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Medicinal plants and their interaction with drugs used to control systemic arterial hypertension

Plantas medicinais e sua interação com medicamentos usados no controle da hipertensão arterial sistêmica

Plantas medicinales y su interacción con medicamentos utilizados para controlar la hipertensión arterial sistémica

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Abstract
Chronic diseases with evidence for systemic arterial hypertension are one of the main causes of mortality in the country. The treatment of these diseases is done through allopathic medicines and medicinal plants, and their association is increasingly frequent and thus also increases the risk of interactions. A literature review was carried out on the implications of the use of medicinal plants and their interaction with drugs used to control arterial hypertension, based on works published between 2014 and 2022, addressing the interactions between medicinal plants with popular knowledge and their drug interactions. The approached plants that showed interactions were *Allium sativum* L., *Passiflora sp*., *Cymbopogon citratus*, *Lippia alba* (Mill.), *Citrus sp*., *Sechium edule* and *Alpinia zerumbet*. The possible interactions of these plants with allopathic medicines were evaluated and it was observed that the main

interactions are of the pharmacodynamic type, so caution is necessary when used concomitantly with other medicines or without guidance of a professional that can bring harm to health and decrease the effect of the drug on the body.
Keywords: Plant-drug interactions; Rational use of medicinal plants; Antihypertensive.

Resumo
As doenças crônicas com evidência para a hipertensão arterial sistêmica são uma das principais causas de mortalidade no país. O tratamento dessas doenças é feito por meio de medicamentos alopáticos e plantas medicinais, sendo que sua associação está cada vez mais frequente e com isso também aumentam os riscos de ocorrência de interações. O objetivo dessa pesquisa foi realizar uma revisão da literatura sobre as implicações do uso de plantas medicinais e sua interação com medicamentos usados no controle da hipertensão arterial com base em trabalhos publicados entre 2014 a 2022, abordando as interações entre plantas medicinais com conhecimento popular e a sua interação com medicamentos. As plantas abordadas que apresentaram interações foram: *Allium sativum* L., *Passiflora sp*., *Cymbopogon citratus*, *Lippia alba* (Mill.), *Citrus sp*., *Sechium edule* e *Alpinia zerumbet*. Foram analisadas as possíveis interações dessas plantas com medicamentos alopáticos e observou-se que as principais interações são do tipo farmacodinâmico, dessa forma faz se necessário ter cautela quando utilizados concomitantemente com outros medicamentos ou sem orientação de um profissional o que pode trazer danos à saúde e diminuição do efeito do fármaco no organismo
Palavras-chave: Interações planta-medicamentos; Uso racional de plantas medicinais; Anti-hipertensivos.

Resumen
Las enfermedades crónicas con evidencia de hipertensión arterial sistémica son una de las principales causas de mortalidad en el país. El tratamiento de estas enfermedades se realiza a través de fármacos alopáticos y plantas medicinales, y su asociación es cada vez más frecuente y con ello también aumentan el riesgo de interacciones. El objetivo de esta investigación fue realizar una revisión bibliográfica sobre las implicaciones del uso de plantas medicinales y su interacción con medicamentos utilizados para controlar la hipertensión a partir de estudios publicados entre 2014 y 2022, abordando las interacciones entre plantas medicinales con conocimiento popular y su interacción con medicamentos. Las plantas abordadas que presentaron interacciones fueron: *Allium sativum* L., *Passiflora sp*., *Cymbopogon citratus*, *Lippia alba* (Mill.), *Citrus sp*., *Sechium edule* y *Alpinia zerumbet*. Se analizaron las posibles interacciones de estas plantas con fármacos alopáticos y se observó que las principales interacciones son del tipo farmacodinámico, por lo que es necesario tener precaución cuando se usa concomitantemente con otros medicamentos o sin la guía de un profesional, lo que puede causar daños a la salud y disminuir el efecto del medicamento en el cuerpo
Palabras clave: Interacciones planta-fármaco; Uso racional de plantas medicinales; Antihipertensivo.

1. Introduction

Systemic arterial hypertension is a comorbidity that does not have a definite cause, characterized by the permanence of high tensoriaus levels. It presents itself as a problem of high magnitude and, according to the VII Brazilian Guidelines on Hypertension (2020), is a multifactorial clinical condition characterized by one of the main causes of mortality and cardiovascular morbidity (Barroso et al, 2021).

According to the Ministry of Health, a patient is considered to have hypertension when he has blood pressure levels greater than or equal to 140mmHg and a diastolic blood pressure above 90mmHg. For blood pressure classified as optimal, systolic and diastolic blood pressure should be less than 120 mmHg and 80 mmHg, respectively. Treatment for the control of hypertension includes, in addition to medications, the modification of habits, whose main objective is to reduce symptoms, since metabolic changes increase the risks of fatal and non-fatal cardiovascular events (Barroso et al, 2021).

The main classes of drugs that can be used to treat systemic arterial hypertension are diuretics, adrenergic inhibitors, vasodilators, calcium channel blockers, angiotensin conversion enzyme inhibitors (ACEI), and angiotensin II receptor blockers (Wright, et al., 2018).

Although systemic arterial hypertension is recognized as a public health problem, it is far from being fully controlled. This is mainly due to the non-follow-up of the recommended treatment that manifests itself with lack of adtake and is related to several factors, such as adverse reactions and cost (Nogueira et al., 2014).

It usually leads patients to seek out or use alternative therapies, which will further affect blood pressure control. In alternative therapies, phytotherapy is characterized by the use of medicinal plants or their parts containing substances responsible for their therapeutic effects (Brasil, 2015).

Co-administration and use of medicinal plants and medications can cause unexpected interactions, which occur due to lack of attention to their use, usually inadequate and guided by philosophy of life, personal and cultural customs. Some of these factors are shared by patients and health professionals who have no experience in the area (Kirchner et al, 2022).

Currently, millions of people are using medicinal plants together with prescription drugs for therapeutic purposes or formulated as herbal medicines to prevent diseases. Despite being considered natural, these means may interact with medications causing potentially dangerous side effects or reducing benefits obtained with conventional treatment. However, these products are not free of toxicity or adverse reactions, depending on the characteristics of the patient and may have interactions with other medicines and/or foods (Brandão et al., 2010, Pontes et al., 2012, Silva, 2018).

With regard to harmfulness and intoxication, plants produce a wide variety of chemicals that may have different biological activities and are still relevant therapeutic resources for a significant part of the world population that does not have access to industrialized medicines (Campos et al., 2016; Oliveira, et al., 2021).

Adverse effects arising from the use of plants may be caused by interactions of the constituents of herbal products with other medicines, or related to user characteristics or physiological conditions (Farias, 2016). Interactions between plants and medications can lead to pharmacological changes and drug toxicity. These interactions can be of the pharmacodynamic type, when there is an increase or decrease in the effect of the drug, due to synergy or antagonism, or even pharmacokinetics, which will lead to changes in the absorption and distribution of the drug in the body, resulting in increased plasma concentration (Carneiro, Comarella, 2016).

Therefore, the aim of this study was to describe the interactions that may be caused by simultaneous use between medicinal plants and antihypertensive drugs.

2. Methodology

The present study is of a basic nature and consists of an integrative literature review with exploratory, descriptive and qualitative approach. The databases of Latin American and Caribbean Literature on Health Sciences (LILACS), Scientific Electronic Library Online (SciELO), BIREME, MedLine and PubMed were used, comprising by 2014 to 2022. The following descriptors were used: "*Drug plant interaction*", "*hypotensive action*", "*medicines*".

As inclusion criteria, were considered the complete articles in English and Portuguese which contained the selected descriptors, together or separately. Duplicate articles, books, book chapters, dissertations, theses and abstracts of congresses that did not meet the established theme were excluded.

The selection of the articles found in the different databases was performed in three stages. The first stage was from the reading of titles of the articles found, the second stage was through the reading of the abstracts of the selected articles and, in the third stage, the articles that were not excluded during the previous steps were read in full for the selection of which ones would be used in the research.

The articles were separated, using an instrument previously validated by Ferreira et al. (2020), into blocks according to the year of publication and the information collected were systematized in a database using Microsoft Excel™, the spreadsheet was organized with title, year of publication and reference, and the information of these articles was tabulated and analyzed in order to verify their interactions with medicines.

3. Results and Discussion

In the literature review performed, 70 eligible articles were found, among which 22 articles met the inclusion criteria. LILACS (1), SciELO (6), BIREME (4), MedLine (3) and PubMed (8). The others were disregarded, because despite appearing in the research bases, they did not address what medicinal plants could cause changes in blood pressure and the interaction with antihypertensive drugs.

According to the articles selected in this survey, seven plants showed potential to alter blood pressure levels and interacted with medications used to control hypertension were: *Allium sativum* L., *Passiflora sp*., *Cymbopogon citratus*, *Lippia alba* (Mill.), *Citrus sp*., *Sechium edule* and *Alpinia zerumbet*.

The search of the bibliography referring to the theme was carried out through the scientific name, to ensure reliable information, since a plant can present several popular names depending on the region.

The (Table 1) shows the 7 species that presented scientific studies that prove their antihypertensive activity as well as scientific name, popular name, part used and phytochemical composition.

Table 1: Medicinal plants that cause interactions when used in association with antihypertensive drugs and that showed hypotensive action.

Medicinal plant	**Popular name**	**Part used**	**Phyrochemical composition**	**Class of antihypertensive that interact**	**Authors and year of publication**
Allium sativum L.	Garlic	Leaf, Composite Bulb	Sulfur compounds, glycosides, monoterpenoids, flavonoids and saponins	Beta-adrenergic antagonist simpaticolytics	(Carneiro and Comarela, 2016, Verma et al., 2021, Lima et al., 2018).
Passiflora sp.	Passion fruit	Leaf	Flavonoids, saponins, alkaloids and volatile oils	Direct vasodilators	(Souza et al., 2017, Costa et al., 2019, Andrade et al., 2018, Santos, Galindo and Queiroz, 2020).
Cymbopogon citratus	Lemon grass	Leaf	Flavonoids, tannins, saponins, anthraquiones, alkaloids and essential oils	Calcium channel blockers and diuretics	(Farias, 2016, Souza et al., 2017, Velazquez et al., 2017, Barros et al., 2018, Carvalho et al., 2021).
Lippia alba (Mill.)	Bushy matgrass	Flower, Leaf	Monoterpenes, flavonoids, iridoids, naphthoquinones and alkaloids	Direct vasodilators	(Gomes et al., 2016, Costa et al., 2019, Barros et al., 2018).
Citrus sp	Orange	Leaf, Fruit	Mono and sesquiterpenes, flavonoids, coumarins, tannins, xanthones and triterpenes	Beta adrenergic antagonists and ACEI	(Silva, Quadros and Neto, 2015, Humenhuk, Leite and Fritsch, 2020).
Sechium edule	Chayote	Flower, seed, bark, kernel or root	Alkaloids, saponins, flavonoids	Diuretics	(Souza et al, 2017, Lombardo-Earl et al., 2014, Saad et al., 2016).
Alpinia zerumbet	Shell ginger	Leaf	Monoterpenes, flavonoids and hydrolysable tannins	Calcium channel blockers and direct vasodilators	(Castro et al., 2016, Cunha et al., 2016, Souza et al., 2017, Lins et al., 2020).

Source: Search data (2022).

In the studies analyzed, it was observed that hypertensive patients use their conventional medications together with medicinal plants, and this practice can generate interferences in the pharmacological effect. The potential for plant and drug interactions depends on the presence and mechanism of action of some secondary antihypertensive metabolites, and may have their antagonistic effects when used with plants with hypertensive, vasoconstrictor and liquid retaining activity, enhanced when used with plants with hypotensive, vasodilator and diuretic properties (Farias, 2016, Carvalho et al., 2021).

A description was made about each species, its effects and interaction with the medicinal products.

3.1 *Allium sativum* L. (Garlic)

Garlic has in its composition sulfurcompounds, such as allicin and ajoene, in addition to glycosides, monoterpenoids, enzymes, vitamins, minerals and flavonoids (canferol and quercetin), saponins. (Lima et al., 2018). Regarding the mechanism of action, Lima et al. (2018) pointed out that sulfur compounds exhibit *in vitro* vasodilator activity mediated by nitric release and the use of garlic can reduce the expression of CYP3A4 isoforms, CYP3A5, CYP3A7, CYP2C9, CYP2C19 and CYP2E1 and glycoprotein-P and can increase the expression of CYP2C9, CYP3A1, CYP1A1.

The research conducted by Carneiro and Comarella, (2016); Verma et al. (2021); Lima et al. (2018) are in agreement and reported that synergistic interactions may occur when garlic is used simultaneously with the drug nebivolol, an antihypertensive β-blocker. This medicine initially acts by decreasing cardiac output, causing decreased rein secretion and readaptation of baroreceptors with the decrease of catecholamines in nerve synapses.

This medicine also acts by providing vasodilation by increasing the synthesis and endothelial release of nitric oxide, which is an effect similar to those sulfur compounds present in garlic, thus suggesting a potentiation of the effect.

According to Lima et al. (2018), there is a similar effect on the sulfur compounds present in garlic, with potentiation of the effect of the drug and interactions with inhibitors of antihypertensive conversion of angiotensin, causing an increase in the effect. Calcium channel antagonist class drugs are metabolized in CYP450, and verapamil is mainly metabolized by CYP3A4 isoform, β-blockers are metabolized by CYP2D6 isoform that changes with the administration of garlic products, suggesting that pharmacokinetic interactions occur when used concomitantly with the plant.

3.2 *Passiflora sp.* (Passion fruit)

Andrade (2018), Santos, Galindo and Queiroz (2020) point out that the most frequent chemical constituents cited for the species are C-glycosylated flavonoids and saponins.

Its mechanism of action lies in the reduction of blood pressure due to the vasodilatory action of polyphenols such as lutein and its glycosides contained in the extract, as it was observed the decrease in systolic blood pressure in spontaneously hypertensive rats after administration of *Passiflora edulis* methanol extract, as well as the antioxidant properties of phenolic compounds (Souza et al., 2017).

Souza et al. (2017) and Costa et al. (2019) mentioned that drug interactions may occur with drugs of the class of direct vasodilators (hydralazine, minoxidil), which act promoting relaxation of the vascular wall muscles, resulting in vasodilation and decreased peripheral vascular resistance, potentiating the pharmacological effect.

3.3 *Cymbopogon citratus* (Lemon grass)

The main components found in *Cymbopogon citratus*, and described in the study by Velazquez et al. (2017), were geraniol, neral and myrcene. As for the mechanism of action, the author describes that the essential oil caused hypotension with the reduction of vascular resistance, which can be caused by inhibition of calcium ion influx and activation of cardiac muscarinic receptors that cause bradycardia.

On drug interactions, Farias, (2016), Velazquez et al. (2017), Souza et al. (2017), Barros et al. 2018) and Carvalho et al. (2021), report in their studies that synergistic interactions of calcium channel antagonists associated with plant use may occur, since the mechanism by which plant constituents cause hypotension is similar to the mechanism of action of the drugs of the classes of phenylachiallamine, benzothiazepins and diidropiridins. When these drugs bind the α1 subunits of the calcium channels L type and interact with each other preventing the opening of the channels, there is a decrease in the intake of calcium generating generalized arterial dilation, which reduces arteriolar resistance, reducing systemic blood pressure, and may affirm the additive interaction between the plant and the ampldipine drug when used concomitantly.

3.4 *Lippia alba* (Bushy matgrass)

Bushy matgrass is composed mainly by citronelol, citral, myrcene, limonen and carvone. Research indicates that its potential mechanism of action involves citronelol, which is responsible for the plant's antihypertensive activity. Studies conducted by Gomes et al. (2016) and Barros et al. (2018) report that the mechanism by which citronelol lowers blood pressure is by direct effect on vascular smooth muscle, thus promoting vasodilation.

With regard to drug interactions, citronelol, because its mechanism of action is similar to direct vasodilators (hydralazine, minoxidil, nitroprusside) that act on the musculature of the vascular wall and provide muscle relaxation, results in vasodilation and decreased peripheral vascular resistance. Therefore, the association between this class of drugs and this species can cause a potentiation of the effect of the drug (Gomes et al., 2016, Costa et al., 2019, Barros et al., 2018).

3.5 *Citrus sp.* (Orange)

Orange has the following chemical constituents: phenols, tannins, (anthocyanidins, flavanones, flavonols), xanthones, saponins, steroids and triterpenoids. Flavanoid hesperidine is, according to Humenhuk et al. (2020), the substance found in citrus juices and fruits. It has hypotensive activity in normal and hypertensive rats and has diuretic action in normal rats, as well as β-blocking effects, culminating in antihypertensive effect that instill the activity of the angiotensin-converter enzyme (ACE).

Regarding the mechanisms of action and drug interactions, the authors Silva, et al., (2015), add that synergistic interactions occur with antihypertensive drugs of the class of β-blockers, because hesperidine has similar action of blocking the β-adrenergic receptors, as occurs in drugs that act in reducing cardiac output, reducing the secretion of renine by the glomerular just cells, besides having central action reducing sympathetic activity. The mechanism of action of *Citrus sp*. may suggest that the additive interaction between the plant and the drugs, propranolol (beta adrenergic) and captopril (ACEI), occurs when used concomitantly.

3.6 *Sechium edule* (Chayote)

The main chemical constituents present in the plant that are responsible for its pharmacological effect are its nutrients such as potassium, calcium, magnesium, phosphorus, zinc, iron, alkaloids, saponins, flavonoids thiamine, riboflavins fibers and proteins (Lombardo-Earl et al., 2014).

As for the mechanism of action of the plant, Lombardo-earl et al. (2014) found that potassium (K) presents in chayote has a great vasodilator effect. Vasodilation in blood vessels can reduce peripheral resistance and increase cardiac output so that blood pressure can be normal. Potassium can affect the central nervous system and when the amount of this mineral falls below the recommended, it can lead to a hypokalemia with abnormal symptoms such as muscle weakness, abnormal heart rhythm, weakness, vomiting, and diarrhea. In addition, chayote, for being a diuretic, reduces sodium levels in the blood through urinary excretion.

Also according to the authors, the hydroalcoholic extract of this plant, when induced with angiotensin II, obtained a satisfactory result as a relaxing vessel, and with this it is possible to prove the efficacy of this plant for the treatment of this comorbidity.

According to Souza et al. (2017), interactions occur when its use is combined with hypotensive, diuretics, sedatives, sedatives and antihistamines.

The research conducted by Saad et al. (2016) states that the pharmacological actions of plants with antihypertensive activity (diuretics, sedative, ACE inhibitor, calcium channel action inhibitor) are similar to those of synthetic substances used in these situations. However, the synergistic interactions that occur between the various constituents of phytocomplex results in smoother action with fewer side effects, and it may be suggested that a hypotensive effect occurs when used simultaneously with the drug furosemide, a drug that belongs to the class of diuretics.

3.7 *Alpinia zerumbet* (Shell ginger)

The research conducted by Castro et al. (2016), Cunha et al. (2016) and Lins et al. (2020), demonstrated that the mechanisms of action and evidence based on the treatment of *Alpinia zerumbet* essential oil reduce blood pressure due to the presence of terpineol and 1.8-cineol (eucalyptus) components improving cardiovascular hemodynamics. Terpineol that acts to block calcium influx into the canals, catechins that act on vascular smooth musculature and alkaloides that have diuretic action.

Regarding drug interactions, the authors Souza et al. (2017) and Lins et al. (2020) are in agreement that the terpineol identified in the plant acts similarly to drugs of the class of antihypertensive calcium antagonists and prevents the entry of calcium into cells. The use of the plant when associated with drugs of this class can cause hypotension because it increases the antihypertensive effect. Catechins present pharmacological action similar to the mechanism of action of direct vasodilator antihypertensives and can potentiate the action of the drug when used in concomitance with the plant, and there may be an interaction of hypotensive effect between the drugs amlodipine and hydralazine.

4. Final Considerations

In this bibliographic survey it was evidenced that the use of plants is something quite old, sometimes it is configured in a single therapy option for the population, since they are low cost, besides the perpetuation that plants because they are of plant origin do not present adverse effects or harmfulness to people who use them, not knowing that even though it is of natural origin its effects can be assimilated to synthetic drugs.

It was shown in this article, studies that state that patients affected by systemic arterial hypertension should not use medicinal plants associated with medications, or as an adjunct treatment, without the guidance of a qualified professional, since they may cause hypotension, as well as potentiate the side effects of medications.

Based on the studies described in this review article, the plants with antihypertensive action are: *Allium sativu*m L, *Passiflora* sp, *Cymbopogom citratus*, *Lippia alba*, *Citrus sp*, *Sechium edule* and *Alpinia zerumbet*. In the granting of the interactions involved in the use of plants associated with drugs to treat systemic arterial hypertension, they showed that all interactions were pharmacodynamic type, with synergistic effects and pharmacokinetic interactions, by interference in liver enzymes.

The pharmacological classes that showed interactions with plants were the antagonists of calcium channels that present interactions with garlic, shell ginger and holy grass; beta-blockers have interactions with garlic, orange; ACE inhibitors that show interaction with orange, passion fruit and bushy matgrass and diuretics interact with chayote.

In this sense, it highlights how important the pharmaceutical professional is in this context, because the guidance of this professional can minimize the adverse effects on the patient on the irrational use of plants and medications, guiding them on the risks of drug interaction with antihypertensivedrugs and changes in blood pressure.

The rational use of medicinal plants is a practice that has been developed and has shown good results. Thus, future studies are needed on the way plant species and their derivatives are used on the different metabolic pathways of the human organism. Promoting its use for various ailments and avoiding possible interactions with synthetic drugs.

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