

Review

Antihypertensive Effects of Brazilian Fruits

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Abstract: Cardiovascular disease is a health problem that generates economic and social impacts worldwide and hypertension is a major risk factor for the development of cardiovascular disease. Currently, conventional medicine offers treatments that control and regulate blood pressure through medication, but the traditional medicines of different cultures have used plants and foods to treat and prevent this type of disease for many years. Brazilian flora has enormous potential due to its wide diversity; however, few studies have evaluated the effects of fruits for reducing or preventing hypertension. This literature review was intended to target current work with Brazilian fruits that sought evidence of species for which consumption could serve as an adjuvant to existing drugs for the control of hypertension. We found studies of five Brazilian fruits which some of them are popularly used to treat hypertension and the results of the research were compared and discussed. *Schinus terebentifolius*, *Passiflora edulis*, *Euterpe oleracea* and *Insignis platonis* demonstrated promising effects, while *Myrciaria dubia* did not show positive effects. Thus, we can conclude that Brazilian fruit has potential for use in the treatment of hypertension; however, further studies need to be conducted to explore these fruits in order to increase knowledge in this area. Thus, these fruits could be incorporated into food and used as adjuvants in the treatment of this chronic disease, which has negative impacts on the quality of life of the population.

Keywords: Blood Pressure, Cardiovascular System, Food, Natural Products

Introduction

The prevalence of Noncommunicable Diseases (NCDs), such as obesity, type 2 diabetes and Cardiovascular Disease (CD), has grown exponentially worldwide. They can result from a combination of several factors, such as diet, aging, urbanization, smoking and physical inactivity (WHO, 2013; Wild *et al.*, 2004). Among NCDs, CD is the main cause of morbidity and mortality worldwide (WHO, 2013).

CD directly influences public health costs and economies of countries, especially developing countries (WHO, 2013). The reason for this is the high costs that arise from the treatment and prevention of CD and a decrease in personal productivity, which causes an impact in the economy (Stevens *et al.*, 2018). CD is sometimes disabling and leads to increased spending on health services. This has a negative impact on developing countries, where health spending resources are fewer and the population is needier (WHO, 2013). In addition, CD

also affects the well-being of individuals and their families, as it is a debilitating disease with associated comorbidities (Malachias *et al.*, 2016; Mozaffarian *et al.*, 2016). In Brazil, it is estimated that the costs and economic losses from this condition exceeds 50 billion of Brazilian reais annually (Stevens *et al.*, 2018).

Hypertension (HA) is one of the major risk factors responsible for the high death rate associated with CD (Malachias *et al.*, 2016; Mozaffarian *et al.*, 2016). The disease has a multifactorial pathogenesis; it is influenced by genetic and environmental factors that contribute to an imbalance in the homeostasis of the cardiovascular system, leading to the development of hypertension (Whelton *et al.*, 2017).

In addition, environmental factors, such as overweight/obesity, a high-fat diet, excess of sodium intake and alcohol consumption, have large impacts on the development and growth of individuals with CD worldwide (Bezerra *et al.*, 2018; Samadian *et al.*, 2016). Thus, especially for populations in developing countries,

where access to modern medicine is difficult, the use of other methods for the treatment or prevention of disease is very important. The use of medicinal plants, as well as dietary interventions using functional foods and nutraceuticals, has been previously investigated and has demonstrated great results (Chen *et al.*, 2014; Magrone *et al.*, 2013; Peluso *et al.*, 2018).

Functional foods are those that provide essential nutrients to the body and also improve general well-being or health. It is different of nutraceuticals, that are considered bioactive compounds that generally are not provided as food, but as medicine in the form of capsules or tablets (ANVISA, 1999).

Currently, much is known about the influence of the consumption of functional foods and nutraceuticals in reducing the development of diseases such as cancer, neurological disorders, cardiovascular disease like hypertension, obesity, inflammation and infections (Aune *et al.*, 2017; Avtanski and Poretsky, 2018). In this sense, fruits are an excellent source of nutrients such as carbohydrates, carotenoids, vitamins and minerals, which are essential to the proper functioning of the body (Brookie *et al.*, 2018; Cassidy *et al.*, 2016; Neri-Numa *et al.*, 2018). In addition to these nutrients, fruits contain secondary metabolites such as phenolic acids, anthocyanins and flavonoids that have many beneficial effects on the body (Aune *et al.*, 2017). Thus, by having these qualities, there is a potential for fruits to act as adjuvants in the treatment of various diseases (Dametto *et al.*, 2017; dos Reis *et al.*, 2018; Johnston, 2009; Silva *et al.*, 2016; Vasudevan *et al.*, 2009).

Brazil has a large land area and a great diversity, which is favorable to the discovery of natural products with biological activity (Valli *et al.*, 2018). Also, the traditional medicine produced by Brazilian people has an enormous potential to produce new medicines. Even with the popular use of these plants by people (Akter *et al.*, 2011; dos Santos *et al.*, 2015; Heinrich *et al.*, 2011; Ricardo *et al.*, 2017; Zibadi *et al.*, 2007), only few studies were conducted to evaluate its effects. In this sense, the determination of important biological properties in Brazilian native fruits can help drive consumption, which, along with global dietary management, can contribute to the prevention of CD, including hypertension and other chronic heart-related diseases (Aune *et al.*, 2017; Hügel *et al.*, 2016; NCGC, 2011).

Therefore, the aim of this study was to conduct a literature review of articles published in major scientific databases that have explored the antihypertensive effects of Brazilian fruits.

Methods

Articles were screened in major databases such as PubMed, ScienceDirect, LILACS, Medline and Scielo using the following indexes: "Brazil", "Fruits" and "Antihypertensive".

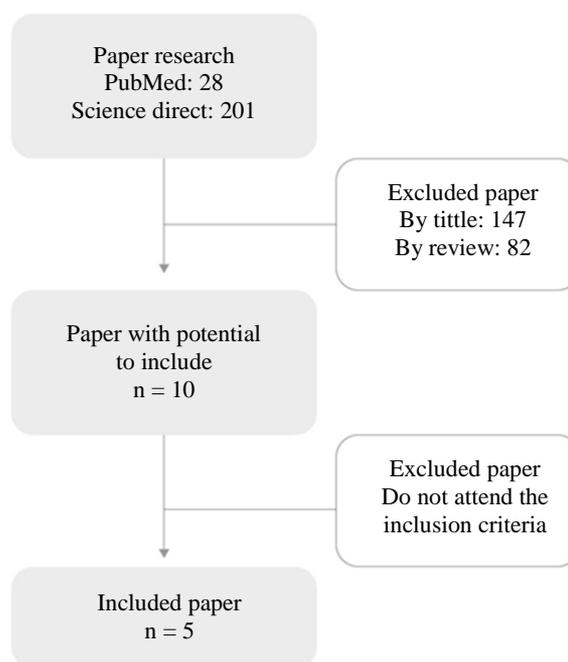


Fig. 1: Flow chart demonstrating the sequence of paper selection and the exclusion of papers for the review

The following inclusion criteria were used: Articles that addressed the antihypertensive effects of Brazilian fruits published between 2008 and 2018. Excluded items included review articles, clinical articles and book chapters (Fig. 1).

Results and Discussion

In recent years, there has been an increase in interest in how food can affect health. It is known that a balanced and healthy diet is important for maintaining health and preventing disease (D'El-Rei *et al.*, 2016; Mochizuki *et al.*, 2017). Thus, the consumption of processed foods, which is associated with a sedentary lifestyle and other practices, increases the likelihood of the development of chronic diseases such as diabetes and CD, especially Hypertension (HA) (Agosti *et al.*, 2017; Gatineau *et al.*, 2017).

HA is a chronic disease that is closely related to lifestyle and eating habits, such as excessive sodium intake and a sedentary lifestyle (Fig. 2) (Gatineau *et al.*, 2017). Patients with this disease generally take many medications that may have unwanted side effects. Therefore, changes in lifestyle and the addition of foods rich in beneficial compounds, such as polyphenols, can help to control the disease (D'El-Rei *et al.*, 2016).

Thus, foods with certain properties or functional claims, commonly known as functional foods, stand out. These are defined as foods that, when consumed, in addition to the nutritional contributions of macro and

micronutrients, have other beneficial aspects, such as the presence of compounds that can assist the body in controlling chronic diseases (Agosti *et al.*, 2017; Ahtesh *et al.*, 2018; Cicero and Colletti, 2015; Cicero *et al.*, 2017; Santini *et al.*, 2017). Which is promoted by control and maintenance of the physiological functions of the human body (ANVISA, 1999). However, for these foods to confer benefits, they must be consumed regularly (Santini *et al.*, 2017).

Studies have indicated that the consumption of functional foods can help to control and treat chronic diseases such as HA and these foods could act as adjuvants to drug therapies (Agosti *et al.*, 2017; Arroyo-Johnson and Mincey, 2016; Cicero and Colletti, 2015; D'El-Rei *et al.*, 2016; Johnston, 2009; Santini *et al.*, 2017). Therefore, functional foods can be incorporated into the diet in order to assist in the control of chronic diseases, also traditional people have use it as

a medicine to treat diseases (Heinrich *et al.*, 2011; Pereira *et al.*, 2016; Pimenta *et al.*, 2018; Vasquez *et al.*, 2018). Proven and available functional foods include some types of fruits (Santini *et al.*, 2017).

Fruits contain a large number of phenolic molecules, which are produced by secondary metabolism and thanks to their chemical characteristics, have antioxidant properties (Felzenszwalb *et al.*, 2013; Tungmunnithum *et al.*, 2018). Antioxidants are compounds capable of inhibiting or reducing Reactive Oxygen Species (ROS) found in the body, thus reducing the damage caused by them (Cicero and Colletti, 2015). Some people already use fruit for the prevention and treatment of diseases (Da Costa *et al.*, 2017; Poli *et al.*, 2018). In Brazil, this is no different and with the country's rich biome, many fruits may have beneficial effects on chronic diseases, including HA (Felzenszwalb *et al.*, 2013; Gloria *et al.*, 2017; Schulz *et al.*, 2017).

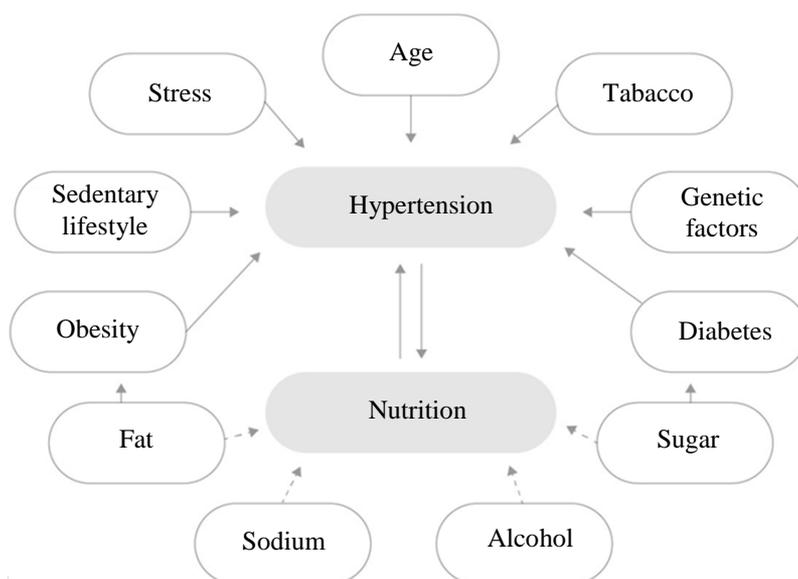


Fig. 2: The multifactorial profile of hypertension. Factors like nutrition, lifestyle, genetic and other diseases help to increase the risk of develop of that disease

Table 1: Summary of main results obtained by papers that study Brazilian fruits as antihypertensive agents

Fruit	Main result	Author/Date
<i>Euterpe oleracea mart.</i>	Extract at a dose of 200mg/kg promoted decrease on blood pressure in 2K1C model of hypertension. Antioxidant effect was show and treatment promote ameliorate on NO-cGMP pathway.	Da Costa <i>et al.</i> (2012)
<i>Myrciaria dubia Mc. Vaugh</i>	Extract at a dose of 10mg/mL did not present ACE inhibitory activity.	Fujita <i>et al.</i> (2015)
<i>Passiflora edulis Sims f. Flavicarpa Deg.</i>	Decrease on blood pressure was observed at a dose of 5, 6 and 8 mg/kg in SHR rats after 5 days of treatment.	Konta <i>et al.</i> (2014)
<i>Platonia insignis Mart.</i>	Ethanollic and ethyl acetate extract from fruit peel promote acute hypotension at 12.5, 25 and 50 mg/kg.	Mendes <i>et al.</i> (2014)
<i>Schinus terebinthfolius Raddi</i>	Polyphenols enrich extract at a dose of 30mg/kg promote decrease in mean, systolic and diastolic blood pressure.	Gloria <i>et al.</i> (2017)

2K1C – two kidney one clip. NO-cGMP – Nitric oxide – cyclic guanosine monophosphate. ACE – Angiotensin converting enzyme. SHR – Spontaneously hypertensive rats

From the research carried out, we found 229 items in the included databases. Taking into account the established criteria, 224 articles were excluded and five species had their antihypertensive properties evaluated: *Euterpe oleracea*, *Myrciaria dubia* Mc. Vaughn, *Passiflora edulis* Sims f. *flavicarpa*., *Insignis platonia* Mart and *Schinus terebinthifolius*. The resume of main results is present at Table 1.

Passiflora edulis Sims f. *flavicarpa*

The genus *Passiflora*'s belongs to family Passifloraceae and its diverse species have been widely used in traditional medicine in many countries as sedatives, tranquilizers, diuretics and painkillers (Appel *et al.*, 2011; Dhawan *et al.*, 2004; Ngan and Conduit, 2011). Known as passion fruit, it is native to Brazil and is often consumed as fresh fruit pulp and is used as a raw material for juice production (Mercandante *et al.*, 1998). Studies investigating the pharmacological properties of the *Passiflora* genus have been performed (Appel *et al.*, 2011; Dhawan *et al.*, 2004; Reginatto *et al.*, 2006). Traditionally, *Passiflora edulis* is indicated to treat anxiety, insomnia, asthma, urinary infections and as a heart tonic (Schotsmans and Fischer, 2011). The antihypertensive effect was demonstrated experimentally, especially for *Passiflora edulis* bark extract; however, the pulp was also evaluated (Konta *et al.*, 2014; Reginatto *et al.*, 2006; Zibadi *et al.*, 2007).

Konta *et al.* (2014) evaluated the effects of passion fruit pulp on Spontaneously Hypertensive Rats (SHR), identified the chemical constituents of passion fruit pulp and demonstrated the presence of phenolic compounds, ascorbic acid and carotenoids. This chemistry may be responsible for the beneficial effects observed on the animals' blood pressure.

Some of these compounds, such as quercetin (Duarte *et al.*, 2001) and caffeic acid (Yeh *et al.*, 2009), have been previously associated with antihypertensive action in SHR rats when administered as single compounds and this effect was related to their antioxidant activities.

The antihypertensive effect of *Passiflora edulis* was evaluated using three different doses (5, 6 and 8 g/kg) applied orally over 5 consecutive days. After the treatment period, a decrease in systolic blood pressure was observed at a dose of 8 g/kg; this reduction was not accompanied by a change in the heart rate. Additionally, renal function and safety of use were evaluated using a micronucleus test. Treatment at the highest dose yielded an increase in the concentration of reduced glutathione (GSH) and a reduction in TBARS

levels in the renal tissue, indicating an important antioxidant effect. No toxicity was observed in the micronucleus test. The authors also concluded that the antihypertensive effect of passion fruit pulp can be attributed, at least in part, to the increase in the antioxidant status; however, the precise mechanisms responsible for this action still need further investigation (Konta *et al.*, 2014).

In the cardiovascular system, imbalances in the production of ROS are closely related to the pathophysiology of inflammation, hypertrophy, cell proliferation, apoptosis, angiogenesis and fibrosis (Montezano and Touyz, 2012). The pathogenesis of hypertension appears to be related, at least in part, to excessive oxidative stress, including an increased local oxidative state in the kidneys (Harrison and Gongora, 2009; Kizhakekuttu and Widlansky, 2010).

Studies have linked the antioxidant effects of polyphenols to their ability to reduce blood pressure (Duarte *et al.*, 2001; Hügel *et al.*, 2016; Yeh *et al.*, 2009). Phenolic compounds, through their antioxidant action, improve endothelial function and normalize vascular tone, resulting in an antihypertensive effect (Hügel *et al.*, 2016). Other mechanisms, such as the vasodilator effect of quercetin and the modulation system of gamma-aminobutyric acid (Appel *et al.*, 2011), could also contribute to a decrease in blood pressure.

Schinus terebinthifolius Raddi

Schinus terebinthifolius Raddi (Anacardiaceae) is a plant native to South America that is popularly known as Aroeira or Pimenta Rosa. It is used by people for the treatment of various diseases, which includes antihypertensive, diarrhea, rheumatism and others (Bae *et al.*, 2015; dos Santos *et al.*, 2015).

Gloria *et al.* (2017) evaluated the effects of *in bolus* administration of a polyphenols- enriched fraction from *Schinus terebinthifolius* fruit in normotensive rats. It was observed that the application of the extract provided a significant reduction in the mean arterial, diastolic and systolic pressures, indicating that the fruit would have the potential to reduce blood pressure. However, the extract showed adverse effects through changes in the locomotor activity such as hypolocomotion, muscular incoordination and immobilization that were observed in the treated animals (30 mg/kg).

The phenolic compounds found in the enriched fraction (naringenin and gallic acid) and other unidentified gallic acid equivalents (659.21±05.06 mg/g) are responsible for antioxidant effects through the neutralization of ROS, which contributed to the hypotension that was observed (D'Sousa'Costa *et al.*,

2015). Thus, Gloria *et al.* (2017) highlight the importance of quantifying the phenolic compounds and determining the antioxidant activity in all studies investigating fruit because this is an important step towards identifying possible sources of bioactive molecules. In their study, the observed effects were primarily attributed to the two major compounds found (naringenin and gallic acid).

Also, Gloria *et al.* (2017) concluded that their study provided evidence for the pharmacological potential of *Schinus terebinthifolius* Raddi fruit extract as antihypertensive and antioxidant, making it a natural fruit source with promise for combating CD.

Myrciaria dubia Mc. Vaughn

The *Myrciaria dubia* Mc. Vaughn, popularly known as Camu Camu, Caçari or Araça d'água, is a fruit tree native to the Amazon region in Brazil. The plant can be found in various states in the northern region of Brazil, including Para, Amazon, Roraima, Rondonia and Tocantins. It is widely known to have a high ascorbic acid content (Langley *et al.*, 2015). Because of its rich vitamin C content, various studies have shown its neuroprotective, antidiabetic, promotes decrease on glucose levels and inflammation (Neri-Numa *et al.*, 2018).

Fujita *et al.* (2015) evaluated the potential of inhibiting Angiotensin-Converting Enzyme I (ACE) according to a method modified by Kwon *et al.* (2006) that used rabbit lungs as a substrate. The authors demonstrated the inhibitory effect on ACE at only the highest concentration of the aqueous extract studied (10 mg/mL); once the dose was too high, the extract was considered ineffective.

Camu Camu has a high concentration of ellagic acid as its main phenolic compound, which could be a reason for the negative result observed. As Kwon *et al.* (2006) demonstrated, these acids do not have ACE inhibitory activity when tested alone.

Although ACE inhibition was not observed in aqueous extracts of Camu Camu at 10 mg/ml, the author mentioned that further analyses needed to be conducted with high concentrations to confirm the findings (Fujita *et al.*, 2015).

Euterpe oleracea Mart.

The açai berry, *Euterpe oleracea* Mart., is a palm species from the Arecaceae family that is cultivated in Brazil because its fruit is a popular food. It is a palm tree native to Brazil and it has small fruits that are round and have a black-purple color. They can be sold frozen or in the form of bottled juice (Yamaguchi *et al.*, 2015).

Additional of its high nutrients content, traditional population use the berries to treat flu, pain, infections and skin problems (Heinrich *et al.*, 2011). Some other authors has demonstrates that its high phenolic content can prevent hypertension (Da Costa *et al.*, 2012).

Da Costa *et al.* (2012) evaluated the effect of a hydro-ethanolic extract of *Euterpe oleracea* on the development of hypertension using two kidneys, one clip (2K1C) model. The induction of hypertension was observed and chronic treatment at a dose of 200 mg/kg/day in drinking water prevented an increase in the systolic blood pressure in the first week of treatment. Additionally, the reduction in the pressure in this group was accompanied by a decrease in renin levels. Moreover, studies in the mesenteric bed demonstrated the reestablishment of vasodilation, promoted by acetylcholine, in these animals (Costa-Júnior *et al.*, 2011).

Chronic treatment also resulted in a reduction in oxidative stress and a decrease in malondialdehyde and carbonylated protein levels in hypertensive treated animals. Furthermore, animals treated with the *Euterpe oleracea* extract were found to have an increase in antioxidant enzyme activity (SOD, catalase and glutathione). These increase in enzyme activity were combined with an increase in protein expression of SOD1 and 2 and a reduction in NOX and eNOS-4, the latter of which is an important oxidizing enzyme. Together, these data demonstrate the strong antioxidant activity of *Euterpe oleracea* fruits (Da Costa *et al.*, 2012).

Additionally, previous research performed by Rocha *et al.* (2007) demonstrated that *Euterpe oleracea* can promote a vasorelaxant effect at the mesenteric bed, which can be associated with the NO-cGMP pathway and the release of Endothelium-Derived Hyperpolarization Factor (EDHF). Also, Cordeiro *et al.* (2017) evaluated the effects of chronic treatment with *Euterpe oleracea* fruit extract (200 mg/kg) in Spontaneously Hypertensive Rats (SHR) and observed a decrease in the systolic blood pressure and a vasodilatory effect on the mesenteric bed of SHR animals. That effect on pressure was accompanied by a decrease in oxidative stress and an amelioration of histological organization in treated animals.

Thus, all of the studies have together demonstrated that chronic treatment with açai berry extract prevents the development of hypertension, endothelial dysfunction and vascular structural alterations in rats with hypertension. This indicates that the fruit may have potential for use in the treatment of hypertension in humans.

Platonia insignis Mart.

Platonia insignis Mart. is popularly known as Bacuri. It belongs to the Clusiaceae family, is native to Brazil and is sourced mainly from the states in the northern of Brazil (Costa-Júnior *et al.*, 2011).

A study performed by Mendes *et al.* (2014) evaluated the acute hypotensive effects of ethanol extract and ethyl acetate at different doses (12.5, 25 and 50 mg/kg) from *Platonia insignis* fruit peel in normotensive animals. The study only demonstrated a significant reduction in the mean arterial pressure at doses of 25 and 50 mg/kg in the ethyl acetate fraction. This was accompanied by hypotension and tachycardia at rates of 12.5 and 25 mg/kg; the latter was also observed for the higher dose (50 mg/kg).

The analysis of pathways by which the extract caused hypotension involved the co-administration of L-NAME, hexamethonium, verapamil, propranolol and yohimbine. The potentiation of the effect by the co-administration with L-NAME was observed. Moreover, the hypotensive effect was completely abolished by the administration of yohimbine, which indicates that the primary mechanism by which the

extract promotes hypotension is via the α -adrenergic receptor (Mendes *et al.*, 2014).

Thus, it is possible to conclude that the results are promising, especially considering that few works have evaluated the cardiovascular effects promoted by *Platonia insignis*. Other studies are important in order to evaluate chronic treatment with fruit, in addition to gaining the ability to determine the compounds responsible for these actions.

Conclusion

We can conclude that even with the wealth of species found in Brazilian flora, few studies have explored the beneficial effects of its fruits on the cardiovascular system. It was possible to observe the influence of phenolic compounds present in fruits and their promising effects in hypertension, in addition to inferring the mechanisms of these compounds in antioxidant antihypertensive actions (Fig. 3). It is therefore necessary that further studies are conducted in order to enrich the knowledge in this area and to bring forth various fruits with potential use in the prevention and treatment of chronic diseases by acting as functional foods and/or nutraceuticals.

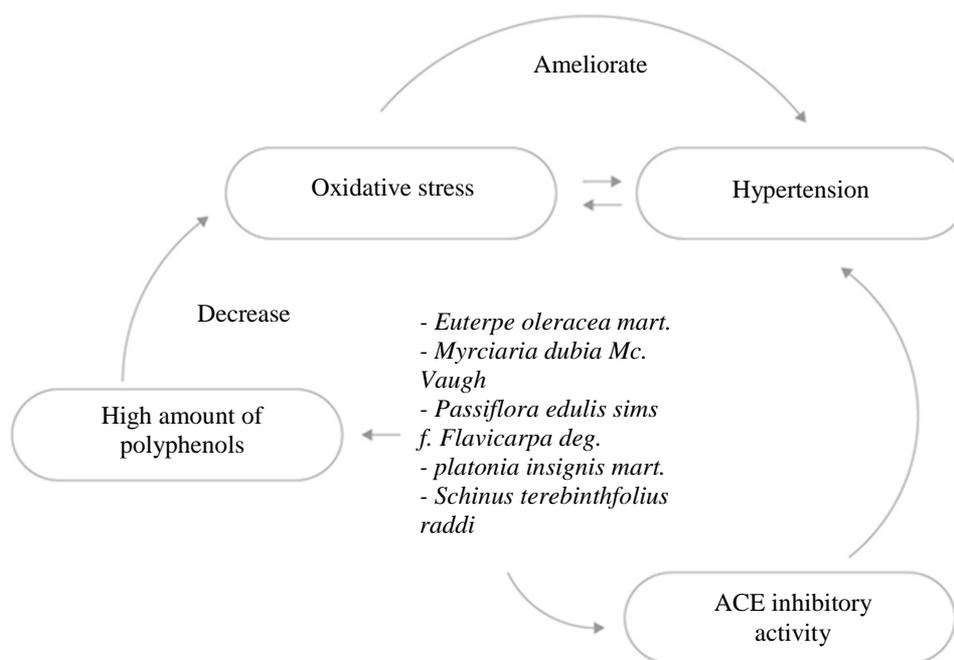


Fig. 3: It is well known the connection between oxidative stress and hypertension. The consume of polyphenols from the Brazilian fruits promote a decrease on oxidative stress, which could help on the decrease of blood pressure observed. That effect are accompanied, in some cases, by the inhibition of angiotensin converting enzyme, which helps to decrease the Renin Angiotensin System (RAS) activation, the main system of blood pressure control and that is augmented in hypertension

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Author's Contributions

Augusto Altoé Puppín: Help with the study design and writing the manuscript.

Christiane Mileib Vasconcelos: Help with the writing of final version of the manuscript.

Mirian de Almeida Silva: Contributed to paper research and with the final version of the manuscript,

Ewelyne Miranda Lima: Contribute with the review of the manuscript, selection of papers and approve the final version of the manuscript.

Tadeu Uggero de Andrade: Contributed with the approval of the final version of the manuscript.

Girlandia Alexandre Brasil: Contributed with the study design, writing the manuscript, approve of final version of the manuscript and paper research.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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