Research, Society and Development, v. 11, n. 8, e52911831364, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i8.31364

Therapeutic potential of flavonoid-rich plants in the treatment of arterial hypertension and diabetes mellitus: focus on antioxidant role

Potencial terapêutico de plantas ricas em flavonoides no tratamento da Hipertensão Arterial e do Diabetes Mellitus: foco no papel antioxidante

Potencial terapéutico de las plantas ricas en flavonoides en el tratamiento de la hipertensión arterial y la diabetes mellitus: centrarse en el papel antioxidante

Received: 06/04/2022 | Reviewed: 06/14/2022 | Accept: 06/16/2022 | Published: 06/28/2022

Matheus Vinicius Barbosa da Silva
ORCID: https://orcid.org/0000-0003-1295-6301
Universidade Federal de Pernambuco, Brazil
E-mail: matheushue30@gmail.com
Gleyciele dos Santos Barbosa
ORCID: https://orcid.org/0000-0002-0020-2193
Universidade Federal de Pernambuco, Brazil
E-mail: gleycielebarbosa20@gmail.com
Alisson Carlos da Rocha
ORCID: https://orcid.org/0000-0003-0573-2529
Universidade Federal de Pernambuco, Brazil
E-mail: alissoncarlos3232@gmail.com
Diego da Rocha
ORCID: https://orcid.org/0000-0002-3475-2724
Centro Universitário AGES, Brazil
E-mail: diegodarocha89@gmail.com
Thais Ana da Silva
ORCID: https://orcid.org/0000-0001-5352-6549
Universidade Federal de Pernambuco, Brazil
E-mail: thais.ana2015@gmail.com
Jackson Alves da Silva
ORCID: https://orcid.org/0000-0003-2484-0939
Universidade Federal de Pernambuco, Brazil
E-mail: ckssilva0011@gmail.com
Alyssa Castelo Branco Alencar Andrade
ORCID: https://orcid.org/0000-0001-8605-1076
Centro Universitário Christus, Brazil
E-mail: alyssaalencar@outlook.com
Bruna Bezerra Pimentel Andrade
ORCID: https://orcid.org/0000-0002-7970-2173
Universidade Federal de Pernambuco, Brazil
E-mail: bru.bezerra@gmail.com
Francisco Antonio da Cruz dos Santos
ORCID: https://orcid.org/0000-0003-1065-5695
Centro Universitário Planalto do Distrito Federal, Brazil
E-mail: facs.francisco.facs@gmail.com
Jonas Laerte Longen Junior
ORCID: https://orcid.org/0000-0003-3732-9216
Centro Universitário de Pato Branco, Brazil
E-mail: jonaslongenjr@gmail.com
Heverton Valentim Colaço da Silva
ORCID: https://orcid.org/0000-0001-7169-4140
Universidade Federal de Pernambuco, Brazil
E-mail: neto_pe6@liv.com

Abstract
Introduction: Chronic non-communicable diseases are the main causes of morbidity and mortality today, among them, Arterial Hypertension (SAH) and Type 2 Diabetes Mellitus (T2DM), which are responsible for a variety of systemic complications. Both conditions share, in their pathophysiology, the state of oxidative stress, justifying the possible use of antioxidant components, such as flavonoids. Objectives: To characterize and describe the therapeutic potential of the main medicinal plants of popular use, rich in flavonoid-type antioxidant constituents, in the treatment of hypertension

and diabetes. Methodology: An integrative literature review study, developed from a survey in PubMed, MEDLINE and LILACS databases. Results: From the survey, the following plants used for hypertension stood out: Hibiscus sabdariffa, Allium sativum L., Phyllathus amarus, Ginkgo biloba and Matricaria chamomilla. As for diabetes, the following stand out: *Syzygium cumini L*., *Caesalpinia sappan*, *Andrographis paniculata* and *Curcuma longa L*. Conclusion: The results showed that the use of medicinal plants rich in flavonoids can serve as an important ally in the prevention, control and treatment. of SAH and T2DM, acting mainly against the state of oxidative stress, a common pathophysiological mechanism in both diseases, and thus preventing the occurrence of complications resulting from this state.
Keywords: Medicinal plants; Hypertension; Antioxidants; Flavonoids; Diabetes Mellitus.

Resumo

Introdução: As doenças crônicas não transmissíveis configuram-se como as principais causas de morbimortalidade na atualidade, entre elas destacam-se a Hipertensão Arterial (HAS) e o Diabetes Mellitus tipo 2 (DM2), as quais são responsáveis por uma variedade de complicações sistêmicas. Ambas as condições compartilham entre si, na sua fisiopatologia, o estado de estresse oxidativo, justificando o possível uso de componentes antioxidantes, como os flavonoides. Objetivos: Caracterizar e descrever o potencial terapêutico das principais plantas medicinais de uso popular ricas em constituintes antioxidantes do tipo flavonoides, no tratamento da hipertensão e diabetes. Metodologia: Estudo de revisão integrativa da literatura, desenvolvida a partir do levantamento nas bases de dados PubMed, MEDLINE e LILACS. Resultados: A partir do levantamento, destacaram-se como plantas utilizadas para a hipertensão: *Hibiscus sabdariffa*, *Allium sativum L*., *Phyllathus amarus*, *Ginkgo biloba* e *Matricaria chamomilla*. Enquanto para o diabetes, destacaram-se: *Syzygium cumini L*., *Caesalpinia Sappan*, *Andrographis paniculata* e *Curcuma Longa L*. Conclusão: Os resultados mostraram que o uso de plantas medicinais ricas em flavonoides pode servir como um importante aliado na prevenção, controle e tratamento da HAS e do DM2, atuando principalmente frente ao estado de estresse oxidativo, mecanismo fisiopatológico comum em ambas as doenças, e dessa forma previne a ocorrência de complicações decorrentes deste estado.
Palavras-chave: Plantas medicinais; Hipertensão; Antioxidantes; Flavonoides; Diabetes Mellitus.
.

Resumen

Introducción: Las enfermedades crónicas no transmisibles son las principales causas de morbilidad y mortalidad en la actualidad, entre ellas, la Hipertensión Arterial (HAS) y la Diabetes Mellitus tipo 2 (DM2), las cuales son responsables de diversas complicaciones sistémicas. Ambas condiciones comparten, en su fisiopatología, el estado de estrés oxidativo, justificando el posible uso de componentes antioxidantes, como los flavonoides. Objetivos: Caracterizar y describir el potencial terapéutico de las principales plantas medicinales de uso popular, ricas en constituyentes antioxidantes de tipo flavonoides, en el tratamiento de la hipertensión arterial y la diabetes. Metodología: Estudio integrador de revisión bibliográfica, desarrollado a partir de una encuesta en las bases de datos PubMed, MEDLINE y LILACS. Resultados: De la encuesta se destacaron las siguientes plantas utilizadas para la hipertensión: *Hibiscus sabdariffa, Allium sativum L., Phyllathus amarus*, *Ginkgo biloba* y *Matricaria chamomilla*. En cuanto a la diabetes se destacan*: Syzygium cumini L., Caesalpinia sappan, Andrographis paniculata* y *Curcuma longa L*. Conclusión: Los resultados mostraron que el uso de plantas medicinales ricas en flavonoides puede servir como un importante aliado en la prevención, control y tratamiento de la HAS y la DM2, actuando principalmente contra el estado de estrés oxidativo, mecanismo fisiopatológico común en ambas enfermedades, y previniendo así la aparición de complicaciones derivadas de este estado.
Palabras clave: Plantas medicinales; Hipertensión; Antioxidantes; Flavonoides; Diabetes Mellitus.

1. Introduction

Chronic non-communicable diseases, including type 2 Diabetes Mellitus (T2DM) and Systemic Arterial Hypertension (SAH), are one of the leading causes of morbidity and mortality in Brazil and worldwide (Neves et al., 2021). These diseases are important risk factors for the development of cardiovascular diseases, with consequences for the quality and life expectancy of individuals and dramatically increasing the risk of death (Silva et al., 2022; Neves et al., 2021; Costa et al., 2020; Malta et al., 2015).

Inadequate control of T2DM and SAH leads to a variety of complications in the long term. In diabetes, nephropathy, diabetic retinopathy and neuropathy, acute myocardial infarction, stroke, and peripheral vascular disease stand out (Tschiedel, 2014). While in SAH, the main complications are infarction, heart failure, kidney disease, and stroke. Preventive strategies are urgently needed to reduce such complications (Hugel et al., 2016).

Antidiabetic and antihypertensive pharmacological treatment have presented numerous advances in recent years.

However, it is still observed that in many patients, the effectiveness of these currently used therapies is still limited. Such limitations have stimulated the search for new drugs of natural plant-based origin (Cogolludo, 2005; Dinda et al., 2019).

Since ancient times, many plants have been used for medicinal purposes, helping to alleviate diseases. There has been a long-standing interest in the search for new herbal drugs, focusing on the prevention and treatment of T2DM and SAH. The discovery of several bioactive substances present in different plant species enabled the development of numerous drugs currently used for the treatment of different diseases, and until today they arouse interest in new research, due to the great diversity of plant species not yet fully understood and studied (Sen & Samanta, 2014).

T2DM and SAH are pathologies that share similarities in their causal risk factors and the mechanisms involved in their pathophysiologies, such as upregulation of the renin-angiotensin-aldosterone system, inflammation, and oxidative stress (Cheung & Li, 2012; Petrie et al., 2018). Given their antioxidant activities, the latter can be attenuated or reversed by antioxidant molecules, such as flavonoids. They act by eliminating and preventing the formation of reactive oxygen species (ROS), such as superoxide anion and peroxynitrite (Cheng et al., 2017).

In this way, the objective of the present study was to characterize and describe the therapeutic potential of the central medicinal plants of widespread use rich in antioxidant constituents, such as flavonoid-type phenolic compounds, as a possible alternative for the treatment of two chronic diseases, systemic arterial hypertension and type 2 diabetes mellitus.

2. Methodology

This is an integrative literature review, one of the most widely used literature review methods in the approach to evidence-based practice. This type of study allows the inclusion of experimental and non-experimental studies to understand a particular phenomenon studied. For its elaboration, the following six steps were followed: identification of the theme and elaboration of the guiding question; choice of criteria and literature search; data collection; critical analysis of included studies; discussion of results and presentation of the review/synthesis of knowledge (Souza et al., 2010; Mota et al., 2017).

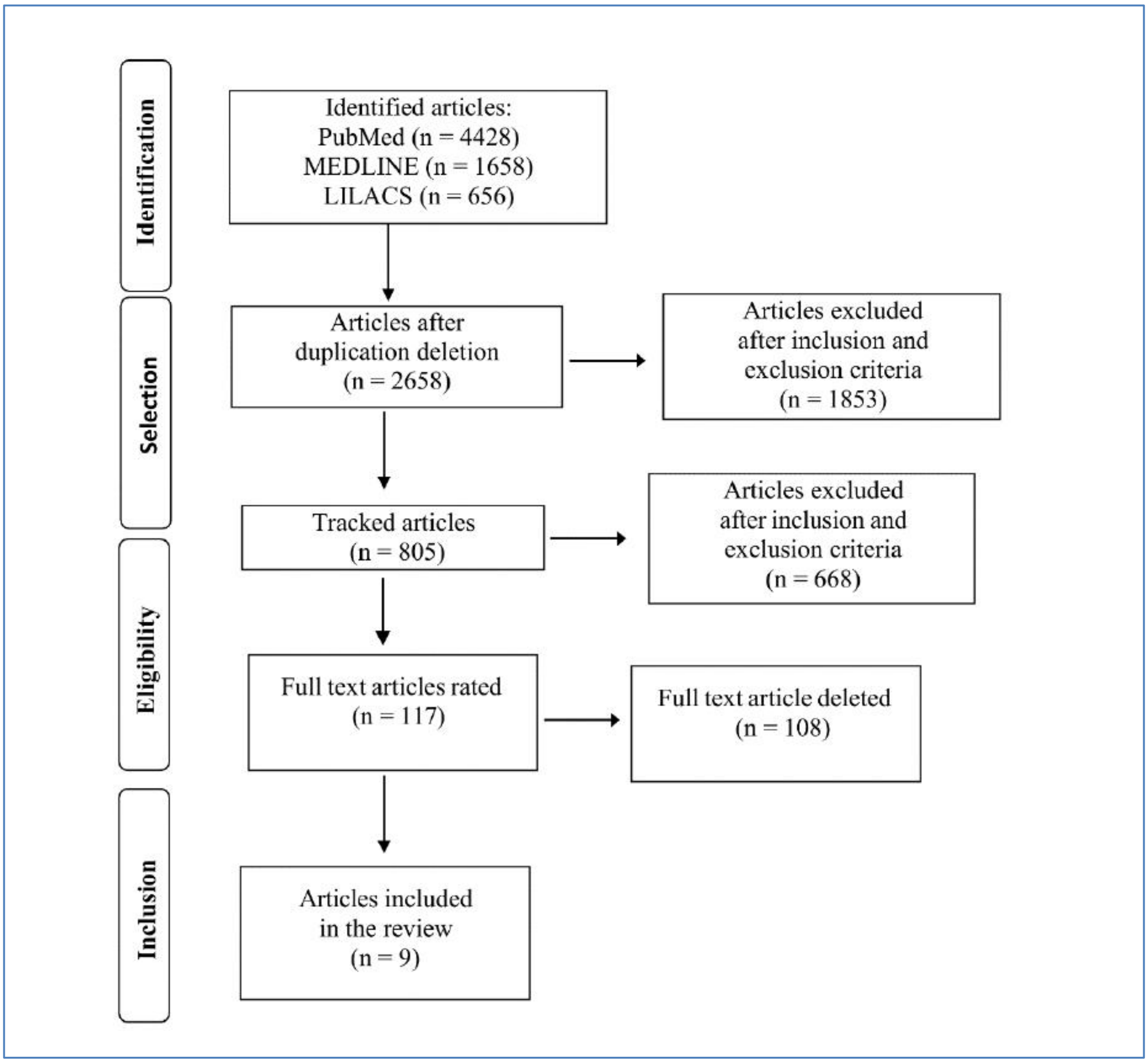
The study was conducted with the following guiding question: “What are the main medicinal plants of popular use rich in flavonoid-like compounds that can be used as a possible alternative for treating Systemic Arterial Hypertension and Type 2 Diabetes Mellitus?”

The survey of studies was carried out in the Medical Literature Analysis and Retrievel System Online (MEDLINE), Latin American and Caribbean Literature in Health Sciences (LILACS), and National Library of Medicine (PubMed) databases. The search in LILACS and MEDLINE was carried out by combining the descriptors in health sciences: “hypertension”, “antioxidants”, “medicinal plants” and “diabetes mellitus”. While at PubMed, the search was performed using the following terms registered in the Medical Subject Headings (MeSH): “plants medical”; “hypertension”; “diabetes mellitus”; "antioxidants" and "flavonoids". All descriptors were linked by the Boolean connector “AND”. To assist in the study selection process, the flowchart of the Statement for Reporting Systematic Reviews and Meta-Analyses of Studies (PRISMA) was used (Moher, 2009).

The following inclusion criteria were defined: full-text articles published between 2012 and 2022 in peer-reviewed journals, in Portuguese and English, indexed in MEDLINE, LILACS, or PubMed. Articles that did not meet the objective, the proposed criteria, and duplicates, as well as theses, case studies, dissertations, and book chapters, were excluded from the study. After reading the selected studies, a systematic review and categorization were performed through a data extraction form, extracting data on the author, year of publication, popular name, species name, part used, and central plant properties.

Research, Society and Development, v. 11, n. 8, e52911831364, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i8.31364

Figure 1. PRISMA flowchart illustrating the process by which the articles in this integrative review were included or excluded.



Source: Flowchart of the PRISMA group adapted by the authors (20220).

3. Results and Discussion

The bibliographic survey in the electronic databases MEDLINE, LILACS, and PubMed enabled the identification of 6742 titles. Subsequently, after applying the inclusion and exclusion criteria, nine were selected to compose the final sample of this study.

The articles included in this review were categorized in two tables according to the author, year of publication, popular name, species name, part used, and central plant properties, one containing the primary plants with therapeutic potential in the treatment of SAH and the other those in T2DM (Table 1 and 2, respectively). Soon after, the discussion of the relationship between the use of flavonoids and the state of oxidative stress was carried out, contextualizing the diseases addressed and the plants evidenced through the survey.

Table 1. Summary of studies related to hypertension included in the study, according to author/year of publication, title, country of study, plant, and properties.

Author/year of publication	Popular name	Species name	Used part	Main properties
Jalalyazdi et al., 2019	Caruru sorrel	***Hibiscus sabdariffa***	Flowers	The daily intake of two cups of *Hibiscus sabdariffa* tea for a month, associated with lifestyle changes, significantly reduced blood pressure in hypertensive patients.
Chen et al., 2021	Garlic	***Allium sativum* L.**	Bulbs	Supplementation with *Allium sativum* extract promoted a reduction in blood pressure in hypertensive animals, an increase in nitric oxide and bradykinin levels, and an increase in the activity of antioxidant enzymes.
Yao et al., 2020	Stonebreaker	***Phyllanthus amarus***	All	Supplementation with *Phyllanthus amarus* extract prevented the increase in blood pressure in DOCA-SAL hypertensive animals, in addition to improving cardiac diastolic function, reducing cardiac wall thickening and oxidative stress.
Zaher et al., 2018	Ginkgo	***Ginkgo biloba***	Sheets	Treatment with standardized extract of *Ginkgo biloba* leaves effectively reduced systolic and diastolic blood pressure, reduced the level of markers of oxidative stress, and prevented the reduction in nitric oxide and glutathione levels induced by hypertension.
Awaad et al., 2018	Chamomile	***Matricaria chamomilla* L.**	Stalk	Treatment of different groups with extracts of *Matricaria chamomilla* L was able to reduce systolic and diastolic blood pressure, and heart rate, and restore the level of antioxidant enzymes.

Source: Authors.

Tabela 2. Summary of studies related to type 2 diabetes mellitus included in the study, according to author/year of publication, title, country of study, plant and properties.

Author/year of publication	Popular name	Species name	Used part	Main properties
Baldissera et al., 2016	Jammelon	***Syzygium cumini* L.**	Sheets	Treatment with *Syzygium cumini* L extract in diabetic rats reduced plasma glucose levels, reduced oxidative stress, and reduced the destruction of pancreatic cells.
Wediasari et al., 2020	Brazilwood	***Caesalpinia sappan***	Heartwood	In an experimental model of diabetes induced by streptozotocin, treatment with *Caesalpinia sappan* extract promoted a reduction in serum glucose concentrations and an increase in pancreatic β cell count.
Jaiyesimi et al., 2020	Green chiretta	***Andrographis paniculata***	Sheets	Treatment with *Andrographis paniculata* polyphenol-rich extract promoted the reduction of oxidative stress in a diabetes model and increased the activity of glycolytic enzymes and insulin levels.
Ramkumar et al., 2022	Turmeric	***Curcuma longa* L.**	Rhizoma	Treatment with extracts of *Curcuma Longa* L. was able to promote the reduction of hyperglycemia, the levels of the marker of chronic hyperglycemia, fructosamine, and inhibiting the activity of pancreatic α-amylase.

Source: Authors.

3.1 Flavonoids and oxidative stress

The production of reactive species occurs naturally in the body and constitutes an essential process for cellular reactions, including cell signaling events, gene expression, and defense against invading microorganisms. The main intracellular sources of these free radicals are mitochondria, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, cyclooxygenases, nitric oxide synthase, and cytochrome p450 enzymes. However, physiologically, the body has mechanisms, enzymatic and non-enzymatic, to protect against free radicals, such as superoxide dismutase, catalase, glutathione peroxidase, β-carotene, α-tocopherol, glutathione, bilirubin, and nicotinamide (Rajendran et al., 2014; Senoner, Dichtl, 2019).

In addition, exogenous antioxidants such as phenolics, including flavonoids, stand out (Liguori et al., 2018). However, in conditions in which ROS production exceeds the capacity of cellular antioxidant systems, we have the so-called oxidative stress state, which can generate considerable damage in the body, causing or accelerating a series of pathological conditions (Rajendran et al., 2014).

A wide variety of constituents can be found in plants, among which phenolic compounds or polyphenols stand out. The leading representative of this class are flavonoids, one of the most abundant bioactive constituents in plants. Flavonoids can be classified according to their structure into six subclasses: flavanols, flavonols, flavanones, flavones, isoflavones, and anthocyanins (Rosário et al., 2020). They can be found in fruits, teas, wine, vegetables, and seeds (Ciurmanean et al., 2020; Ress, 2018).

Flavonoids have numerous biological activities, such as antioxidant, anti-inflammatory, anticancer, and antimutagenic. In plants, flavonoids play an essential role in destroying free radicals and in the defense against harmful agents (Ciurmanean et al., 2020). The antioxidant activity is evidenced by reducing the oxidative stress state through different mechanisms, reducing the expression and activation of ROS-forming protein subunits, such as NADPH oxidase, in addition to helping to regulate the expression of ROS, antioxidant enzymes such as superoxide dismutase and catalase (Cheng et al., 2017).

Phenolic compounds, such as flavonoids, have made these compounds the target of many studies due to their various activities beneficial to health, especially the potent antioxidant activity (Ferrerra et al., 2016). Several studies have shown positive effects of the use of plants rich in flavonoids in diseases that present the state of oxidative stress as one of the mechanisms related to their pathophysiology. They are effective in improving endothelial function, blood pressure, insulin sensitivity, and action, regulating glucose metabolism, as well as helping to prevent DM2 (Ferrerra et al., 2016; Rees, 2018; Paéz et al., 2013; Dinda et al., 2013; Dinda et al. al., 2020).

3.2 Systemic Arterial Hypertension

SAH is one of the most prevalent and incident diseases worldwide, where it is estimated that approximately 1.4 billion people have hypertension, with only a tiny portion of those affected with controlled disease. SAH is defined by high and sustained blood pressure levels and is a significant risk factor for cardiovascular diseases (WHO, 2021). When uncontrolled, it dramatically increases the risk of heart, kidney, and brain disease (Noone et al., 2018).

The ways of treating SAH include pharmacological and non-pharmacological approaches. Pharmacological treatment prescribes the primary drugs to treat the disease, belonging to the following classes: thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and calcium channel antagonists, either alone or in combination (Flack, 2019). Non-pharmacological strategies include reducing daily sodium intake, increasing fruit and vegetable intake, exercising regularly, and controlling the intake of trans and saturated fats (WHO, 2021; Noone et al., 2018). Evidence shows the critical role of diet in controlling hypertension, through the intake of grains, vegetables, fruits, and vegetables, as they are rich in components beneficial to health, such as flavonoids (Gibbs et al., 2021).

The consumption of flavonoids is related to a range of beneficial effects on the cardiovascular system and blood pressure control through the improvement of endothelial function, increased nitric oxide bioavailability, reduction of oxidative stress, and inhibition of matrix metalloproteinase activity (Hugel et al., 2016). As also shown in the Australian longitudinal, which showed that higher consumption of flavonoids, such as flavones, isoflavones, and flavanones, was effective in reducing the incidence of hypertension (Rosário et al., 2020).

According to the bibliographic survey, the plants that can be used as an alternative for SAH treatment are *Phyllanthus amarus, Hibiscus sabdariffa, Allium sativum* L., *Matricaria chamomilla* L. and *Ginkgo biloba*, which will be broken down below.

3.2.1 *Phyllanthus amarus*

Phyllanthus amarus, also popularly known as stonebreaker, is a tropical plant used throughout the world, belonging to the family of Euphorbiaceaes, being traditionally used to treat various pathologies. Among the various applications in traditional medicine, the plant is used for diabetes, hypertension, malaria, asthma, kidney, liver, gastrointestinal and skin disorders.

According to phytochemical studies, several active metabolites can be found in the plant, such as flavonoids, triterpenes, sterols, and alkaloids. Such constituents are related to the broad spectrum of pharmacological activities linked to the plant (Patel et al., 2011; Yao et al., 2018; Ogunmoyole et al., 2020).

The use of the aqueous extract of *Phyllanthus amarus* in a model of hypertension induced by desoxycorticosterone showed that treatment with the extract could reduce systolic and diastolic blood pressure, oxidative stress state, and cardiac hypertrophy generated by hypertension (Yao et al., 2020). In agreement with previous findings, treatment with plant preparations promoted potent diuretic activity, evidenced by the increase in urinary output associated with greater sodium excretion and significantly reducing systolic and diastolic blood pressure (Srividya, 1995; Yao et al., 2018).

3.2.2 *Hibiscus sabdariffa*

Hibiscus sabdariffa is a tropical plant, commonly known as caruru sorrel, it is used for several diseases, including SAH, due to a large number of beneficial compounds present in its composition, such as flavonoids, organic acids, such as citric and malic acids, in addition to minerals (Serban et al., 2015; Hopkins et al., 2013). Studies report that *Hibiscus sabdariffa* has several biological activities, such as antibacterial, antioxidant, diuretic, antidiabetic, and antihypertensive. The latter is possibly mediated by angiotensin-converting enzyme inhibition, endothelium-mediated vasodilation, calcium influx block, and cyclooxygenase inhibition (Hopkins et al., 2013; Serban et al., 2015; Jalalyazdi et al., 2019). Its use is considered an essential ally for the prevention of cardiovascular diseases and their risk factors (Serban et al., 2015; Jalalyazdi et al., 2019).

A randomized clinical trial with stage 1 hypertensive patients showed that the daily use of *hibiscus sabdariffa* tea for one month, combined with improvements in dietary and physical lifestyle, promoted a reduction in blood pressure in these patients (Jalalyazdi et al., 2019). In another study carried out in Jordan, uncontrolled hypertensive patients were treated adjuvantly with *hibiscus sabdariffa* tea, in which a reduction in systolic and diastolic blood pressure was observed (Anbaki et al., 2019). Similar to what was shown in a previous study, where standardized powdered extract of hibiscus sabdariffa offered to hypertensive patients for daily use for four weeks, showed excellent tolerability and was influential in lowering blood pressure (Herrera et al., 2004).

3.2.3 *Allium sativum* L.

Allium sativum L., also known as garlic, is a plant belonging to the alliaceae family. It is one of the main herbs used around the world. Among the various presentations, it is commonly used as a seasoning, food, and medicine. It is considered an essential ally in the prevention and treatment of cardiovascular diseases and their risk factors, such as SAH (Ried, 2016). *Allium sativum L.* contains several bioactive compounds such as flavonols, organosulfur compounds such as allicin, alllin, 1-propenyl allylthiosulfonate, g-L-glutamyl-S-alkyl-L-cysteine, diallyl sulfide, diallyl disulfide, diallyl trisulfide (Ried, 2014; Bahadoran et al., 2017). Studies have shown that *Allium sativum L.* has antihypertensive activities, with blood pressure reductions similar to those obtained with classic antihypertensive drugs (Ried, 2014).

The mechanisms by which *Allium sativum* L. reduces blood pressure include decreased peripheral vascular resistance by acting similarly to prostaglandins, inhibiting endothelial contractile factors such as endothelin-1, increased vasorelaxation mediated by nitric oxide, and by blocking the production of angiotensin -II (Ried, 2013; Ried, 2014; Bahadoran et al., 2017). As also shown in a study by Chen et al., 2021 where supplementation of hypertensive rats for four weeks with extracts and nanoemulsions of black garlic, rich in flavonoids, was able to reduce blood pressure, increase bradykinin and nitric oxide levels, two vasodilating agents, attenuate oxidative stress, evidenced by increased activity of antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase, in addition to reducing serum levels of angiotensin-II and aldosterone.

3.2.4 *Matricaria chamomilla L.*

Chamomile or *Matricaria chamomilla* L. is a medicinal plant used worldwide for various ailments (Bas et al., 2021). The plant has several beneficial constituents for human health, such as flavones, flavanones, and lipophilic actives. These confer numerous biological activities to the plant, such as antioxidant, anti-inflammatory, antiulcerogenic, antimicrobial, anxiolytic and sedative, immunomodulatory, and antihypertensive (Bas et al., 2021; Chauhan et al., 2021).

As shown in a study carried out in Saudi Arabia, extracts of *Matricaria chamomilla L.* were able to reduce the activity of the angiotensin-converting enzyme, a key enzyme related to blood pressure control, where its upregulation is related to the pathophysiology of SAH (Bas et al., 2021). In line with a previous study, which showed that ingestion of *Matricaria chamomilla L.* extracts in humans was effective in reducing heart rate, systolic and diastolic blood pressure, attenuating oxidative stress, restoring the level of antioxidant components such as superoxide dismutase and glutathione, in addition to having little or no side effects associated with their use (Awaad et al., 2018).

3.2.5 *Ginkgo biloba*

Ginkgo biloba, also known as ginkgo or maiden tree, is one of the most used medicinal plants in the world. It is also known as a "living fossil" because it is estimated that its emergence occurred thousands of years ago (Shaito et al., 2020). The plant has numerous constituents that play essential activities for human health, such as terpenoids, sesquiterpenes, acids, organic compounds, and flavonoids, the latter being highly present, mainly flavone glycosides. Flavonoids are mainly responsible for the plant's remarkable antioxidant and anti-inflammatory activity. *Ginkgo biloba* leaves are popularly used to treat a range of diseases, including SAH (Shaito et al., 2020; Park, 2014).

A study showed that the use of a standardized extract of *Ginkgo biloba* in hypertensive rats was able to reduce the blood pressure of these animals, both in systolic and diastolic values. In addition, the treatment was shown to attenuate oxidative stress, evidenced by the reduction of stress markers, such as malonaldehyde, in addition to preventing the reduction of nitric oxide and glutathione bioavailability, as well as being able to protect against kidney damage, secondary to hypertension (Zaher et al., 2018). Although such beneficial effects in experimental models, other previous studies show disagreement, where it was seen that the treatment with *Ginkgo biloba* was not shown to be statistically effective in reducing blood pressure in the elderly, and more robust studies are needed to consolidate the application of the plant as a future alternative for the treatment of SAH (Brinkley, et al, 2010; Xiong et al., 2014)

3.3 Type 2 diabetes mellitus

Diabetes mellitus is a chronic disease (WHO, 2016) caused by defects in the production and secretion of insulin by pancreatic beta cells, defects in insulin receptors on target cells, or both, causing hyperglycemia, which can cause various damages to the organism, altering the metabolism of carbohydrates, proteins, and lipids. When not properly treated, it can progress to microvascular and macrovascular complications, markedly increasing the risk of death (Dallaqua, 2011; Abhar, 2014). The primary forms of treatment for T2DM include non-pharmacological strategies, through lifestyle changes, with the regular practice of physical activity and a controlled diet. From the pharmacological point of view, synthetic oral hypoglycemic agents and insulin stand out (Abhar, 2014).

Among the mechanisms related to the pathophysiology of T2DM is oxidative stress, a critical event for the activation of redox-sensitive signaling pathways that lead to the generation of cell damage (Petrie et al., 2018). In addition to autonomic dysfunction, inflammation (Agashe, 2018), endothelial dysfunction evidenced by low NO synthesis and increased vascular contractile tone (Kanter, 2017), and insulin resistance (Awar et al., 2016).

Currently, a wide variety of plants are known that are used to prevent and manage diabetes mellitus. It is known that among the various plants widely used worldwide for the treatment of T2DM, many of them are still based on empirical knowledge, where the properties and adverse effects have not yet been confirmed or scientifically proven (Dallaqua, 2011).

Several studies have shown that teas, vegetables, and fruits in a diet rich in flavonoids can help in the treatment of T2DM, which are cheap, effective options with an excellent safety profile, emerging as promising alternatives to replace some current antidiabetic drugs, which have several limitations with prolonged use (Dinda et al., 2019). Flavonoids may act on pathways that stimulate insulin release, increase expression and translocation of glucose transporters, and improve insulin sensitivity in target organs (Martin, 2021; Gandhi et al., 2020).

Evidence shows that plants rich in antioxidant constituents such as flavonoids are a potential alternative for treating T2DM, especially: *Syzygium cumini*, *Curcuma longa L.*, *Caesalpinia sappan* and *Andrographis paniculata*.

3.3.1 *Syzygium cumini L.*

Plants such as *Syzygium cumini* L., from the Myrtaceae family, popularly known as Jambolan or Purple Olives, are widely used in folk medicine to treat a variety of disorders, including T2DM. Through phytochemical analysis, constituents such as phenols, terpenoids, tannins, saponins, phytosterols, and flavonoids were observed in the bark of its stem, fruits, seeds, and leaves (Ayyanar, 2012; Veber et al., 2015; Qamar et al., 2022). Due to the presence of a range of bioactive constituents identified in the plant, a variety of pharmacological activities are related to it, such as antioxidant, anti-inflammatory, anticancer, and antidiabetic (Qamar et al., 2022).

A study carried out in diabetic rats, where treatment with hydroalcoholic extract made with *Syzygium cumini* leaves was performed, showed the extract's ability to reduce hyperglycemia, improved the oxidative profile by increasing the expression of antioxidant enzymes such as superoxide dismutase and catalase, preventing damage to DNA and target organs, in addition to attenuating the destruction of pancreatic β cells (Baldissera et al., 2016).

Another study carried out in an experimental model of DM2, induced by treatment with alloxan, a diabetogenic chemical agent (Awar et al., 2016), showed that treatment with *Syzygium cumini* seed extract promoted antidiabetic activities and antihyperglycemic effect, showing is a potent and safe ally for the treatment of T2DM (Bansode et al., 2017). Similar to what was previously observed in an *in vitro* study with L6 myogenic cells, where *Syzygium cumini* promoted increased expression of phosphoinositide 3 (PI3) kinase, an essential enzyme in insulin signaling. In addition to increasing the transcription of glucose transporter type 4 (GLUT4) mRNA, improving glucose reuptake (Anandharajan et al., 2006).

3.3.2 *Curcuma longa* L.

Turmeric or scientifically known as *Curcuma longa* L., is a plant of the Zingiberaceae family that is used worldwide as a remedy for the treatment of various conditions such as dyslipidemias, T2DM, Alzheimer's, and multiple sclerosis (Bodalska et al., 2017). The main active constituents present in turmeric are curcuminoids, a subclass derived from flavonoids, in particular curcumin and its derivatives, demethoxycurcumin, and bisdemethoxycurcumin (Thota et al., 2019). A wide variety of biological activities are related to the plant, such as anti-inflammatory, antioxidant, antiangiogenic, antidiabetic, and anti-infectious (Bodalska et al., 2017).

A randomized study with diabetic patients showed that curcumin supplementation improved insulin sensitivity, promoting a reduction in serum hormone, plasma triglycerides, and atherogenic plasma index (Thota et al., 2019). Similar to what was exposed in another study, where treatment with *Curcuma longa* L. extract could reduce hyperglycemia, observed by reducing pancreatic α-amylase activity and serum fructosamine levels, in addition to improving hepatic and renal parameters altered by diabetes (Ramkumar et al., 2021).

3.3.3 *Caesalpinia sappan*

Caesalpinia sappan is a medicinal plant belonging to the Caesalpiniaceae family, widely used in different regions of the world to treat diseases such as T2DM, anemia, and heart problems. A range of activities is related to the plant, such as antioxidant and anti-inflammatory (Syamsunarmo et al., 2021). Among the main bioactive constituents found in the plant, flavonoids stand out, which are related to the notorious antioxidant effects performed by the plant (Syamsunarmo et al., 2021; Uddin et al., 2015).

The antidiabetic effects of the plant are related to effects on several pathways and genes related to the pathophysiology of T2DM (Adnan et al., 2022). According to a study carried out in diabetic rats, treatment with *Caesalpinia sappan* extract promoted significant antidiabetic activity to reduce serum glucose concentrations and increase pancreatic β cell count (Wediasari et al., 2020). In addition, the plant showed an essential effect on dipeptidyl peptidase 4, the enzyme responsible for cleaving incretins such as glucagon-like peptide-1, a hormone related to the improvement of pancreatic function, promoting increased insulin secretion (Setyaningsih et al., 2019).

3.3.4 *Andrographis paniculata*

Andrographis paniculata, popularly known as green chiretta, is a medicinal plant native to the Asian continent, used to treat various pathological conditions such as tonsillitis, cancer, typhoid fever, T2DM, eczema, diphtheria, epilepsy, gonorrhea, syphilis and dandruff (Wediasari et al., 2020). The plant has several pharmacological activities, such as antioxidant and antidiabetic, related to the effect of its constituents, which include flavonoids and other terpenoids such as andrographolide, the latter being a metabolite with potent antidiabetic activity (Dai et al., 2018).

Several studies have shown positive effects of treatment with *Andrographis paniculata* extracts for diabetes, promoting significant effects on mechanisms involved in the development and progression of diabetes (Dai et al., 2018; Akhtar et al., 2018; Nugroho et al., 2012). According to a study carried out in an experimental model of diabetes-induced by treatment with alloxan, treatment with an extract rich in polyphenols from *Andrographis paniculata* was able to reduce oxidative stress, increase the activity of glycolytic enzymes and increase insulin levels (Jaiyesimi et al., 2020). In addition, it can reduce blood glucose levels, increase the activity of antioxidant enzymes such as SOD, CAT, and glutathione (Hidayat, 2021; Nugroho et al., 2012; in addition to promoting cardioprotective effects, attenuating the process of diabetic cardiomyopathy by reducing oxidative stress and cardiac inflammation (Liang et al., 2018).

4. Final Considerations

The results showed that medicinal plants rich in flavonoids can serve as an important ally in preventing, controlling, and treating SAH and T2DM, as evidenced in experimental and non-experimental studies. Flavonoids and other antioxidant constituents present in these plants act mainly against the state of oxidative stress, a common pathophysiological mechanism in both diseases, and thus prevent the occurrence of complications resulting from this state. However, further clinical studies are still needed to consolidate information about the properties of these plants and the effectiveness of long-term treatment for SAH and T2DM.

References

Abdel-Zaher, A. O., Farghaly, H. S. M., El-Refaiy, A. E. M., & Abd-Eldayem, A. M. (2018). Protective effect of the standardized leaf extract of Ginkgo biloba (EGb761) against hypertension-induced renal injury in rats. *Clinical and Experimental Hypertension*, 40(8), 703–714. https://doi.org/10.1080/10641963.2018.1425421

Adab, Z., Eghtesadi, S., Vafa, M., Heydari, I., Shojaii, A., Haqqani, H., & Eghtesadi, M. (2019). Effect of turmeric on glycemic status, lipid profile, hs-CRP, and total antioxidant capacity in hyperlipidemic type 2 diabetes mellitus patients. *Phytotherapy Research*, *33*(4), 1173–1181. https://doi.org/10.1002/ptr.6312

Adnan, Md., Jeon, B.-B., Chowdhury, Md. H. U., Oh, K.-K., Das, T., Chy, Md. N. U., & Cho, D.-H. (2022). Network Pharmacology Study to Reveal the Potentiality of a Methanol Extract of Caesalpinia sappan L. *Wood against Type-2 Diabetes Mellitus. Life,* 12(2), 277. https://doi.org/10.3390/life12020277

Agashe, S., & Petak, S. (2018). Cardiac Autonomic Neuropathy in Diabetes Mellitus. *Methodist DeBakey Cardiovascular Journal*, *14*(4), 251. https://doi.org/10.14797/mdcj-14-4-251

Akhtar, M., Bin Mohd Sarib, M., Ismail, I., Abas, F., Ismail, A., Lajis, N., & Shaari, K. (2016). Anti-Diabetic Activity and Metabolic Changes Induced by Andrographis paniculata Plant Extract in Obese Diabetic Rats. *Molecules*, 21(8), 1026. https://doi.org/10.3390/molecules21081026

Al-Anbaki, M., Nogueira, R. C., Cavin, A.-L., Al-Hadid, M., Al-Ajlouni, I., Shuhaiber, L., & Graz, B. (2019). Treating Uncontrolled Hypertension with Hibiscus sabdariffa When Standard Treatment Is Insufficient: Pilot Intervention. *The Journal of Alternative and Complementary Medicine*, *25*(12), 1200–1205. https://doi.org/10.1089/acm.2019.0220

Al-awar, A., Kupai, K., Veszelka, M., Szűcs, G., Attieh, Z., Murlasits, Z., & Varga, C. (2016). Experimental Diabetes Mellitus in Different Animal Models. *Journal of Diabetes Research*, *2016*, 1–12. https://doi.org/10.1155/2016/9051426

Anandharajan, R., Jaiganesh, S., Shankernarayanan, N. P., Viswakarma, R. A., & Balakrishnan, A. (2006). *In vitro* glucose uptake activity of Aegles marmelos and Syzygium cumini by activation of Glut-4, PI3 kinase and PPARγ in L6 myotubes. *Phytomedicine*, *13*(6), 434–441. https://doi.org/10.1016/j.phymed.2005.03.008

Awaad, A. A., El-Meligy, R. M., Zain, G. M., Safhi, A. A., AL Qurain, N. A., Almoqren, S. S., & Al-Saikhan, F. I. (2018). Experimental and clinical antihypertensive activity of Matricaria chamomilla extracts and their angiotensin-converting enzyme inhibitory activity. *Phytotherapy Research*, *32*(8), 1564–1573. https://doi.org/10.1002/ptr.6086

Ayyanar, M., & Subash-Babu, P. (2012). Syzygium cumini (L.) Skeels: A review of its phytochemical constituents and traditional uses. *Asian Pacific Journal of Tropical Biomedicine*, *2*(3), 240–246. https://doi.org/10.1016/s2221-1691(12)60050-1

Bahadoran, Z., Mirmiran, P., Momenan, A. A., & Azizi, F. (2017). Allium vegetable intakes and the incidence of cardiovascular disease, hypertension, chronic kidney disease, and type 2 diabetes in adults. *Journal of Hypertension*, *35*(9), 1909–1916. https://doi.org/10.1097/hjh.0000000000001356

Baldissera, G., Sperotto, N. D. M., Rosa, H. T., Henn, J. G., Peres, V. F., Moura, D. J., & Saffi, J. (2016). Effects of crude hydroalcoholic extract of Syzygium cumini (L.) Skeels leaves and continuous aerobic training in rats with diabetes induced by a high-fat diet and low doses of streptozotocin. *Journal of Ethnopharmacology*, *194*, 1012–1021. https://doi.org/10.1016/j.jep.2016.10.056

Bansode, T., Salalkar, B., Dighe, P., Nirmal, S., & Dighe, S. (2017). Comparative evaluation of antidiabetic potential of partially purified bioactive fractions from four medicinal plants in alloxan-induced diabetic rats. AYU (an International Quarterly Journal of Research in Ayurveda), 38(2), 165. https://doi.org/10.4103/ayu.ayu_18_17

Bas, Z., Turkoglu, V., & Goz, Y. (2021). Investigation of inhibition effect of butanol and water extracts of Matricaria chamomilla L. on angiotensin-converting enzyme purified from human plasma. *Biotechnology and Applied Biochemistry*. https://doi.org/10.1002/bab.2106

Brinkley, T. E., Lovato, J. F., Arnold, A. M., Furberg, C. D., Kuller, L. H., Burke, G. L., & Williamson, J. D. (2010). Effect of Ginkgo biloba on Blood Pressure and Incidence of Hypertension in Elderly Men and Women. *American Journal of Hypertension*, *23*(5), 528–533. https://doi.org/10.1038/ajh.2010.14

Chauhan, R., Singh, S., Kumar, V., Kumar, A., Kumari, A., Rathore, S., & Singh, S. (2021). A Comprehensive Review on Biology, Genetic Improvement, Agro and Process Technology of German Chamomile (Matricaria chamomilla L.). *Plants*, *11*(1), 29. https://doi.org/10.3390/plants11010029

Chen, C.-Y., Tsai, T.-Y., & Chen, B.-H. (2021). Effects of Black Garlic Extract and Nanoemulsion on the Deoxy Corticosterone Acetate-Salt Induced Hypertension and Its Associated Mild Cognitive Impairment in Rats. *Antioxidants*, *10*(10), 1611. https://doi.org/10.3390/antiox10101611

Cheng, Y.-C., Sheen, J.-M., Hu, W. L., & Hung, Y.-C. (2017). Polyphenols and Oxidative Stress in Atherosclerosis-Related Ischemic Heart Disease and Stroke. *Oxidative Medicine and Cellular Longevity*, *2017*, 1–16. https://doi.org/10.1155/2017/8526438

Cheung, B. M. Y., & Li, C. (2012). Diabetes and Hypertension: Is There a Common Metabolic Pathway? *Current Atherosclerosis Reports*, *14*(2), 160–166. https://doi.org/10.1007/s11883-012-0227-2

Ciumărnean, L., Milaciu, M. V., Runcan, O., Vesa, Ș. C., Răchișan, A. L., Negrean, V., & Dogaru, G. (2020). The Effects of Flavonoids in Cardiovascular Diseases. Molecules, 25(18), 4320. https://doi.org/10.3390/molecules25184320

Cogolludo, A., Pérez-Vizcaíno, F., & Tamargo, J. (2005). New insights in the pharmacological therapy of arterial hypertension. *Current Opinion in Nephrology & Hypertension*, *14*(5), 423–427. https://doi.org/10.1097/01.mnh.0000168334.09454.1c

Costa, J. M. B. da S., Barreto, M. N. S. de C., Gomes, M. F., Fontbonne, A., & Cesse, E. Â. P. (2020). Avaliação da estrutura das farmácias das Unidades de Saúde da Família para o atendimento aos portadores de hipertensão arterial sistêmica e diabetes mellitus em Pernambuco. Cadernos Saúde Coletiva, 28(4), 609–618. https://doi.org/10.1590/1414-462x202028040243

Dai, Y., Chen, S.-R., Chai, L., Zhao, J., Wang, Y., & Wang, Y. (2018). Overview of pharmacological activities of Andrographis paniculata and its major compound andrographolide. Critical Reviews in Food Science and Nutrition, 59(sup1), S17–S29. https://doi.org/10.1080/10408398.2018.1501657

Dinda, B., Dinda, M., Roy, A., & Dinda, S. (2020). Dietary plant flavonoids in prevention of obesity and diabetes. *Advances in Protein Chemistry and Structural Biology*, 159–235. https://doi.org/10.1016/bs.apcsb.2019.08.006

Dinda, B., Dinda, M., Roy, A., & Dinda, S. (2020). Dietary plant flavonoids in prevention of obesity and diabetes. *Advances in Protein Chemistry and Structural Biology*, 159–235. https://doi.org/10.1016/bs.apcsb.2019.08.006

El-Abhar, H. S., & Schaalan, M. F. (2014). Phytotherapy in diabetes: Review on potential mechanistic perspectives. *World Journal of Diabetes*, *5*(2), 176. https://doi.org/10.4239/wjd.v5.i2.176

Ferrera, T. S., Heldwein, A. B., Dos Santos, C. O., Somavilla, J. C., & Sautter, C. K. (2016). Substâncias fenólicas, flavonoides e capacidade antioxidante em erveiras sob diferentes coberturas do solo e sombreamentos. *Revista Brasileira de Plantas Medicinais*, 18(2 suppl 1), 588–596. https://doi.org/10.1590/1983-084x/15_197

Flack, J. M., & Adekola, B. (2020). Blood pressure and the new ACC/AHA hypertension guidelines. *Trends in Cardiovascular Medicine*, *30*(3), 160–164. https://doi.org/10.1016/j.tcm.2019.05.003

Gandhi, G. R., Vasconcelos, A. B. S., Wu, D.-T., Li, H.-B., Antony, P. J., Li, H., & Gan, R.-Y. (2020). Citrus Flavonoids as Promising Phytochemicals Targeting Diabetes and Related Complications: A Systematic Review of *In Vitro* and *In Vivo* Studies. *Nutrients*, *12*(10), 2907. https://doi.org/10.3390/nu12102907

Ghiasi, S., Jalalyazdi, M., Ramezani, J., Izadi-Moud, A., Madani-Sani, F., & Shahlaei, S. (2019). Effect of hibiscus sabdariffa on blood pressure in patients with stage 1 hypertension. *Journal of Advanced Pharmaceutical Technology & Research*, *10*(3), 107. https://doi.org/10.4103/japtr.japtr_402_18

Gibbs, J., Gaskin, E., Ji, C., Miller, M. A., & Cappuccio, F. P. (2020). The effect of plant-based dietary patterns on blood pressure: a systematic review and meta-analysis of controlled intervention trials. *Journal of Hypertension*, *39*(1), 23–37. https://doi.org/10.1097/hjh.0000000000002604

Herrera-Arellano, A., Flores-Romero, S., Chávez-Soto, M. A., & Tortoriello, J. (2004). Effectiveness and tolerability of a standardized extract from Hibiscus sabdariffa in patients with mild to moderate hypertension: a controlled and randomized clinical trial. *Phytomedicine*, *11*(5), 375–382. https://doi.org/10.1016/j.phymed.2004.04.001

Hidayat, R., & Wulandari, P. (2021). Effects of Andrographis paniculata (Burm. F.) Extract on Diabetic Nephropathy in Rats. *Reports of Biochemistry and Molecular Biology*, 10(3), 445–454. https://doi.org/10.52547/rbmb.10.3.445

Hopkins, A. L., Lamm, M. G., Funk, J. L., & Ritenbaugh, C. (2013). Hibiscus sabdariffa L. in the treatment of hypertension and hyperlipidemia: A comprehensive review of animal and human studies. *Fitoterapia*, *85*, 84–94. https://doi.org/10.1016/j.fitote.2013.01.003

Hügel, H. M., Jackson, N., May, B., Zhang, A. L., & Xue, C. C. (2016). Polyphenol protection and treatment of hypertension. *Phytomedicine*, 23(2), 220–231. https://doi.org/10.1016/j.phymed.2015.12.012

Jaiyesimi, K. F., Agunbiade, O. S., Ajiboye, B. O., & Afolabi, O. B. (2020). Polyphenolic-rich extracts of Andrographis paniculata mitigate hyperglycemia via attenuating β-cell dysfunction, pro-inflammatory cytokines and oxidative stress in alloxan-induced diabetic Wistar albino rat. *Journal of Diabetes & Metabolic Disorders*, 19(2), 1543–1556. https://doi.org/10.1007/s40200-020-00690-2

Kanter, J. E., & Bornfeldt, K. E. (2016). Impact of Diabetes Mellitus. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *36*(6), 1049–1053. https://doi.org/10.1161/atvbaha.116.307302

Karlowicz-Bodalska K; Han S; Freier J; Smolenski M; & Bodalska A. (2017). Curcuma Longa As Medicinal Herb In The Treatment Of Diabet- IC COMPLICATIONS. *Acta Poloniae Pharmaceutica*, 74(2). https://pubmed.ncbi.nlm.nih.gov/29624265/

Liang, E., Liu, X., Du, Z., Yang, R., & Zhao, Y. (2018). Andrographolide Ameliorates Diabetic Cardiomyopathy in Mice by Blockage of Oxidative Damage and NF-κB-Mediated Inflammation. Oxidative Medicine and Cellular Longevity, 2018, 1–13. https://doi.org/10.1155/2018/9086747

Liguori, I., Russo, G., Curcio, F., Bulli, G., Aran, L., Della-Morte, D., & Abete, P. (2018). Oxidative stress, aging, and diseases. *Clinical Interventions in Aging*, *Volume 13*, 757–772. https://doi.org/10.2147/cia.s158513

Malta, D. C., Stopa, S. R., Szwarcwald, C. L., Gomes, N. L., Silva Júnior, J. B., & Reis, A. A. C. dos. (2015). A vigilância e o monitoramento das principais doenças crônicas não transmissíveis no Brasil - Pesquisa Nacional de Saúde, 2013. *Revista Brasileira de Epidemiologia*, 18(suppl 2), 3–16. https://doi.org/10.1590/1980-5497201500060002

Martín, M. Á., & Ramos, S. (2021). Dietary Flavonoids and Insulin Signaling in Diabetes and Obesity. *Cells*, *10*(6), 1474. https://doi.org/10.3390/cells10061474

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine*, 6(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Mota, M., Marques-Vieira, C., Severino, S., & Antunes, V. (2017). Metodologia de Revisão Integrativa da Literatura em Enfermagem. *ResearchGate; unknown*. https://www.researchgate.net/publication/321319742_Metodologia_de_Revisao_Integrativa_da_Literatura_em_Enfermagem

Neves, R. G., Duro, S. M. S., Nunes, B. P., Facchini, L. A., & Tomasi, E. (2021). Atenção à saúde de pessoas com diabetes e hipertensão no Brasil: estudo transversal do Programa de Melhoria do Acesso e da Qualidade da Atenção Básica, 2014. Epidemiologia E Serviços de Saúde, 30(3). https://doi.org/10.1590/s1679-49742021000300015

Noone, C., Dwyer, C. P., Murphy, J., Newell, J., & Molloy, G. J. (2018). Comparative effectiveness of physical activity interventions and anti-hypertensive pharmacological interventions in reducing blood pressure in people with hypertension: protocol for a systematic review and network meta-analysis. *Systematic Reviews*, *7*(1). https://doi.org/10.1186/s13643-018-0791-9

Nugroho, A., Warditiani, N., Pramono, S., Andrie, M., Siswanto, E., & Lukitaningsih, E. (2012). Antidiabetic and antihiperlipidemic effect of Andrographis paniculata (Burm. f.) Nees and andrographolide in high-fructose-fat-fed rats. Indian Journal of Pharmacology, 44(3), 377. https://doi.org/10.4103/0253-7613.96343

Ogunmoyole, T., Awodooju, M., Idowu, S., & Daramola, O. (2020). Phyllanthus amarus extract restored deranged biochemical parameters in rat model of hepatotoxicity and nephrotoxicity. *Heliyon*, *6*(12), e05670. https://doi.org/10.1016/j.heliyon.2020.e05670

Páez, M. T., Rodríguez, D. C., López, D. F., Castañeda, J. A., Buitrago, D. M., Cuca, L. E., & Guerrero, M. F. (2013). Croton schiedeanus Schltd prevents experimental hypertension in rats induced by nitric oxide deficit. Brazilian Journal of Pharmaceutical Sciences, 49(4), 865–871. https://doi.org/10.1590/s1984-82502013000400027

Park, H.-J., & Kim, M.-M. (2014). Flavonoids in Ginkgo biloba fallen leaves induce apoptosis through modulation of p53 activation in melanoma cells. *Oncology Reports*, *33*(1), 433–438. https://doi.org/10.3892/or.2014.3602

Patel, J. R., Tripathi, P., Sharma, V., Chauhan, N. S., & Dixit, V. K. (2011). Phyllanthus amarus: Ethnomedicinal uses, phytochemistry and pharmacology: A review. *Journal of Ethnopharmacology*, *138*(2), 286–313. https://doi.org/10.1016/j.jep.2011.09.040

Petrie, J. R., Guzik, T. J., & Touyz, R. M. (2018). Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. *Canadian Journal of Cardiology*, *34*(5), 575–584. https://doi.org/10.1016/j.cjca.2017.12.005

Qamar, M., Akhtar, S., Ismail, T., Wahid, M., Abbas, M. W., Mubarak, M. S., & Esatbeyoglu, T. (2022). Phytochemical Profile, Biological Properties, and Food Applications of the Medicinal Plant Syzygium cumini. *Foods*, *11*(3), 378. https://doi.org/10.3390/foods11030378

Rajendran, P., Nandakumar, N., Rengarajan, T., Palaniswami, R., Gnanadhas, E. N., Lakshminarasaiah, U., & Nishigaki, I. (2014). Antioxidants and human diseases. *Clinica Chimica Acta*, *436*, 332–347. https://doi.org/10.1016/j.cca.2014.06.004

Ramkumar, S., Thulasiram, H. V., & RaviKumar, A. (2021). Improvement in serum amylase and glucose levels in diabetic rats on oral administration of bisdemethoxycurcumin from Curcuma longa and limonoids from Azadirachta indica. Journal of Food Biochemistry, 45(4). https://doi.org/10.1111/jfbc.13674

Rees, A., Dodd, G., & Spencer, J. (2018). The Effects of Flavonoids on Cardiovascular Health: A Review of Human Intervention Trials and Implications for Cerebrovascular Function. *Nutrients*, *10*(12), 1852. https://doi.org/10.3390/nu1012185

Ried, K. (2016). Garlic Lowers Blood Pressure in Hypertensive Individuals, Regulates Serum Cholesterol, and Stimulates Immunity: An Updated Meta-analysis and Review. *The Journal of Nutrition*, *146*(2), 389S396S. https://doi.org/10.3945/jn.114.202192

Ried, K., & Fakler, P. (2014). Potential of garlic (Allium sativum) in lowering high blood pressure: mechanisms of action and clinical relevance. *Integrated Blood Pressure Control*, 71. https://doi.org/10.2147/ibpc.s51434

Ried, K., Frank, O. R., & Stocks, N. P. (2012). Aged garlic extract reduces blood pressure in hypertensives: a dose–response trial. *European Journal of Clinical Nutrition*, *67*(1), 64–70. https://doi.org/10.1038/ejcn.2012.178

Rosario, V. A., Schoenaker, D. A. J. M., Kent, K., Weston-Green, K., & Charlton, K. (2020). Association between flavonoid intake and risk of hypertension in two cohorts of Australian women: a longitudinal study. *European Journal of Nutrition,* 60(5), 2507–2519. https://doi.org/10.1007/s00394-020-02424-9

Sen, T., & Samanta, S. K. (2014). Medicinal Plants, Human Health and Biodiversity: A Broad Review. *Biotechnological Applications of Biodiversity*, 59–110. https://doi.org/10.1007/10_2014_273

Senoner, T., & Dichtl, W. (2019). Oxidative Stress in Cardiovascular Diseases: Still a Therapeutic Target? Nutrients, 11(9), 2090. https://doi.org/10.3390/nu11092090

Serban, C., Sahebkar, A., Ursoniu, S., Andrica, F., & Banach, M. (2015). Effect of sour tea (Hibiscus sabdariffa L.) on arterial hypertension. *Journal of Hypertension*, *33*(6), 1119–1127. https://doi.org/10.1097/hjh.0000000000000585

Setyaningsih, F. Saputri, & A. Mun'im. (2019). The Antidiabetic Effectivity of Indonesian Plants Extracts via DPP-IV Inhibitory Mechanism. Undefined; https://www.semanticscholar.org/paper/The-Antidiabetic-Effectivity-of-Indonesian-Plants-Setyaningsih-Saputri/490cce5165d54db33633c8ed2233086eb3d2462c

Shaito, A., Thuan, D. T. B., Phu, H. T., Nguyen, T. H. D., Hasan, H., Halabi, S., & Pintus, G. (2020). Herbal Medicine for Cardiovascular Diseases: Efficacy, Mechanisms, and Safety. *Frontiers in Pharmacology*, *11*. https://doi.org/10.3389/fphar.2020.00422

Souza, M. T. de, Silva, M. D. da, & Carvalho, R. de. (2010). Integrative review: what is it? How to do it? *Einstein (São Paulo)*, 8(1), 102–106. https://doi.org/10.1590/s1679-45082010rw1134

Silva, MVB., Vitória, B., Sales, S., Antonio, C., Aline, Lopes, G., & Amanda. (2022). Caracterização do perfil epidemiológico da mortalidade por doenças cardiovasculares no Brasil: um estudo descritivo. *Enfermagem Brasil,* 21(2), 154–165. https://doi.org/10.33233/eb.v21i2.5030

Srividya N;Periwal S. (2019). Diuretic, hypotensive and hypoglycaemic effect of Phyllanthus amarus. *Indian Journal of Experimental Biology*, 33(11). https://pubmed.ncbi.nlm.nih.gov/8786163/

Syamsunarno, M. R. A., Safitri, R., & Kamisah, Y. (2021). Protective Effects of Caesalpinia sappan Linn. and Its Bioactive Compounds on Cardiovascular Organs. *Frontiers in Pharmacology*, 12. https://doi.org/10.3389/fphar.2021.725745

Thota, R. N., Acharya, S. H., & Garg, M. L. (2019). Curcumin and/or omega-3 polyunsaturated fatty acids supplementation reduces insulin resistance and blood lipids in individuals with high risk of type 2 diabetes: a randomised controlled trial. *Lipids in Health and Disease*, 18(1). https://doi.org/10.1186/s12944-019-0967-x

Tschiedel, B. (2014). *Complicações crônicas do diabetes*. *102*. Retrieved from http://files.bvs.br/upload/S/0047-2077/2014/v102n5/a4502.pdf

Uddin, G. M., Kim, C. Y., Chung, D., Kim, K.-A., & Jung, S. H. (2015). One-step isolation of sappanol and brazilin from Caesalpinia sappan and their effects on oxidative stress-induced retinal death. *BMB Reports*, 48(5), 289–294. https://doi.org/10.5483/bmbrep.2015.48.5.189

Wediasari, F., Nugroho, G. A., Fadhilah, Z., Elya, B., Setiawan, H., & Mozef, T. (2020). Hypoglycemic Effect of a Combined Andrographis paniculata and Caesalpinia sappan Extract in Streptozocin-Induced Diabetic Rats. *Advances in Pharmacological and Pharmaceutical Sciences*, 2020, 1–9. https://doi.org/10.1155/2020/8856129

World Health Organization. (2021). *Guideline for the pharmacological treatment of hypertension in adults*. https://apps.who.int/iris/bitstream/handle/10665/344424/9789240033986-eng.pdf

World Health Organization. World Health Organization; France: 2016. Global Report on Diabetes WHO. (2016). *Global Report On Diabetes*. https://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf

Xiong, X. J., Liu, W., Yang, X. C., Feng, B., Zhang, Y. Q., Li, S. J., & Wang, J. (2014). Ginkgo biloba extract for essential hypertension: A systemic review. *Phytomedicine*, 21(10), 1131–1136. https://doi.org/10.1016/j.phymed.2014.04.024

Yao, A. N., Kamagaté, M., Amonkan, A. K., Chabert, P., Kpahé, F., Koffi, C., & Die-Kakou, H. (2018). The acute diuretic effect of an ethanolic fraction of Phyllanthus amarus (Euphorbiaceae) in rats involves prostaglandins. *BMC Complementary and Alternative Medicine*, *18*(1). https://doi.org/10.1186/s12906-018-2158-0

Yao, N. A., Niazi, Z. R., Najmanová, I., Kamagaté, M., Said, A., Chabert, P., & Schini-Kerth, V. (2020). Preventive Beneficial Effect of an Aqueous Extract of Phyllanthus amarus Schum. and Thonn. (Euphorbiaceae) on DOCA-Salt–Induced Hypertension, Cardiac Hypertrophy and Dysfunction, and Endothelial Dysfunction in Rats. *Journal of Cardiovascular Pharmacology*, 75(6), 573–583. https://doi.org/10.1097/fjc.0000000000000825