







Medicinal plants with potential antihypertensive properties: emphasis on natural products from the Brazilian Cerrado¹

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ABSTRACT – (Medicinal plants with potential antihypertensive properties: emphasis on natural products from the Brazilian Cerrado). Arterial hypertension is a worldwide public health problem and the search for new medicines is one of the biggest challenges for the treatment of this pathology. Secondary metabolites of plants exhibit pharmacological properties of great phytotherapeutic interest. Cerrado is one of the largest biomes in Brazil and research with Cerrado plants as therapeutic resources is of growing interest. Our objective was to compile data regarding the Cerrado plants that already have some of their active compounds described and may potentially be used to treat arterial hypertension. We concluded that flavonoids, tannins, steroids and saponins exhibit important properties to low blood pressure. Thus, the species from Cerrado Brazilian such as pau-paraíba (*Simarouba versicolor*), pau-santo (*Kielmeyera coriacea*), abiu-do-cerrado (*Pouteria torta*), guarandi (*Calophyllum brasiliense*), bacaba (*Oenocarpus bacaba*), puçá-amarelo (*Mouriri elliptica*), fava-de-anta (*Dimorphandramollis*), murici (*Byrsonima crassifolia*) and cereja-do-cerrado (*Eugenia calycina*) are strong candidates for future herbal studies in this field.

Keywords: antihypertensive plants, Brazilian Savanna, hypertension, plant secondary metabolites, phytotherapy

RESUMO – (Plantas medicinais com potenciais propriedades anti-hipertensivas: ênfase em produtos naturais do Cerrado Brasileiro). A hipertensão arterial é um problema de saúde pública mundial e a busca por novos medicamentos é um dos maiores desafios para o tratamento dessa patologia. Os metabólitos secundários das plantas apresentam propriedades farmacológicas de grande interesse fitoterápico. O Cerrado é um dos maiores biomas do Brasil e cresce o interesse em pesquisas com plantas desta região como recurso terapêutico. Nosso objetivo foi compilar dados sobre as plantas do Cerrado que já possuem alguns de seus compostos ativos descritos e que podem ser potencialmente utilizadas no tratamento da hipertensão arterial. Concluímos que flavonóides, taninos, esteróides e saponinas apresentam propriedades importantes para a redução da pressão arterial. Assim, as espécies do Cerrado brasileiro, pau-paraíba (*Simarouba versicolor*), pau-santo (*Kielmeyera coriacea*), abiu-do-cerrado (*Pouteria torta*), guarandi (*Calophyllum brasiliense*), bacaba (*Oenocarpus bacaba*), puçá-amarelo (*Mouriri elíptica*), fava-de-anta (*Dimorphandramollis*), murici (*Byrsonima crassifolia*) e cereja-do-cerrado (*Eugenia calycina*) são fortes candidatas para futuros estudos fitoterápicos.

Palavras-chave: fitoterapia, hipertensão, metabólitos secundários de plantas, plantas anti-hipertensivas, savana brasileira

Introduction

Systemic arterial hypertension (SAH) is characterized by the sustained maintenance of blood pressure (BP) above 130 and 139 mmHg for systolic and/or 80 mmHg for diastolic blood pressure. The causes of SAH range from genetic, metabolic, behavioral factors and may even be caused by pathophysiological changes in other organs (Précoma *et al.* 2019).

Given the different factors involved in the triggering of SAH, it is expected that several signaling pathways are involved in the regulation of BP and that dysregulation in those pathways are associated to SAH. Among the pathways involved in BP control, nitric oxide (NO), angiotensin II and

the production of reactive oxygen species (ROS) occupy prominent place (Förstermann *et al.* 2017).

The ideal treatment for SAH depends on the causes of the disease and on the patient's response (Malachias *et al.* 2016). Currently, drug resistant SAH has been a concern, as it has become more and more frequent. Also, the available drugs or their combination may not be effective for the treatment and many patients may present a silent evolution of symptoms, which may cause other cardiovascular diseases and culminate in death (Pijacka *et al.* 2016, Pike *et al.* 2017).

In this way, there is a growing interest in developing research focused at identifying new approaches for SAH treatment. The use of herbal medicines has increased in recent years which leveraged the research on the identification and characterization of bioactive molecules (Lorenzi & Matos

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2003, Barbosa *et al.* 2012). Plants from the Brazilian Cerrado are recognized by the population for their wide application in home medicine and research has shown that some of these species present compounds that can provide BP by distinct mechanisms (Pereira & Cardoso 2012, Silva *et al.* 2010). Therefore, the present Review aimed to compile results from different studies that point out to the anti-hypertensive and regulatory potential of some Brazilian Cerrado plants.

Material and Methods

This study is a systematic review of the literature. Searches were performed in the following databases: PubMed, *Periódicos CAPES* and Google Scholar. Articles published in the last 20 years (from 2000 to 2020) were selected, except for prestigious works in the area, which were used regardless of the publication date. Works published in English, Portuguese or Spanish were considered.

References were searched for the terms in association “Systemic Arterial Hypertension”, “Brazilian Cerrado”, “Medicinal plants” and “Antihypertensive action” without the use of controlled vocabulary (descriptors). With this strategy, there was a recovery of a greater number of references, ensuring the detection of most of the works published within the pre-established criteria.

Review and original articles with experimental design (clinical trials, randomized or not) and observational studies, which studied the use of Cerrado plants to reduce blood pressure or treat hypertension *in vitro* and/ or *in vivo* were considered. Duplicate references (present in more than one database), outside the topic of interest and those that did not meet the criteria defined above were excluded.

The total number of articles found in the three databases with the combinations of terms was 2044: 68 in the PubMed platform, 26 in CAPES Journals and 1950 inside Google Scholar. Of this total, 1943 were excluded for not meeting the criteria previously defined. Finally, 101 eligible references containing the most cited Cerrado species exhibiting some antihypertensive properties were selected to compose the present Review with the additional descriptions presented.

Results

Systemic Arterial Hypertension - According to a survey by the World Health Organization (WHO) cited by the Brazilian Society of Cardiology (Précoma *et al.* 2019), systemic arterial hypertension (SAH) is responsible for 7.5 million premature and preventable deaths worldwide, being the main risk factor for several complications related to the development of cardiovascular diseases, such as stroke, acute myocardial infarction, heart failure, peripheral arterial disease and chronic kidney disease (Malachias *et al.* 2016). About 30% of the general Brazilian population is affected by SAH, generating a strong impact on the deaths caused by its complications and a challenge for public health (Précoma *et al.* 2019).

SAH is related to different factors like advanced age (Li *et al.* 2018, Mendes *et al.* 2014); genetic predisposition (Whelton *et al.* 2017); functional and/ or structural changes in target organs such as kidneys, arteries, heart, and brain (Cesar *et al.* 2014); changes in metabolism, overweight, poor diet and physical inactivity and drugs and pharmaceuticals (Bloch *et al.* 2016, Malachias *et al.* 2016). In physiological terms, SAH is the result of homeostatic

loss between two determining factors: the volume of blood pumped by the heart in one minute (cardiac output) and the resistance of blood vessels, especially arterioles, to blood flow (systemic or peripheral vascular resistance) (Krieger *et al.* 1996), resulting in the loss of the ability of the endothelium to normally vasodilate (Cohen 2007). Such pathology is continuously influenced by complex pressure systems (as the sympathetic nervous system, catecholamines, angiotensin, endothelin, etc.) and depressants (as nitric oxide (NO), bradykinin, etc.) (Krieger *et al.* 1996).

The initial stage (stage 1) of SAH is characterized by the sustained elevation of systemic blood pressure, with values between 130 and 139 mmHg for systolic blood pressure and/ or 80 mmHg for diastolic blood pressure. At a more advanced stage (stage 2), these values can exceed 140 mmHg for systolic pressure and 90 mmHg for diastolic pressure (Whelton *et al.* 2017). The individual affected by primary SAH (also called essential hypertension), that is, unrelated to other pathologies, is usually asymptomatic; however, some patients may experience suboccipital headache, drowsiness, visual disturbance, nausea, tinnitus, and fatigue. In turn, the person affected by secondary SAH, which is related to other pathologies, can present a diversity of symptoms associated with the initial pathology (Oigman 2014).

The major concern related to hypertension is the fact that it evolves silently, and most of the affected people are only diagnosed after crises and hypertensive emergencies (Freitas Filho *et al.* 2017). Then, early diagnosis is essential to prevent possible complications. The measurement of blood pressure (BP) levels is done at the doctor's office in all consultations, using manual, semi-automatic or automatic sphygmomanometers. Outside the office, BP can be measured using residential BP measurement (RBPM) and/ or 24-hour ambulatory BP measurement (ABPM), with ABPM allowing BP measurement in moments of sleep and wakefulness (Malachias *et al.* 2016).

Blood pressure assessments are used to classify the BP condition in normotensive - BP levels within those considered normal; prehypertension - BP values close to the recommended upper limit; stage 1 hypertension and stage 2 hypertension - BP levels above normal. After diagnosis, the best form of treatment is defined, which can be non-medicated and/ or medicated (Malachias *et al.* 2016, Whelton *et al.* 2017).

Signaling pathways activated during arterial hypertension - The SAH manifests itself in response to the activation of some cell signaling pathways, which involve endothelial dysfunction, vascular remodeling, and immune infiltration, with a consequent increase in the production of reactive oxygen species (ROS) (Roy *et al.* 2018). Thus, some signaling pathways are more frequently activated or inhibited in this pathology, such as the NO pathway, angiotensin II and the production of ROS (Förstermann *et al.* 2017).

The endothelium plays an important role in the vasculature, being responsible for the synthesis of vasomotor molecules such as NO (Carvalho *et al.* 2001), which plays an important vasodilating action (Piotrkowski *et al.* 2015) by inhibiting the entry of calcium ions (Ca⁺) inside the cell (Moneer *et al.* 2003). Because of endothelial dysfunction in hypertension there is an imbalance in the production and release of vasomotor molecules, including a decrease in the release of NO, an increase in ROS and the consequent increase in vascular tone (Carvalho *et al.* 2001).

Angiotensin II presents different actions that influence blood pressure levels. On one hand, it has a direct vasoconstrictor action,

acting via AT1 receptors present in vascular smooth muscle; on the other hand, it activates the secretion of aldosterone, an antidiuretic hormone, which reduces the excretion of water and salts, increasing vascular tone (Lima *et al.* 2007). In 1996, the hypertensive action of angiotensin II was characterized by activating the production of superoxide via membrane NADH/NADPH, causing oxidative stress (Rajagopalan *et al.* 1996). In addition, in 2001 it was discovered that this molecule also stimulates collagen secretion through the activation of type 1 receptors. Therefore, activation of the angiotensin II pathway is one of the characteristics of SAH (Lijnen *et al.* 2001, Li *et al.* 2016).

The production of ROS in moderate concentrations has an important signaling role, helping to maintain homeostasis in physiological conditions. The excessive and sustained production of these molecules, however, concomitant with the low availability of antioxidant agents, leads to oxidative stress (Förstermann *et al.* 2017). Oxidative stress is characterized by the high reactivity of ROS that cause the degradation of cellular components and initiate degradative processes (Bonomini *et al.* 2015). In the cardiovascular system, NADPH oxidases and mitochondrial oxidases produce ROS; and, evidence shows that, during hypertension, this production is increased, contributing to the symptoms of the disease (Harrison & Gongora 2009, Sinha & Kumar Dabla 2015).

As a result of the participation of these signaling pathways in the development of SAH, the antihypertensive effects of many drugs and medicinal plants are observed from their regulation.

Antihypertensive therapies available - The choice of the therapeutic approach for SAH depends on the stage of hypertension and the cardiovascular risks associated with it and can include everything from non-medication until the use of antihypertensive drugs. The treatment aims to reduce BP to levels close to normal, to protect target organs from injuries and/ or changes caused by high BP and to prevent outcomes of cardiovascular and renal damage (Malachias *et al.* 2016).

Non-drug approaches can be effective in preventing SAH and reducing BP, but they are limited to patient compliance in the medium and long term. In addition, these interventions may assist in the effectiveness of drug treatment (Malachias *et al.* 2016, Whelton *et al.* 2017). Non-drug approaches mainly involve changes in eating habits and adherence to physical activity (Kohlmann Júnior *et al.* 1999). Thus, non-drug treatments include weight loss for overweight or obese people, adherence to a healthy diet such as DASH (Dietary Approaches to Stop Hypertension), reduced sodium intake, potassium supplementation, adherence to physical activities (of 90 to 150 minutes per week), moderation in the consumption of alcoholic beverages and smoking and stress control (Malachias *et al.* 2016, Freitas Filho *et al.* 2017, Whelton *et al.* 2017).

Drug treatment, in turn, aims to reduce BP levels more efficiently and prevent/ treat cardiovascular risks. Among the main classes of current antihypertensive drugs used are angiotensin-converting enzyme (ACE) inhibitors, angiotensin AT1 receptor blockers, diuretics, calcium channel blockers, beta-blockers, alpha-blockers, centrally acting sympatholytics, direct vasodilators and antagonists' mineralocorticoids (Cesar *et al.* 2014).

In general, ACE inhibitors work by blocking the formation of angiotensin II, increasing the availability, and reducing the degradation of vasodilators. AT1 receptor blockers also inhibit the vasoconstrictor effect activated by the renin-angiotensin system. Diuretics, in turn, act on the nephrons, increasing the excretion

of sodium and reducing its concentration in the circulation and, consequently, the levels of blood pressure (Cesar *et al.* 2014).

Calcium channel blockers act by reducing the entry of calcium into smooth muscle cells in arterioles, thus decreasing the contraction of these cells and peripheral vascular resistance. Beta-blockers act by blocking the action of catecholamines on β receptors, causing vasodilation and reducing cardiac output. Alpha-blockers act as competitive antagonists of α receptors, blocking the action of catecholamines and reducing peripheral vascular resistance (Malachias *et al.* 2016).

The centrally acting sympatholytics act directly on the central nervous system (CNS), reducing sympathetic influx and is reserved as one of the last drugs of choice for having a direct action on the CNS (Cesar *et al.* 2014, Whelton *et al.* 2017). Besides, direct vasodilators cause vasodilation, but are not used as monotherapy, they are generally associated with the administration of diuretics because they lead to sodium and water retention (Whelton *et al.* 2017). Finally, mineralocorticoid antagonists have a discrete diuretic action and are efficient in the treatment of SAH in patients with heart failure (Cesar *et al.* 2014).

Despite the existence of this range of classes of antihypertensive drugs, many of them cause side effects in some patients, which limits their use. In addition, currently, between 2% and 16% of hypertensive individuals have resistant SAH and do not respond satisfactorily to available treatments (Pike *et al.* 2017). Together, these conditions led to the use of a combination of antihypertensive drugs, which, in many cases, is not efficient. In view of this high incidence of SAH resistant to antihypertensive medication and/ or that with low adherence or tolerance to this medication, it is necessary to identify new targets and develop new drugs to ensure a better treatment of this condition (Pijacka *et al.* 2016).

Natural resources - The use of natural resources like leaves, flowers, peels and roots of plants for therapeutic purposes dates back thousands of years (Deviene *et al.* 2004). The biological activity of some plants is described in the literature as classic phytotherapies. This is the case with morphine, derived from opium extracted from the poppy (*Papaver somniferum*), isolated in the early 19th century, used to control pain; caffeine, isolated in 1820 from *Coffea arabica* (Dutra *et al.* 2016), used as a stimulant; the quinine used to treat malaria and cardiac arrhythmias, isolated from species of *Cinchona sp.*, native from the Andes, in 1819, among others (Schulz *et al.* 2001).

According to the WHO, "any and all plants that contain substances that can be used as therapeutic purposes or are precursors of semi-synthetic drugs in one or more organs" are called "Medicinal plants" (Geneva, 1998). Such isolated substances consist of active principles generated through the plant's natural biochemical metabolism, originating from simple and complex reactions responsible for the growth, development, and reproduction of the plant (Schaaf *et al.* 1995).

The primary metabolism of plants occurs through the synthesis of essential compounds for the performance of vital functions, such as the photosynthetic processes that originate the formation of fatty acids, glycolysis, the citric acid cycle, the synthesis of proteins, nucleic acids, enzymes and coenzymes, structural and genetic materials (Schaaf *et al.* 1995).

Secondary metabolism consists of a set of reactions apparently not essential for the survival of the species. They are characterized by a complex structure, low molecular weight, remarkable biological activities and are found in low concentrations in only certain groups of plants (Di Stasi 1995). The secondary metabolites generated are important for the

adaptation, defense, and protection of the plant to various oscillating external environmental factors, such as seasonality, circadian rhythm, rainfall, UV radiation, atmospheric composition, altitude, temperature, micro and macro nutrients (Gobbo-Neto *et al.* 2007). Therefore, the accumulation and bioavailability of secondary metabolites varies according to specific needs faced by the plant (Savithamma *et al.* 2011).

Secondary metabolites with potential pharmacological activity are classified into alkaloids, terpenes, and phenolic compounds (Savithamma *et al.* 2011) and have great phytotherapy, nutraceutical and industrial value, since the producer can adapt the external conditions to obtain the metabolite of interest (Briskin 2000).

Medicinal plants with recognized antihypertensive action - Several medicinal plants are elucidated with pharmacological action in the treatment of cardiovascular disorders, including SAH. *Panax ginseng* and *Allium sativum*, for example, are described with potent vasodilating action by different systems (blocking calcium channels, NO releasing), due to the presence of hypotensive molecules such as ginsenosides, saponins and sulfur compounds (Lorenzi & Matos 2003, Barbosa *et al.* 2012).

Schulz *et al.* (2001) and Simões *et al.* (2007) reported plants such as *Achillea millefolium* rich in artemetin, *Rosmarinus officinalis* with resveratrol, hydroxybenzoic acid, coumaric acid and phenolic compounds, and *Cecropia pachystachya* with flavones, in the antihypertensive action due to ACE inhibition.

Flavonoids, polyphenols and other compounds have also been reported in several plants such as *Equisetum arvense*, *Viscum album*, *Cymbopogon citratus*, *Anethum graveolens*, *Scutiabuxifolia*, *Cuphea carthagenensis*, *Sechium edule*, *Echinodorus macrophyllus* and *Melissa officinalis*, presenting important vasodilating properties application in the treatment of hypertensive cases (Mahran *et al.* 1991, Martins *et al.* 2000, Bevilaqua *et al.* 2001, Di Stasi *et al.* 2002, Moraes 2004, Simões *et al.* 2007, Whelton *et al.* 2007, Conceição 2011).

It is known that Brazil is one of the countries with the greatest biodiversity in the world, and for this reason, it is characterized as an important and potent storehouse of natural resources, with about 30% of the known plant species in the world, distributed in their different ecosystems (Myers *et al.* 2000). Therefore, the Brazilian flora represents a potential source of phytotherapeutic agents and molecules for the development of new medicines (Gurib-Fakim 2006).

Brazilian Cerrado - The Cerrado biome is in the Central region of Brazil and covers an area of approximately 2 million km². This biome covers the provinces of Goiás, part of Minas Gerais, Bahia and the Federal District, Tocantins, Mato Grosso, and Mato Grosso do Sul (Oliveira *et al.* 2008), occupying around 21% of the national territory and being considered the second largest biodiversity in South America (Instituto Cerrado e Sociedade 2011). In addition, its vast extent makes it the second largest biome in Brazil, behind only the Amazon (Klink *et al.* 2005).

The Cerrado is characterized by a high diversity of plant and animal species and a high variety of environments (Machado *et al.* 2014). It has more than 10,000 species of plants, of which around 4000 of these are endemic (Scolforo & Ferraz Filho 2013), making the Brazilian Cerrado a global hotspot, serving as the target of many research and public policies for its conservation and enhancement (Oliveira *et al.* 2008).

The seasonal tropical climate with dry winters and rainy summers, soils with high acidity, deficient in nutrients and

rich in aluminum, and supplied by six of the eight largest hydrographic basins in Brazil (Marouelli 2003) favor the existence of such biodiversity in this region. Facing all these environmental conditions, plant species need to develop physical and physiological mechanisms to ensure their survival, the latter being the focus of this review. Secondary metabolites are physiological mechanisms of plant adaptation and are complex in structure, not linked to obtaining nutrients and energy for the cell, but rather adapting to the environment in which it is located. In this way, they are identified in variable quantities, depending on the conditions in which the plant is (Pereira & Cardoso 2012).

A study aimed at carrying out phytochemical tests on plant species in a protected area located in the Brazilian Cerrado identified that the secondary metabolites most present in these species were tannins, alkaloids, flavonoids, and terpenes (Silva *et al.* 2010). These compounds already have their action recognized as antioxidants and cardiovascular protectors (Pereira & Cardoso 2012).

Studies focused on the potential of Cerrado plants in the identification of medicinal compounds, however, are still scarce and closely related to their popular use. Over the years, a change has been sought in this scenario, with an increase in the number of studies, and with phytochemical tests of different species already available in the literature. Based on this, it is recognized that the Cerrado plants have great potential for the treatment of several diseases, including SAH (Borges 2002).

Cerrado plants with potential antihypertensive action - There are reports of the antihypertensive action of some plants in the Cerrado, which point to secondary metabolites and their mechanism of action for the observed effect. Thus, it is known that *mangabeira* (*Hancornia speciosa*) has a hypotensive effect by inhibiting ACE, increasing NO levels and exhibit antioxidant action (Silva *et al.* 2011); *gabirola* (*Campomanesia xanthocarpa*) exhibits dose-dependent hypotensive action by blocking AT1 receptors and acting on the autonomic nervous system (Sant'anna *et al.* 2017); and *sangue-de-Cristo* (*Sabicea brasiliensis*) has anti-inflammatory and antioxidant actions (Batista *et al.* 2014).

However, there are many other species of the Cerrado with secondary metabolites like those already studied and that have not yet been researched regarding their ability to lower blood pressure levels. These species are less known by the population and by the researchers, however they deserve attention since they present antioxidant metabolites with anti-inflammatory and hypotensive potential. After reviewing these less known species from Brazilian Cerrado and considering the concentration of secondary metabolites with potential anti-hypertensive action present in such plants, we have identified *Pau-paraíba* (*Simarouba versicolor*), *Pau-santo* (*Kielmeyera coriacea*), *Abiu do cerrado* (*Pouteria torta*), *Guarani* (*Calophyllum brasiliense*), *Bacaba* (*Oenocarpus bacaba*), *Puçá-amarelo* (*Mouriri elliptica*), *Fava-de-anta* (*Dimorphandramollis*), *Murici* (*Byrsonima crassifolia*) and *Cereja-do-cerrado* (*Eugenia calycina*) as promising for future studies of isolation of active ingredients to be applied as alternative approaches to the treatment of SAH. The results regarding the analysis of all these plant species, considering the secondary metabolites present, their described biological activities and their potential hypotensive activity are summarized in table 1.

Table 1. Brazilian Cerrado species with potential antihypertensive action: main metabolites, recognized medicinal action and secondary metabolites with potential hypotensive action.

Plant species	Secondary metabolites described	Recognized medicinal action	Secondary metabolites with known or potential hypotensive action
Pau-paraíba (<i>Simarouba versicolor</i>)	Quassinoids, triterpenoids, mixture of steroids, a derivative of squalene and the flavonoid canferol (Arriaga <i>et al.</i> 2002)	Antifungal action of its extract (Simote <i>et al.</i> 2006), antitumor action (Ghosh <i>et al.</i> 1977; Carvalho 2008), acetylcholinesterase enzyme (Carvalho 2008), antioxidant, antiviral, amebicidal and anti-fertility action male (Almeida <i>et al.</i> 2007)	Flavonoids to antioxidant and anti-inflammatory action (Almeida <i>et al.</i> 2007)
Pau-santo (<i>Kielmeyera coriacea</i>)	Hydrocarbons sesquiterpenes and oxygenated sesquiterpenes (Martins <i>et al.</i> 2015), xanthones, biphenyl and triterpenes, (Cortez <i>et al.</i> 1998)	Antimicrobial activity and low cytotoxicity (Martins <i>et al.</i> 2015), antifungal activity (Cortez <i>et al.</i> 1998), anti-inflammatory (Toledo <i>et al.</i> 2011), alpha-amylase inhibitor (Silva 2008)	Xanthones for the regulation of vascular tone (Peres & Nagem 1997)
Abiu-do-cerrado (<i>Pouteria torta</i>)	Lupeol acetate (Perfeito <i>et al.</i> 2005), triterpenes (Che <i>et al.</i> 1980) and flavonoids (Costa <i>et al.</i> 2014)	Mutagenic activity (Costa <i>et al.</i> 2014), insecticide and antifungal (Boleti <i>et al.</i> 2007) and alpha-amylase inhibitor with the potential to control type 2 diabetes (Sales <i>et al.</i> 2017)	Triterpenes and flavonoids to antioxidant and anti-inflammatory action (Sales <i>et al.</i> 2017)
Guarandi (<i>Calophyllum brasiliense</i>)	Hyperine (hyperoside), amentoflavone, quercetin, gallic acid and protocatechuic acid (Silva <i>et al.</i> 2001), coumarins and xanthones (Ito <i>et al.</i> 2003)	Analgesic action (Silva <i>et al.</i> 2001), cancer chemopreventive activity (Ito <i>et al.</i> 2003), antiproliferative and antitumor (Ruiz-Marcial <i>et al.</i> 2007), antioxidant (Blanco-Ayala <i>et al.</i> 2013; Gonçalves <i>et al.</i> 2013) and HIV-1 reverse transcriptase inhibitor (Huerta-Reyes <i>et al.</i> 2004; César <i>et al.</i> 2011)	Xanthones and other polyphenols as ACE inhibitors (Braga <i>et al.</i> 2007).
Bacaba (<i>Oenocarpus bacaba</i>)	Polyunsaturated fatty acids (Pinto <i>et al.</i> 2018), phenolic compounds (Finco <i>et al.</i> 2012), hydroxycinnamic acids and flavonoids (Leba <i>et al.</i> 2016)	Antioxidant action (Mafra, 2019), rich in omega-3,6 and 9 and cardioprotective potential (Pinto <i>et al.</i> 2018)	Polyunsaturated fatty acids and flavonoids to the antioxidant and cardioprotective potential (Pinto <i>et al.</i> 2018) Terpenes and flavonoids to the antioxidant potential and increases the production of endogenous NO (Andréo 2008)
Puçá-amarelo (<i>Mouriri elliptica</i>)	Terpenes, flavonoids and tannins (Andréo 2008)	Gastroprotective, antiulcerogenic and anti- <i>Helicobacter pylori</i> activity (Moleiro <i>et al.</i> 2009), inhibition of alpha-amylases and acetylcholinesterase (Silva <i>et al.</i> 2020)	Flavonoid with antioxidant potential (Petacci <i>et al.</i> 2010)
Fava-de-anta (<i>Dimorphandra mollis</i>)	Flavonoids (Petacci <i>et al.</i> 2010), neoisoastilbine, catechin, astilbine and tannins (Cintra <i>et al.</i> 2005)	Insecticidal activity (Cintra <i>et al.</i> 2002; Cintra <i>et al.</i> 2005; Tavares <i>et al.</i> 2014), peroxidase inhibiting and ROS eliminating activity (Petacci <i>et al.</i> 2010)	Triterpenes and flavonoids to antioxidant, anti-inflammatory and anti-platelet aggregation (Villar <i>et al.</i> 1997; Moreno León 2015)
Murici (<i>Byrsonima crassifolia</i>)	Triterpenes, steroids and flavonoids (Bejar <i>et al.</i> 1995)	Spasmogenic activity (Bejar <i>et al.</i> 1995), anti-inflammatory (Maldini <i>et al.</i> 2009), antidepressant (Herrera-Ruiz <i>et al.</i> 2011), anti-platelet aggregation action (Villar <i>et al.</i> 1997) and antioxidant (Moreno León 2015)	Flavonoids and terpenes to antioxidant action (Ferreira <i>et al.</i> 2014)
Cereja-do-cerrado (<i>Eugenia calycina</i>)	Flavonoids, fatty acids, terpenes, steroids and tannins (Ferreira <i>et al.</i> 2014)	Action as antibiotic and antifungal (Ferreira <i>et al.</i> 2014; Sousa <i>et al.</i> 2015; Souza <i>et al.</i> 2018)	Terpenes and flavonoids to the antioxidant potential and increases the production of endogenous NO (Andréo 2008)
Puçá-amarelo (<i>Mouriri elliptica</i>)	Terpenes, flavonoids and tannins (Andréo 2008)	Gastroprotective, antiulcerogenic and anti- <i>Helicobacter pylori</i> activity (Moleiro <i>et al.</i> 2009), inhibition of alpha-amylases and acetylcholinesterase (Silva <i>et al.</i> 2020)	

Discussion

The Brazilian Cerrado has an extensive number of plant species with potential pharmacological properties. The active compounds from the metabolism of plant species are an alternative for the treatment of several diseases, including arterial hypertension, since the presence of secondary metabolites, such as steroids, flavonoids, catechins, isoflavones, saponins, stilbenes and tannins, they can act as antioxidants, anti-inflammatories, enzyme inhibitors, channel blockers, among others. Cerrado plant species such as pau-paraíba (*Simarouba versicolor*), pau-santo (*Kielmeyera coriacea*), abiu-do-cerrado (*Pouteria torta*), guarandi (*Calophyllum brasiliense*), bacaba (*Oenocarpus bacaba*), puçá-amarelo (*Mouriri elliptica*), fava-de-anta

(*Dimorphandra mollis*), murici (*Byrsonima crassifolia*) and cereja-do-cerrado (*Eugenia calycina*), have many bioactive compounds that have already been studied in relation to their properties for controlling blood pressure. Figure 1 summarizes the idea of the present review, which is to point out new species from the Brazilian Cerrado that are little explored and with potential application in the development of new medicines for the treatment of systemic arterial hypertension. Therefore, future research to elucidate the mechanisms involved in a possible antihypertensive action of Cerrado plants is of fundamental importance, given the relevance of the pathology in the context of cardiovascular diseases, especially for individuals resistant to the currently available treatments.

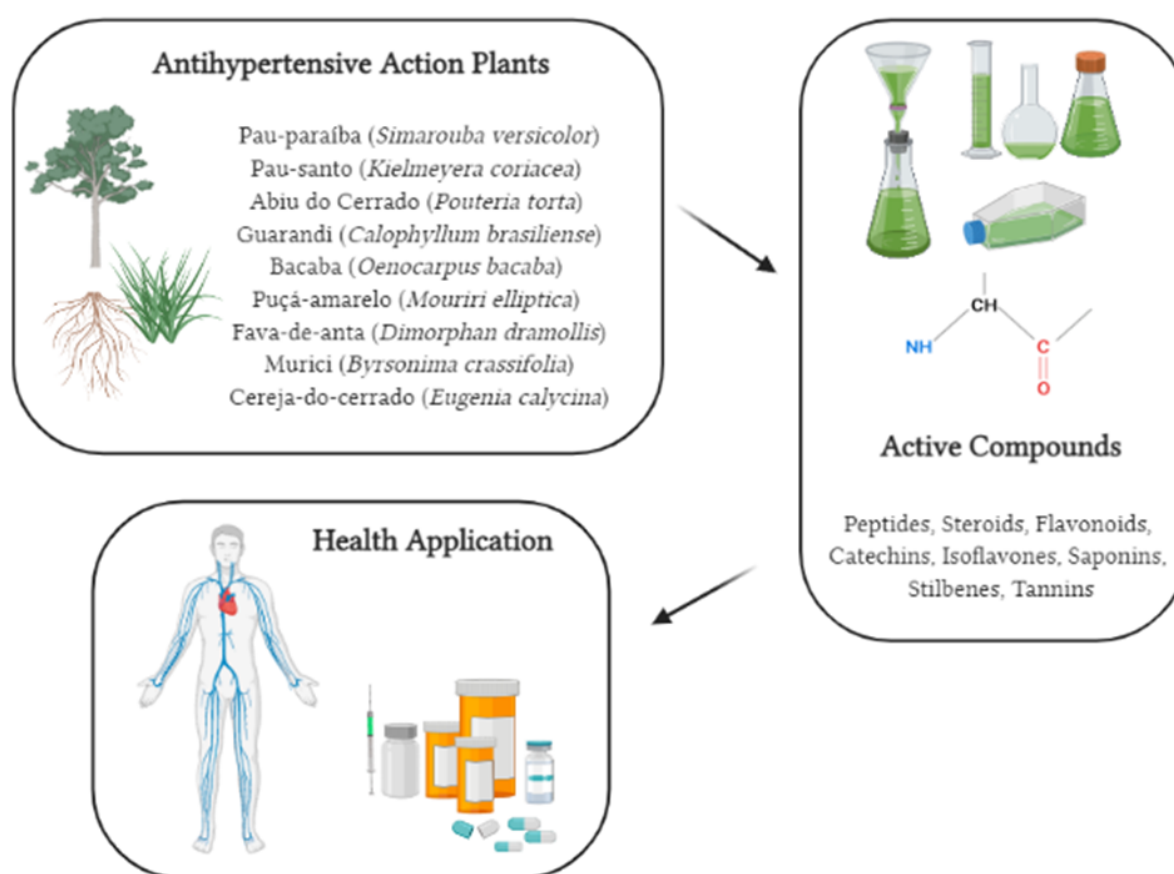


Figure 1. Scheme of Brazilian Cerrado plants identified as potential blood pressure lowering agents based on their described secondary metabolites. This figure also suggests the isolation of active compounds from these plant species and, finally, their potential application in health, especially in the field of arterial hypertension.

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Conflict of Interest Statement

The authors declare no conflict of interest.

Author Contributions

Marcelo Antônio da Trindade: Substantial contribution in the concept and design of the study; Substantial contribution in the choice of articles; Contribution to data interpretation; Contribution to manuscript preparation.

Fernanda Cardoso da Silva: Substantial contribution in the choice of articles; Contribution to data interpretation; Substantial contribution to manuscript preparation.

Bruna Juber de Araújo: Contribution to data interpretation and manuscript preparation.

Janayne Luihan Silva: Substantial contribution in the choice of articles; Contribution to data interpretation; Substantial contribution to manuscript preparation.

Thaise Gonçalves de Araújo: Contribution to critical revision, adding intellectual content.

Cristina Ribas Fürstenau: Substantial contribution to data interpretation and manuscript preparation; Contribution to critical revision, adding intellectual content; Was Marcelo Antônio da Trindade's supervisor and research coordinator.

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