Review Article

South African medicinal plants displaying angiotensin-converting enzyme inhibition: Potential use in the management of preeclampsia

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A B S T R A C T

In resource-limited settings, such as South Africa, hypertensive disorders of pregnancy such as preeclampsia is the most common direct cause of maternal deaths. Current management strategies of preeclampsia primarily involve the use of pharmaceutical drugs, which are frequently associated with undesirable side-effects. Moreover, these drugs are often not easily accessible due to financial and economic constraints. Consequently, many patients rely on traditional medicine obtained from medicinal plants to manage health-related conditions.

Angiotensin-converting enzyme inhibitors are widely used drugs for the management of preeclampsia. This narrative review aims to highlight the use of indigenous medicinal plants from South Africa with Angiotensin-converting enzyme inhibitory activity whilst also evaluating their potential use in the treatment of hypertension in pregnancy. This information will influence traditional healers and sangomas in their patient management. Furthermore, the antihypertensive potential of these plants will be unraveled thus facilitating the development of new naturally occurring pharmaceutical products to reduce maternal and neonatal mortality and morbidity.

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1. Introduction

Globally, hypertensive disorders of pregnancy (HDP) such as chronic hypertension, gestational hypertension, preeclampsia, severe preeclampsia, eclampsia and the HELLP syndrome (haemolysis, elevated liver enzymes and low platelet levels) are a major cause of maternal and perinatal morbidity and mortality. In 2019, Rana et al. (2019) reported that preeclampsia (PE) accounts for >70,000 maternal and >500,000 foetal deaths each year [1]. PE affects up to 8% of pregnancies worldwide [2], with a higher prevalence in low and middle-income countries (LMICs) [3]. Complications associated with PE are common in resource-limited settings such as South Africa (SA) [4]. Despite a decline in the triennium, HDP remains the second cause of maternal deaths, which emanate from patients attending antenatal clinics during the late stages of pregnancy, poor antenatal care such as failure to detect women at risk of PE, and inadequate emergency transport services to transfer women with complications associated with this disorder timeously [4].

Preeclampsia, a pregnancy-specific disorder, is defined as new-onset hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) coupled with one or more of the following conditions: with/without proteinuria (urinary protein ≥300 mg per 24 h), maternal organ dysfunction, liver, and renal injury or foetal growth restriction; such clinical characteristics are usually detected at or after 20 weeks of gestation [5]. Clinical evidence suggests that hypertension is the most severe symptom influencing maternal and neonatal health in PE [6]. Whilst the exact aetiology of PE remains unknown, its pathogenesis is most likely...
dependent on the complex interaction among increased angiotensin II activity, endothelial dysfunction, neurovascular anomalies, and excessive vasoconstriction [7]. Therefore, the management of hypertension in PE involves pharmaceutical agents that target specific physiological mechanisms involved in blood pressure regulation, such as the renin-angiotensin-aldosterone system (RAAS) [8]. To-date, angiotensin-converting enzyme inhibitors (ACEI’s) have proven to be valuable in the management of hypertensive disorders. ACEI’s interfere with RAAS by inhibiting angiotensin II production and thereby stimulating blood vessel dilation that causes a decrease in blood pressure (Fig. 1) [9]. Notably, this inhibitory effect increases sodium and urine excretion, reduces resistance in renal blood vessels, increases venous capacity, whilst decreasing cardiac output [9].

2. Issues related to the current pharmaceutical management of hypertensive disorders during pregnancy

In addition to synthetic antihypertensive agents such as diuretics, beta-blockers, calcium channel blockers, ACEI’s are recommended for the management of hypertension in pregnancy (Table 1). Nonetheless, the use of ACEI’s is costly, thus inaccessible to patients from lower socioeconomic backgrounds [10]. Other limitations include a reduced efficacy with prolonged use, various adverse side effects, and teratogenic effects if used during the last two trimesters of pregnancy (Table 1) [5,10,11].

Clinically in South Africa, ACEI’s and beta-blockers are the most commonly prescribed drugs in the management of HDP, especially PE [23]. Despite the frequent prescribing of ACEIs for the treatment of HDP, evidence suggests that synthetic ACEIs are contraindicated during the second and third trimesters as a result of suspected fetopathy [24]. However, data pertaining to the consequences observed during first-trimester exposure in pregnant women with chronic hypertension is poorly described, resulting in conflicting opinions regarding their safety [24–28]. For example, Cooper et al. (2006) suggests that the use of ACEIs may be associated with possible teratogenicity, since an increased risk of foetal cardiac valve and central nervous system defects was shown after first trimester ACEI exposure [26] in contrast to no reported teratogenic risk by others [29,30]. Likewise, a systematic analysis of published cases involving intrauterine exposure to ACEI’s, highlights that most complications are less frequent in first trimester exposure compared to exposure during the second and third trimesters or throughout gestation [26,31,32]. This may be attributed to the possibility that Angiotensin II is responsible for foetal kidney development towards the end of pregnancy rather than early foetal development [32]. Moreover, prenatal renal development is dependent on a fully functional RAAS, hence it is possible that abnormalities arising after in-utero ACEI exposure may be due to the drug itself or underlying maternal ailments [31]. Antenatal screening of underlying complications prior to administration of ACEI’s should be a perquisite in pregnant women predisposed to

Fig. 1. Diagrammatic representation of the effect of medicinal plants on the angiotensin-converting enzyme I renin-angiotensin system (ACE1 RAS) pathway. Renin is produced by the kidneys in response to low blood volume, low sodium, or high potassium levels. Renin’s primary substrate is angiotensinogen, which is produced in the liver. Renin catalyzes the cleavage of circulating angiotensinogen, resulting in angiotensin I. Angiotensin II stimulates the secretion of aldosterone and is involved in sodium retention. The retention of water and sodium causes an increase in blood volume and thus blood pressure. ACEIs such as medicinal plants inhibit the action of ACE, reducing the conversion of angiotensin I to angiotensin II. Muscle contraction around blood vessels is reduced, successfully dilating vessels, and lowering blood pressure. Aldosterone levels drop, as does water/sodium reabsorption, lowering blood pressure. Image created with BioRender.com.
hypertension. Of note, babies delivered by pregnant women managed with captopril, a drug with a short elimination half-life, throughout pregnancy or towards the end of the pregnancy, revealed no neonatal complications in 95% of these babies [31]. Thus, during pregnancy, ACEIs should be discontinued early in the first trimester to prevent potential harmful effects associated with late pregnancy exposure [25]. Based on the conflicting evidence and side effects associated with the use of synthetic antihypertensive drugs, there is an urgent need for safer, more effective, and less expensive treatment alternatives with minimal or no side effects for the management of HDP. Modern medicine includes the use of several drugs that are derived from medicinal plants [33]. Medicinal plants are accessible in low-income environments [34] and represent a valuable source in the development of new therapeutic compounds.

2.2. Medicinal plants targeting the ACE1 RAS pathway for the potential management of preeclampsia

Medicinal plants (together with their common names, location, traditional uses, and bioactive compounds) currently in use, that potentially lower blood pressure by modifying the ACE 1 RAS pathway is summarized in Table 2. Plants that are considered to have potential antihypertensive properties are required to inhibit the ACE enzyme (and the subsequent conversion of angiotensin I to angiotensin II) by more than 50%. These medicinal plants are widespread throughout SA. Different morphological parts of the plant are used for treatment, with the leaves mainly being used, which is in line with accepted protocols for plant conservation and sustainable use [34]. Most plant extracts isolated use polar solvents such as water, methanol, and ethanol and have high ACE inhibitory potential. However, clinical trials are required to verify its therapeutic potential.

2.2.1. Adenopodia spicata

The in vitro inhibition of ACE by Adenopodia spicata aqueous and ethanolic leaf extracts [40] were 97% and 72%, respectively but were not significant (8%) when using root extracts [40]. The phytochemical analysis confirmed flavonoids and saponins as the plant’s main bioactive components [54]. While saponins isolated from A. spicata has not been researched for their antihypertensive effect, oral administration for five days of saponin isolated from the leaves of Camellia sinensis to spontaneously hypertensive rats showed a time-dependent decrease in blood pressure and mean blood pressure [55]. A single administration of saponin also showed a long-lasting hypotensive effect in these rats [55]. Likewise, partially purified soybean saponin also significantly reduced blood pressure in spontaneously hypertensive rats [56]. This data suggests that the saponin found in A. spicata may have antihypertensive potential, however, clinical trials are required to verify its therapeutic potential.
2.2.2. Asystasia gangetica

The in vitro inhibition of ACE by Asystasia gangetica aqueous and methanolic leaf extracts were 20% and 51%, respectively [41]. Furthermore, an in-vivo study on the effects of the aqueous leaf extract of A. gangetica (200 mg/kg) on blood pressure and heart rate of spontaneously hypertensive rats [57] significantly reduces the systolic, diastolic, and mean arterial blood pressure [57]. This reduction in systolic, diastolic, and mean arterial blood pressure produced by co-infusion with angiotensin I can be attributed to A. gangetica inhibiting the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor [58].

2.2.3. Clausena anisata

Clausena anisata is a medicinal plant indigenous to Southern Africa [59]. The in vitro inhibition of ACE by C. anisata aqueous [40] and ethanolic leaf extracts were 54% and 1%, respectively [40]. An in-vivo study that administered bolus injections of the aqueous leaf extract of the plant (400 mg/kg/bw) to spontaneously hypertensive rats significantly reduced aortic blood pressure [59]. The report further demonstrated that the same amount of extract added daily to the drinking water of spontaneously hypertensive rats significantly decreases systolic, diastolic, and mean arterial blood pressure after 40 days of treatment [59]. The bioactive phytomolecules in the plant are carbozole alkaloids and coumarins [40,60], in which coumarins (Fig. 3) demonstrates antihypertensive properties [61]. C. anisata extracts were shown to significantly reduce the blood pressure of hypertensive rats, most likely by reducing the angiotensin II levels, which act via the ACE inhibitory mechanism [40]. This report delivers an essential basis for further studies into the isolation and characterization of active biomolecules that might be responsible for lowering blood pressure.

2.2.4. Dietes iridioides

Infusions of Dietes iridioides made from the inner part of its rhizomes are taken orally or in enemas, are utilized in childbirth and to treat hypertension [62]. The in vitro, antihypertensive impact of the leaf extracts of D. iridioides show 80% and 7% ACE inhibition using water and ethanol, respectively [40] in comparison to their roots which have low inhibition (13%) [40]. A study conducted on the cardiovascular effects of the leaf extract of D. iridioides (400 mg/kg/bw) in spontaneously hypertensive rats demonstrated significant decline of short- and long-term blood pressure (systolic, diastolic and mean arterial pressure parameters) within 20 min for 20 days, using bolus injections of the plant [63]. In addition, following the administration of the plant extract to the rats, an increase in plasma nitric oxide levels was noted indicating that the vasodilatory nitric oxide may be responsible for the decrease in aortic blood pressure [64]. Furthermore, a study that compared the blood pressure effects of D. iridioides with a combination of D. iridioides and perindopril (a known angiotensin-converting enzyme inhibitor) demonstrated a remarkable decrease in aortic blood pressure compared to both treatments alone [63].

2.2.5. Sclerocarya birrea

An in vitro study by Ojewole (2006) found that an aqueous extract of Sclerocarya birrea stem bark induced concentration-dependent relaxations of endothelium-intact rat isolated aortic rings precontracted with noradrenaline. Bolus intravenous administrations of the stem-bark extract (25–400 mg/kg) significantly decreases systemic arterial blood pressure and heart rate in anesthetized normotensive and hypertensive Dahl salt-sensitive rats [65]. Acute intravenous administration of S. birrea crude stem bark extract (120 mg/kg) to non-diabetic and streptozocin-
treated diabetic rats resulted in momentary vasodepressive effects, with maximal activity occurring within 60 min of the extract’s infusion. Long-term administration of the plant’s stem-bark extract (120 mg/kg for 5 weeks) resulted in a significant reduction in mean arterial blood pressure. Compared to the control group, blood pressure was lower over the course of the 5-week study [56]. Furthermore, in a study conducted by Masoko et al. (2008), dichloromethane, hexane and acetone S. birrea stem, bark and leaves displayed strong antioxidant activity [57]. Polyphenols such as galloylate catechins contributed significantly to the antioxidant activity of S. birrea [58].

2.2.6. Tulbaghia violacea

The ACE inhibitory potential of Tulbaghia violacea was demonstrated in vitro using aqueous (68%) and methanolic (71%) leaf extracts [40,41,69]. The aqueous extracts of the leaf and bark also exhibited an ACE inhibitory potential of 72% and 49%, respectively, whilst the ethanolic leaf extracts inhibited the activity of ACE by 61% [40]. Analyses of the methanolic leaf extract tested at varying concentrations accentuated the reduction in systolic, diastolic, and mean arterial pressure of normotensive and spontaneously hypertensive rats in a dose-dependent manner, underpinning its antihypertensive impact. The reduction in blood pressure may be stimulated by the plant’s actions on the ACE and β-adrenoceptors. Furthermore, T. violacea decreased systolic blood pressure in Dahl salt-sensitive rats by reducing renal angiotensin II type 1 receptor gene expression [69]. Antioxidant studies of the extracts reveal potent antioxidant activity with low IC50 values [53,70]. In addition, a two-week co-treatment with the T. violacea extracts significantly decreased elevated thiobarbituric reacting substance (TBARS) and

Table 2

| Plant Species (Family) | English Name/Traditional Name | Traditional uses | Location | Phytochemicals | References |
|------------------------|-------------------------------|-----------------|----------|----------------|------------|
| Adenopodia spicata     | Spiny splinter bean (Ubobo)   | Bark - chest or breast pain, syphilis, hypertension | Southern Africa | Flavonoids, Saponins | [40]       |
| Agapanthus africanus   | African lily (Ubani)          | Leaves and roots - chest pains, coughs, heart disease, ease labor | South Africa | Flavonoids, sitosterol, yuccagenin, agapanthagenin, spirrostan sapogenins | [40]       |
| Amaranthus dubius       | Wild spinach (Imbuya)         | Leaves - kidney problems, anemia, fever, hemorrhage, stomach problems, hypertension | Found worldwide | Flavonoids, Nicin, thiamine, riboflavin, ascorbic acid, hydroxyacetic acid, oxalic acid | [41,42]    |
| Asystasia gangetica    | Creeping foxglove (Ishobo)    | Leaves - asthma | Tropics | Flavonoids, Alkaloids, terpenes, phenols, salidroside, apigenin, ajugol, megastigmaenoglucoside, benzyl-β-o-glucopyranoside, cardiac glycosides, tannins | [41,43]    |
| Clausena anisata       | Horsewood (Umukumkhubha)      | Leaves and roots - heart disease, tapeworms, fever, liver disease | Africa | Not reported | [40,44]    |
| Dietes tridoides       | African iris (Ishishuphe somfula) | Leaves, roots, and rhizomes - dysentry, hypertension | Sub-Saharan Africa | Flavonoids | [40,45]    |
| Dombeya rotundifolia   | Wild pear (Nblizinyonkhulu)   | Leaves and roots - heart problems, ulcers, stomach problems, fever, nausea, diarrhea | Southern Africa and northwards to central and eastern tropical Africa | Saponins, tannins and cardiac glycosides | [40,46]    |
| Proteorhiza longifolia | Red beech (Uzintwiva)         | Bark and leaves - HBP, heartburn, internal bleeding, diarrhea, dysentry | South Africa, Swaziland | Flavonoids, glycosides and steroids | [40,47]    |
| Rhus chirdinensis      | Red currant (Umhlabamvudu)    | All plant parts - measles, cough, chest pain, syphilis, convulsions, epilepsy, HBP | KwaZulu/Natal, Swaziland, Zimbabwe, and Mozambique | Flavonoids | [40,48]    |
| Scleroxarya birrea     | Marula (Ukanyi)               | Bark, leaves, and stems - dysentry, diarrhea, rheumatism, malaria, hemorrhoids. | North-eastern South Africa and parts of eastern Botswana. | Polyphenols, tannins, flavonoids, alkaloids, anthocyanins, and saponosides coumarins, triterpenoids, and phytoesterols (β-sitosterol) Quercetin, kaempferol, gallic acid, (−)-epicatechin 3-O-gallol ester, (−)-epigallocatechin 3-O-gallol ester | [40,49]    |
| Stangeria eriopus      | Natal Grass Cycad (Umfigwani) | Root and leaves - headaches, internal parasites, HTN. | East coast of South Africa and southern Mozambique | Alkaloids, amino acids, biflavones, fatty acids, glycosides, polyphenols, saponins, and tannins | [40,50]    |
| Tulbaghia violacea     | Garlic (isihaqa)              | Rhizome, bulb, leaves and roots- sinus conditions, headaches, cough, colds, asthma, tuberculosis, intestinal worms and hypertension | Eastern Cape, Limpopo and KwaZulu-Natal | Bioflavonoids, saponoids | [51–53]    |
reversed endothelial dysfunction and tissue antioxidant enzyme activity to near normal concentration [71]. The activity of serum markers of liver and kidney damage in extract-treated groups were significantly reduced, confirming this protective effect [71]. Treatment with the extract also decreased liver TBARS levels, improved liver superoxide dismutase, catalase, and glutathione peroxidase, and increased plasma nitric oxide concentrations in rats, supporting the antioxidant and hepatoprotective effects [72]. Additionally, the in vitro antioxidant activities of the plant extract validates its use in preventing oxidative stress and, thereby, concomitant disorders such as hypertension [53].

2.3. Concerns regarding traditional medicines

The widespread accessibility and use of herbal medicines, potential herbal toxicity and herb–drug interactions are major global concerns; particularly the lack of scientific evidence with regards to efficacy and/or safety is worrying. Medicinal plants comprise a

Table 3
Toxicity studies of some South African medicinal plants.

| Plant                     | Acute/sub-chronic toxicity | Model of experimentation                                                                 | Parts of plant/solvent used         | Result                                                                                                                                                                                                 | References |
|---------------------------|----------------------------|--------------------------------------------------------------------------------------------|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| **Asystasia gangetica**   | Acute toxicity             | A single dose of 1000, 2000 and 5000 mg/kg of the extract were administered orally to male and female Wistar rats | Whole plant/methanolic extract       | No mortality reported nor was there any sign of toxicity after 24 h and for 14 days thereafter.                                                                                                          | [74]       |
| **Clausena anisata**      | Acute toxicity             | A single dose of between 500 and 5000 mg/kg body weight was administered orally to male Swiss mice | Leaves/hexane extract                | No mortality observed within 48 h. Physical signs observed (Decreased motor activity, respiration and feeding, closure of eyes)                                                                         | [75]       |
|                           |                            |                                                                                             | Leaves/Chloroform extract            | Doses of 5000 and 2811 mg/kg produced 60% and 40% mortality, respectively, within 48 h. Oral LD₅₀ of the extract was calculated to be 4166.7 mg/kg.                                               | [75]       |
| **Sclerocarya birrea**    | Acute toxicity             | A single dose of 3000 mg/kg body weight was administered to male and female albino rats.     | Kernel/aqueous extract               | No sign of toxicity or mortality observed within 48 h.                                                                                                                                                  | [76]       |
|                           | Sub-chronic toxicity      | Animals were orally administered with doses of 1000, 2000, 3000 and 4000 mg/kg body weight of the extract once daily for 28 days. |                                                        | Doses of 3000 and 4000 mg/kg/day revealed liver and kidney abnormalities                                                                                                                               | [76]       |
| **Tulbaghia violacea**    | Acute toxicity             | A single dose of 5/kg body weight was administered orally to male and female Wistar rats    | Rhizomes/methanolic extract          | No mortality observed and no indication of toxicity, behavioural or physiological changes.                                                                                                          | [77]       |
|                           | Sub-chronic toxicity      | Animals were orally administered with doses of 125, 250 and 500 mg/kg daily for 28 days      |                                                        | No mortality observed and no signs of toxicity reported                                                                                                                                             | [77]       |

Fig. 3. Distribution of reported secondary metabolites in the plants displaying ACE inhibitory potential.
complex mixture of approximately 400 or more chemicals in comparison to synthetic drugs which are typically made up of a single chemical [73]. It is relatively simple to determine the activity and side effects of a single chemical, however, it is increasingly difficult to record the composite interactions and synergies occurring amongst the several chemicals found in a plant, or crude plant extract that is traditionally used. Toxicological issues linked with the use of traditional medicines are associated with serious adverse events including cardiovascular issues, liver toxicity or malfunction, hematologic, renal toxicity, and fatality (Table 3). The low frequency of adverse reports associated with traditional medicine in developing countries could be because consumers commonly esteem them as safe and thus assume their symptoms are unrelated to their use.

Therefore, it is imperative that more evidence-based studies demonstrating the efficacy of traditional medicine is conducted. Furthermore, medicinal plants should be phytochemically characterized to identify their bioactive compounds since other compounds present in crude extracts may cause unfavorable side effects. Albeit the phytochemical analysis should be complemented by studies on the mechanism of action and the toxicological profile of the medicinal plants. Additionally, there is a paucity of data on the toxicity of medicinal plants in SA during pregnancy. This warrants further toxicological studies that profile the potential use of medicinal plants and pre-clinical toxicological research during pregnancy. Since PE requires close monitoring and management across the gestational period, there is a need for chronic toxicity studies.

3. Conclusion and future perspective

Phytotherapy continues to create broader awareness and publicity due to its therapeutic properties and negligible side effects. We provide a summary of the effects of South African medicinal plants in the ACE1 RAS pathway, as a potential treatment of HDP. However, a better understanding of the efficacy of these medicinal plants is required for further clinical trials and translation for ACE1 inhibitors' safety in pregnancy. We recommend more evidence-based research in this field.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization: RR, SB, RM and NG; methodology and study design, SB, RM, NG; all authors contributed to the formal analysis and investigation; original draft preparation, RR; Review and editing, SB, RM, JM, TN, and NG. All authors have read and agreed to the final version of the manuscript.

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