Tropical Journal of Pharmaceutical Research June 2015; 14 (6): 1111-1117
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v14i6.25

Review Article

Potential Beneficial Effects of *Tulbaghia violacea* William Henry Harvey (Alliaceae) on Cardiovascular System - A Review

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Received: 9 May 2014 *Revised accepted: 19 April 2015*

Abstract

Tulbaghia violacea William Henry Harvey (Harv. Alliaceae) is a small bulbous herb belonging to the family Alliaceae. It is used in South Africa to treat fever, colds, asthma, paralysis, and hypertension. Meanwhile, cardiovascular disease accounts for about 30 % of total global death, with most of these deaths occurring in low and middle-income countries. Furthermore, people in low-income countries are still largely dependent on plants in their surroundings for both prophylaxis and treatment of diseases, partly due to limited access to and cost of pharmaceuticals, and folkloric evidence of the potency of medicinal plants and/or local belief systems. Therefore, the present review aims to proffer possible ways by which T. violacea may improve cardiovascular outcomes. An extensive and systematic review of the literature was carried out, and relevant findings presented in this review. There is evidence that T. violacea may modulate the renin-angiotensin system, the autonomic nervous system, oxidative stress and haemostasis, with resultant protection of the cardiovascular system in both health and disease.

Keywords: *Tulbaghia violacea, Spontaneously hypertensive rats, Hypertension, Blood pressure, Heart rate, Renin-angiotensin aldosterone system*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Cardiovascular disease (CVD) is a complex multi-factorial disease [1]. It accounts for 29.2 % of total global deaths, with approximately 80 % of these deaths occurring in low and middle-income countries [2]. Epidemiologic studies indicate that hypertension (HTN), elevated serum lipids, increased plasma fibrinogen and coagulation factors, increased platelet activation, alterations in glucose metabolism (diabetes mellitus, DM), and smoking are factors positively associated with CVD [3]. Sixty per cent of the burden of CVD and about 50 % of that of coronary heart disease (CHD) globally is caused by HTN [3]. Age [4], gender [5], urbanization [6], obesity [7] and certain dietary factors [8] strongly influence the occurrence of essential HTN. Although, some of the present chemical drugs have shown a lot of promise in the treatment of HTN, many patients usually need to use a combination of agents from the different classes of antihypertensive agents presently in the market to achieve the desired therapeutic goals, leading to problems with adherence to therapeutic regimes [9]. Furthermore, uncontrolled blood pressure (BP) has also been reported in a high number of hypertensive patients who adhere to the available antihypertensive drugs and/or therapy [10], given impetus to intensive research towards

discovering better, cheaper and equally effective medicines, including herbs [11].

PLANTS IN CARDIOVASCULAR DISEASE

Plants have formed the basis of sophisticated traditional medicine systems that have been in existence for thousands of years and continue to provide mankind with new remedies, and about 80 % of the population of the world may still rely on plant-derived medicines for their healthcare needs [12]. In recent times, there has been a rekindling of interest in 'rediscovering natural products' [13]. Previous works on medicinal plants led to the isolation of early drugs such as cocaine, codeine, digitoxin, quinine, diosgenin, reserpine, pilocarpine and morphine [12]. Some plants which have been previously reported to have potential beneficial effects against CVD include *Allium sativum* (garlic) [14], *Rauwolfia serpentina* (Apocynaceae) *Radix rauwolfiae* (snake-root) [15], *Curcuma longa* (turmeric) [16], *Crataegus monogyna* (Hawthorn) and *Crataegus laevigata* (Hawthorn thorny) leaves, flowers and berries [17], *Salvia miltiorrhiza* (red sage, Danshen) [18], *Ocimum gratissimum* L. (Labiatae) [19], *Andrographis paniculata* [20], and *Tulbaghia violacea* [21-23]. The list is endless, however this review will be geared towards one of such plant: *T. violacea.*

Tulbaghia violacea

Tulbaghia violacea Harv. (Alliaceae) is a small bulbous herb, with attractive purple flowers, arising from a white fleshy stalk (figure 1 below). It belongs to the same family as onions and garlic, Alliaceae. The plant is widespread throughout Africa, with the greatest concentration in Southern Africa, where it is known locally as wilde knoffel (Afrikaans), isihaqa (Zulu) or itswele lomlambo (Xhosa) [24]. It is widely used as herbal remedy for various ailments such as fever, colds, asthma, tuberculosis, rheumatism, paralysis, HTN, stomach problems and oesophageal cancer; with its leaves and bulbs being the parts most commonly used. However, adverse effects such as gastroenteritis, abdominal pain, acute inflammation, sloughing of the intestinal mucosa, contraction of the pupils, as well as fatalities has also been reported with treatment with extracts of the plant [23,24].

T. violacea has been postulated to have similar secondary metabolites and hence biological activities as garlic since they belong to the same family; and both have the characteristic sulphur smell associated with garlic [23,24]. Sulphur compounds have been isolated from both garlic and *T. violacea*, and are credited with the medicinal properties of garlic [25,26]. These sulphur-containing compounds are produced when alliinase, an enzyme present in all plants belonging to the Allium species, reacts with alliin when the plant is bruised/ crushed [25]. Numerous odour forming compounds [25,26] and bioflavonoids such as quercetin [27] have also been isolated from extracts of *T. violacea*. The optimum pH for activity of alliinase from both garlic and *T. violacea* is 6.5, and that for onion 8 [28].

Figure 1: *Tulbaghia violacea (*with green leaves and purple flowers)

There is extensive clinical, epidemiological, *in-vivo* and *in-vitro* research on the beneficial effects of garlic on the cardiovascular system (CVS) [14]. However, there are only a few *in-vivo* and *in-vitro* reports in literature for *T. violacea* and these are due to a recent burst of research into it [11,21,22,29-33]. The present review will discuss the possible modulatory action of *T. violacea* on the renin-angiotensin aldosterone system, the autonomic nervous system, oxidative stress and haemostasis and the beneficial effects for cardiovascular diseases.

Effects of TV on the renin angiotensin aldosterone system

The renin angiotensin aldosterone system (RAAS) is a key physiologic regulator of vascular tone, salt and water balance, blood pressure (BP), bradykinin system and pituitary gland hormones [34]. Chronic activation of the RAAS results in HTN, vascular and myocardial hypertrophy, left ventricular remodelling, atherosclerosis , and glomerulosclerosis [34]. *T. violacea* has been reported to display angiotensin converting enzyme (ACE) inhibitory activity *in vitro* [31] and *in vivo* [11,22,32,33]. Extracts of *T. violacea* have been reported to reduce systolic blood pressure (SBP) in response to infusion of ang I in anaesthetized male spontaneously hypertensive Wistar rats (SHR) [11,21] and in normotensive male Wistar rats [33] when compared to the corresponding values in the control rat groups in acute experiments. A similar finding was replicated in chronic experiments involving Dahl salt sensitive rats (DSS) [22,32], but not in SHR [21] (Table 1, Figure 2).

Angiotensin II (ang II) is the most powerful biologically active product of the RAAS. It directly constricts vascular smooth muscle (VSM) and the cells (VSMCs), enhances myocardial contractility, stimulates aldosterone production, blunts the baroreflex, stimulates the release of catecholamines from the adrenal medulla and sympathetic nerve endings, increases sympathetic nervous system activity, stimulates thirst and salt appetite, and increases sodium and water reabsorption. It also induces inflammation, cell growth, mitogenesis, apoptosis, migration, and differentiation, regulates the gene expression of bioactive substances, reactive oxygen species, and activates multiple intracellular signalling pathways [38,39]. Consequently, ang II plays an important role in atherosclerosis, with most of its hypertensinogenic actions mediated through the angiotensin II type 1 (AT_1) receptor; although an angiotensin II type 2 (AT_2) receptor exists [34]. The lack of a significant change in final BP values obtained with co-infusion of *T. violacea* and ang II, when compared to the infusion of ang II alone in the SHR in the study conducted by Raji *et al* [11] may suggest that *T. violacea*

Table 1: Cardiovascular effects of *Tulbaghia violacea* extracts

Reference number	Animal used	Type of study	Plant part	Plant preparation	Results
[35]	N/A	*in-vitro*	Leaf, Roots	Aqueous & Methanol	ACE inhibition
[24]	N/A	*in-vitro*	Leaf, Bulb	Aqueous & methanol	Anticoagulant & antithrombotic activities
[36]	N/A	*in-vivo*	Whole plant	Aqueous	Antioxidant activity
[33]	NWR	*in-vitro* *in-vivo*	Leaf	Aqueous & methanol	ACE inhibition; reduction in MAP
[29]	N/A	*in-vitro*	Bulb	Methanol	Anticoagulant & antithrombotic activities
[32]	DSS	*in-vivo*	Leaf	Aqueous	Reduction in AT_1a mRNA expression & SBP; increased diuresis & natriuresis
[37]	NWR	*in-vivo*	Root	Methanol	Antioxidant activity
[30]	DIATR	*in-vivo*	Root	Methanol	Improved lipid profile & antioxidant activity
[11]	SHR	*in-vivo*	Leaf	Methanol	Reduced SBP, MAP, DBP & HR; ACE inhibition & β1 adrenoceptor blockade
[22]	DSS	*in-vivo*	Root	Methanol	Decrease SBP; increased diuresis & natriuresis
[21]	SHR	*in-vivo*	Leaf	Methanol	Reduced plasma aldosterone levels, SBP, MAP, DBP & HR; stimulated muscarinic receptors

NWR; normotensive Wistar rats, DIATR; diet-induced atherosclerogenic rats, DSS; Dahl salt sensitive rats, ACE; angiotensin converting enzyme, AT1a mRNA; angiotensin II type 1a mRNA, SBP; systolic blood pressure, MAP; mean arterial pressure, DBP; diastolic blood pressure, HR; heart rate, TG; triglyceride, TC; total cholesterol, LDL; low-density lipoprotein, VLDL; very low-density lipoprotein, HDL; high density lipoprotein; N/A, not applicable.

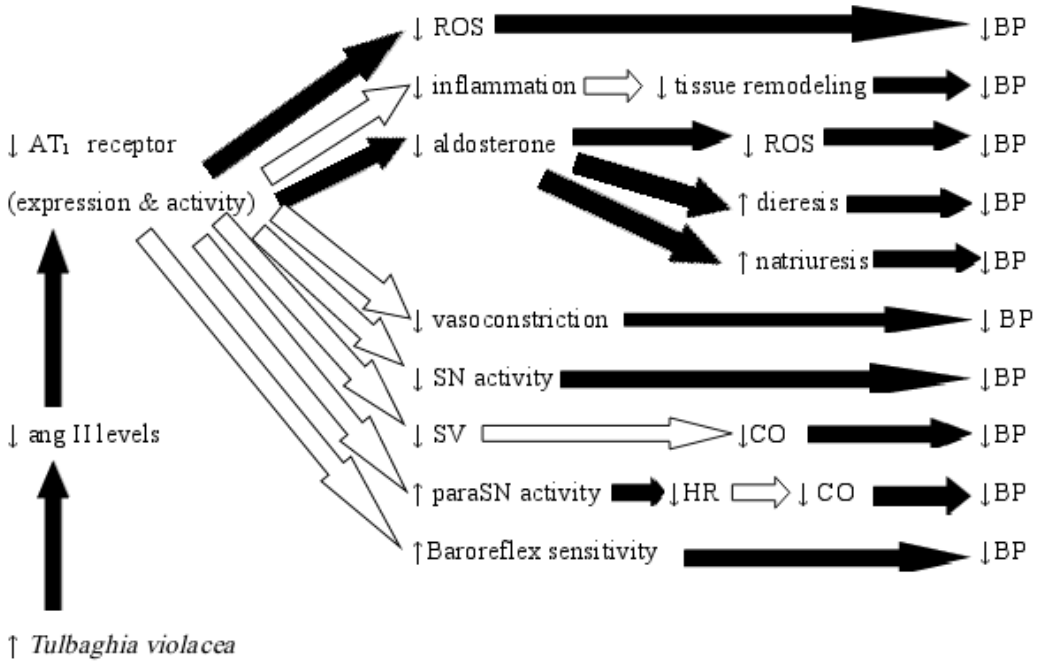

Figure 2: Possible mechanism of action of *Tulbaghia violacea.* The dark arrows indicate mechanisms already reported in literature, while the light arrows indicate proposed mechanisms. Increased (↑), decreased (↓), blood pressure (BP), angiotensin II (ang II), angiotensin II type 1 (AT_1) receptor, reactive oxygen species (ROS), sympathetic nerve (SN), parasympathetic nerve (paraSN), stroke volume (SV), cardiac output (CO), heart rate (HR)

may not directly inhibit the AT_1 receptor. However, enhanced natriuresis has been reported with chronic treatment of DSS with *T. violacea* [22,32]. This was associated with down-regulation of the AT_1a mRNA in one study [32], but was not associated with down-regulation of the AT_1a mRNA in another [22] (Table 1, Figure 2), which may suggest that the plant may produce its natriuretic action via other mechanisms or receptors, aside the AT_1a.

Aldosterone is a mineralocorticoid synthesized in the zona glomerulosa of the adrenal gland in response to ang II, adrenocorticotropin and potassium. It regulates electrolyte, fluid balance and BP homeostasis [40]. It also mediates maladaptive tissue remodelling throughout the cardiovascular and central nervous system. Primary hyperaldosteronism leads to a greater frequency of resistant HTN, as well as CVD and chronic kidney disease (CKD) morbidity and mortality, compared with essential HTN [41]. Reducing plasma aldosterone levels may be a third point of intervention of *T. violacea* in the RAAS, with inhibition of ACE and AT1a mRNA expression being the first and second respectively. Interestingly, chronic infusion of *T. violacea* resulted in significant reduction ($p < 0.05$) in plasma aldosterone levels in two studies in SHR [21] and DSS [32] (Table 1, Figure 2), but this reduction was not observed in a third study [22].

Effects of TV on the autonomic nervous system

The VSMCs are the major cellular component of the vascular media and mediate vasodilatation and vasoconstriction; and are innervated by both sympathetic and parasympathetic fibres [42]. The autonomic nervous system (ANS) consists of both the sympathetic and parasympathetic nervous systems, the activities of both systems are normally in dynamic balance, and plays a vital role in the control of cardiovascular activity [43]. Interestingly, a large proportion of patients with HTN have increased sympathetic activity, associated with decreased parasympathetic activity [44]. Adrenoceptors mediate the actions of the sympathetic nervous system [45]. Stimulation of the beta 1 (β1) adrenoceptors in the heart produces increases in heart rate (HR), cardiac output, and ultimately BP [46]. Inhibition of the β1 adreonoceptors by *T. violacea* may have contributed to the bradycardia, associated with reduction in BP observed in the SHR [11] (Table 1, Figure 2). Resting HR is an independent predictor of both cardiovascular and "all-cause" mortality in men and women with or without a diagnosed CVD [45], therefore agents that can reduce HR are beneficial to the CVS. The neurotransmitter of the parasympathetic nervous system is acetylcholine, and it acts via nicotinic and muscarinic receptors. Activation of

the muscarinic receptors in the heart leads to bradycardia [47]. *T. violacea* may have an effect on the muscarinic receptors, since pre-treatment of SHR with atropine, blocked the bradycardia of its methanolic extract [21] (Table 1, Figure 2).

Effects of TV on oxidative stress and haemostasis

Oxidative stress, characterized by an imbalance between the generation of reactive oxygen species (ROS) and the capacity of the intrinsic antioxidant defense system, has been implicated in the pathogenesis of CVD, including HTN [39]. ROS are important as signaling molecules and are produced continuously from oxygen in cells to support normal cellular functions such as proliferation and migration [48,49], but may result in cell injury when excessively produced, and have been implicated in a host of pathological processes, including vascular hypertrophy and remodelling, HTN, inflammation and atherosclerosis [38,49]. The established therapeutics against atherosclerosis are largely focused on alleviating hypertension and hyperlipidaemia or controlling haemostasis to prevent thrombotic complications [50]. To this end, *T. violacea* has been reported to improve lipid profile [30]; and have both anti-oxidant [30,37], and anti-thrombotic [24,29] properties (Table 1, Figure 2).

RECOMMENDATIONS

The traditional use of *T. violacea* in the treatment of HTN may be encouraged, although further studies are required, to not only ascertain its safety and optimal dose, but to also isolate and remove constituents that may negate the potency of the anti-hypertensive constituent(s). It will also be crucial to investigate the effect of temperature on the active constituent(s), as well as the first pass metabolism, the bioavailability when taken orally, the rate of metabolism in the body, the distribution, the half life, toxicity and also the route(s) of elimination of its constituents. Finally, an assessment into its interaction with other herbs, drugs or food in both experimental animals and in clinical trials would be required.

CONCLUSION

Various studies have shown that *T. violacea* has a wide-ranging effect on the cardiovascular system by modulating the renin-angiotensin aldosterone system, the autonomic nervous system, oxidative stress and haemostasis.

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