizes on effectively controlling BP, especially with regard to reducing BP variability (BPV).[5]

Considerable progress has been made in the field of antihypertensive drugs. For example, renin–angiotensin–aldosterone system (RAAS) has a crucial role in the regulation of BP and cardiovascular remodeling. The RAAS inhibitor is currently considered an important cornerstone of reducing the risk of cardiovascular events.[6] Aside from the commonly used oral antihypertensive drugs, such as angiotensin-converting enzyme inhibitor (ACEI), angiotensin II type 1 receptor

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(AT1R) blockers, beta blockers and aldosterone receptor antagonist, new RAAS inhibitors have been recently researched and developed. For instance, Aliskiren, the first orally active direct rennin inhibitor, is a novel antihypertensive drug that inhibits the first step of RAAS. It blocks the conversion of angiotensinogen to angiotensin I (Ang I) to reduce the secretion of Ang II.[7] Compared with ACEI and ARB, direct rennin inhibitors stop the 'ACE escape phenomenon' and do not influence the plasma rennin activity during long-term use.[8–10] Furthermore, angiotensin II type 2 receptor, a new type of RAAS inhibitor, can prevent the production of anti-vascular smooth muscle cells (anti-VSMC), relax blood vessels and reverse cardiovascular remodeling. Aldosterone synthase (CYP11B2) inhibitors can inhibit the final step of biochemical reactions catalyzed by the enzymes of *in vivo* aldosterone synthesis process, thereby reducing aldosterone synthesis. Preventing the reactive elevation of aldosterone, compared with aldosterone receptor antagonist, is a new way to antagonize aldosterone. In addition, a significant amount of valuable research has come from modern medicine and pharmacology. Recently, other, newer agents, including a antihypertensive vaccine against Ang I, Ang II, AT1R, endothelin receptor antagonist (Bosantan, Darusentan, Siaxsentan and Tezosentan), chymase, Ang 1-7, neutral endopeptidase-ACE dual inhibitors (omapatrilat, sampatfilt) and so on, are being developed. Despite their proven benefits, achieving an ideal BP level in patients with hypertension is not satisfactory because only 25% of patients achieve this goal, and recurrent cardiovascular events still occur in those who take antihypertensive drugs. At the same time, numerous adverse reactions, including headache, dizziness, orthostatic hypotension and decreased sexual function, limit the clinical practice of antihypertensive drugs. Thus, reducing the occurrence and development of hypertension is necessary to prevent TOD and decrease the vascular morbidity and mortality related to hypertension.[11,12] Developed novel classes of antihypertensive agents must possess high efficacy. As always, fewer adverse effects are the research focus to prevent CVD.

The study of Chinese herbal formulas for treating hypertension is the most active area of research within TCM and integrative medicine in China. Over the past 30 years, significant progress has been made from theory and experiments in the clinical fields based on the inheritance and innovation of thoughts in TCM, to clarify the treatment regulations and principles of hypertension. Currently, much attention has been paid to the holistic, multitarget and multidimensional pharmacological studies of TCM.[13,14] Moreover, the efficacy of TCM for treating hypertension is demonstrated by numerous published cases and randomized trials.[15–17] However, some trials have found null results.[18–21] Numerous randomized controlled trials have been conducted in China to evaluate the efficacy of novel Chinese herbal formulas generated from well-known Chinese medicine formulas or from currently effective practices to treat hypertension. Some trials have effectively treated hypertension.[22,23] An increasing number of systematic reviews and meta-analyses have been conducted to assess the efficiency of TCM for treating hypertension, providing the best evidence supporting the use of TCM for patients who suffer from hypertension.[24–34] The majority of these studies have positive findings that favor the practice of TCM. These studies reveal the multi-protective mechanisms of Chinese herbal formulas for treating hypertension. A recent study showed a strong association between TCM syndrome (also called 'zheng' or 'pattern') and hypertension.[35] Thus, Chinese herbal formulas, including classical prescriptions, experienced prescriptions, traditional Chinese patent medicine and others based on syndrome differentiation, were analyzed further with regard to the aspects shown in Table 1.

THE ANTIHYPERTENSIVE MECHANISM OF CHINESE HERBAL FORMULAS FOR TREATING HYPERTENSION

Reduce BPV

For many decades, the major goal of antihypertensive treatment was to lower BP to a defined level. Recently, several investigators have shown that BPV is another critical cardiovascular risk factor that should also be emphasized in the treatment of hypertension.[36] BPV refers to the physiological fluctuations of BP over time that result from the complex interactions of the dynamic regulations of *in vivo* neuroendocrine systems. These interactions are multifaceted phenomena that include both short- and long-term components that can be estimated using the s.d. of the BP values over a day or using the night-to-day BP ratio. Studies show that, aside from increasing average BP, the load and circadian rhythm of BP are closely associated with cardiac and vascular remodeling as well as TOD.[37] If patients clearly have TOD, then their BPV will increase because of their constantly high systolic pressure at night. Furthermore, increased BPV is associated with a higher incidence of the cardiovascular morbidity complications related to hypertension. The mechanisms of BPV that lead to TOD might be relevant to vascular endothelial injury, RAAS activation, inflammatory response stimulation and the acceleration of target organ apoptosis. Because of the relevant predictions of these associated mechanisms, the adverse prognostic significance of increased BPV has clinical experts increasingly concerned.

Recent studies have shown that various syndromes are highly correlated with BPV. Liver fire (*Gan huo shang yan*)/liver-yang hyperactivity (*Gan yang shang kang*) syndrome and phlegm-fluid retention (*tan zhuo nei zu*) syndrome are two major types of hypertension discussed in TCM. Compared with patients who suffer from liver fire/liver-yang hyperactivity syndrome, patients with phlegm-fluid retention syndrome have more significant BP day-night circadian reductions and BP overload increases. Furthermore, it might injure target organs easily.[38] Chinese herbal formulas for treating liver fire/liver-yang hyperactivity syndrome and phlegm-fluid retention syndromes, such as *Qingxuanjiangya decoction*,[39,40] *Niuhuangjiangya pill*,[41] *Songlingxuemaikang capsule*[42–44] and *Banxia baizhu tianma decoction*,[45] can reduce BPV, control BP and improve clinical symptoms both *in vitro* and *in vivo*.

Inhibiting the activity of sympathetic nerve

Does sympathetic activation initiate and maintain BP elevation in patients with hypertension? Strong historical and contemporary evidence supports this claim. The chronic activation of the sympathetic nervous system is the dominant contributor to systemic hypertension that directly leads to elevation and fluctuation of BP by increasing renin release and cardiac output as well as by promoting vasoconstriction. Therefore, maintaining BP by suppressing sympathetic activity and balancing the sympathetic vagus nerve system is necessary.[46,47]

Verticil, also known as the alkaloid of *Rauwolfia verticallata*, is an antihypertensive drug that is independently produced in China. It consists of *reserpine* and ingredients such as α-receptor blockade. In addition, both *berberine* and *isoliensinine* have a strong effect with regard to blocking the α1 receptor that can reduce BP and the left ventricular mass/body mass ratio in renovascular hypertensive rats (as shown in Figures 1 and 2).[48,49] Other TCM chemical components, *rhynchophylline* and *isorhynchophylline*, can dilate peripheral vessels by

Table 1 Chinese herbs and formulas with antihypertensive effect that are recommended in TCM

Disease	*Syndrome*	*Chinese herbs and formulas*	*Components*	*TCM efficacy*	*Antihypertensive effect*	*Label*
Hypertension	Fire syndrome	*Tianma Gouteng Yin* (decoction of *Gastrodia* and *Uncaria*)	*Rhizoma Gastrodiae* (tall gastrodis tuber), *Ramulus Uncariae Cum Uncis* (gambir plant), *Concha Haliotidis* (sea-ear shell), *Cortex Eucommiae* (eucommia bark), *Radix Achyranthis Bidentatae* (two-toothed achyranthes root), *Herba Taxilli* (Chinese taxillus herb), *Fructus Gardeniae* (Cape jasmine fruit), *Radix Scutellariae* (scutellaria root), *Herba Leonuri* (Motherwort Herb), *Sclerotium Poriae Pararadicis* (Indian bread with hostwood), and *Caulis Polygoni Multiflori* (fleeceflower stem)	Suppressing liver yang hyperactivity, clearing heat, activating blood and nourishing the kidney	Reversing myocardial and interstitial remodeling	Classical prescription of *New Meanings of Treatment in miscellaneous diseases with Traditional Chinese Medicine*
		Huanglian Jie Du Tang (detoxicant decoction of *Coptis*)	*Rhizoma Coptidis* (golden thread), *Radix Scutellariae* (scutellaria root), *Radix et Rhizoma Rhei* (rhubarb root and rhizome), and *Cortex Phellodendri Chinensis* (amur cork-tree bark)	Counteracting heart fire syndrome, clearing heat and toxic materials and relieving headache and dizziness	Lowering the level of ET and TXA_2, increasing the level of NO, 6-K-PG, and 6-K-PG/TXA_2, and improving the balance of ET and NO	Classical prescription of *Arcane Essentials from the Imperial Library* dispensed by *Wang Tao* in *Tang* dynasty
		Niuhuangjiangya pill	Extract of scutellaria, *Radix Codonopsis Tangshen* (codonopsis root), *Radix Astragali* (milk-vetch root; astragalus root), *Rhizoma Chuanxiong* (cnidium), *Radix Paeoniae Alba* (white peony root), *Borneolum Syntheticum* (borneol), *Semen Cassiae* (cassia seed), *Radix et Rhizoma Nardostachyos* (nardostachys root), *Radix Curcumae* (turmeric root tuber), *Herba Menthae* (field mint), *Calculus Bovis Artifactus* (bistort rhizome), *Cornu Saigae Tataricae* (antelope horn), *Cornu Bubali* (buffalo horn), and Margarita (pearl)	Clearing liver heat, dissolving phlegm, resting heart and calming the mind	Reducing BPV, suppressing sympathetic activity, enhancing vagal activity, blocking AT1R, activating AT2R and inhibiting platelet adhesion and aggregation	Traditional Chinese patent medicine
		Songlingxuemaikang capsule	*Radix Puerariae Lobatae* (kudzuvine root), Margarita (pearl layer powder), and *Pinus armandi Franch* (fresh pine needles)	Calming the liver and subduing yang, tranquilizing the heart and calming the mind	Reducing BPV, improving blood rheological condition and inhibiting inflammation and atherosclerosis	Traditional Chinese patent medicine
		Qingxuanjiangya decoction	*Folium Ilicis Latifoliae* (ilex kudingcha), *Rhizoma Gastrodiae* (tall gastrodis tuber), *Radix Uncariae Macrophyllae* (large leaf gambir plant root), *Radix Scutellariae* (scutellaria root), *Radix Cyathulae* (cyathula root), *Cortex Eucommiae* (eucommia bark), *Caulis Polygoni Multiflori* (fleeceflower stem; caulis polygoni multiflori), *Radix Rehmanniae* (rehmannia root), *Folium Mori* (mulberry leaf), and *Flos Chrysanthemi Indici* (chrysanthemum flower)	Clearing liver heat, calming the liver and subduing yang and enriching and nourishing the liver and kidney	Reducing BPV, block ing RAAS, protecting hypertensive renal damage and inhibiting inflammation	Experienced prescription dispensed by Academician *Chen Keji*
		Jiangyatongmai decoction	*Radix et Rhizoma Salviae Miltiorrhizae* (danshen root), *Flos Carthami* (Safflower), *Radix Curcumae* (turmeric root tuber), *Rhizoma Cyperi* (nutgrass galingale rhizome), *Caulis Spatholobi* (suberect spatholobus stem), *Fructus Trichosanthis* (snakegourd fruit), *Bulbus Allii Macrostemi* (long stamen onion bulb), *Radix Scutellariae* (scutellaria root), *Flos Chrysanthemi* (chrysanthemun flower), *Semen Cassiae* (cassia seed; foetid cassia seed), and *Concha Margaritiferae Usta* (mother-of-pearl)	Calming the liver and subduing yang, invigorating blood and dissolving stasis	Reversing LVH	Experienced prescription dispensed by famous TCM physician *Guo Shikui*
		Jiangya capsule	*Radix Cyathulae* (cyathula root), *Radix Achyranthis Bidentatae* (two-toothed achyranthes root), *Rhizoma Gastrodiae* (tall gastrodis tuber), *Rhizoma Chuanxiong* (Sichuan lovage root), *Pheretima* (earth worm), and *Fructus Lycii* (Chinese wolfberry fruit)	Calming the liver, nourishing the kidney and invigorating blood	Lowering the level of ET, increasing the level of NO and improving the balance of ET and NO	Experienced prescription dispensed by famous TCM physician *Zhou Wenquan*
		Xiaxi oral liquid	*Spica Prunellae* (common self-heal fruit-spike), *Radix Cyathulae* (cyathula root), and *Fructus Leonuri* (leonurus fruit)	Calming the liver fire	Decreasing the content of myocardial AT1Rs by downregulating the expression of AT1 mRNA, lowering the level of ET, increasing the level of NO and improving the balance of ET and NO	Experienced prescription
		Zhengejiangya decoction	*Concha Margaritiferae Usta* (mother-of-pearl), *Radix Puerariae Lobatae* (pueraria root), *Flos Chrysanthemi Indici* (wild chrysanthemum flower), *Semen Cassiae* (cassia seed), and *Cortex Eucommiae* (eucommia bark)	Calming the liver and clearing the fire	Lowering the level of ET, increasing the level of NO and improving the balance of ET and NO	Experienced prescription
		Tongmaining granule	*Rhizoma Gastrodiae* (tall gastrodis tuber), *Radix Achyranthis Bidentatae* (two-toothed achyranthes root), *Radix Paeoniae Alba* (white peony root), *Radix et Rhizoma Salviae Miltiorrhizae* (danshen root), *Rhizoma Chuanxiong* (Sichuan lovage root), *Radix Puerariae Lobatae* (kudzuvine root) and so on	Calming the liver and subduing yang and dissolving blood stasis	Reversing vascular remodeling	Experienced prescription
		Qingxin capsule	*Cortex Eucommiae* (eucommia bark), *Ramulus Uncariae Cum Uncis* (gambir plant), *Radix Scrophulariae* (figwort root), *Cortex Moutan* (tree peony bark), *Plumula Nelumbinis* (lotus plumule) and so on	Calming the liver fire and clearing heart fire	Blocking RAAS, lowering levels of plasma ET and ratio of ET/CGRP and elevating plasma levels of CGRP	Experienced prescription
	Fluid retention syndrome	*Banxia Baizhu Tianma Tang* (decoction of *Pinellia ternata*, *Atractylodes macrocephala*, and *Gastrodia elata*)	*Rhizoma Pinelliae Praeparatum* (pinellia rhizome in ginger juice), *Rhizoma Atractylodis Macrocephalae* (white atractylodes rhizome), *Rhizoma Gastrodiae* (tall gastrodis tuber), *Pericarpium Citri Reticulatae* (aged tangerine peel), *Poria* (Indian bread), and *Radix et Rhizoma Glycyrrhizae* (liquorice root)	Calming the liver, strengthening the spleen and dissipating excessive fluid	Blocking RAAS, reversing LVH, regulating metabolism of glucose and lipid, lowering the level of insulin and enhancing the insulin sensitivity	Classical prescription of *Medical Revelations* dispensed by *Cheng Zhongling* in *Qing* dynasty
		Zexietang jiawei decoction (modified decoction of Alisma)	*Rhizoma Alismatis* (water plantain rhizome), *Rhizoma Atractylodis Macrocephalae* (white atractylodes rhizome), *Herba Lycopi* (hirsute shiny bugleweed herb), and *Rhizoma Acori Tatarinowii* (grassleaf sweetflag rhizome)	Dissolving phlegm and draining water-dampness	Protecting hypertensive renal damage	Modified classical prescription of Synopsis of Golden Chamber
		Wendantang jiawei decoction (modified decoction for clearing away gallbladder heat)	*Caulis Bambusae in Taenia* (bamboo shavings), *Fructus Aurantii Immaturus* (immature orange fruit), *Rhizoma Pinelliae* (pinellia rhizome), *Pericarpium Citri Reticulatae* (aged tangerine peel), *Poria* (Indian bread), *Radix et Rhizoma Glycyrrhizae* (liquorice	Dissolving phlegm and boosting *qi*	Lowering IMT, scores and areas of carotid plaque and improving endothelium-dependent dilation of brachial artery	Modified classical prescription of Prescriptions Assigned to the Three Categories of Pathogenic Factors of Diseases

Table 1 (Continued)

Disease	*Syndrome*	*Chinese herbs and formulas*	*Components*	*TCM efficacy*	*Antihypertensive effect*	*Label*
			root), *Radix Codonopsis* (codonopsis root), *Radix Curcumae* (turmeric root tuber) and so on			
	Deficiency syndrome	*Yinianjiangya* decoction	*Ramulus Uncariae Cum Uncis* (gambir plant), *Concha Haliotidis* (sea-ear shell), *Plastrum Testudinis* (Tortoise plastron), *Rhizoma Pinelliae* (pinellia rhizome), *Pericarpium Citri Reticulatae* (aged tangerine peel), *Fructus Aurantii* (orange fruit), *Radix Achyranthis Bidentatae* (two-toothed achyranthes root), *Herba Leonuri* (Motherwort Herb), *Herba Taxilli* (Chinese taxillus herb), *Radix Polygoni Multiflori Praeparata cum Succo Glycines Sotae* (prepared fleeceflower root) and so on	Enriching and nourishing kidney yin, calming the liver and subduing yang	Lowering the level of ET, increasing the level of NO and improving the balance of ET and NO	Experienced prescription
		Jiangzhitiaoya granule	*Radix Polygoni Multiflori* (fleeceflower root), *Fructus Lycii* (Chinese wolfberry fruit), *Semen Cassiae* (cassia seed), *Fructus Crataegi* (Chinese hawthorn fruit), *Flos Chrysanthemi* (chrysanthemun flower), *Rhizoma seu Herba Gynostemmatis Pentaphylli* (gold theragran), *Folium Nelumbinis* (lotus leaf), *Theae* (Tea) and so on	Supplementing kidney, invigorating blood and calming the liver	Lowering levels of plasma ET and ratio of ET/CGRP and elevating plasma levels of CGRP	Experienced prescription
		Jiangyamaijing liquid	*Herba Taxilli* (Chinese taxillus herb), *Semen Cassiae* (cassia seed), *Fructus Crataegi* (Chinese hawthorn fruit), *Fructus Lycii* (Chinese wolfberry fruit), *Fructus Schisandrae Chinensis* (Chinese magnolivine fruit), *Concha Ostreae* (oyster shell) and *Flos Chrysanthemi* (chrysanthemun flower)	Supplementing liver and kidney, fortifying the spleen, harmonizing the stomach dissolving phlegm and blood stasis	Protecting hypertensive renal damage	Experienced prescription
		Bushenyixin tablet	*Herba Epimedii* (aerial part of epimedium herb), *Semen Plantaginis* (plantago seed) and so on	Supplementing kidney, boosting the heart, clearing liver heat and draining water	Regulating metabolism of glucose and lipid, lowering the level of insulin and serum uric acid and enhancing the insulin sensitivity	Experienced prescription
	Others	*Tongxinluo* capsule	*Scorpio* (scorpion), *Scolopendra* (centipede), Hirudo (leech), *Eupolyphaga seu Steleophaga* (ground beetle), *Periostracum Cicadae* (cicada moulting), *Radix et Rhizoma Ginseng* (ginseng), *Borneolum Syntheticum* (borneol), *Radix Paeoniae Rubra* (red peony root) and so on	Invigorating blood and unblocking the collaterals	Lowering the level of ET, increasing the level of NO, improving the balance of ET and NO, inhibiting the platelet activation and vascular inflammation	Traditional Chinese patent medicine
		Shexiangbaoxin pill	*Moschus* (musk), Ginseng Extract, *Calculus Bovis Artifactus* (bistort rhizome), *Cortex Cinnamomi* (cassia bark), Styrax (storax), *Venenum Bufonis* (toad venom), and *Borneolum Syntheticum* (borneol)	Warming and dredge with aromatics, boosting *qi* and nourishing the heart	Reversing myocardial and interstitial remodeling	Traditional Chinese patent medicine
		Xue ling	Angelica	Invigorating blood	Blocking calcium channel	Experienced prescription
		Gadol	—	Supplementing *qi* and activating blood circulation	Elevating the mRNA expression of CPT-1 in heart by improving the hemodynamic index and enhancing the level of adiponectin and the expression of its related signal transduction molecules	Chinese herb
		Ganoderma spore	—	Supplementing *qi*, relieving uneasiness and relieving cough and asthma	Elevating the mRNA expression of CPT-1 in heart by improving the hemodynamic index and enhancing the level of adiponectin and the expression of its related signal transduction molecules	Chinese herb
		Astragalus injection	*Astragalus saponin*	Supplementing *qi*	Reverse myocardial and interstitial remodeling	Traditional Chinese medicine injection
		Erigeron injection	4,5,6-Trihydroxy flavonoids-7 glucuronide	Activating blood and removing stasis and dredging the collaterals to stop pain	Reversing myocardial, interstitial and vascular remodeling	Traditional Chinese medicine injection
		Puerarin injection	8-β-D-Glucopyranosyl-4′,7-dihydroxy isoflavone	—	Decreasing the mRNA expression of AT1 and ACE2 mRNA in heart and clearing free radicals	Traditional Chinese medicine injection
		Verticil	—	—	Inhibiting the activity of sympathetic nerve	Active ingredients
		Berberine	—	—	Blocking α1 receptor	Active ingredients
		Isoliensinine	—	—	Blocking α1 receptor	Active ingredients
		Rhynchophylline	—	—	Inhibiting vasomotor center and blocking sympathetic nerves or ganglions	Active ingredients
		Isorhynchophylline	—	—	Inhibiting vasomotor center and blocking sympathetic nerves or ganglions	Active ingredients
		Tetrandrine	—	—	Blocking calcium channel, reducing the total intracellular calcium, relaxing arteriolar smooth muscle and decreasing peripheral resistance	Active ingredients

Abbreviations: ACE2, angiotensin converting enzyme; AT(1/2)R, angiotensin II type (1/2) receptor; BPV, blood pressure variability; CGRP, calcitonin gene-related peptide; CPT-1, carnitine palmitoyl transferase; ET, endothelin; LVH, left ventricular hypertrophy; NO, nitric oxide; RAAS, renin–angiotensin–aldosterone system; TXA_2, thromboxane A2.

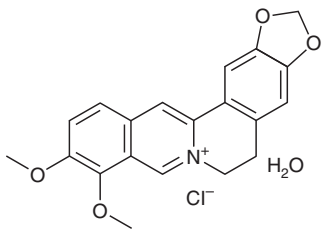

Figure 1 Chemical structure of berberine.

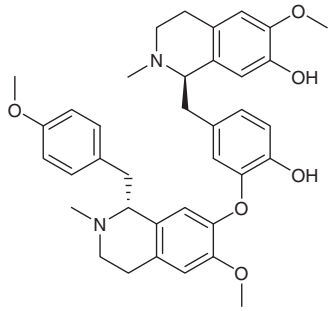

Figure 2 Chemical structure of isoliensinine.

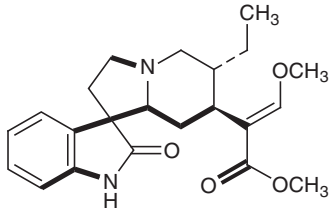

Figure 3 Chemical structure of rhynchophylline.

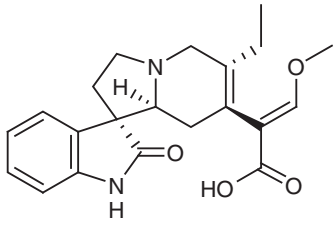

Figure 4 Chemical structure of isorhynchophylline.

directly inhibiting the vasomotor center and blocking the sympathetic nerves or ganglions (as shown in Figures 3 and 4).[50] *Niuhuangjiangya pill* can suppress sympathetic activity and enhance vagal activity, thereby significantly lowering plasma rennin activity and epinephrine after a grip-strength test to stabilize BP under stress and effectively control 24-h BP levels.[51]

Blocking the renin–angiotensin system

For the past three decades, the renin–angiotensin system has been a major focus in high BP research. RAAS has an important role in the acute and chronic regulation of BP. Excessive RAAS activation not only causes sustained increases in BP but also leads to arterial vasoconstriction, fibrosis and cardiac remodeling. Ang II, a crucial vasoactive peptide, which is one of the strongest hormones among the endogenesis active peptides used to reduce BP, is involved in

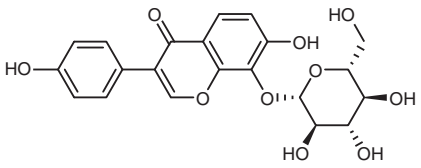

Figure 5 Chemical structure of Puerarin.

vasoconstriction as well as the proliferation and migration of smooth muscle cells, formation of foam cells, aggregation and adhesion of platelets, bradykinin degradation, nitric oxide (NO) reduction and endothelin (ET) increases by acting on AT1R.[52] *Qingxuanjiangya decoction* and *Qingxin capsule* might safely and effectively lower BP in patients with mild or moderate degrees of hypertension, improve their clinical symptoms and more effectively improve their quality of life. This mechanism might be related to their ability to inhibit the activity of the circulatory renin–angiotensin system.[39,53]

AT1R activation can cause arterial vasoconstriction, smooth muscle cell proliferation and strengthen myocardial contraction, which can lead to hypertension, vascular remodeling and cardiac hypertrophy.[54] Several studies have demonstrated that *Xiaxi oral liquid* lowers BP and the content of myocardial AT1Rs by downregulating the expression of AT1 mRNA in spontaneously hypertensive rats (SHR).[55] Furthermore, the antihypertensive effect of *Niuhuangjiangya pill*, another traditional Chinese patent medicine, is related to directly blocking AT1R and indirectly activating angiotensin II type 2 receptor.[56,57]

ACE2 is a zinc-dependent metalloproteinase that has a strong homology with ACE. In addition, ACE2 is similar to the endogenous ACEI that can degrade ACE substrates and decompose ACE products such as Ang II (1–7), thereby resulting in lowered BP and inhibited myocardial hypertrophy. Much research has shown that *Banxia Baizhu Tianma Tang* (a decoction of *Pinellia ternata*, *Atractylodes macrocephala* and *Gastrodia elata*) can improve the expression of factors in cardiac RAAS via a dynamic long-term process. The expression of ACE2 mRNA gradually increases with the extension of delivery time. Importantly, the effect was similar with captopril.[58] Puerarin, also called 4′–7-dihydroxy-8-beta-D-glucose isoflavones, is the major active ingredient extracted from the roots of the kudzuvine, which induces anti-platelet aggregation, activates blood vessels and lowers BP (as shown in Figure 5). Study has demonstrated that low dose of puerarin decreases the mRNA expression of AT1 and ACE2 mRNA in the heart, whereas high doses increase these expression levels in the kidney. A feedback correlation might exist between AT1 and ACE2.[59]

Improving endothelial function

Vascular endothelial factors also have a crucial role in the regulation of BP. Under the stimulation of hypertension, vessel endothelial cells (VEC) release a series of endothelial growth factors that can result in the proliferation and hypertrophy of VSMC, increase intimal collagen, thicken vascular walls and increase peripheral vascular resistance. Finally, all these actions contribute to a vicious circle.[60,61] The research concerning VEC, an initiating factor and carrier of the 'endothelium-hypertension-cardiovascular event' chain, has become a hot issue in the field of hypertension. Thus, early endothelial dysfunction interventions can delay and control the development of cardiovascular and cerebrovascular events.

VEC-stimulated synthesis releases a variety of vasoactive substances through paracrine, autocrine and endocrine systems to regulate

vascular tone, stimulate smooth muscle cell growth and proliferation, promote blood/endothelial cell adhesion, reverse vascular remodeling and participate in blood coagulation, fibrinolysis and immune system.[62] The endothelium-dependent contraction factors produced and released by VEC include ET-1, thromboxane A2 (TXA_2), Ang II, asymmetric dimethyl arginine, O^{2-} (superoxide anion (O^{2-})), urotensin and coupling factor 6. The endothelium-dependent relaxing factors produced and released by the VEC include NO, prostacyclin (PGI_2), calcitonin gene-related peptide (CGRP), endothelium-derived hyperpolarizing factor and C-type natriuretic peptide.

NO, which is synthesized by endothelial nitric oxide synthase, maintains vasodilatation and contraction as well as a balance between anticoagulants and procoagulants.[63] ET is a strong vasoconstrictor that can produce long-lasting concentration-dependent vasoconstriction and cause vascular spasms.[64] It can also stimulate VSMC proliferation, thicken the vascular wall in atherosclerosis and eventually lead to high BP and vascular structural changes. Therefore, the imbalance between the synthesis and release of NO and ET-1 is one of the most important mechanisms in the occurrence and development of hypertension. In addition, this balance is a characteristic of VEC damage. Several studies have demonstrated that certain classic prescriptions lower the level of ET while increasing the level of NO and improve the balance of ET and NO, prevent endothelial injury and improve the peroxidation pathological hyperactivity state in the cardiovascular system of patients with hypertension. These types of classic prescriptions include *Huanglian Jie Du Tang* (*Arcane Essentials from the Imperial Library* written by *Wang Tao* in *Tang* dynasty),[65] *Xiaxi oral liquid*,[66] *Tongxinluo capsule*,[67] *Zhengejiangya decoction*,[68] *Yinianjiangya decoction*[69,70] and *Jiangya capsule*.[71–73]

CGRP is the strongest vasodilator, and it has a crucial role in the systolic and diastolic functions of the cardiovascular system. CGRP fights against the vascular effects of ET and Ang II, enhances the left ventricular systolic function and reduces myocardial ischemia. Both *Qingxin capsule* and *Jiangzhitiaoya granule*[74] could lower levels of plasma ET and the ET/CGRP ratio and elevate the plasma levels of CGRP.

PGI_2 is the strongest *in vivo* platelet depolymerization and vasodilator. 6-keto-prostaglandin $F_{1\alpha}$ (6-K-$PGF_{1\alpha}$) is a metabolite of PGI_2 that may indicate the content of PGI_2 because of its stable nature. TXA_2 is a strong platelet aggregation substance and vasoconstrictor. Therefore, PGI_2 and TXA_2 are important vasoactive substances in the regulation of vascular wall tension. The balance between these elements has an important role in maintaining hemodynamics and vasoconstriction. Studies have shown that *Huanglian Jie Du Tang* can increase the levels of 6-keto-prostaglandin (6-K-PG) and 6-K-PG/TXA_2 while lowering TXA_2 in SHR. These findings indicate that PGI_2 and TXA_2 improve hemodynamics and maintain the balance between the coagulation and anticoagulation.[65]

Preventing TOD

Given the progress of research on hypertension, the structure and function of target organs such as the heart, brain, kidneys and blood vessels have been reconsidered to certain extent. Consequently, much attention should be paid to preventing and treating TOD while lowering BP.[75] Recent research showed that a strong association exists between TCM syndromes and the clinical symptoms of TOD.[35] That is, a liver-fire blazing upward pattern was related to cerebrovascular and eye disease and heart disease (HD); the obstruction of phlegm and the dampness of the heart/liver/gallbladder pattern were related to kidney disease; *qi* and blood deficiencies leading to liver-yang rising patterns were related to HD and kidney disease; and kidney yin/yang deficiency patterns were related to cerebrovascular and eye disease and HD.

Left ventricular hypertrophy is often assumed to be a serious TOD for hypertension. In fact, left ventricular hypertrophy is an independent risk factor for sudden death, coronary HD, congestive heart failure, arrhythmia and other cardiovascular events. Because of the increased long-term pressure load, catecholamine, Ang II and other growth factors can stimulate myocardial hypertrophy and interstitial fibrosis. Therefore, simply lowering BP might not solve the problem of TOD. Furthermore, reversing left ventricular hypertrophy, improving cardiac function and protecting target organs have become the primary goals of hypertension treatment.[76–78] *Gadol* (*Sedum rhodiola* medicinal plants) and *Ganoderma spore* (the dissemination of spores during the maturation of the medicinal fungus *Ganoderma lucidum* fruiting bodies) might treat a variety of CVDs. *Gadol* and *Ganoderma* spore medications, either alone or in combination, might significantly reduce systolic BP, diastolic BP and the myocardial hypertrophy index as well as elevate the mRNA expression of carnitine palmitoyl transferase in the heart by improving the hemodynamic index in SHR, thereby enhancing the level of adiponectin and the expression of its related signal transduction molecules.[79] In addition, liver fire/liver-yang hyperactivity syndrome is strongly related to HD in TOD. Chinese herbal medicine such as *Banxia Baizhu Tianma Tang*, *Jiangyatongmai decoction* and *Tianma Gouteng Yin*, which are used to treat liver fire/liver-yang hyperactivity syndrome, all have potential effects on HD. *Banxia Baizhu Tianma Tang* might significantly decrease the cardiac hypertrophy of 18-week and 24-week-old SHR by regulating the mRNA expression of the RAS factor. The therapeutic effect of this herbal medicine is similar to that of captopril.[58] *Jiangyatongmai decoction*, a Chinese medicine for invigorating blood circulation and eliminating blood stasis, is a historical prescription dispensed by the famous TCM doctor Guo Shikui. This herb might reduce BP, reverse left ventricular remodeling and enhance left ventricular function by inhibiting the AKT protein, decreasing the levels of ET and Ang II and increasing the level of CGRP.[80,81] In addition to substantial myocardium reconstruction, myocardial collagen remodeling is common in hypertension. Much research has demonstrated that *Tianma Gouteng Yin* (a decoction of *Gastrodia* and *Uncaria*),[82–84] *Astragalus injection*,[85] *Erigeron injection*[86] and *Shexiangbaoxin pill*[87] can reverse myocardial and interstitial remodeling and significantly reduce perivascular collagen area, the levels of left ventricular mass index, left ventricular wall thickness and interventricular septum thickness, the content of Type I and Type III collagen, the diameter of myocardial cells, myocardial collagen synthesis and extracellular matrix deposition. This mechanism might be related to the reduction in myocardial transforming growth factor-β1 expression.

Hypertensive renal injury is another major TOD. Long-term hypertension can cause renal sclerosis and gradually progress to chronic renal failure. Positive control of hypertension is the key to preventing hypertensive renal damage. According to recent studies, hypertensive renal injury is strongly related to fluid, phlegm and dampness retention syndrome and liver-yang hyperactivity syndrome, which are caused by deficiency syndrome. Chinese medicines such as *Zexietang jiawei* decoction (a modified decoction of Alisma), *Jiangyamaijing liquid* and *Qingxuanjiangya decoction*, which are used to treat fluid, phlegm and dampness retention syndrome, deficiency syndrome and liver-yang hyperactivity syndrome, respectively, have certain advantages with regard to treating hypertensive renal injury.

Clinical research indicates that prescriptions such as *Zexietang jiawei decoction*,[88] *Jiangyamaijing liquid*[89] and *Qingxuanjiangya decoction*[90] might control increased systolic BP, inhibit the glomerular and tubular hyperplasia caused by high BP in SHR and significantly reduce urinary albumin and β2-microglobulin by increasing the activity of renal rennin and the level of Ang II.

Vascular remodeling is a series of adaptive structural and functional changes in the blood vessels caused by hemodynamics and humoral factors. In addition, it primarily manifests as VSMC hypertrophy and hyperplasia, increased perivascular collagen, decreased vascular compliance and changes in its reactivity to vasoactive substances. Furthermore, the structure and functional changes of large vessels might lead to atherosclerosis. Recent studies have shown that the active ingredients of Chinese medicine might improve vascular remodeling by regulating RAAS and inhibiting a variety of cytokines (inflammatory factors).[91,92] *Erigeron injection*[86] and *Tongmaining granule*[93] might reduce perivascular Type I collagen, improve vascular compliance and reverse vascular remodeling through the inhibition of PKC activity in addition to lowering BP. Other studies have found that *Wendantang jiawei* decoction (a modified decoction for clearing away gallbladder heat and a classic TCM prescription for treating phlegm turbid retention syndrome) might significantly lower intima-media thickness scores and carotid plaque areas as well as improve the endothelium-dependent dilation of the brachial artery.[94]

Improving insulin resistance as well as glucose and lipid metabolism

Hypertension is often associated with lipid and glucose metabolism disorders. The interaction between these disorders might continue to diminish arterial elasticity, increase peripheral resistance and change hemorheology, thereby leading to microcirculation disturbance and high rates of CVD. Therefore, intervening and treating risk factors such as impaired glucose tolerance, dyslipidemia, abdominal obesity and hyperhomocysteinemia are equally important in hypertension treatment.[95,96] In addition, several recent studies have shown that the fasting insulin levels in patients with hypertension were significantly higher than normal. Moreover, insulin resistance is one of the most important aspects of the pathological basis of hypertension. Clinical studies have also shown that Chinese herbal formulas for treating hypertension, such as *Puerarin*, *Banxia baizhu tianma Tang* and *Bushenyixin pill*, might reverse the risk factors of hypertension, regulate glucose and lipid metabolisms, lower insulin levels and enhance insulin sensitivity.[97–101] Furthermore, *Puerarin* has a crucial role in eliminating free radicals.[98] *Banxia baizhu tianma Tang* might improve salt sensitivity and lower cholesterol, low-density lipoprotein cholesterol, triglycerides and the body mass index of patients with hypertension and abundant phlegm-dampness syndrome.[99,100] *Bushenyixin pill* might reduce the serum uric acid level in patients with essential hypertension and insulin resistance.[101]

Other mechanisms

In addition to the above mechanisms, calcium ions have a vital role in the development of hypertension. The activation of potential-dependent calcium channel and receptor regulation of calcium channel might cause an extracellular calcium influx, release of intracellular calcium and lead to a higher concentration of intracellular free Ca^{2+}. Chinese herbal formulas also have calcium channel antagonists and lower BP. *Tetrandrine*, a well-known extract of *Fangji* (*Radix stephaniae tetrandrae*), is both a natural, non-selective calcium channel blocker and a calmodulin antagonist; moreover, it lowers BP by blocking calcium channels, thereby reducing total intracellular calcium, relaxing arteriolar smooth muscle and decreasing peripheral resistance.[102] In addition, *Xue ling*, the primary component of angelica, has a similar effect on verapamil, which indicates that antihypertensive activity is also associated with calcium channel blocking.[103]

Chinese herbal formulas might also improve blood rheological conditions, such as blood flow, viscosity, deformability and coagulation, in patients with hypertension. Because of the enhancement of platelet adhesion, aggregation, releasing reaction and the erythrocyte deformability dysfunction in patients with hypertension, red blood cell deformability improvement and platelet activation inhibition might help in treating patients with hypertension. Studies show that *Songlingxuemaikang capsule* improves the hemorheology of patients with hypertension, especially high shear blood viscosity, plasma viscosity and whole-blood-reduced viscosity.[104] *Tongxinluo capsule* inhibits the platelet activation and vascular inflammation of essential hypertension patients with comorbid diabetes and reduces the levels of serum high-sensitivity C-reactive protein (Hs-CRP), plasma fibrinogen C (FIB-C), CD62p and glycoprotein b/a (GP b/a).[67] *Niuhuangjiangya pill* significantly inhibits platelet adhesion and aggregation in normal rats by inhibiting the release of the TXA_2 platelets induced by adenosine diphosphate, which might block platelet activation and aggregation as well as regulate the positive feedback between the release of adenosine diphosphate and TXA_2.[105]

The important role of inflammation in the incidence and complications of CVD has received much attention. Inflammation, which most likely acts as a trigger and may be associated with CRP to a large extent, tumor necrosis factor-α and other related inflammatory factors most likely have vital roles in the process of remodeling of the vessels, myocardium and renal interstitial cells in patients with hypertension. For instance, *Qingxuanjiangya decoction* not only lowers Hs-CRP and inhibits the inflammatory response but also regulates lipid metabolism and increases the level of endogenous estrogen in perimenopausal women. Furthermore, *Qingxuanjiangya decoction* can reduce the occurrence of cardiovascular events in addition to lowering BP. *Songlingxuemaikang capsule* has a better therapeutic effect than *Qingxuanjiangya decoction* for inflammatory and carotid atherosclerosis, which reduces the content of Hs-CRP and the atherosclerotic plaque index in patients with hypertension.[106] *Niuhuangjiangya pill* also has a role in anti-atherosclerosis. The tumor necrosis factor among patients with atherosclerosis was significantly lower after taking this medicine.[107]

DISCUSSION AND PERSPECTIVES

TCM has a long history and abundant experience with regard to treating the clinical manifestations frequently reported by patients with hypertension and probable TOD.[108,109] With the increasing popularity of complementary and alternative medicines among patients with hypertension,[110–112] TCM is being more frequently used in China and the West.[113,114] TCM also has a unique way of diagnosing and treating this disease. Furthermore, a variety of TCM practices, including Chinese herbal formulas, acupuncture, moxibustion, cupping, qigong, Tai Chi (a shadow-boxing exercise), diet and exercise therapy, originated in China.[115–121] Among these practices, Chinese herbal formulas are a key research area. Great amount of effective Chinese herb and formulas including classical prescriptions originated from a 'classic' textbook, experienced prescriptions dispensed by famous TCM physicians, traditional Chinese patent medicines and others have been widely used in clinical practice by TCM practitioners for thousands of years. Under the guidance of holistic concept and treatment based on

syndrome differentiation and formula syndrome differentiation,[122] TCM practitioners diagnose certain syndromes and prescribe certain formulas according to the clinical manifestations of patients with hypertension. Thus, corresponding Chinese herbal formulas are prescribed based on a TCM diagnosis. In most cases, selected classical prescriptions should be modified (either added or deleted) based on individual symptoms. Current research demonstrates that Chinese herbal formulas possess the advantage of whole body regulation in many ways for many targets. Recently, the continued study of the anti-hypertensive mechanisms of Chinese herbal formulas for hypertension has made great progress with regard to the etiology and pathogenesis of this disease. In addition, progress has been made with regard to treatment regulations and the principles of antihypertensive drugs as well as concerning active ingredients, traditional Chinese patent medicine and Chinese herbs and formulas. Chinese herbal formulas not only stabilize BP but also improve clinical symptoms and quality of life, reverse hypertension-related risk factors and protect targeted organs to improve the chances of long-term survival. Thus, therapeutic advantages exist for overall regulation. Importantly, the effectiveness of Chinese herbal formulas with regard to the uncontrollable factors of BP such as insomnia, constipation, mood swings, obesity, pain and so forth will be the focus of future research on Chinese medicine/integrative medicine for treating hypertension.[123]

As previously mentioned, antihypertensive therapy research on Chinese herbal formulas for treating hypertension has made rapid progress over the past 30 years, but certain problems remain that seriously limit the progress of this research; these problems should be solved as soon as possible. Currently, the clinical hypertensive treatment trials using TCM have been limited to small samples of curative effects, and multicenter, large-scale random samples with controlled methods are rarely employed. This limitation leaves the clinical practice of Chinese herbal formulas for treating hypertension short of definitive clinical evidence. Thus, the evaluation criteria of the clinical outcomes of hypertension must also attend to BPV rather than the value of casual BP (clinical BP) as a medical efficacy appraisal standard. Moreover, many experiments have primarily focused on the mechanisms of one aspect of specific Chinese herbal formulas for treating hypertension. The experimental methodology requires rigor, and only a few studies have included *in vitro* and *in vivo* samples in the same design.

Because of many of the problems regarding the effectiveness and security of current antihypertensive Western drugs, a great need has arisen to develop efficacious medicines to treat hypertension. Screening highly efficient antihypertensive drugs with fewer adverse effects based on Chinese herbal formulas has attracted much research attention, and the target mechanisms of Chinese herbal formulas for hypertension are a hot topic in the research and development of antihypertensive drugs. Active ingredients with potential antihypertensive effects are the material basis of Chinese herbal formulas for treating hypertension. However, Chinese herbs contain many active ingredients, and a commonly used formula usually contains more than two Chinese herbs. Thus, a large quantity of active ingredients must be identified, extracted and purified from a formula, which is difficult for medical researchers. Furthermore, certain active ingredients are chemically unstable, which limits large-scale synthesis. These pressing issues should be resolved in future research. However, the primary task of the current study was to discuss the antihypertensive effects of Chinese herbal formulas. Multicenter, large-scale random samples using controlled trials are needed to reasonably evaluate the efficacy and safety of Chinese herbal formulas for treating hypertension within the 'concept of holism' and the 'syndrome differentiation' in TCM.[124,125] Furthermore, the experiments on classic and experienced prescriptions should also be strengthened. By providing intensive research on the antihypertensive effects of Chinese herbal formulas, we can develop many new antihypertensive drugs that possess definite curative effects that target clear mechanisms to significantly advance the research on hypertensive treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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