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Edible Seeds in the Fight Against Hypertension: A Review of In Vitro, In Vivo, and Clinical Evidences With a Mechanistic Insight of Bioactive Compounds

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ABSTRACT

Hypertension, often referred to as a silent killer, is responsible for 7.5 million deaths, representing approximately 12.8% of all global mortality. This study aimed to (1) catalogue traditional uses of edible seeds for hypertension as recorded in ethnopharmacological surveys, (2) elucidate the antihypertensive attributes of these seeds based on in vitro, in vivo, and clinical studies, and (3) assess the mechanisms of action of primary bioactive compounds derived from these seeds. Data were sourced from online databases, including Scopus, PubMed, Google Scholar, and Web of Science, resulting in 155 reviewed studies, 47 of which were ethnopharmacological surveys. Data extracted from the studies included the species names of edible seeds, family names, year, countries where the study was conducted, study design, model used, extract, method of preparation, solvent used, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MABP), pulse pressure (PP), and heart rate (HR). Predominant seeds included *Nigella sativa* L. (black seed), *Peganum harmala* L. (harmala), *Persea americana* Mill. (avocado seed), *Linum usitatissimum* L. (flaxseed), and *Moringa oleifera* Lam. (drumstick seed). The protein extract of *Arachis hypogaea*

Abbreviations: Cu/Zn-SOD, copper zinc superoxide dismutase; CVDs, cardiovascular diseases; DBP, diastolic blood pressure; DHFR, dihydrofolate reductase; DOCA, deoxycorticosterone acetate; FDA, Food and Drug Administration; GPx, glutathione peroxidase 1; HR, heart rate; IL 1 β , interleukin 1 beta; IL 6, interleukin 6; MABP, mean arterial blood pressure; MCT, monocrotaline; MMP2, matrix metalloproteinase 2; NADPH, nicotinamide adenine dinucleotide phosphate; NCDs, noncommunicable diseases; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; p ERK, extracellular signal-regulated kinase; p38-MAPK, p38 mitogen-activated protein kinases; PASMCs, pulmonary artery smooth muscle cell; PP, pulse pressure; SBP, systolic blood pressure; SHR, spontaneously hypertensive rats; T&CM, traditional and complementary medicines; TGF- β 1, transforming growth factor β 1; TNF α , tumor necrosis factor alpha; TQ, thymoquinone; T-SOD, total superoxide dismutase; WHO, World Health Organization.

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L. (peanut) demonstrated the most potent inhibition of angiotensin-converting enzyme (ACE) with IC_{50} values ranging from 0.07 to 0.08 mg/mL, whereas *Hordeum vulgare* L. (barley) exhibited the highest ACE inhibitory activity at 91.8%. Notably, *N. sativa* was observed to be especially effective in lowering both diastolic and SBP. This review highlights the potential antihypertensive benefits of traditionally employed edible seeds, presenting new perspectives and avenues for future research.

1 | Introduction

Hypertension or high blood pressure (BP) is one of the leading risk factors for cardiovascular diseases and a major cause of mortality. Hypertension is primarily characterized by a persistent increase in blood vessel pressure. When BP increases, the heart has to pump blood harder and faster than normal (WHO 2023). Normal BP is less than 120/80 mmHg. Prehypertension is defined as diastolic BP (DBP) (80–89 mmHg) or systolic BP (SBP) (120–139 mmHg), where these individuals are at higher risk of developing hypertension. An individual is diagnosed with hypertension when his SBP exceeds 140 mmHg and DBP exceeds 90 mmHg (Khatib and El-Guindy 2005). Hypertension can be a significant threat to the heart. Excessive pressure hardens the arteries, reducing the amount of oxygen the heart can pump. High BP and low blood flow can lead to angina, heart attacks, and irregular heartbeats (Amir Masoud et al. 2024; D. Li et al. 2024).

Globally, an estimated 1.28 billion adults aged between 30 and 79 years suffer from hypertension; the majority of these cases (two-thirds) are found in low- and middle-income countries. The highest prevalence of hypertension is predominantly in African nations (27%), whereas the lowest prevalence is noted in American regions (18%) (WHO 2023). It is considered a leading cause of death globally, responsible for approximately 13.5% of cardiovascular deaths and 70% of heart attacks, chronic heart failures, and strokes (Ried and Fakler 2014). The global incidence of hypertension continues to rise due to an aging population and increased exposure to lifestyle risk factors such as physical inactivity and poor diets high in salt and low in potassium (Mills et al. 2020). Cardiovascular diseases are the primary cause of mortality, causing 17.9 million deaths annually. They are followed by cancers (9.3 million deaths), chronic respiratory diseases (4.1 million deaths), and diabetes (2.0 million deaths). As a result, noncommunicable diseases (NCDs) claim the lives of 41 million people (74%) each year (WHO 2023).

Currently, several methods are available for managing hypertension, primarily encompassing lifestyle modifications and pharmacological interventions. Lifestyle changes incorporate increased physical activity, healthy dietary practices, weight loss, avoidance of smoking and alcohol consumption, and regular BP monitoring, among others (H. Zheng et al. 2023). Commonly prescribed medications include angiotensin-converting enzyme (ACE) inhibitors, beta blockers, diuretics, calcium channel blockers, angiotensin II antagonists, centrally acting alpha-adrenergic agents, vasodilators, peripherally acting alpha-adrenergic blockers, combination drugs, and renin inhibitors (FDA 2021; Kajal and Ramanlal 2023; Wen et al. 2024; T.-T. Zhang et al. 2024). However, these drugs often present numerous side effects such as swelling, headache, dizziness, fatigue, cough, and sleep disturbances (FDA 2021). Consequently, ongoing research efforts aim to discover new

medicines from natural sources, including traditional medicinal plants (Priyono et al. 2024).

Traditional medicines, which have a long history of use, are the result of assimilating various skills, abilities, and traditions acquired through diverse cultural experiences, theories, and beliefs. Since their inception, they have been employed to maintain good health, as well as to prevent, diagnose, and treat both physical and psychological ailments (WHO 2023). Among these traditional medicinal products, medicinal plants have been extensively used for the treatment and management of various diseases. These remedies are now globally prevalent, with both consumers and medical professionals such as doctors incorporating them into their practices (Saleem et al. 2019). In contemporary times, approximately 40% of pharmaceutical products, primarily drugs, have a foundation in natural products. The integration of new technology in healthcare and medicine has the potential to broaden our understanding of conventional medicine, potentially leading to the realization and production of innovative natural-based pharmaceutical drugs (WHO 2023).

Seeds, integral to plant reproduction, serve dual purposes—as a food reserve and a source of bioactive compounds (R.-L. Zheng et al. 2024). Although certain seeds possess toxic properties harmful to humans, many edible seeds are rich in beneficial nutrients. Notably, seeds are replete with essential bioactive components such as tannins, polyphenolic compounds, glycosides, alkaloids, carotenoids, flavonoids, saponins, terpenoids, and steroids. These components exhibit potent anti-inflammatory and antioxidant properties and have proven effective against a range of diseases, including cancer, diabetes, obesity, hyperlipidemia, neurological disorders, cardiovascular disease, and various chronic ailments (Chandrasekar and Sivagami 2021; M.-Y. Li, Gu, et al. 2025; M.-Y. Li, Zhang, et al. 2025).

The antihypertensive properties of medicinal plants have been extensively researched and summarized in recent reviews. For example, Baharvand-Ahmadi and Asadi-Samani (2016) identified 40 species of medicinal plants used for hypertension treatment in Iran, whereas Meresa et al. (2017) noted 66 plants employed as hypotensives in Ethiopia. However, there appears to be no comprehensive review focusing specifically on traditionally utilized edible seeds for hypertension, despite numerous field studies documenting their therapeutic use worldwide. Thus, this study aims to thoroughly examine the literature and elucidate the pharmacological properties of edible seeds traditionally used globally in hypertension management. The study's objectives are threefold: (1) to document the traditional uses of edible seeds against hypertension as reported in ethnopharmacological surveys, (2) to highlight the biological properties of these traditionally used seeds based on in vitro, in vivo, and clinical reports,

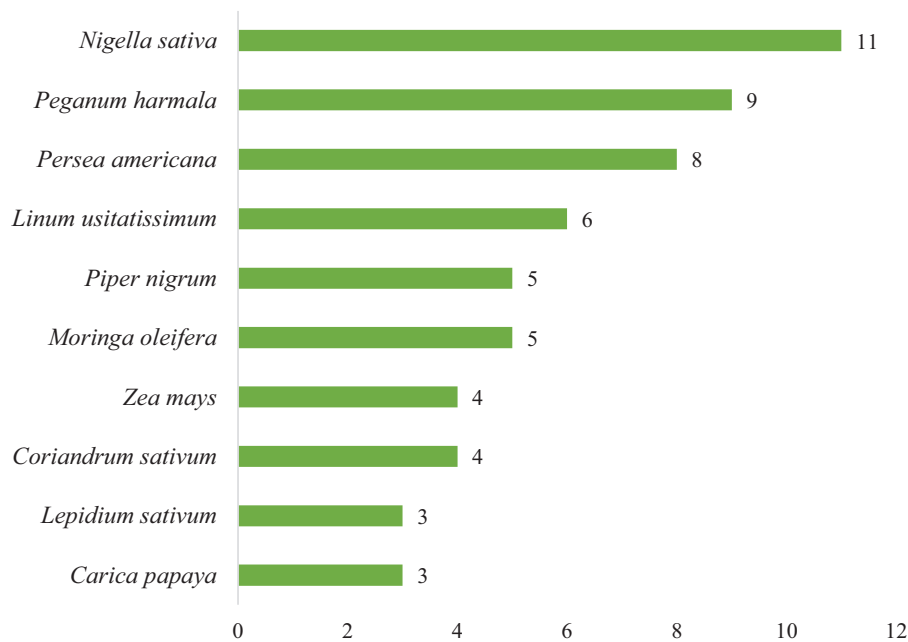


FIGURE 1 | Seeds most reported against hypertension.

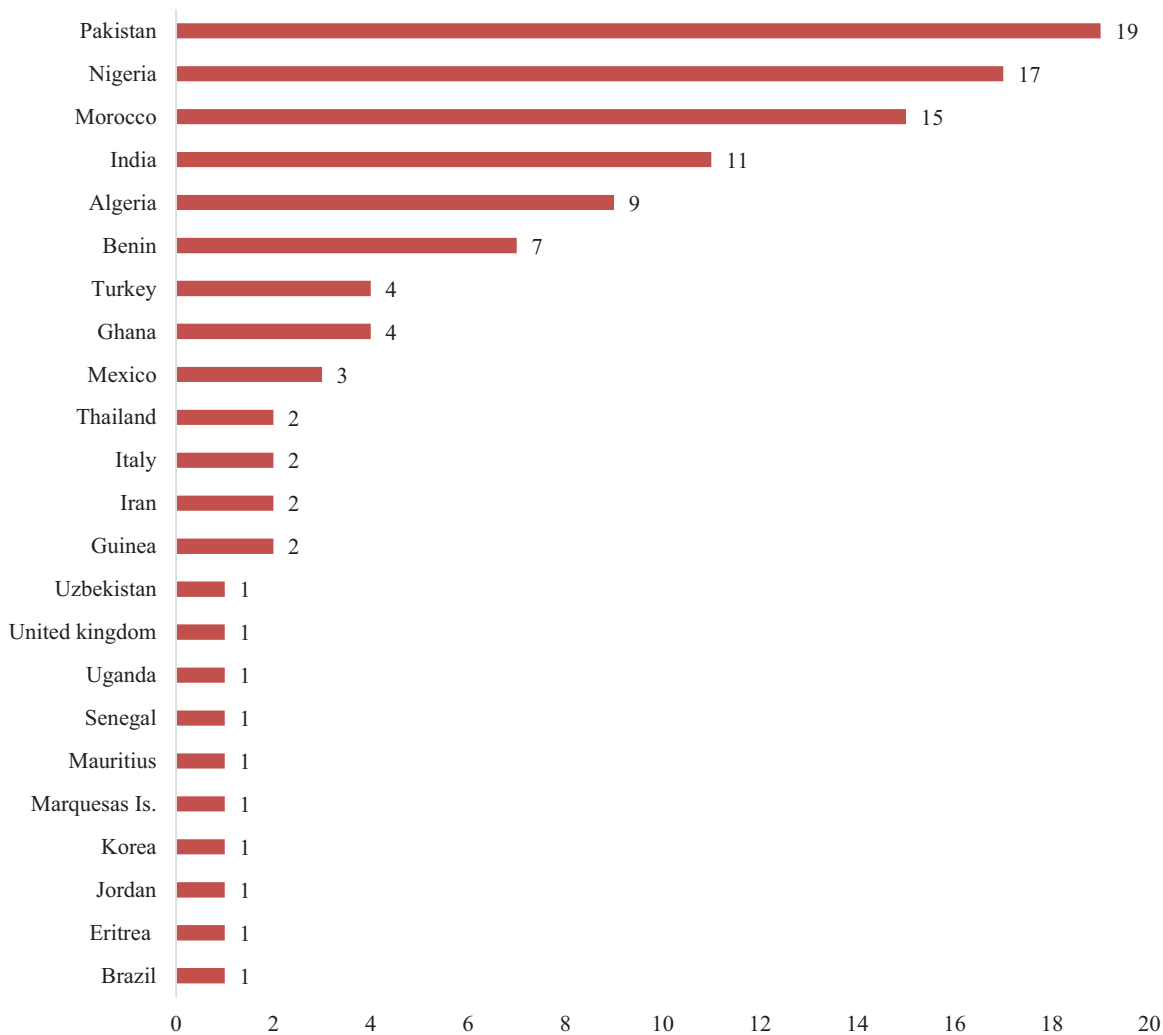


FIGURE 2 | Number of field studies in different countries.

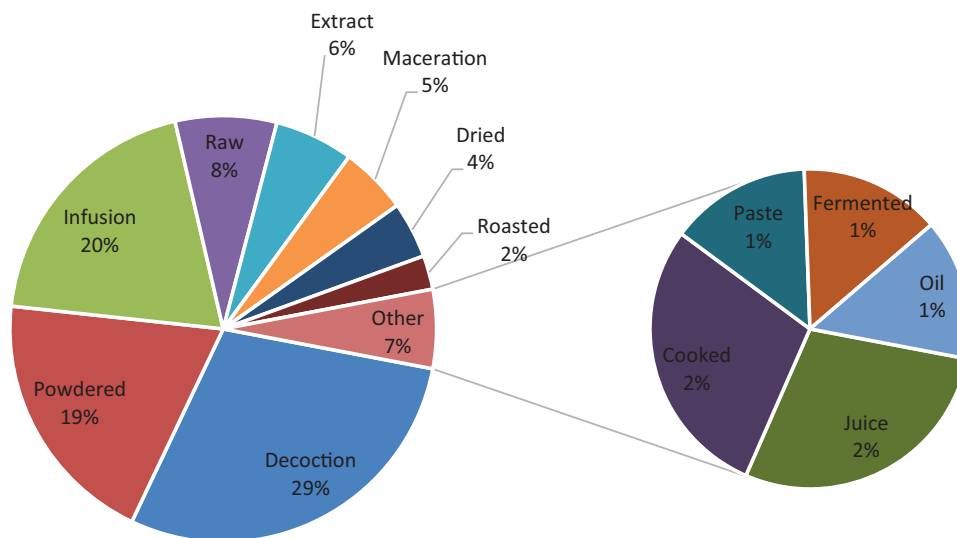


FIGURE 3 | Method of preparation of seeds.

and (3) to review the antihypertensive activity of the primary bioactive compounds isolated from clinically tested seeds.

2 | Methodology

2.1 | Databases

Scopus, Google Scholar, Web of Science, and PubMed were the main databases that were scrutinized. The database “PubChem” was then used to search and design the chemical structure of compounds. The scientific names of plants were authenticated using The Plants of the World Online and The World Flora Online. The databases described above were used to confirm the misspelt names of plants that were double-checked on Google.

2.2 | Search Strategy

For the traditional uses, the main keywords that were used in addition to “hypertension” and “high blood pressure” were “ethnomedicinal,” “ethnobotanical,” “ethnomedicine,” “ethnomedical,” “ethnopharmacological,” “traditional,” “indigenous,” “folk,” “plants,” “natural products,” and “herbal.” A hyphen (-) after the word “ethno” (e.g., ethno-medicinal, ethno-botanical, and ethno-pharmacological) was put to not miss those research articles which use this symbol in the title. For the pharmacological part, the keywords that were used to search in those databases were “seed,” “hypertension,” “angiotensin converting enzyme,” “blood pressure,” “systolic blood pressure,” “diastolic blood pressure,” “mean arterial blood pressure,” “pulse pressure,” and “heart rate.” The names of the main compounds along with the word “hypertension” were used to search for studies on compounds isolated from clinically tested species.

2.3 | Data Extraction

Data extracted from the studies included the species names of edible seeds, family names, year, and countries where the study

was conducted, study design, model used, extract, method of preparation (if indicated), solvent used, SBP, DBP, mean arterial BP (MABP), pulse pressure (PP), and heart rate (HR). Any reported adverse effects were also extracted.

After screening through various databases (Scopus: $n = 118$; Google Scholar: $n = 166$; PubMed: $n = 61$; Web of Science: $n = 45$), a total of 390 studies were found. There were 199 duplicate articles found across the four databases. Thirty-six articles were eliminated following the examination of the inclusion and exclusion criteria. There were 155 studies included in the current evaluation.

3 | Results

3.1 | Ethnopharmacological Uses of Seeds

A total of 50 distinct seed types have been traditionally utilized to combat hypertension (Table 1). The plant *Nigella sativa* has the highest number of field studies attached to it, amounting to 11 studies. This is closely followed by *Peganum harmala* and *Persea americana* with nine studies each, and *Linum usitatissimum* with six studies. Both *Moringa oleifera* and *Piper nigrum* have five studies conducted on them, whereas *Coriandrum sativum* and *Zea mays* have four studies each. Three studies have been reported for both *Carica papaya* and *Lepidium sativum* (Figure 1).

The most frequent field studies were conducted in Pakistan ($n = 19$), Nigeria ($n = 17$), Morocco ($n = 15$), India ($n = 11$), Algeria ($n = 9$), and Benin ($n = 7$). Ghana and Turkey had four studies each, whereas Mexico only had three (Table 1). Guinea, Italy, and Thailand included two studies. Finally, only one study was reported for Brazil, Eritrea, Jordan, Korea, Marquesas Island, Mauritius, Senegal, Uganda, the United Kingdom, and Uzbekistan (Figure 2).

The predominant method of preparation reported was decoction ($n = 34$), followed by an equal number of reports for both infusion and powdered preparation. There were nine reports for the use of raw materials, seven for extracts, six for maceration, and five for

TABLE 1 | Traditional uses of edible seeds against hypertension.

Family	Species	Country	Method of preparations	References
Amaryllidaceae	<i>Allium cepa</i> L.	Pakistan	Decoction	Malik et al. (2018)
	<i>Allium paniculatum</i> L.	Algeria	—	Chermat and Gharzouli (2015)
Annonaceae	<i>Rollinia mucosa</i> (Jacq.) Baill.	Pakistan	—	Malik et al. (2018)
Apiaceae	<i>Anethum graveolens</i> L.	India	—	Esakkimuthu et al. (2016)
		Turkey	Decoction, oral administration, drink one teacup three times a day for 7–8 days	Olçay and Kültür (2020)
	<i>Apium graveolens</i> L.	Algeria	Eaten raw, decoction	Hassaïne et al. (2019)
	<i>Carum carvi</i> L.	Morocco	Decoction	Tahraoui et al. (2007)
		Algeria	Powder ingested	Hassaïne et al. (2019)
	<i>Coriandrum sativum</i> L.	Brazil	Infusion	Di Stasi et al. (2002)
		India	—	Esakkimuthu et al. (2016)
		Syria	Decoction	Alachkar et al. (2011)
		Pakistan	Infusion	Malik et al. (2018)
	<i>Cuminum cyminum</i> L.	India	—	Esakkimuthu et al. (2016)
	<i>Foeniculum vulgare</i> Mill.	Pakistan	Infusion; collect healthy seed, wash, and dry at room temperature for 15 days. Then 20 g seed powdered and soaked in 100 mL water	Malik et al. (2018)
		India	—	Esakkimuthu et al. (2016)
	<i>Petroselinum crispum</i> (Mill.) Fuss	Morocco	Decoction	Tahraoui et al. (2007)
	<i>Pimpinella anisum</i> L.	Algeria	Decoction, powder ingested	Hassaïne et al. (2019)
		Morocco	Decoction	Tahraoui et al. (2007)
	<i>Pimpinella hazariensis</i>	Pakistan	Powder ingested with water Drink two cups of hot water and add three teaspoons of crushed plant mix and use twice a day	Malik et al. (2018)
Apocynaceae	<i>Picralima nitida</i> (Stapf) T. Durand & H. Durand	Guinea	Infusion	Traore et al. (2022)
Berberidaceae	<i>Berberis vulgaris</i> L.	Pakistan	Extract	Malik et al. (2018)
Brassicaceae	<i>Lepidium sativum</i> L.	Morocco	—	Jouad et al. (2001)
		Pakistan	Extracts of seeds are taken for 5 days	Malik et al. (2018)
		Algeria	Infusion	Hassaïne et al. (2019)
Burseraceae	<i>Canarium schweinfurthii</i> Engl.	Uganda	Paste	Okullo et al. (2014)
Capparaceae	<i>Capparis spinosa</i> L.	Morocco	Decoction	El Abbouyi et al. (2014)
		Pakistan	Powder ingested with water Powder of the seed is given with water thrice a day	Malik et al. (2018)

(Continues)

TABLE 1 | (Continued)

Family	Species	Country	Method of preparations	References
Caricaceae	<i>Carica papaya</i> L.	Marquesas Islands	—	Girardi et al. (2015)
		Nigeria	Decoction; leaf of <i>Musanga cecropioides</i> , <i>Talinum triangulare</i> , dried <i>Carica papaya</i> , and a bulb of <i>Allium sativum</i> boil (decoction) in water; half glass cup two times a day	Gbolade (2012)
		Benin	Infusion, decoction, chewing	Aboua et al. (2024)
Clusiaceae	<i>Garcinia kola</i> Heckel	Nigeria	Eaten raw	Akin-Osanaiye et al. (2015)
Compositae	<i>Helianthus annuus</i> L.	Morocco	—	Eddouks et al. (2002)
		Italy	Roasted seed to prepare a decoction	Leporatti and Corradi (2001)
Cucurbitaceae	<i>Citrullus lanatus</i> (Thunb.) Matsum. and Nakai	South Africa	Juice is pressed, squeezed, and fermented for 2 days. One tin cup of the extract is taken three times a day	Semenya and Potgieter (2013)
Euphorbiaceae	<i>Plukenetia conophora</i> Müll.Arg.	Nigeria	4–5 seeds chewed daily; eaten raw	Chima et al. (2013)
Ginkgoaceae	<i>Ginkgo biloba</i> L.	Korea	Decoction	Kim and Song (2011)
Juglandaceae	<i>Juglans nigra</i> L.	Nigeria	Partially cooked	Akin-Osanaiye et al. (2015)
Lamiaceae	<i>Lallemantia royleana</i> (Benth.) Benth.	Pakistan	Ingested directly with water Seeds are swallowing orally with water	Malik et al. (2018)
Lauraceae	<i>Persea americana</i> Mill.	Nigeria	Decoction	Akin-Osanaiye et al. (2015)
		Nigeria	Seed powder added to drinks	Atawodi et al. (2014)
		Nigeria	Decoction; boil (decoction) leaf and seed of <i>Persea americana</i> , and leaf of <i>Acalypha godseffiana</i> in water; half glass cup injected thrice a day Powder; <i>Persea americana</i> seeds are grinded and mixed to pap; one teaspoonful taken two times daily Powder ingested with honey Powder; ground seed of <i>Persea americana</i> , with leaf of <i>Viscum album</i> mixed with honey; Lick twice a day Powder; grinded seeds of <i>Persea americana</i> and <i>Zea mays</i> are added into a tea as beverage; one teaspoonful taken daily Infusion; <i>Persea americana</i> seed, <i>Zingiber officinale</i> rhizome, and <i>Sida acuta</i> leaf made into tea; one glass cup taken twice daily	Gbolade (2012)

(Continues)

TABLE 1 | (Continued)

Family	Species	Country	Method of preparations	References
Leguminosae	<i>Parkia biglobosa</i> (Jacq.) G.Don	Nigeria	Powdered and ingested with pap	Ekpo et al. (2008)
		Mexico	Infusion or decoction	Castillo-España et al. (2009)
		Benin	Decoction, infusion, maceration, chewing	Aboua et al. (2024)
		Guinea	Decoction, powder	Traore et al. (2022)
		Ghana	Grind dried seeds into powder	Asafo-Agyei et al. (2023)
		Nigeria	Powder ingested with honey <i>Allium sativum</i> bulb, <i>Parkia biglobosa</i> seed, <i>Allium ascalonicum</i> leaf, <i>Allium cepa</i> bulb, and <i>Zingiber officinale</i> tuber were ground into a powder and combined with honey. Once day, two tablespoons are given orally	Olorunnisola et al. (2015)
	<i>Prosopis africana</i> (Guill. & Perr.) Taub.	Benin	Infusion, maceration, chewing	Aboua et al. (2024)
		Ghana	Decoction	Oppong Bekoe et al. (2017)
		Ghana	—	Ofori et al. (2012)
	<i>Tetrapleura tetraptera</i> (Schum. & Thonn.) Taub.	Ghana	—	Ofori et al. (2012)
	<i>Trigonella foenum-graecum</i> L.	Pakistan	Extract	Malik et al. (2018)
	<i>Vigna radiata</i> (L.) R.Wilczek	Morocco	Powder ingested	Haouari et al. (2018)
		India	—	Esakkimuthu et al. (2016)
		India	—	Esakkimuthu et al. (2016)
Linaceae	<i>Linum aroanium</i> Boiss. & Orph.	Turkey	Roasted and grinded seed/boil (decoction) and drunk as coffee	Güzel et al. (2015)
	<i>Linum usitatissimum</i> L.	Italy	Infusion	Vitalini et al. (2015)
		Pakistan	Dried powdered mixed with water and juice is extracted and taken	Malik et al. (2018)
Malvaceae	<i>Theobroma cacao</i> L.	Mexico	—	Castillo-España et al. (2009)
		Algeria	Powder ingested, infusion	Hassaïne et al. (2019)
		Morocco	—	Eddouks et al. (2002)
		Turkey	Decoction	Olçay and Kültür (2020)
		Nigeria	Hot infusion of powered seed/cotyledons	Akin-Osanaiye et al. (2015)
Moringaceae	<i>Moringa oleifera</i> Lam.	Benin	Decoction/Maceration/Infusion/Powder	Lagnika et al. (2016)
		Nigeria	Seeds are roasted or eaten raw	Popoola and Obembe (2013)
		Thailand	Boil (decoction) fresh materials/Drink instead of plain water	Neamsuvan et al. (2018)
		Benin	Decoction, crushing, maceration, infusion	Aboua et al. (2024)

(Continues)

TABLE 1 | (Continued)

Family	Species	Country	Method of preparations	References
Myrtaceae	<i>Syzygium aromaticum</i> (L.) Merr. & L.M. Perry	Senegal	Chew the seeds of pods morning and evening/Drink or swallow a teaspoon morning and evening	Lyoussi et al. (2023)
		Nigeria	Decoction; <i>Zingiber officinale</i> rhizome, <i>Xylopia aethiopica</i> , and <i>Syzygium aromaticum</i> seeds are boiled (decoction) in water and consumed twice a day in a glass cup	Gbolade (2012)
Nitrariaceae	<i>Peganum harmala</i> L.	Morocco	—	Jouad et al. (2001)
		Jordan	—	Abu-Irmaileh and Affi (2003)
		Morocco	Infusion, powder ingested	Tahraoui et al. (2007)
		Morocco	—	Eddouks et al. (2002)
		Algeria	Powder ingested	Madani et al. (2012)
		Pakistan	Seed extract	Malik et al. (2018)
		Pakistan	Grind seeds take this powder daily	Ayub et al. (2023)
Piperaceae	<i>Piper guineense</i> Schumach. & Thonn.	Morocco	Decoction	Lyoussi et al. (2023)
		Turkey	Decoction, infusion	Olçay and Kültür (2020)
		Benin	Maceration	Lagnika et al. (2016)
	<i>Piper nigrum</i> L.	Nigeria	Decoction, as soup ingredients	Akin-Osanaiye et al. (2015)
		Thailand	Boil (decoction) fresh ingredients with a small amount of alum, magnesium sulfate, and aloe resin. Drink one teacup before each of the three meals each day Infusion: Powder dried ingredients and infuse in hot water/drink two teaspoons after three meals a day Boil (decoction) fresh materials/drink 3/4 cup after three meals daily	Neamsuvan et al. (2018)
		India	—	Esakkimuthu et al. (2016)
		Benin	Maceration, powder, chewing, infusion	Aboua et al. (2024)
		Pakistan	Grind seeds take with honey or brown sugar daily	Ayub et al. (2023)
		India	—	Esakkimuthu et al. (2016)
		Morocco	Dried/Scorched	Tahraoui et al. (2007)
Poaceae	<i>Hordeum vulgare</i> L. <i>Zea mays</i> L.	Nigeria	Powder; ground seed of <i>Persea americana</i> and <i>Zea mays</i> are mixed in tea as beverage; one teaspoonful consumed a day	Gbolade (2012)
		Pakistan	Infusion: Dried seeds are dipped whole night in water	Malik et al. (2018)

(Continues)

TABLE 1 | (Continued)

Family	Species	Country	Method of preparations	References
Ranunculaceae	<i>Nigella sativa</i> L.	United Kingdom	Ingestion, eaten raw	Ceuterick et al. (2011)
		Pakistan	Eaten raw; in empty stomach at morning	Ishtiaq Ch et al. (2012)
		Iran	Mixed with honey, infusion	Sadeghi et al. (2014)
		India	—	Esakkimuthu et al. (2016)
		Eritrea	—	Sium Demoz et al. (2015)
		Morocco	Powder ingested	Tahraoui et al. (2007)
		Iran	—	Sadeghi et al. (2014)
		Pakistan	—	Ishtiaq Ch et al. (2012)
		Morocco	—	Eddouks et al. (2002)
		Algeria	—	Amel (2013)
		Pakistan	Twice day, drink one cup of water and 0.5 teaspoons of seed oil orally	Malik et al. (2018)
Rosaceae	<i>Amygdalus communis</i> var. <i>amara</i> DC. (Unresolved species in http://www.theplantlist.org)	Algeria	Infusion	Hassaïne et al. (2019)
		Uzbekistan	5–10 of seeds are eaten	Sezik et al. (2004)
Rubiaceae	<i>Pyrus communis</i> L.	Nigeria	—	Agunu et al. (2017)
	<i>Morinda citrifolia</i> L.	Mauritius	Crush about 20 mg of the seed and add to water, bring water to the boil (decoction) for about 30 min. Drink	F. Mahomoodally et al. (2018)
Sapotaceae	<i>Butyrospermum paradoxum</i> (C.F.Gaertn.) Hepper (Syn: <i>Vitellaria paradoxa</i> C.F.Gaertn.)	Nigeria	—	Olowokudejo et al. (2008)
	<i>Manilkara zapota</i> (L.) P.Royen	Mexico	Infusion	Castillo-España et al. (2009)
	<i>Mimusops elengi</i> L.	India	—	Esakkimuthu et al. (2016)
Vitaceae	<i>Vitis vinifera</i> L.	India	—	Esakkimuthu et al. (2016)
Zingiberaceae	<i>Aframomum melegueta</i> K.Schum.	Nigeria	Powder; one teaspoon of <i>Aframomum melegueta</i> seed and one teaspoon of <i>Talinum triangulare</i> leaf powder are mixed to pap Concoction; <i>Phyllanthus amarus</i> leaves, stems, and roots are boiled (decoction) with seven <i>Aframomum melegueta</i> seeds and a little amount of palm kernel oil (<i>Elaeis guineensis</i>); sip it like soup	Gbolade (2012)

(Continues)

TABLE 1 | (Continued)

Family	Species	Country	Method of preparations	References
		Ghana	Decoction: boil together with <i>Zingiber officinale</i> and <i>Khaya senegalensis</i> stem bark	Asafo-Agyei et al. (2023)
	<i>Zingiber officinale</i> Roscoe	Pakistan	Extract	Malik et al. (2018)

Note: “—”: Not mentioned specifically.

dried preparations. Three reports existed for the roasted method of preparation, whereas two reports were found for the juice and cooked methods. Only one report was noted for each of the paste, fermented, and oil methods of preparation (Figure 3) (Table 1).

3.2 | In Vitro Studies

Out of the 50 seed species with traditional use against hypertension, only 17 species have been subjected to in vitro (Figure 7) cell-free enzyme inhibition assays. The most common assay was ACE inhibition. The ACE inhibition assay evaluates a substance's capacity to block the ACE, which is essential for controlling BP by changing angiotensin I into the vasoconstrictor angiotensin II (Serra et al. 2005). Before doing in vivo research, this in vitro assay offers a helpful indicator of the antihypertensive potential of plant extracts or bioactive substances. The most frequently studied species were *M. oleifera* ($n = 7$), *Z. mays* ($n = 4$), and *Vigna radiata* and *Arachis hypogaea* ($n = 3$). Furthermore, two studies were retrieved for each of the following plant species; *Anteaeolidiella indica*, *C. sativum*, *Hordeum vulgare*, *L. usitatissimum*, *N. sativa*, *Parkia biglobosa*, and *Theobroma cacao*. For the rest of the six plant species, only one study was retrieved for each (Figure 4).

The family most frequently tested was Fabaceae ($n = 8$), followed by Moringaceae ($n = 7$), Poaceae ($n = 6$), Apiaceae ($n = 4$), and Ranunculaceae ($n = 3$). Two studies were identified for the Linaceae, Malvaceae, and Meliaceae families. For the remaining families—Lythraceae, Myristicaceae, Nitrariaceae, and Vitaceae—only one study was found for each (Figure 5).

In terms of the type of extract utilized, protein extract was the most prevalent, having been used in 16 studies. This was followed by aqueous extract, which was employed in seven studies. Fermented and essential oil extracts were used in three studies each, whereas polyphenol and phenol extracts were used in two studies each. One study was conducted on ethanol, crude, and methanol extracts (Figure 6). As for the control, captopril was used as a positive control in six studies, and ramipril was used in one study. The results were expressed either as IC_{50} or as a percentage inhibition of ACE.

3.2.1 | Comparison of ACE Inhibition

The ACE inhibition assay was conducted to determine the anti-hypertensive property of the seed extracts and peptide fractions. This assay measures the ability of a sample to inhibit ACE activity, an enzyme involved in BP regulation through the conversion of

angiotensin I into angiotensin II (Li, Le, et al. 2005). The efficacy of various seed species in inhibiting ACE is amplified with an increase in the percentage of inhibition. It was determined that *H. vulgare* demonstrated the highest percentage of ACE inhibitory values when protein concentrate extracts were used. Among 15 synthesized peptides, four—FQLPKF, ALPYFM, NFLARF, and GFTLKIF—exhibited the most substantial ACE inhibitory activity, with respective values of 91.8%, 90.3%, 89.0%, and 88.3% (Gangopadhyay et al. 2016). The crude extract of *N. sativa* yielded the second-highest ACE inhibitory efficacy, measuring nearly 89% (Javaid et al. 2021), followed by the aqueous extract of *Z. mays*, which recorded 87.26 ± 2.68 $\mu\text{g/mL}$ (C.-C. Li et al. 2019). The results from the ACE inhibitory activity of the aqueous extract with varying enzymes reveal that the maximum ACE activity (85.26%) resulted from the extraction using alcalase, then trypsin (72.80%), neutrase (47.43%), and protamex (13.94%) sequentially. Furthermore, the peptide fraction III (CIII) of *Z. mays* exhibited the highest ACE activity (82.92%), succeeded by fraction V (CV) (21.38%), fraction II (CII) (18.56%), fraction I (CI) (13.54%), fraction VI (CVI) (12.36%), and fraction IV (CIV) (10.78%) (Yang et al. 2007). The protein isolates and hydrolysates extract (alcalase) of *M. oleifera* demonstrated superior potency (79.30%) compared to the pepsin (43.01%) and trypsin hydrolysates (75.05%) (T. A. Aderinola et al. 2019). Additionally, the membrane fraction's inhibition of the globulin hydrolysates extracts against ACE progressively increased, achieving 73% inhibition. T. A. Aderinola et al. (2018) also reported 72.48% ACE inhibition by the globulin protein extract. In addition, the ACE activity of the peptide fractions of *V. radiata* indicated that fraction C2 had the highest ACE activity (78.87%), followed by C3 (74.05%), C1 (49.03%), C4 (40.35%), T2 (33.88%), T1 (25.49%), and T3 (7.15%) sequentially (Viernes et al. 2012). The methanol extract of *P. harmala* had the highest level of ACE inhibition at 1.0 μg (48.7%), followed by 0.5 μg (42.5%), 0.25 μg (32.3%), and 0.1 μg (23.5%) (Hivrale and Lomate 2013). The crude extract revealed the highest ACE activity (66.4%). The most minimal ACE inhibition was demonstrated in the protein extract of *V. radiata*, with values of 4.02% in the chymotryptic digest and 10.26% in the tryptic digest (Viernes et al. 2012) (refer to Table 2).

3.2.2 | Comparison of IC_{50} Values

The IC_{50} is the concentration required to inhibit 50% of ACE activity. It was calculated for each extract or peptide in order to allow a quantitative comparison of their potency in the study (Li, Liu et al. 2005). The efficacy of a seed species in suppressing ACE is inversely proportional to the value of IC_{50} ; that is, a smaller IC_{50} value indicates greater efficacy. The protein extract of *A. hypogaea*

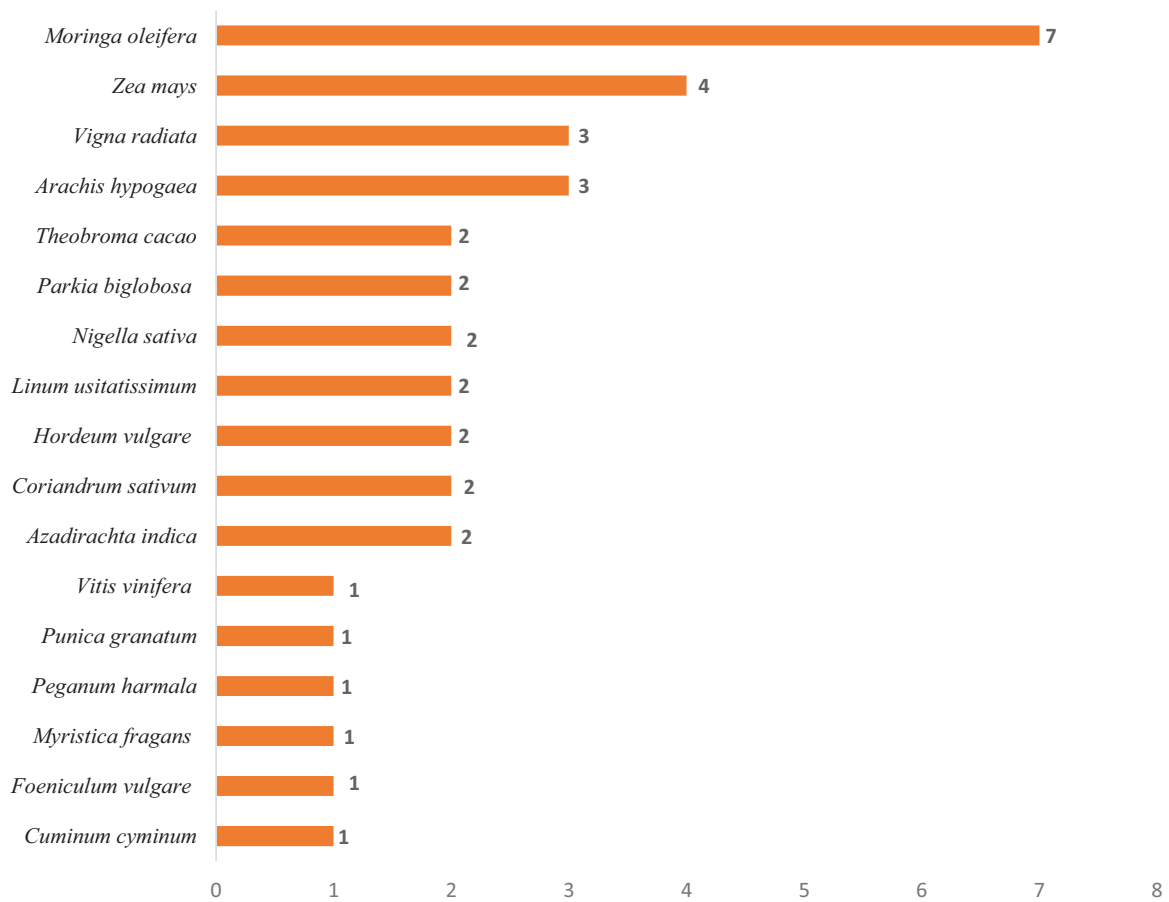


FIGURE 4 | Ten most frequently cited plant species in vitro against hypertension.

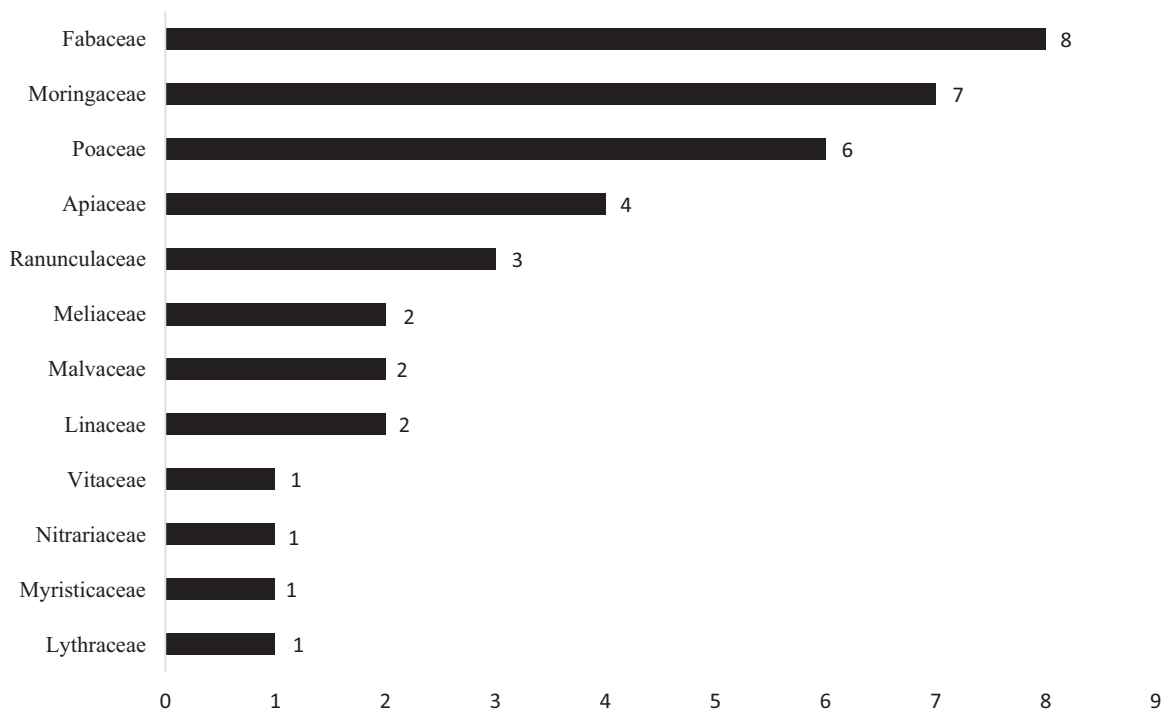


FIGURE 5 | Plant families tested in vitro against hypertension.

TABLE 2 | Seed species tested in vitro against hypertension.

Plant species	Extract	Findings		References
		Treatment (extract)	Positive control	
<i>Arachis hypogaea</i> L. (Fabaceae)	Enzyme hydrolysates	IC₅₀ (μg/mL) of fractions from Alcalase digestion: 8.7–122 Roasted flour: 12–235 The pepsin–pancreatic system yielded IC ₅₀ values for raw and roasted peanuts of 7.9–65.9 and 11–36 μg/mL, respectively	NI	Quist et al. (2009)
<i>Arachis hypogaea</i> L. (Fabaceae)	Protein hydrolysates	IC₅₀ (mg/mL): 0.489 ± 0.002	NI	Olusola and Ekun (2018)
<i>Arachis hypogaea</i> L. (Fabaceae)	Protein fraction hydrolysates and fractions less than 5 kDa	Light-roasted protein fraction hydrolysates (PFH) IC₅₀ (mg/mL) Crude PFH 0 h: 24.91 1 h: 6.45 2 h: 2.28 4 h: 1.86 Fractions less than 5 kDa 0 h: 5.65 1 h: 3.74 2 h: 3.91 4 h: 1.19 Dark roasted protein fraction hydrolysates (PFH) IC₅₀ values (mg/mL) of Crude PFH 0 h: 24.49 1 h: 4.12 2 h: 1.91 4 h: 1.50 Fractions less than 5 kDa 0 h: 4.70 1 h: 1.92 2 h: 1.17 4 h: 1.16	NI	Fang et al. (2021)
<i>Azadirachta indica</i> A.Juss. (Meliaceae)	Protein hydrolysates	Compared to peptides with molecular weights more than 3 kDa, the smaller peptides (less than 3 kDa) exhibited superior ACE inhibitory effects	NI	Acho et al. (2023)
<i>Azadirachta indica</i> A.Juss. (Meliaceae)	Protein hydrolysates	IC₅₀ values (mg/mL) Pepsin neem seed protein hydrolysate (PNSPH): 0.21 ± 0.12 Trypsin neem seed protein hydrolysate (ANSPH): 0.57 ± 0.14 Alcalase neem seed protein hydrolysate (ANSPH): 0.86 ± 0.10	NI	Arise et al. (2019)
<i>Coriandrum sativum</i> L. (Apiaceae)	Fermented	Fermented: 0.056 CapEq/mL Non-fermented: increased ≥10-fold	NI	Takamiya et al. (2023)
<i>Coriandrum sativum</i> L. (Apiaceae)	Essential oil	IC₅₀ (μg/mL): 34.8 ± 2.3	NI	Chaudhary et al. (2012)
<i>Cuminum cyminum</i> L. (Apiaceae)	Fermented	Fermented: 0.31 CapEq/mL Non-fermented: increased ≥10-fold	NI	Takamiya et al. (2023)
<i>Foeniculum vulgare</i> Mill. (Apiaceae)	Essential oil	IC₅₀ (μg/mL): 40.7 ± 3.5	NI	Chaudhary et al. (2012)
<i>Hordeum vulgare</i> L. (Poaceae)	Protein concentrates	ACE-I inhibitory activity of peptides (%) DSWRPW: 25.80 ± 4.96 FQLPKF: 91.83 ± 0.33 Four peptides: FQLPKF, ALRYFM, NFLARF, and GFPTLKIF. Out of the 15 synthesized peptides were selected for IC ₅₀ analysis because they had the greatest ACE-I inhibitory activity (91.8%, 90.3%, 89.0%, and 88.3%, respectively) IC₅₀ values of the four peptides (μM) FQLPKF: 28.2 ALRYFM: 200 NFLARF: 100 GFPTLKIF: 41.2	NI	Gangopadhyay et al. (2016)

(Continues)

TABLE 2 | (Continued)

Plant species	Extract	Findings		References
		Treatment (extract)	Positive control	
<i>Hordeum vulgare</i> L. (Poaceae)	Polyphenols	IC₅₀ (μM) 3- <i>O</i> -feruloylquinic acid: 43.8 ± 0.6 Lutonarin: 15.9 ± 1.1 Saponarin: 24.4 ± 1.2 Isoorientin: 7.3 ± 0.1 Orientin: 24.4 ± 1.6 Isovitexin: 26.1 ± 0.5 Isoorientin-7- <i>O</i> -[6-sinapoyl]-glucoside: 36.2 ± 0.8 Isoorientin-7- <i>O</i> -[6-feruloyl]-glucoside: 29.8 ± 0.5 Isovitexin-7- <i>O</i> -[6-sinapoyl]-glucoside: 40.7 ± 0.1 Isovitexin-7- <i>O</i> -[6-feruloyl]-glucoside: 35.4 ± 0.1 Quercetin: 25.2 ± 0.2	NI	Ra et al. (2020)
<i>Linum usitatissimum</i> L. (Linaceae)	Aqueous	IC₅₀ (μg/mL): 28.7	Captopril exhibited a significant percentage inhibition with a value of 74.5 at a dose of 25 μg/mL concentration	Gokhale and Sahu (2016)
<i>Linum usitatissimum</i> L. (Linaceae)	Fermented	IC₅₀ (mg/mL): 0.36	NI	Pihlanto et al. (2012)
<i>Moringa oleifera</i> Lam. (Moringaceae)	Protein	IC₅₀ (mg/mL): 1.057	NI	Liu et al. (2023)
<i>Moringa oleifera</i> Lam. (Moringaceae)	Aqueous	ACE inhibitory activity (U/mg) Crude: 0.04 Acetone precipitation: 0.16 Gel filtration: 1.99	NI	Mansurah et al. (2015)
<i>Moringa oleifera</i> Lam. (Moringaceae)	Alkaloid, flavonoid, and saponin	IC₅₀ values (mg/mL) Alkaloid-rich: 2.04 ± 0.95 Flavonoid-rich: 2.16 ± 0.56 Saponin-rich: 24.32 ± 2.31 IC₅₀ values of partially purified fractions of alkaloid rich fractions-A (mg/mL) A1: 0.07 ± 0.01 A2: 0.82 ± 0.04 A3: 0.18 ± 0.03 A4: 0.11 ± 0.01 A5: 0.25 ± 0.02 IC₅₀ values of partially purified fractions of flavonoid rich fractions-F (mg/mL) F1: 1.20 ± 0.02 F2: 0.88 ± 0.05 F3: 1.06 ± 0.03 F4: 0.42 ± 0.03	IC₅₀ value of Captopril (mg/mL): 0.22 ± 0.01	Mansurah et al. (2015)
<i>Moringa oleifera</i> Lam. (Moringaceae)	Globulin hydrolysates	The membrane fraction's inhibition against ACE increased gradually, with the 5–10 kDa having a much larger (73%) inhibition than the other membrane fractions. There was no discernible pattern in the inhibition of renin Nevertheless, in comparison to other membrane fractions, the 5–10 kDa still demonstrated superior inhibition (57%) ability	NI	T. A. Aderinola et al. (2018)
<i>Moringa oleifera</i> Lam. (Moringaceae)	Globulin protein	The peptides' ability to inhibit ACE was improved; the 1–3 kDa peptide had the best ACE inhibition (72.48%) but the lowest (17.64%, 1–3 kDa) inhibition against renin	NI	T. A. Aderinola et al. (2019)
<i>Moringa oleifera</i> Lam. (Moringaceae)	Aqueous	IC₅₀ (μg/mL): 273.82 ± 0.71	NI	Obubanjo et al. (2017)

(Continues)

TABLE 2 | (Continued)

Plant species	Extract	Findings		References
		Treatment (extract)	Positive control	
<i>Moringa oleifera</i> Lam. (Moringaceae)	Protein isolates and hydrolysates	No inhibitory potential against ACE activity up to the maximum 0.5 mg protein/mL Alcalase hydrolysates showed higher potency (79.30%) when compared to the 43.01% and 75.05% for pepsin hydrolysates and trypsin hydrolysates, respectively	NI	Aderinola et al. (2018)
<i>Myristica fragrans</i> Houtt. (Myristicaceae)	Aqueous	IC ₅₀ (µg/mL): 205.51 ± 0.71	NI	Odubanjo et al. (2018)
<i>Nigella sativa</i> L. (Ranunculaceae)	Crude	ACE inhibition: About 89% Extract separated into three fractions (1) AS-30 (2) AS-60 (3) AS-Sat Only two fractions (AS-30 and AS-60) were found active against ACE with 61% and 29% inhibitory activity	NI	Javaid et al. (2021)
<i>Nigella sativa</i> L. (Ranunculaceae)	Essential oil	IC ₅₀ (µM) Xanthine-xanthine oxidase: 0.1 Phenazine methosulfate method: 1.2	NI	Khattab and Nagi (2007)
<i>Parkia biglobosa</i> Benth. (Fabaceae)	Phenol	IC ₅₀ (mM gallic acid equivalent) Free extract: 1.00 ± 0.4 Bound extract: 1.07 ± 0.6	NI	Ademiluyi and Oboh (2012)
<i>Parkia biglobosa</i> Benth. (Fabaceae)	Phenol	IC ₅₀ values for the inhibition of ACE (µg/mL) Bound extract: 46.85 ± 3.3 Free extract: 15.35 ± 4.0	IC ₅₀ values for the inhibition of ACE (µg/mL) Ramipril: 0.173 ± 0.04	Komolafe et al. (2018)
<i>Peganum harmala</i> L. (Nitrariaceae)	Methanol	ACE inhibition at different concentrations (%) 0.1 µg: 23.5 0.25 µg: 32.3 0.5 µg: 42.5 1.0 µg: 48.7	IC ₅₀ of Captopril (%) 1.0 µg: 49.1	Hivrale and Lomate (2013)
<i>Punica granatum</i> L. (Lythraceae)	Aqueous	IC ₅₀ (%): 53.43 ± 14.09	NI	Das and De (2013)
<i>Theobroma cacao</i> L. (Malvaceae)	Hydrolysates	IC ₅₀ (mg/mL): 0.49	NI	Coronado-Cáceres et al. (2021)
<i>Theobroma cacao</i> L. (Malvaceae)	Aqueous	EC ₅₀ (mg/mL) ACE (lungs): 0.674 ± 0.06 ACE (heart): 1.006 ± 0.08	NI	Oboh et al. (2014)
<i>Vigna radiata</i> L. R.Wilczek (Fabaceae)	Protein	ACE inhibitory activity of extract (IU × 10 ⁻³) Tryptic digest: 0.342 ± 0.070 Chymotryptic digest: 0.134 ± 0.057 Inhibitory activity (IU × 10 ⁻³) Tryptic digest: 1.786 ± 0.070 Chymotryptic digest: 1.994 ± 0.057 ACE inhibitory activities of peptide fractions (%) C1: 49.03 ± 0.36 C2: 78.87 ± 0.49 C3: 74.05 ± 1.15 C4: 40.35 ± 1.55 T1: 25.49 ± 0.71 T2: 33.88 ± 0.49 T3: 7.15 ± 0.36 IC ₅₀ of peptide fractions (µg) C1: 0.826 ± 0.046 C2: 0.203 ± 0.014 C3: 0.286 ± 0.007 C4: 0.852 ± 0.027 T1: 1.325 ± 0.142 T2: 1.151 ± 0.005 T3: 1.367 ± 0.001	ACE inhibitory activities of peptide fractions (%) Captopril: 96.75 ± 0.80 IC ₅₀ value (µg) Captopril: 0.028 ± 0.001	Viernes et al. (2012)
<i>Vigna radiata</i> L. R.Wilczek (Fabaceae)	Protein	IC ₅₀ (mg/mL): 0.64	NI	G.-H. Li, Shi, et al. (2006)
<i>Vigna radiata</i> L. R.Wilczek (Fabaceae)	Protein	IC ₅₀ (mg/mL): 0.64	IC ₅₀ of Captopril: 0.019 µM	G. H. Li, Le, et al. (2005)

(Continues)

TABLE 2 | (Continued)

Plant species	Extract	Findings		
		Treatment (extract)	Positive control	References
<i>Vitis vinifera</i> L. (Vitaceae)	Ethanol	IC ₅₀ (mmol/L): 0.480 ± 0.03	NI	Eriz et al. (2011)
<i>Zea mays</i> L. (Poaceae)	Aqueous	ACE inhibition at different substrates (μg/mL) Substrate 1: 53.95 ± 0.58 Substrate 2: 87.26 ± 2.68	Captopril inhibited the hydrolysis substrates 1 and 2 by ACE in a dose-dependent manner	C.-C. Li et al. (2019)
<i>Zea mays</i> L. (Poaceae)	Protein hydrolysates	IC ₅₀ of different molecular-weight peptides (mg protein/mL) <i>M_w</i> < 1 kDa: 0.44 <i>M_w</i> < 3 kDa: 0.29 <i>M_w</i> < 5 kDa: 1.27	NI	Huang et al. (2011)
<i>Zea mays</i> L. (Poaceae)	Peptide hydrolysates	ACE inhibitory activity of extract with various enzymes (%) Protamex: 13.94 Neutrase: 47.43 Alcalase: 85.26 Trypsin: 72.80 ACE inhibitory activity of peptide fractions (%) CI: 13.54 CII: 18.56 CIII: 82.92 CIV: 10.78 CV: 21.38 CVI: 12.36	NI	Yang et al. (2007)
<i>Zea mays</i> L. (Poaceae)	Peptides	The results of ultrafiltration indicated the presence of strong ACE inhibitory peptides in the 3–10 kDa fraction (IC ₅₀ = 15.98 μg/mL) Reverse-phase chromatography and size exclusion chromatography were used to further separate the peptides in the fraction. The most potent ACE inhibitor was found to be the new peptide DLLGCS (IC ₅₀ = 39.0 μM)	NI	Wongngam et al. (2023)

Abbreviation: NI, not indicated.

recorded the lowest IC₅₀ value (0.079–0.0659 mg/mL) (Quist et al. 2009), followed by the phenolic-free extract of *P. biglobosa* (0.01535 mg/mL) (Komolafe et al. 2018), protein extract of *Z. mays* (0.01598 mg/mL) (Wongngam et al. 2023), and the aqueous extract of *L. usitatissimum* (0.0287 mg/mL) (Gokhale and Sahu 2016).

Among the essential oil extracts, *C. sativum* recorded the next lowest IC₅₀ value (0.0348 ± 0.0023 mg/mL) (Chaudhary et al. 2012), followed by *Foeniculum vulgare* (0.0407 ± 0.0035 mg/mL) (Chaudhary et al. 2012). The aqueous extract of *M. fragrans* had an IC₅₀ value of 0.20551 ± 0.00071 mg/mL (Odubanjo et al. 2018),

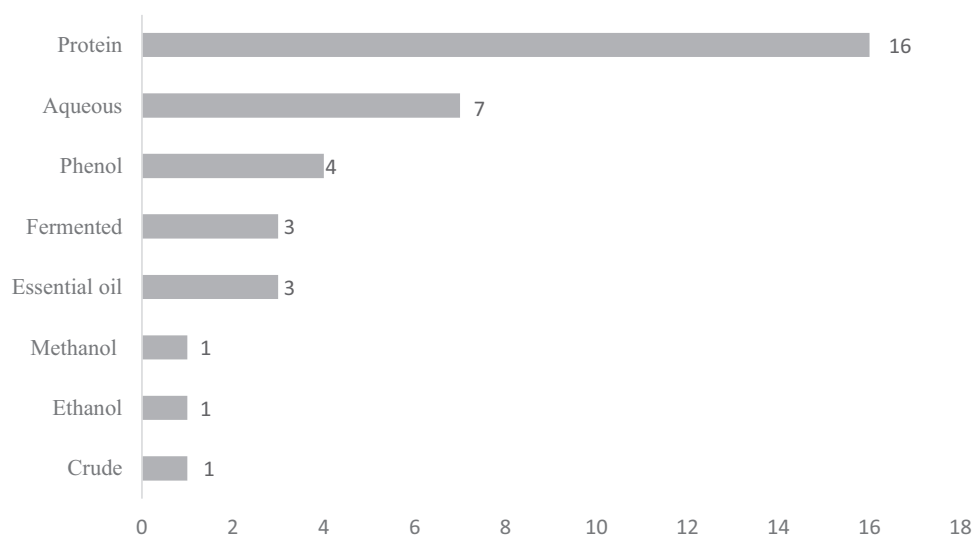


FIGURE 6 | Different types of extract tested in vitro.

whereas the protein hydrolysates extract of *A. indica* yielded IC₅₀ values (in the order of pepsin > trypsin > alcalase) of 0.21 ± 0.12 , 0.57 ± 0.14 , and 0.86 ± 0.10 mg/mL, respectively (Arise et al. 2019). The aqueous extract of *M. oleifera* recorded the next lowest IC₅₀ value (0.27382 ± 0.00071 mg/mL) (Odubanjo et al. 2018), followed by the protein hydrolysates extract of *Z. mays* (in the order of Mw < 3 kDa, Mw < 1 kDa, Mw < 5 kDa) with IC₅₀ values of 0.29, 0.44, and 1.27 mg/mL, respectively (Arise et al. 2019). Subsequent IC₅₀ values were for the fermented extract of *L. usitatissimum* (0.36 mg/mL) (Pihlanto et al. 2012), protein hydrolysates extract of *A. hypogaea* (0.489 ± 0.002 mg/mL) (Olusola and Ekun 2018), hydrolysates extract of *T. cacao* (IC₅₀ = 0.49 mg/mL) (Coronado-Cáceres et al. 2021), and protein extract of *V. radiata* (IC₅₀ = 0.64 mg/mL) (G. H. Li, Le, et al. 2005), with the latter being repeated for the protein extract of *V. radiata* (G.-H. Li, Shi, et al. 2006). The plant species with the second-lowest IC₅₀ value was the aqueous extract of *T. cacao*, which exhibited an IC₅₀ value of 0.674 ± 0.06 mg/mL (lung) and 1.006 ± 0.08 mg/mL (heart). This was followed by the protein extract of *M. oleifera*, which had an IC₅₀ value of 1.057 mg/mL (Liu et al. 2023). The lowest IC₅₀ value for the light-roasted protein fraction hydrolysates of *A. hypogaea* was 1.86 mg/mL, whereas fractions less than 5 kDa recorded an IC₅₀ value of 1.19 mg/mL after 4 h. For the dark roasted protein fraction hydrolysates, the IC₅₀ value was 1.50 mg/mL, and fractions less than 5 kDa had an IC₅₀ value of 1.16 mg/mL, also after 4 h. Notably, the fractions less than 5 kDa were more effective, as they exhibited the lowest IC₅₀ values (Fang et al. 2021). The alkaloid-rich extract of *M. oleifera* demonstrated the lowest IC₅₀ value of 2.04 ± 0.95 mg/mL, compared to the flavonoid-rich and saponin-rich extracts, which had IC₅₀ values of 2.16 ± 0.56 and 24.32 ± 2.31 mg/mL, respectively (Mansurah et al. 2015) (Table 2).

As the units of the IC₅₀ values are presented in mg/mL, only one study (*M. oleifera*) was comparable with the positive control among the six studies that used captopril as a positive control. The alkaloid-rich extract of *M. oleifera* had the best IC₅₀ value (2.04 ± 0.95 mg/mL) compared to the IC₅₀ value of captopril (0.22 ± 0.01 mg/mL) (Mansurah et al. 2015). For the one study that used ramipril as a positive control, the IC₅₀ value was comparable as both are presented in µg/mL. The phenolic-free extract of *P. biglobosa* had better efficacy (15.35 ± 4.0 µg/mL) compared to the IC₅₀ of ramipril (0.173 ± 0.04 µg/mL) (Komolafe et al. 2018). In the rest of the studies, the IC₅₀ values of captopril were presented in percentage (%) and µM, whereas the IC₅₀ values of the extracts were presented as µg/mL and mg/mL (Table 2).

3.3 | In Vivo Studies

Out of the 50 seed species traditionally employed against hypertension (Table 1), 20 species underwent in vivo testing (Table 3). Metrics, such as SBP, DBP, PP, and MABP, were consistently recorded across all studies. Additionally, some studies measured HR and plasma ACE activity. The most frequently studied plant species was *N. sativa* ($n = 9$), with *P. americana* and *Z. mays* each having five studies, followed by *L. usitatissimum*, *M. oleifera*, and *Trigonella foenum-graecum* with four studies each. Both *Garcinia kola* and *P. biglobosa* had only two studies each. For species like *Aframomum melegueta*, *Anethum graveolens*, *Capparis spinosa*, *Citrullus lanatus*, *Cuminum cyminum*, *H. vulgare*, *Petroselinum*

crispum, *Picralima nitida*, *Piper guineense*, *T. cacao*, *V. radiata*, and *V. vinifera*, only a single study was available for each (Figure 7) (Table 3).

The most frequently sampled family was Ranunculaceae ($n = 9$), followed by Fabaceae ($n = 7$), Poaceae ($n = 6$), and Lauraceae ($n = 5$). Both Linaceae and Moringaceae had four studies, whereas five studies were available for Apiaceae. Only two studies were retrieved for Clusiaceae. For the remaining families—Apocynaceae, Capparaceae, Cucurbitaceae, Malvaceae, Piperaceae, Vitaceae, and Zingiberaceae—only one study was found (Figure 8) (Table 3).

The most common extract type used for in vivo studies was aqueous extract ($n = 18$), followed by powdered extract ($n = 8$), ethanol extract ($n = 6$), and methanol and protein extract ($n = 4$). Three studies were found with the use of essential oil and hydroalcoholic extracts, respectively. Similarly, two studies were found with the use of hexane extract. Only one study was found with the use of raw seed as an extract in in vivo studies (Figure 9) (Table 3).

The most frequently used in vivo model was Wistar rats ($n = 28$), followed by Sprague–Dawley rats/mice ($n = 4$). Other models, namely, Balb/c mice, *Rattus norvegicus* rats, *Oryctolagus cuniculus* rabbits, and normal rabbits, were employed in a single study each (Figure 10) (Table 2).

The predominant route of administration was oral ($n = 39$), followed by intraperitoneal injection ($n = 4$). Other routes, including intragastric, intravenous, orogastric, and subcutaneous injections, were each reported in only two studies (Figure 11) (Table 3).

3.3.1 | Comparison of SBP, Plasma ACE Activity, and MABP

Out of 20 species examined in vivo, the highest reduction in SBP (74.6 mmHg) was found with 700 mg/kg of the aqueous of *P. americana* (Imafidon and Igbinaduwa 2010), followed by *G. kola* (46.1 mmHg) at a dose of 200 mg/kg of the ethanol extract (Olatoye et al. 2023). The next most potent was the aqueous extract of *Z. mays* where hypercholesterolemic rats exhibited the highest decrease in SBP (45 mmHg) (Guzmán-Gerónimo et al. 2017), followed by 500 mg/kg of the aqueous extract of *P. americana* (41 mmHg) (Imafidon and Igbinaduwa 2010). Another study with *G. kola* reported the greatest efficacy with 3.0 mg/kg extract, reducing the SBP by 40 mmHg (Naiho and Ugwu 2011). The next plant is *N. sativa* where its hydroalcoholic extract (600 mg/kg) reduced the SBP by 34.8 mmHg (Enayatfard et al. 2018). The SBP in *L. usitatissimum* was decreased by 32.4 mmHg with an 800 mg/kg dose of extract (Sawant and Bodhankar 2016). The rest of the studies showed a much lower reduction ranging from 15 to 30 mmHg (Table 3).

Only four studies measured plasma ACE activity for *A. melegueta*, *C. spinosa*, *N. sativa*, and *Z. mays*. In the study with *N. sativa*, ACE activity was decreased by 56.2 pg/g in animals administered with 2.5 mg/kg (Jaarin et al. 2015). The remaining ACE activities of

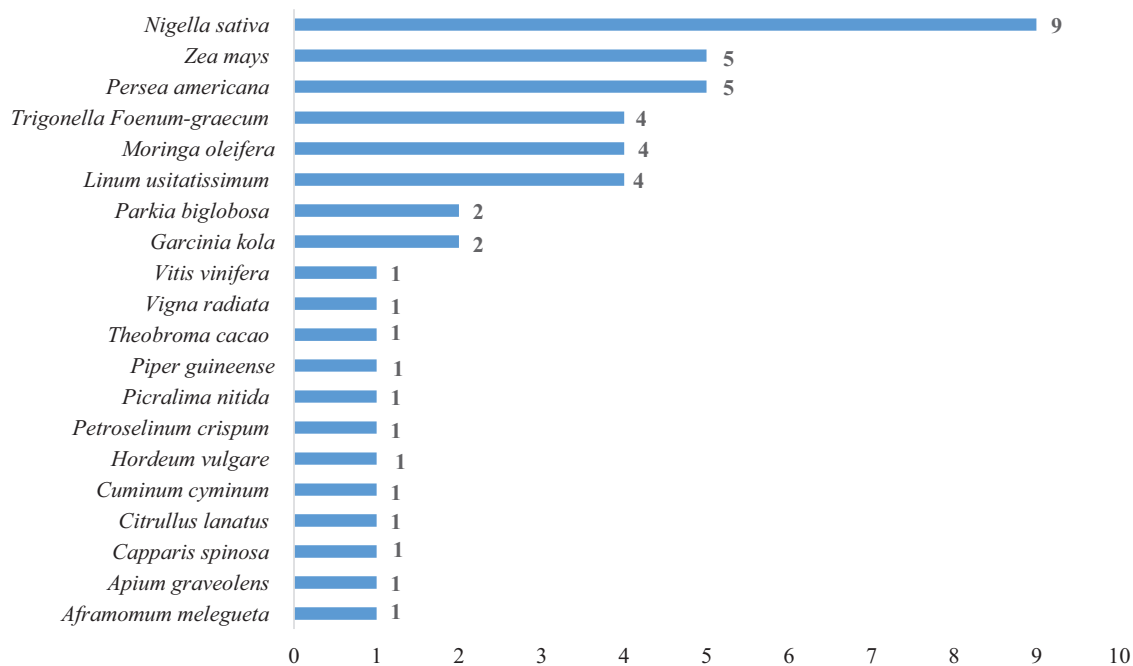


FIGURE 7 | Seed species tested in vivo against hypertension.

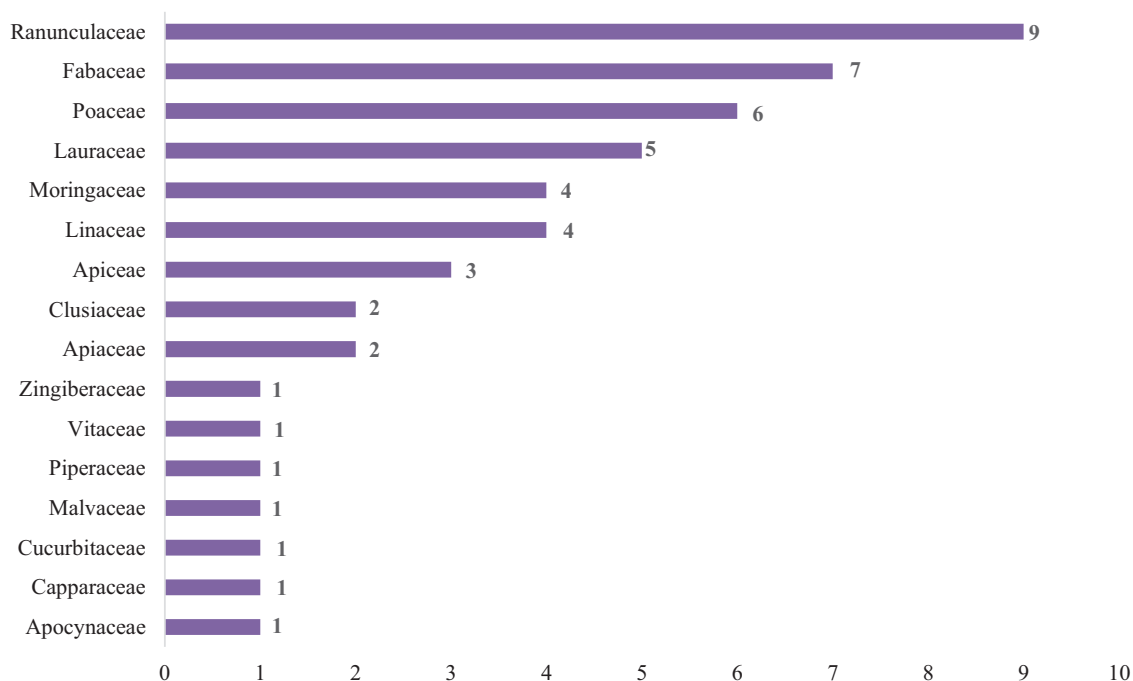


FIGURE 8 | Plant families tested in vivo against hypertension.

the other three plant species were reported in different units and therefore could not be compared (Table 3).

With respect to MABP, the plant species that presented the greatest reduction in this parameter was *P. americana* (61.4 mmHg) with the administration of 500 mg/kg of extract (Imafidon and Igbinaduwa 2010). Another species that significantly reduced the MABP was *L. usitatissimum*, where the administration of 800 mg/kg of aqueous extract reduced the MABP (35.6 mmHg)

(Sawant and Bodhankar 2016). Other results point to *G. kola* that had its MABP reduced by 34.9 mmHg (Olatoye et al. 2023), followed by the administration of 3.0 mg/kg of extract of the same species that reduced the MABP (30.3 mmHg) (Naiho and Ugwu 2011). The hydroalcoholic extract of *N. sativa* at a dose of 600 mg/kg also showed a reduction in MABP (28.34 mmHg) (Enayatfard et al. 2018). Furthermore, the administration of 260 mg/kg of the aqueous extract of *P. americana* caused a decrease in the MABP (18.1 mmHg) greater than the doses of

TABLE 3 | Seed species tested in vivo against hypertension.

Plant species	Extract	Model used	Dosage	Findings		Reference
				Treatment (extract)	Control	
<i>Aframomum melegueta</i> K.Schum. (Zingiberaceae)	Aqueous	Male Wistar rats	Normal	Plasma ACE (units/mg protein)	Plasma ACE (units/mg protein)	Adelegha et al. (2016)
			Group 1: Normal control (normal diet)	Group 3: 135.42 ± 2.99	Group 1: 122.75 ± 3.14	
			Hypercholesterolemic (HC)	Group 4: 102.08 ± 3.88	Group 2: 139.51 ± 4.37	
			Group 2: HC control (HC rat diet)	Group 5: 89.46 ± 4.13		
			Group 3: HC diet + simvastatin in normal saline (0.2 mg/kg)			
			Group 4: HC diet + Extract (2%)			
			Group 5: HC diet + Extract (4%)			
			Administration: Oral			
			Duration: 30 days			
			Hypertensive			
<i>Apium graveolens</i> L. (Apiaceae)	Hexanic, methanolic, and aqueous ethanolic	Male Wistar rats	Group 1: DOCA (20 mg/kg) + hexanic extract (100 mg/kg)	SBP (mmHg)	SBP (mmHg)	Moghadam et al. (2013)
			Group 2: DOCA (20 mg/kg) + hexanic extract (200 mg/kg)	The data showed that BP was decreased in Groups 6 and 1, 2, and 3, in comparison with negative control groups	Administration of DOCA to Groups 7 and 8 increased the BP from 10.5 to 15 mmHg in a period of 7 weeks, but BP in Group 9 remained unchanged during this time	
			Group 3: DOCA (20 mg/kg) + hexanic extract (300 mg/kg)	At the end of Week 7, the BP values in Groups 3 and 6 were 112 and 97 mmHg, respectively. After stopping the treatment, the BP increased to 125 and 134 mmHg, in Groups 3 and 6	HR (beats/min)	
			Group 4: DOCA (20 mg/kg) + methanolic extract (300 mg/kg)		Administration of DOCA in Groups 7 and 8 diminished the HR from 350 to 260 beats/min in a period of 7 weeks, whereas the HR in Group 9 remained unchanged	
			Group 5: DOCA (20 mg/kg) + aqueous-ethanolic extract (300 mg/kg)	The antihypertensive effect of hexanic extracts was significantly higher than methanolic and aqueous-ethanolic extracts of celery seeds in rats		
			Group 6: DOCA (20 mg/kg) + spironolactone (50 mg/kg)	HR (beats/min)		
			Normotensive			
			Group 7: Normal saline (0.9%) (solvent of methanolic + aqueous ethanolic extracts)	The data showed that Group 6 and Groups 1, 2, and 3 experienced an increased HR, in comparison with negative control groups, in hypertensive rats		
			Group 8: Liquid paraffin (0.5 mL) (solvent of the hexanic extract)	At the end of Week 7, the HR values in Groups 3 and 6 were 330 and 380 beats/min, respectively		
			Group 9: Normal saline (0.5 mL) + hexanic extract (300 mg/kg)	After stopping the treatment, the HR altered to 310 and 290 beats/min, in Groups 3 and 6 at the end of Week 9		
			Administration: Subcutaneous injection + Oral	The effect of hexanic extracts on HR was significantly higher than those of methanolic and aqueous-ethanolic celery seed extracts		(Continues)
			Duration: 9 weeks			

TABLE 3 | (Continued)

Plant species	Extract	Model used	Dosage	Findings		Reference
				Treatment (extract)	Control	
<i>Capparis spinosa</i> L. (Capparaceae)	Aqueous	Male SHR rats	Hypertensive Group 1: Distilled water (control) Group 2: Extract (140 mg/kg) Administration: Oral Duration: 20 days	A significant decrease on SBP was observed after 8 days of extract administration leading to 13.5 ± 2.63 mmHg reduction of baseline SBP No significant change in HR was observed Plasma ACE activity (mmol/mL/min) Group 2 Day 0: 98.120 ± 1.91 Day 20: 101.02 ± 2.74 No significant change in plasma ACE was observed after 20 days administration of extract	Plasma ACE activity (mmol/mL/min) Group 1 Day 0: 103.25 ± 2.06 Day 20: 102.06 ± 1.96	Zeggwagh et al. (2007)
			Normotensive Group 1: Normal saline (10 mL/kg) Group 7: Extract (150 mg/kg/day) Hypertensive Group 2: ISO (5 mg/kg/day) Group 3: Carvedilol (10 mg/kg/day) Group 4: Verapamil (10 mg/kg/day) Group 5: Extract (75 mg/kg/day) Group 6: Extract (150 mg/kg/day) Administration: Oral Duration: 21 days	Normotensive rats: The hypotensive response of extract was dose-dependent at doses 0.1, 0.3, 0.5, and 1 mg/kg. The extract decreased MABP in ranges 104, 57, 41, and 55 at respective doses of 0.1, 0.3, 0.5, and 1 mg/kg Hypertensive rats: Extract (0.1, 0.3, 0.5, and 1 mg/kg) resulted in a significant drop in MABP as 177.37 ± 7.35 , 111.8102 ± 3.1 , 63.084 ± 2.15 , and 36.48 ± 6.165 mmHg at doses 0.1, 0.3, 0.5, and 1 mg/kg	Normotensive rats: In the presence of atropine, the hypotensive effect was attenuated. MABP decreased in the range of 107, 108, 104, 99 at doses 0.1, 0.3, 0.5, and 1 mg/kg, respectively. The verapamil decreased MABP in normotensive anesthetized rats in the range of 92, 75, and 53 at respective doses 1, 3, and 10 µg/kg	Saqib et al. (2022)
<i>Cuminum cyminum</i> L. (Apiaceae)	Aqueous	Male Sprague Dawley rats	Normotensive Group 1: Sham control (vehicle) Hypertensive Group 2: 2K/1C (two-kidney one-clipped) + vehicle Group 3: 2K/1C + extract Administration: Oral Duration: 9 weeks	Systolic blood pressure—SBP Treatment with extract reduced SBP in 2K/1C rats when compared to vehicle-treated rats Extract improved eNOS expression in common carotid arteries	NI	Kalaivani et al. (2013)

(Continues)

TABLE 3 | (Continued)

Plant species	Extract	Model used	Dosage	Findings		Reference
				Treatment (extract)	Control	
<i>Garcinia kola</i> Heckel (Clusiaceae)	Crude	Wistar rats	Experiment 1 Group 1: Rat chow + water Group 2: Rat chow (90 g) + extract (10 g) Group 3: Rat chow (85 g) + extract (15 g)	Experiment 1 Changes in SBP (mmHg) Group 2	Experiment 1 Changes in SBP (mmHg) Group 1	Naiho and Ugwu (2011)
			Experiment 2 Group 1: Basal diet Group 2: Solvent Group 3: Extract (0.5 mg/kg) Group 4: Extract (1.0 mg/kg) Group 5: Extract (2.5 mg/kg) Group 6: Extract (3.0 mg/kg) Administration: Oral Duration: 6 weeks	Week 1: 123.2 ± 5 Week 2: 118.4 ± 5 Week 3: 104.0 ± 4 Week 4: 100.5 ± 5 Week 5: 102.2 ± 4 Week 6: 106.8 ± 5 Group 3 Week 1: 124.0 ± 5 Week 2: 106.2 ± 4 Week 3: 104.5 ± 5 Week 4: 96.4 ± 5 Week 5: 95.4 ± 5 Week 6: 100.8 ± 5 Experiment 2 SBP (mmHg) Group 3: 125 ± 7 Group 4: 118 ± 5 Group 5: 103 ± 6 Group 6: 88 ± 3 DBP (mmHg) Group 3: 80.8 ± 6 Group 4: 76 ± 7 Group 5: 71 ± 4 Group 6: 55 ± 6 MAP (mmHg) Group 3: 95.7 ± 8.2 Group 4: 90.5 ± 4 Group 5: 82.6 ± 2.4 Group 6: 66.8 ± 1.2 HR (beats/min) Group 3: 363 ± 19 Group 4: 370 ± 18.2 Group 5: 375 ± 19 Group 6: 395 ± 20	Week 1: 122.3 ± 5 Week 2: 120.8 ± 4 Week 3: 123 ± 5 Week 4: 122.8 ± 5 Week 5: 123.1 ± 6 Week 6: 121.5 ± 5 Experiment 2 SBP (mmHg) Group 1: 128 ± 6 Group 2: 128 ± 6 DBP (mmHg) Group 1: 84 ± 5 Group 2: 83 ± 4 MAP (mmHg) Group 1: 98.0 ± 5.0 Group 2: 97.1 ± 2.1 HR (beats/min) Group 1: 360 ± 18.0 Group 2: 365.8 ± 19	

(Continues)

TABLE 3 | (Continued)

Plant species	Extract	Model used	Dosage	Findings		Reference
				Treatment (extract)	Control	
<i>Garcinia kola</i> . Heckel (Clusiaceae)	Ethanol	Male Wistar rats	Normotensive Group 1: Normal control Hypertensive Group 2: L-NAME (40 mg/kg/day) Group 3: L-NAME (40 mg/kg/day) + extract (50 mg/kg) Group 4: L-NAME (40 mg/kg/day) + extract (100 mg/kg) Group 5: L-NAME (40 mg/kg/day) + extract (200 mg/kg) Group 6: L-NAME (40 mg/kg/day) + lisinopril (0.14 mg/kg) Administration: Oral Duration: 28 days	SBP (mmHg) Group 3: 188.50 ± 4.77 Group 4: 141.20 ± 2.83 Group 5: 148.40 ± 4.72 Group 6: 156.00 ± 3.69	SBP (mmHg) Group 1: 123.70 ± 11.44 Group 2: 194.50 ± 6.63	Olatoye et al. (2023)
				DBP (mmHg) Group 3: 144.70 ± 1.74 Group 4: 113.10 ± 2.68 Group 5: 120.70 ± 2.51 Group 6: 125.50 ± 0.93	DBP (mmHg) Group 1: 106.25 ± 2.83 Group 2: 148.60 ± 4.25	
				MAP (mmHg) Group 3: 148.10 ± 4.83 Group 4: 123.30 ± 0.79 Group 5: 127.00 ± 2.85 Group 6: 130.10 ± 3.35	MAP (mmHg) Group 1: 113.00 ± 3.58 Group 2: 158.20 ± 2.68	
				HR (beats/min) Group 3: 389.30 ± 12.72 Group 4: 384.00 ± 14.05 Group 5: 402.70 ± 10.91 Group 6: 385.30 ± 9.33	HR (beats/min) Group 1: 390.70 ± 13.13 Group 2: 393.30 ± 14.11	
				Pulse pressure PP (mmHg) Group 3: 30.33 ± 2.49 Group 4: 29.40 ± 1.89 Group 5: 29.14 ± 3.19 Group 6: 33.82 ± 6.65	Pulse pressure PP (mmHg) Group 1: 31.08 ± 4.88 Group 2: 30.29 ± 1.18	

(Continues)

TABLE 3 | (Continued)

Plant species	Extract	Model used	Dosage	Findings		Reference
				Treatment (extract)	Control	
<i>Hordeum vulgare</i> L. (Poaceae)	Ethanollic	Male Wistar rats	Normotensive	Treatment with amlodipine and extract mitigated high salt-induced hypertension compared with the HSD group. However, amlodipine treatments are more effective in decreasing blood pressure than the extract treatment	Rats on high-salt diet (HSD) displayed a significant increase of 34.5% in SBP and 23.6% in DBP levels compared to group	Ahmed-Farid et al. (2023)
			Group 1: Control (basal diet) (10 weeks)			
			Hypertensive			
			Group 2: Basal diet with NaCl (8%) (5 weeks only)			
			Group 3: Basal diet with NaCl (8%) + amlodipine (1 mg/kg) [5 weeks]			
			Group 4: Diet with NaCl (8%) + extract (1000 mg/kg) (5 weeks)			
<i>Linum usitatissimum</i> L. (Linaceae)	Aqueous	Male Wistar rats	Group 5: Diet with NaCl (8%) + amlodipine (1 mg/kg) [10 weeks]	Fructose treatment was related to the significant increase in SBP. Prolonged treatment with the extract decreases BP in fructose-fed rats	HR (beats/min) Group 1: 335 ± 8 Group 2: 334 ± 9.7 Group 6: 334 ± 2.3	Gokhale and Sahu (2016)
			Group 6: Diet with NaCl (8%) + extract (1000 mg/kg) (10 weeks)			
			Administration: Oral Duration: 10 weeks			
			Normotensive			
			Group 1: Water + carboxymethylcellulose (CMC) (2%)			
			Hypertensive			
<i>Linum usitatissimum</i> L. (Linaceae)	Aqueous	Male Wistar rats	Group 2: Fructose in water (10%) + Captopril (0.05 mg/kg)	SBP was significantly lower in Groups 3, 4, and 5 compared with the fructose-fed group	HR (beats/min) Group 3: 347 ± 1.12 Group 4: 349 ± 1.2 Group 5: 378 ± 8.75	Gokhale and Sahu (2016)
			Group 3: Fructose in water (10%) + extract (50 mg/kg)			
			Group 4: Fructose in water (10%) + extract 2 (100 mg/kg)			
			Group 5: Fructose in water (10%) + extract 3 (200 mg/kg)			
			Group 6: Fructose in water (10%)			
			Administration: Oral Duration: 2 weeks			

(Continues)

TABLE 3 | (Continued)

Plant species	Extract	Model used	Dosage	Findings		Reference
				Treatment (extract)	Control	
<i>Linum usitatissimum</i> L. (Linaceae)	Aqueous	Male Wistar rats	Normotensive	Group 4 rats did not show any significant effect on hemodynamic parameters	Group 2 rats showed significant increase in:	Sawant and Bodhankar (2016)
			Group 1: Drinking water	Compared to Group 3 rats	SBP: 160.7 ± 3.879 mmHg	
			Hypertensive	Group 5 rats showed significant decrease in	DBP: 123.9 ± 2.891 mmHg	
			Group 2: L-NAME (40 mg/kg/day)	SBP: 140.2 ± 4.57 mmHg DBP: 108.9 ± 2.42 mmHg MABP: 124.2 ± 2.82 mmHg	MABP: 136.2 ± 2.46 mmHg	
			Group 3: L-NAME (40 mg/kg/day) + captopril (30 mg/kg)		HR (beats/min)	
			Group 4: L-NAME (40 mg/kg/day) + extract (200 mg/kg)		Group 1	
			Group 5: L-NAME (40 mg/kg/day) + extract (400 mg/kg)		0th week: 364.50 ± 4.62	
			Group 6: L-NAME (40 mg/kg/day) + extract (800 mg/kg)		1st week: 357.00 ± 3.69	
			Administration: Oral		2nd week: 360.33 ± 4.10	
			Duration: 4 weeks		3rd week: 362.67 ± 4.63	
				SBP: 128.3 ± 2.57 mmHg DBP: 86.83 ± 2.91 mmHg MABP: 100.6 ± 1.78 mmHg	4th week: 359.17 ± 3.32	
				HR (beats/min)	Group 2	
					0th week: 355.33 ± 4.51	
					1st week: 347.00 ± 2.97	
					2nd week: 336.17 ± 2.55	
					3rd week: 340.33 ± 3.84	
					4th week: 327.00 ± 4.04	
					Group 3	
					0th week: 362.17 ± 6.26	
					1st week: 351.83 ± 2.60	
				SBP: 128.3 ± 2.57 mmHg DBP: 86.83 ± 2.91 mmHg MABP: 100.6 ± 1.78 mmHg	2nd week: 354.17 ± 3.00	
					3rd week: 358.00 ± 2.50	
					4th week: 359.33 ± 4.13	
					Group 4	
					0th week: 364.00 ± 2.56	
					1st week: 353.67 ± 3.45	
					2nd week: 344.50 ± 3.17	
					3rd week: 342.67 ± 5.09	
					4th week: 338.67 ± 3.71	
					Group 5	
				SBP: 128.3 ± 2.57 mmHg DBP: 86.83 ± 2.91 mmHg MABP: 100.6 ± 1.78 mmHg	0th week: 361.17 ± 3.48	
					1st week: 351.83 ± 2.60	
					2nd week: 352.50 ± 2.81	
					3rd week: 355.33 ± 3.01	
					4th week: 345.83 ± 2.80	
					Group 6	
					0th week: 363.00 ± 5.03	
					1st week: 355.33 ± 4.06	
					2nd week: 355.67 ± 3.90	
					3rd week: 357.83 ± 3.18	
				SBP: 128.3 ± 2.57 mmHg DBP: 86.83 ± 2.91 mmHg MABP: 100.6 ± 1.78 mmHg	4th week: 358.50 ± 4.72	
					Effect of extract on angiotensin-converting enzyme (ACE)	
					The result revealed that increased blood pressure in the L-NAME hypertensive rats was linked with significant increase in the heart and aortic tissue ACE activity compared with control group	
					Groups 3, 5, and 6 showed the significant inhibitory effect on ACE activity in the heart and aortic tissues	

(Continues)

TABLE 3 | (Continued)

			Findings		Reference
Plant species	Extract	Model used	Dosage	Treatment (extract)	
<i>Linum usitatissimum</i> L. (Linaceae)	Aqueous	Male Wistar rats	Normotensive Group 1: Diet with casein (20%) + saline solution (0.9%) Hypertensive Group 2: Diet with casein (20%) + ouabain in saline solution (10 µg/kg) Group 3: Diet with casein (20%) + extract (1%) Administration: Subcutaneous injection Duration: 21 days	The results showed that treatment with extract had a significant effect in decreasing SBP, DBP, MABP, and HR in hypertensive rats	Berzou et al. (2020)
			Uninephrectomized (UNITZD) rats Normotensive Group 1: Water only Hypertensive Group 2: NaCl (1%) + DOCA salt control (25 mg/kg) Group 3: NaCl (1%) + DOCA-salt (25 mg/kg) + captopril (30 mg/kg) Group 4: NaCl (1%) + DOCA-salt (25 mg/kg) + extract (200 mg/kg) Group 5: NaCl (1%) + DOCA-salt (25 mg/kg) + extract (400 mg/kg) Group 6: NaCl (1%) + DOCA-salt (25 mg/kg) + extract (800 mg/kg) Administration: Oral Duration: 5 weeks	Group 4 rats showed a significant decrease only in SBP: 137.9 ± 4.51 mmHg Group 4 rats did not show any significant decrease in DBP: 97.5 ± 3.20 mmHg MABP: 117.7 ± 3.85 mmHg Compared to Group 2, Group 5 rats showed a significant decrease in SBP: 132.9 ± 2.86 mmHg DBP: 93.16 ± 1.9 mmHg MABP: 113 ± 2.38 mmHg Group 6 rats showed a significant decrease in SBP: 129.3 ± 3.88 mmHg DBP: 90.65 ± 2.6 mmHg MABP: 110 ± 3.2 mmHg	Sawant and Bodhankar (2016)
			Group 3: NaCl (1%) + DOCA-salt (25 mg/kg) + extract (200 mg/kg) Group 4: NaCl (1%) + DOCA-salt (25 mg/kg) + extract (200 mg/kg) Group 5: NaCl (1%) + DOCA-salt (25 mg/kg) + extract (400 mg/kg) Group 6: NaCl (1%) + DOCA-salt (25 mg/kg) + extract (800 mg/kg) Administration: Oral Duration: 5 weeks	Compared to Group 1, Group 2 rats showed an increase in SBP: 152.5 ± 4.41 mmHg DBP: 107.1 ± 3.13 mmHg MABP: 129.8 ± 3.76 mmHg Group 3 rats showed a significant decrease in SBP: 124.8 ± 3.9 mmHg DBP: 87.55 ± 2.9 mmHg MABP: 106.2 ± 3.4 mmHg	
<i>Moringa oleifera</i> Lam. (Moringaceae)	Protein	Hypertensive male rats and healthy adult mice	Normotensive Group 1: Normal saline Group 2: Extract (100 mg/kg) Hypertensive Group 3: Captopril (10 mg/kg) Administration: Oral Duration: 14 days	SBR Group 2 Decrease in SBR by approximately 17 mmHg when compared with Group 1 Group 3 Decrease in SBR by more than 40 mmHg compared with Group 1	Liu et al. (2023)
			Normotensive Group 1: Normal control (basal diet) Group 2: Basal diet + extract (5%) Group 3: Basal diet + extract (10%) Hypertensive Group 4: Basal diet + L-NAME (40 mg/kg) Group 5: Basal diet + extract (5%) Group 6: Basal diet + extract (10%) Administration: Oral Duration: 14 days	Compared to the normotensive control rats, the hypertension model was confirmed in this investigation due to the considerable increase in the final SBP and following the oral administration of L-NAME by gavage, which was decreased in the treated groups	
<i>Moringa oleifera</i> Lam. (Moringaceae)	Powdered	Male albino Wistar rats		NI	Oyeleye et al. (2019)

(Continues)

TABLE 3 | (Continued)

Plant species	Extract	Model used	Dosage	Findings		Reference
				Treatment (extract)	Control	
<i>Moringa oleifera</i> Lam. (Moringaceae)	Powder	Male Wistar rats	Normal control Group 1: Basal diet	Diets supplemented with seed extract caused a significant reduction in ACE activities	There was a significant increase in ACE activity in the HC rat group compared with normal control	Oyeleye et al. (2019)
			Hypercholesterolemia (HC)			
			Group 2: Basal diet + cholesterol (2%)			
			Group 3: Basal diet + cholesterol (2%) + statin (0.5 mg/kg)			
			Group 4: Cholesterol (2%) + extract (2%) Group 5: Cholesterol (2%) + extract (4%) Administration: Oral Duration: 14 days			
<i>Moringa oleifera</i> Lam. (Moringaceae)	Powder	Wistar Kyoto rats	Hypertensive Group 1: Normal food Group 2: Food + extract (750 mg/day) Administration: Oral Duration: 8 weeks	Treatment did not modify blood pressure in hypertensive rats but reduced nocturnal heart rate and improved cardiac diastolic function	NI	Randriamboavonjy et al. (2016)
			Normotensive Group 1: Control			
			Hypertensive Group 2: L-NAME (25 mg/kg) Group 3: L-NAME (25 mg/kg) + Nicardipine (3 mg/kg) Group 4: L-NAME (25 mg/kg) + extract (2.5 mg/kg) Administration: Oral Duration: 8 weeks			
<i>Nigella sativa</i> L. (Ranunculaceae)	Oil	Male Sprague–Dawley rats	Normotensive Group 1: Normal control	There was a significant increase in systolic blood pressure in Group 1 treated rats. However, the treatment in Group 4 resulted in a significantly lower blood pressure Angiotensin-converting enzyme—ACE (pg/g) Group 2: 637.40 ± 14.95 Group 3: 483.07 ± 31.29 Group 4: 464.07 ± 31.29	The blood pressures in Groups 1 and 3 were similar ACE (pg/g) Group 1: 520.27 ± 42.59	Jaarin et al. (2015)
			Hypertensive Group 2: L-NAME (40 mg/kg/day)			
			Group 5: L-NAME (40 mg/kg/day) + extract (300 mg/kg/day) Administration: Oral Duration: 14 days			
			SBP Group 3			
			DBP Group 3			
<i>Nigella sativa</i> L. (Ranunculaceae)	Powder	Wistar rats	SBP Group 3	Decreased in SBP by 8.7% compared with Group 2 DBP Group 3 Decreased in DBP by 10.52% compared with Group 2 MAP Group 3 Decreased in MAP by 9.71% compared with Group 2 HR Group 3 Decreased in HR by 1.32% compared with Group 2	SBP Group 1 Decrease in SBP by 8.7% compared with Group 2	Bin Jardan et al. (2021)
			SBP Group 3			
			DBP Group 3			
			MAP Group 3			
			HR Group 3			

(Continues)

TABLE 3 | (Continued)

Plant species	Extract	Model used	Dosage	Findings		Reference
				Treatment (extract)	Control	
<i>Nigella sativa</i> L. (Ranunculaceae)	Volatile oil	Male Wistar albino rats	Normotensive Group 1: Control (water only) Group 2: Extract (0.5 mg/kg) Group 3: Extract (1.0 mg/kg) Hypertensive Group 4: L-NAME (50 mg/kg) Group 5: L-NAME (50 mg/kg) + extract (0.5 mg/kg) Group 6: L-NAME (50 mg/kg) + extract (1 mg/kg) Administration: Oral Duration: 4 weeks	Groups 5 and 6 reduced the increase in SBP induced by L-NAME in a dose-dependent manner No significant effect of extract from Groups 2 and 3 was observed	No effect was observed in Group 1 Group 4 rats showed a progressive increase in SBP (approximately 50 mmHg)	Khatab and Nagi (2007)
			Normotensive Group 1: Control Hypertensive Group 2: Angiotensin II (Ang II) (300 ng/kg) Group 3: Ang II + losartan (10 mg/kg) Group 4: Thymoquinone (TQ) (40 mg/kg) + Ang II Group 5-7: Three doses of extract (200, 400, and 600 mg/kg) + Ang II Administration: Intraperitoneal injection Duration: 30 min	ΔSBP (mmHg) and Δmean arterial pressure (MAP) (mmHg) Group 5: ΔSBP: 63.75 ± 4.1 ΔMAP: 57.3 ± 6.1 Group 6: ΔSBP: 55.8 ± 5.2 ΔMAP: 42.8 ± 5.7 Group 7: ΔSBP: 43.9 ± 4.9 ΔMAP: 34.76 ± 4.7	ΔSBP (mmHg) and ΔMAP (mmHg) Group 2: ΔSBP: 78.7 ± 6.4 ΔMAP: 63.1 ± 7.1	Enayatifard et al. (2018)
<i>Nigella sativa</i> L. (Ranunculaceae)	Ethanol	Balb/c mice	Normotensive Group 1: Negative control group Hypertensive Group 2: Positive control group (pregnant mice injected with severe preeclampsia (SPE)) Group 3: Maternal preeclampsia serum without extracts Group 4: Treatment with extracts (500, 1000, 1500, and 2000 mg/kg/day) Administration: Intraperitoneal injection + Oral Duration: 19 days	The 2000 mg/kg/day dose of extract was the optimum dose to reduce systolic blood pressure	NI	Rahma et al. (2017)

(Continues)

TABLE 3 | (Continued)

Plant species	Extract	Model used	Dosage	Findings			Reference	
				Treatment (extract)	Control			
<i>Nigella sativa</i> L. (Ranunculaceae)	Oil	Male Wistar albino rats	Normotensive	BP (mmHg)	BP (mmHg)	Reference		
			Group 1: Control				Group 1	
			Group 2: Extract (0.2 mL/kg/day)					0 week: 121 ± 1.9
			Hypertensive					3rd week: 122 ± 2.1
Group 3: Vehicle-treated renovascular hypertension—RVH (1.0 mL/kg/day)	9th week: 125 ± 2.2	Group 3	0 week: 116 ± 2.0					
Group 4: RVH (1.0 mL/kg/day) + extract (0.2 mL/kg/day)	3rd week: 156 ± 3.2	9th week: 185 ± 4.8						
Administration: Intraperitoneal								
Duration: 9 weeks								
<i>Nigella sativa</i> L. (Ranunculaceae)	Aqueous and hydro-methanol	Male albino rats	Hypertensive	Caused partial blockage in AT1 receptors. Hydro-methanolic was more potent than aqueous	NI	ALI et al. (2020)		
			Hydro-methanolic (extract 1)					
			Group 1: Angiotensin II (0.3, 1.0, 3.0, 10, 30 & 100 µM) + extract 1 (1, 2, 3, and 4 mg/mL)					
			Aqueous (extract 2)					
Group 2: Angiotensin II (0.3, 1.0, 3.0, 10, 30 & 100 µM) + extract 2 (1, 2, 3, and 4 mg/mL)								
Administration: NI								
Duration: NI								
<i>Nigella sativa</i> L. (Ranunculaceae)	Powder	Wistar albino rats	Hypertensive	SBP (mmHg)	SBP (mmHg)	Ahad et al. (2020)		
			Group 1: L-NAME (40 mg/kg/day)				Group 1	
			Group 2: L-NAME (40 mg/kg/day) for 2 weeks + losartan (10 mg/kg)					At 1 h: 182.20 ± 10.99
			Group 3: L-NAME					At 12 h: 177.20 ± 8.14
(40 mg/kg/day) + extract (300 mg/kg)	At 0 h: 165.20 ± 3.35	Group 2	At 2 h: 140.80 ± 1.48					
Group 4: L-NAME	At 12 h: 156.40 ± 3.78							
(40 mg/kg/day) + extract (300 mg/kg) for 2 weeks + losartan (10 mg/kg)								
Administration: Oral								
Duration: 2 weeks								

(Continues)

TABLE 3 | (Continued)

Plant species	Extract	Model used	Dosage	Findings			Reference
				Treatment (extract)	Control		
<i>Nigella sativa</i> L. (Ranunculaceae)	Seed	<i>Rattus norvegicus</i> female rats	Normotensive	Mean difference values of BP Group 3 compared to	Mean difference values of BP Group 1 compared to	Marpaung et al. (2020)	
			Group 1: Food + drink (ad libitum)	Group 1: 27.77	Group 2: -33.85		
			Hypertensive	Group 2: -6.07	Group 3: -27.77		
			Group 2: Lipopolysaccharide injection (LPS) + <i>Escherichia coli</i> (0.5 µg/kg)	Group 4: 7.24	Group 4: -20.54		
			Group 3: LPS injection + extract (500 mg/kg/day)	Group 4 compared to Group 2: 20.54	Group 2 compared to		
			Group 4: LPS injection + extract (2000 mg/kg/day)	Group 1: -13.31	Group 1: 33.85		
			Administration: Oral	Group 3: -7.24	Group 3: 6.07		
			Duration: 15 days	Mean difference values of MAP Group 3 compared to	Mean difference values of MAP Group 1 compared to		
			Group 1: 28.57	Group 2: -41.92			
			Group 2: -12.34	Group 3: 28.57			
<i>Parkia biglobosa</i> (Jacq.) R.Br. ex G.Don (Fabaceae)	Methanol	Wistar rats	Normotensive	Group 4 compared to	Group 2 compared to	Airadion and Oghuagu (2020)	
			Group 1: Normal feed diet	Group 2: 21.76	Group 1: 41.92		
			Hypertensive	Group 1: -20.15	Group 3: 13.34		
			Group 2: Egg feed diet [24 egg yolks + normal rat diet (1 kg)]	Group 3: -6.81	Group 4: 20.15		
			Group 3: Egg feed diet [24 egg yolks + normal rat diet (1 kg)] + extract (400 mg/kg)				
			Administration: Oral				
			Duration: 21 days				
				A significant increase was observed in the blood pressure of animals fed with egg-yolk formulated diet without extract treatment when compared with those fed with egg-yolk formulated diet and treated with extract and Group 1, respectively			
				However, this effect was neutralized when animals fed with egg-yolk formulated diet and treated with extract were compared with those in Group 1			
				BP (mmHg) Group 2: 58.4 ± 3	BP (mmHg) Group 1: 59.6 ± 2.8		
<i>Parkia biglobosa</i> (Jacq.) R.Br. ex G.Don (Fabaceae)	Aqueous	<i>Oryctolagus cuniculus</i> rabbits	Hypertensive	Group 3: 57.7 ± 3.7	HR (beats/min) Group 1: 245 ± 4.2	Apedjinou et al. (2023)	
			Group 1: Ethyl carbamate (1.2 g)	Group 4: 40.6 ± 3.9			
			Group 2: Ethyl carbamate (1.2 g) + extract (17.5 mg/kg)	Group 5: 32.5 ± 2.9			
			Group 3: Ethyl carbamate (1.2 g) + extract (35 mg/kg)	HR (beats/min) Group 2: 241.7 ± 7.8			
			Group 4: Ethyl carbamate (1.2 g) + extract (70 mg/kg)	Group 3: 246 ± 8.3			
			Group 5: Ethyl carbamate (1.2 g) + extract (140 mg/kg)	Group 4: 232.2 ± 10.4			
			Administration: Intravenous	Group 5: 217 ± 4.2			
			Duration: NI				

(Continues)

TABLE 3 | (Continued)

Plant species	Extract	Model used	Dosage	Findings		Reference
				Treatment (extract)	Control	
<i>Persea americana</i> Mill. (Lauraceae)	Aqueous	Albino rats	Normotensive Group 1: Normal control (growers mash only)	SBP (mmHg) Group 3: 145.0 ± 2.8 Group 4: 125.0 ± 21.5	SBP (mmHg) Group 1: 81.0 ± 3.1 Group 2: 166.0 ± 5.1	Imafidon and Ighinaduwa (2010)
			Hypertensive Group 2: Growers mash (92%) + NaCl (8%)	DBP (mmHg) Group 3: 76.6 ± 11.6	DBP (mmHg) Group 1: 52.3 ± 4.3	
			Group 3: Growers mash (92%) + NaCl (8%) + extract (200 mg/kg)	Group 4: 56.4 ± 4.0	Group 2: 128.0 ± 6.1	
			Group 4: Growers mash (92%) + NaCl (8%) + extract (500 mg/kg)	Pulse (mmHg) Group 3: 68.4 ± 10.0 Group 4: 68.6 ± 3.1	Pulse (mmHg) Group 1: 28.7 ± 1.9 Group 2: 74.0 ± 5.1	
<i>Persea americana</i> Mill. (Lauraceae)	Aqueous	Sprague-Dawley rats	Administration: Oral Duration: 4 weeks	MAP (mmHg) Group 3: 99.4 ± 2.3 Group 4: 79.2 ± 4.5	MAP (mmHg) Group 1: 60.2 ± 4.0 Group 2: 140.6 ± 6.5	Anaka et al. (2009)
			Normotensive naive Group 1: Extract at	MAP (mmHg) Group 1	NI	
			Dose 1: 240 mg/kg	Dose 1: 92.2 ± 12.0		
			Dose 2: 260 mg/kg	Dose 2: 74.0 ± 12.9		
<i>Persea americana</i> Mill. (Lauraceae)	Aqueous	Albino rats	Dose 3: 280 mg/kg	Dose 3: 77.18 ± 15.6		Imafidon and Ighinaduwa (2010)
			Pretreated rats Group 2: Extract (260 mg/kg)	Group 2: 92.1 ± 8.5		
			Administration: Oral Duration: 10 days	HR (beats/min) Group 1: 274.6 ± 39.3 Group 2: 161.6 ± 11.6		
			Normotensive Group 1: Growers mash	SBP (mmHg) Group 3: 145.0 ± 27.5 Group 4: 125.0 ± 21.2	SBP (mmHg) Group 1: 81.0 ± 3.05 Group 2: 166.0 ± 1.0	
<i>Persea americana</i> Mill. (Lauraceae)	Ethanol	Male Wistar rats	Hypertensive Group 2: Growers mash + NaCl (8%)	Group 5: 91.4 ± 5.5	DBP (mmHg) Group 1: 52.3 ± 4.3	Omodamiro et al. (2021)
			Group 3: Growers mash + NaCl (8%) + extract (200 mg/kg)	DBP (mmHg) Group 3: 76.6 ± 11.6	Group 2: 128.6 ± 6.1	
			Group 4: Growers mash + NaCl (8%) + extract (500 mg/kg)	Group 4: 66.6 ± 2.3		
			Group 5: Growers mash + NaCl (8%) + extract (700 mg/kg)	Group 5: 56.4 ± 4.0		
<i>Persea americana</i> Mill. (Lauraceae)	Ethanol	Male Wistar rats	Administration: Oral Duration: 4 weeks			Omodamiro et al. (2021)
			Normotensive Group 1: Normal control		NI	
			Hypertensive Group 2: Hypertensive untreated			
			Group 3: NaCl (18%) + frusemide (10 mg/kg)			
<i>Persea americana</i> Mill. (Lauraceae)	Ethanol	Male Wistar rats	Group 4: NaCl (18%) + extract (200 mg/kg)			Omodamiro et al. (2021)
			Group 5: NaCl (18%) + extract (400 mg/kg)			
			Group 6: NaCl (18%) + extract (600 mg/kg)			
			Administration: Oral Duration: 3 weeks			

(Continues)

TABLE 3 | (Continued)

Findings						
Plant species	Extract	Model used	Dosage	Treatment (extract)	Control	Reference
<i>Persia americana</i> Mill. (Lauraceae)	Aqueous	Albino Wistar rats and rabbits	Normotensive rabbits	The BP lowering pattern of the extract showed a high degree of potency as the dose of 5 mg/kg caused the highest decrease in the mean SBP and MABP of 89.79 ± 9.4, 56.90 ± 11.9, and 67.86 ± 10.15 mmHg, respectively	NI	Amaechina et al. (2017)
			Group 1: Urethane (1750 mg/kg) + extract (0.624–2.5 mg/kg) Normotensive rats Group 2: Urethane (1750 mg/kg) + extract (0.624–2.5 mg/kg) Administration: Intravenous Duration: NI			
<i>Petroselinum crispum</i> (Mill.) Fuss (Apiaceae)	Aqueous	Wistar rats	Normotensive Group 1: Filtered water (1.0 mL) Hypertensive Group 2: Extract (20%) Administration: Oral Duration: 90 min	The maximal effective and tolerable dose of the extract in rats was 2.5 mg/kg, which caused a decrease in the mean SBP and MABP of 61.5 ± 10.78, 33.40 ± 7.89, and 43.10 ± 11.15 mmHg, respectively Group 2 decreased arterial pressure All the parameters presented these modifications after 30 min of administration of extract These results show that the treatment with the extract has hypotensive effects in anesthetized Wistar rats	Group 1 did not show any differences	Campos et al. (2009)
<i>Pterilima nitida</i> (Stapf) T.Durand & H.Durand (Apocynaceae)	Aqueous	Rabbits	Hypertensive Group 1: Ethyl-urethane (40%) + different doses of extract + atropine Group 2: Ethyl-urethane (40%) + different doses of extract Administration: Intraperitoneal injection Duration: 14 days	Doses ranging from 3 × 10 ^{−6} to 2 × 10 ^{−5} g/kg provokes a transient decrease ranging from 20 to 36 mmHg That corresponds to a decrease of the blood pressure of 39.83% ± 1.88% and 103.33% ± 6%	In the presence of atropine, the hypotension induced by extract for doses ranging from 3.10 ^{−6} to 1.2 × 10 ^{−5} g/kg was reduced, respectively, from 22.22% ± 6% to 55.56% ± 5%	KouassiNdri et al. (2015)
<i>Piper guineense</i> . Schumach. & Thonn. (Piperaceae)	Aqueous	Male Wistar rats	Normal Group 1: Basal diet + citrate buffer (1 mL/kg) Hypercholesterolemic (HC) Group 2: HC diet only Group 3: Simvastatin in normal saline (0.2 mg/kg) Group 4: Extract (2%) Group 5: Extract (4%) Administration: Oral Duration: 30 days	Diabetic rats administered with extract had decreased ACE activity similar to that observed in normal control rats	NI	Adefegha et al. (2016)
<i>Theobroma cacao</i> L. (Malvaceae)	Hexane–chloroform	Male Wistar rats	Normotensive Group 1: Standard diet (3.1 kcal/g) Hypertensive Group 2: High-fat diet (4.5 kcal/g) Group 3: HF diet + extract (150 mg/kg/day) Administration: Orogastric Duration: 8 weeks	The intake of an HF diet significantly increased SBP, DBP, and MBP However, the oral administration of HF diet + extract reverted these effects, and the blood pressure significantly reduced No effects of extract on the HR were observed, being similar in Group 2 and Group 3 at the end of the assay	NI	Coronado-Cáceres et al. (2021)

(Continues)

TABLE 3 | (Continued)

Plant species	Extract	Model used	Dosage	Findings			Reference
				Treatment (extract)	Control		
<i>Trigonella foenum-graecum</i> Mill. (Fabaceae)	Powder	Wistar rats	Normotensive	Systolic blood pressure—SBP	SBP	Bin Jardan et al. (2021)	
			Group 1: normal control	Group 3	Group 1		
			Hypertensive	Decrease in SBP by 8.5% compared with Group 2	Decrease in SBP by 8.7% compared with Group 2		
			Group 2: L-NAME (40 mg/kg/day)	Diastolic blood pressure—DBP			
			Group 3: L-NAME (40 mg/kg/day) + extract (300 mg/kg/day)	Decrease in DBP by 10.82% compared with Group 2			
			Administration: Oral	Mean arterial pressure—MAP			
			Duration: 14 days	Group 3			
				Decrease in MAP by 9.76% compared with Group 2			
				Heart rate—HR			
				Group 3			
				Decrease in HR by 6.13% compared with Group 2			
				SBP (mmHg)	Group 3 (mmHg)	Sudheendra et al. (2009)	
			Normotensive	Group 1	Decrease from 162.2 ± 5.25 to 73.86 ± 5.28 [88.34]		
			Group 1: Extract (100 mg/kg)				
			Group 2: Extract (200 mg/kg)	Decrease from 178.4 ± 11.79 to 159.3 ± 11.76 [19.1]			
			Hypertensive	Group 2			
			Group 3: Enalapril maleate (3 mg/kg)	Decrease from 169.9 ± 7.74 to 117.9 ± 6.90 [52.0]			
			Administration: Oral				
			Duration: 4 weeks				
			Hypertensive	SBP was significantly reduced in the rats when administered with	NI	Ahad et al. (2020)	
			Group 1: L-NAME (40 mg/kg/day)	L-NAME + <i>Trigonella foenum-graecum</i> in contrast to the rats administered with			
			Group 2: L-NAME (40 mg/kg/day) for 2 weeks + losartan (10 mg/kg)	L-NAME alone. A more prominent decline in SBP was detected in rats administered with L-NAME + <i>Trigonella foenum-graecum</i> + losartan			
			Group 3: L-NAME (40 mg/kg/day) + extract (300 mg/kg)				
			Group 4: L-NAME (40 mg/kg/day) + extract (300 mg/kg) for 2 weeks + losartan (10 mg/kg)				
			Administration: Oral				
			Duration: NI				

(Continues)

TABLE 3 | (Continued)

Plant species	Extract	Model used	Dosage	Findings		Reference
				Treatment (extract)	Control	
<i>Trigonella foenum-graecum</i> Mill. (Fabaceae)	Methanol extract (ME) and methanol fraction (MF)	Wistar rats	DOCA-salt-induced hypertension model Group 1: Cottonseed oil (0.2 mL) + saline (1%) + KCl ad libitum (0.2%) Group 2: Cottonseed oil (0.2 mL) + KCl ad libitum (0.2%) + DOCA-salt (15 mg/kg) Group 3: Cottonseed oil (0.2 mL) + saline (1%) + KCl ad libitum (0.2%) + DOCA-salt (15 mg/kg) + methanol extract (30 mg/kg) Group 4: Cottonseed oil (0.2 mL) + saline (1%) + KCl ad libitum (0.2%) + methanol extract (30 mg/kg) Group 5: Saline (1%) + KCl ad libitum (0.2%) + DOCA-salt (15 mg/kg) + methanol fraction (15 mg/kg) Group 6: Cottonseed oil (0.2 mL) + saline (1%) + KCl ad libitum (0.2%) + methanol fraction (15 mg/kg) Administration: Oral Duration: 4 weeks Fructose-induced hypertension model Group 1: Tap water Group 2: Fructose solution (10%) Group 3: Fructose solution (10%) + methanol extract (100 mg/kg) Group 4: Tap water + methanol extract (100 mg/kg) Administration: Oral Duration: 6 weeks	-DOCA-salt hypertensive ratsNoninvasive (indirect) methodAdministration of methanol extract and fraction in DOCA-salt unilateral nephrectomized rats significantly reduced the MABP at the end of the 3rd week and showed further reduction at the end of the 4th week as compared with DOCA-salt hypertensive rats aloneInvasive (direct) methodAdministration of DOCA for 4 weeks in uninephrectomized rats showed a significant elevation of MABP (130.0 ± 2.9 mmHg) when compared with sham control rats (98.4 ± 3.4 mmHg)In sham control rats, chronic administration of methanol extract and fraction for 4 weeks did not change any BP parameters as compared with sham-operated control ratsHowever, chronic administration of methanol extract and fraction for 4 weeks in uni-nephrectomized DOCA-treated rats significantly reduced MABP (ME-30: 106.7 ± 2.8 mmHg; MF-15: 108.0 ± 4.2 mmHg) as compared with MABP (130.0 ± 2.9 mmHg) of DOCA-salt hypertensive rats implying an antihypertensive effect -Fructose-induced hypertensive rats Noninvasive (indirect) methodFructose feeding for 6 weeks in rats produced a significant elevation in SBP (177 ± 5.3 mmHg) as compared with control rats (147.6 ± 6.2 mmHg)However, chronic administration of methanol extract in fructose-fed rats significantly decreased SBP (154.1 ± 5.7 mmHg) as compared with fructose-fed hypertensive rats (177 ± 5.3 mmHg) implying an antihypertensive effect	-DOCA-salt hypertensive ratsIn sham control rats, chronic administration of methanol extract and fraction for 4 weeks did not change any BP parameters as compared with sham-operated control rats In -Fructose-induced hypertensive rats In control rats, chronic administration of ME-100 for 6 weeks did not change SBP (146 ± 3.8 mm Hg) as compared with control rats (147.6 ± 6.2 mm Hg).	Balaraman et al. (2006)

(Continues)

TABLE 3 | (Continued)

			Findings		Reference
Plant species	Extract	Model used	Dosage	Treatment (extract)	
<i>Vigna radiata</i> L. R. Wilczek (Fabaceae)	Protein hydrolysate	Male spontaneous hypertensive rats	Hypertensive Group 1: Distilled water (1.5 mL) Group 2: Extract dissolved in distilled water (1.5 mL) Administration: Oral Duration: 12 h	The mean SBP of SHR was 187.9 ± 8.7 mmHg. The SBP significantly diminished after 2, 4, 6, and 8 h administration. Maximum SBP reduction of 30.8 mmHg was observed 6 h after administration The heart rate in SHR was also measured in order to check the effect of the administration of the hydrolysate on the physical condition. There was no significant change in the heart rate of SHR at 2, 4, 6, 8, and 12 h after administration	Li, Le, et al. (2005)
			Normotensive Group 1: Tap water + regular pellet food Hypertensive Group 2: Lead acetate in water (100 ppm) Group 3: Lead acetate in water (100 ppm) + extract (100 mg/kg) Group 4: Extract (100 mg/kg) Administration: Oral Duration: 45 days	There was a sustained increase of SBP in lead exposed rats that significantly increased at Day 18 (lead treated, 112.7 ± 207 mmHg, vs. control, 105.6 ± 2.6 mmHg) and reached a maximum level at Day 36 (lead treated, 124.9 ± 2.3 mmHg, vs. control, 103.6 ± 3.1 mmHg) The three other groups showed no significant changes in SBP	Badavi et al. (2008)
<i>Vitis vinifera</i> L. (Vitaceae)	Powder	Male Wistar rats	Normotensive Group 1: Distilled water (400 µL) Hypertensive Group 2: Captopril (10 mg/kg) Group 3: Extract (0.1 mg/kg) Group 4: Extract (1.0 mg/kg) Group 5: Extract (10 mg/kg) Administration: Oral Duration: 90 days	Oral administration of extract significantly decreased the SBP levels in a dose-dependent manner The SBP level of Group 5 was 26.57 ± 9.03 mmHg lower than that of Group 1	C.-C. Li et al. (2019)
			Normotensive Group 1: Distilled water (400 µL) Hypertensive Group 2: Captopril (10 mg/kg) Group 3: Extract (0.1 mg/kg) Group 4: Extract (1.0 mg/kg) Group 5: Extract (10 mg/kg) Administration: Oral Duration: 90 days	The SBP level of Group 2 was 47.6 ± 4.34 mmHg lower than that of Group 1	
<i>Zea mays</i> L. (Poaceae)	Aqueous	Male spontaneous hypertensive rats			

(Continues)

TABLE 3 | (Continued)

Plant species	Extract	Model used	Dosage	Findings		Reference
				Treatment (extract)	Control	
<i>Zea mays</i> L. (Poaceae)	Ethanollic	Male Wistar rats	Normal	SBP (mmHg)	SBP (mmHg)	Guzmán- Gerónimo et al. (2017)
			Group 1: Standard diet + water	Group 3: 112 ± 5.7	Group 1: 103 ± 3.0	
			Group 2: Standard diet + sucrose (30%)	Group 5: 110 ± 3.5	Group 2: 162 ± 7.2	
			Group 3: High-sucrose diet + extract (2 mL)		Group 4: 155 ± 3.4	
			Hypercholesterolemic (HC)			
<i>Zea mays</i> L. (Poaceae)	Aqueous	Wistar rats	Group 4: High-sucrose diet + cholesterol (1 g)			Pinheiro et al. (2011)
			Group 5: High-sucrose diet + cholesterol (1 g) + extract (2 mL)			
			Administration: Orogastric			
			Duration: 4 weeks			
			Normotensive			
<i>Zea mays</i> L. (Poaceae)	Aqueous	Wistar rats	Group 1: Distilled water (1 mL)			Pinheiro et al. (2011)
			Group 2: Extract (1 mL)			
			Hypertensive			
			Group 3: Solution containing furosemide (1 mL)			
			Administration: Intragastric			
<i>Zea mays</i> L. (Poaceae)	Aqueous	Wistar rats	Duration: 90 min			Pinheiro et al. (2011)

(Continues)

TABLE 3 | (Continued)

Plant species	Extract	Model used	Dosage	Findings			Reference
				Treatment (extract)	Control	Acute oral administration experiment	
<i>Zea mays</i> L. (Poaceae)	Protein hydrolysate	Male spontaneously hypertensive rats and Wistar-Kyoto rats	Acute oral administration experiment	Acute oral administration experiment	Acute oral administration experiment	Acute oral administration experiment	Huang et al. (2011)
			Hypertensive	After oral administration of captopril and extract samples with several dosages, significant SBP reductions were found at 1 h compared to Group 1	There were little SBP changes observed in Group 1	The maximum SBP reduction levels were (mmHg):	
			Group 1: Saline water (5 mL/kg)	The maximum SBP reduction levels were (mmHg):	Group 2: 38.42	Group 2: 38.42	
			Group 2: Captopril (2 mg/kg)		Long-term experiment: SBP (mmHg)	Long-term experiment: SBP (mmHg)	
			Group 3: Extract (25 mg/kg)	Group 3: 17.91	Group 1	Group 1	
			Group 4: Extract (50 mg/kg)	Group 4: 19.57	0 day: 188.21 ± 2.17	0 day: 188.21 ± 2.17	
			Group 5: Extract (100 mg/kg)	Group 5: 26.57	6 days: 186.69 ± 5.0	6 days: 186.69 ± 5.0	
			Administration: Oral	Long-term experiment: SBP (mmHg)	12 days: 186.72 ± 2.24	12 days: 186.72 ± 2.24	
			Duration: 7 h	Group 3	18 days: 182.68 ± 3.9	18 days: 182.68 ± 3.9	
			Spontaneous hypertensive rats	0 day: 189.86 ± 3.34	24 days: 191.51 ± 8.93	30 days: 186.15 ± 7.27	
<i>Zea mays</i> L. (Poaceae)	Peptides hydrolysate	Male spontaneously hypertensive rats	Group 1: Saline water (5 mL/kg)	6 days: 158.70 ± 2.02	Group 2	Group 2	Yang et al. (2007)
			Group 2: Captopril (2 mg/kg)	12 days: 157.84 ± 2.91	0 day: 189.68 ± 4.84	0 day: 189.68 ± 4.84	
			Group 3: Extract (100 mg/kg)	18 days: 157.15 ± 3.25	6 days: 157.42 ± 4.85	6 days: 157.42 ± 4.85	
			Group 4: Extract (50 mg/kg)	24 days: 156.91 ± 11.09	12 days: 153.03 ± 2.83	12 days: 153.03 ± 2.83	
			Group 5: Extract (25 mg/kg)	30 days: 155.41 ± 3.48	18 days: 154.86 ± 2.70	18 days: 154.86 ± 2.70	
			Normal Wistar Kyoto rats	Group 4	24 days: 150.29 ± 11.87	24 days: 150.29 ± 11.87	
			Group 6: Extract (100 mg/kg) [normal control]	0 day: 189.80 ± 4.21	30 days: 152.4 ± 1.77	30 days: 152.4 ± 1.77	
			Administration: Intragastric	6 days: 165.98 ± 4.74	Group 6	Group 6	
			Duration: 30 days	12 days: 163.12 ± 3.28	0 day: 119.97 ± 5.63	0 day: 119.97 ± 5.63	
				18 days: 163.25 ± 4.43	6 days: 113.46 ± 5.42	6 days: 113.46 ± 5.42	
<i>Zea mays</i> L. (Poaceae)	Peptides hydrolysate	Male spontaneously hypertensive rats	Group 1: Extract in saline (1.0 mL)	24 days: 160.59 ± 7.82	12 days: 111.04 ± 4.95	12 days: 111.04 ± 4.95	Yang et al. (2007)
			Group 2: Saline only (1.0 mL)	30 days: 158.85 ± 3.21	18 days: 117.84 ± 9.85	18 days: 117.84 ± 9.85	
			Administration: Oral	Group 5	24 days: 120.97 ± 10.97	24 days: 120.97 ± 10.97	
			Duration: 4 h	0 day: 186.01 ± 2.49	30 days: 114.79 ± 5.01	30 days: 114.79 ± 5.01	
				6 days: 166.57 ± 3.13	ACE activity in the heart (mU/mg)	ACE activity in the heart (mU/mg)	
				12 days: 166.04 ± 3.78	Group 1: 67.02 ± 20.45	Group 1: 67.02 ± 20.45	
				18 days: 165.62 ± 5.88	Group 2: 68.64 ± 20.27	Group 2: 68.64 ± 20.27	
				24 days: 166.61 ± 4.49			
				30 days: 158.52 ± 5.53			
				ACE activity in the heart (mU/mg)			
<i>Zea mays</i> L. (Poaceae)	Peptides hydrolysate	Male spontaneously hypertensive rats	Group 3: 64.36 ± 8.62	Group 3: 64.36 ± 8.62			Yang et al. (2007)
			Group 4: 69.80 ± 5.08	Group 4: 69.80 ± 5.08			
			Group 5: 68.69 ± 14.10	Group 5: 68.69 ± 14.10			
<i>Zea mays</i> L. (Poaceae)	Peptides hydrolysate	Male spontaneously hypertensive rats	Group 1: Extract in saline (1.0 mL)				Yang et al. (2007)
			Group 2: Saline only (1.0 mL)				
			Administration: Oral				
			Duration: 4 h				

Abbreviation: NI, not indicated.

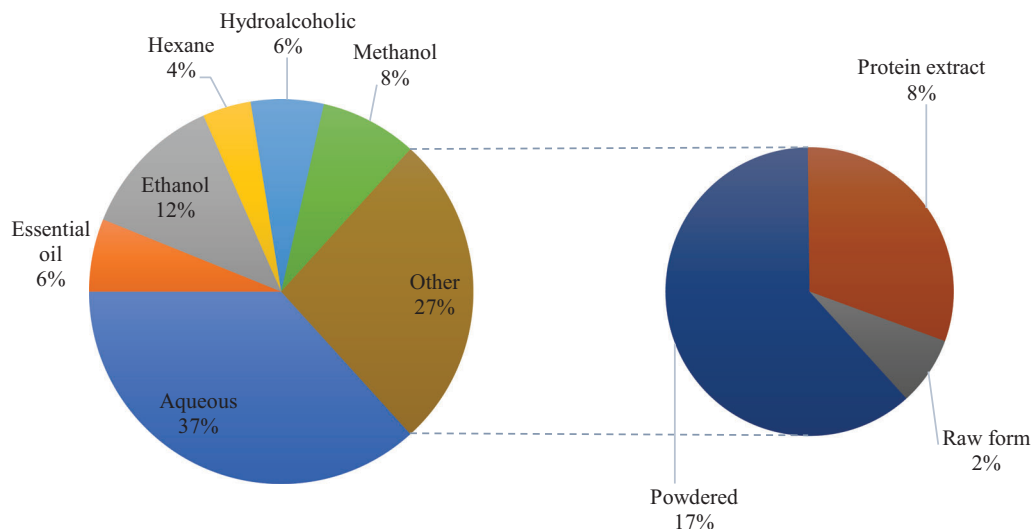


FIGURE 9 | Type of extracts tested in vivo studies.

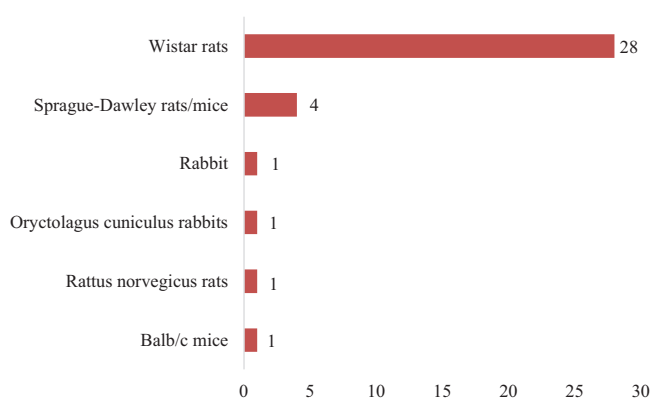


FIGURE 10 | Model used during in vivo studies.

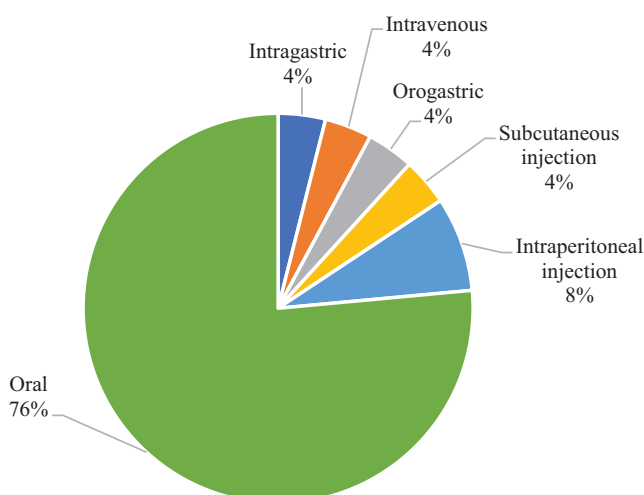


FIGURE 11 | Mode of administration during in vivo studies.

240 and 280 mg/kg, respectively (Anaka et al. 2009). The other results were not expressed in the same units, so they could not be compared, and some of the results found were not quantitative (Table 3).

3.3.2 | Comparison of BP, DBP, HR, and PP

BP was assessed in only two studies, one on *N. sativa* and the other on *P. biglobosa*. In the first study, administration of *N. sativa* extract via intraperitoneal injection at a dose of 0.2 mL/kg/day resulted in a reduction of 34 mmHg in hypertensive rats (Taşar et al. 2012). In the second study, an intravenous administration of 140 mg/kg of *P. biglobosa* (Jacq.) aqueous extract led to a decrease of 27.1 mmHg in rabbits (Apedjinou et al. 2023) (Table 3).

The maximum decrease in DBP (72.2 mmHg) was reported from *P. americana* (Imafidon and Igbinauwa 2010), followed by the same plant species with a decrease of 71.6 mmHg (Imafidon and Igbinauwa 2010). *G. kola* has the second highest reduction in DBP (35.5 mmHg) (Olatoye et al. 2023). Another study reported that the administration of the same species at 3.0 mg/kg of extract orally reduced the DBP by 28 mmHg (Naiho and Ugwu 2011). The DBP of *L. usitatissimum* was decreased to a lesser extent (16.45 mmHg) (Sawant and Bodhankar 2016). The other two studies that showed an effect on the DBP were expressed as a percentage (%); these were *N. sativa* and *T. foenum-graecum*, with reductions in the DBP of 10.52% and 10.82%, respectively (Bin Jordan et al. 2021) (Table 3).

HR was reported in eight in vivo studies with the highest efficacy seen in *P. americana* where an HR reduction of 113 beats/min was recorded in pretreated rats following a dose of 260 mg/kg of the aqueous extract compared to normotensive rats (Anaka et al. 2009). This was followed by *P. biglobosa*, where HR was reduced by 28 beats/min when 140 mg/kg of extract was administered intravenously to *O. cuniculus* rabbits (Apedjinou et al. 2023). A reduction of 25.33 beats/min was also seen following 200 mg/kg of the aqueous extract of *L. usitatissimum* (Sawant and Bodhankar 2016), then the ethanol extract of *G. kola* that decreased HR by 9.3 beats/min. Another study conducted by Naiho and Ugwu (2011) observed that the crude extract of *G. kola* caused HR (0.5 mg/kg) to decline by 2.8 beats/min. As previously stated, two plant species—*T. foenum-graecum* and *N. sativa*—results were expressed in percentage (%) with *T. foenum-graecum* showing the highest efficacy, reducing HR by 6.13% compared to 1.32% for *N.*

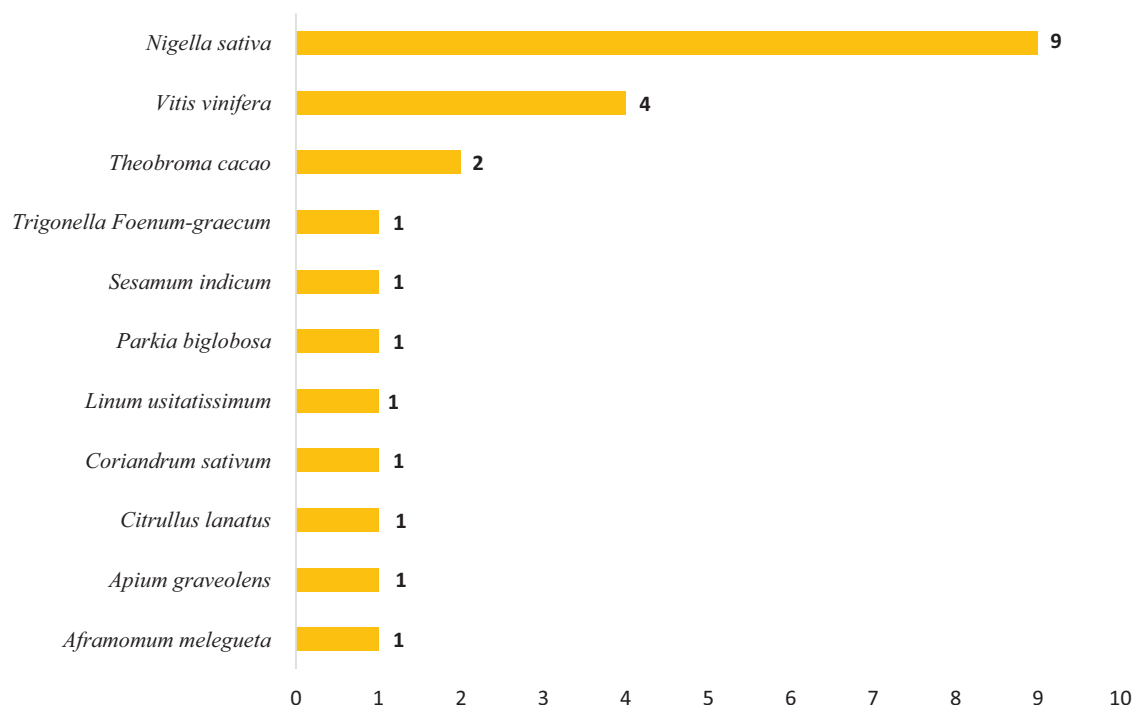


FIGURE 12 | Seed species tested in clinical studies against hypertension.

sativa (Bin Jordan et al. 2021). The remaining 27 studies were not quantitative and therefore could not be compared (Table 3).

PP was evaluated in only two studies involving the species *G. kola* and *P. americana*. Notably, *P. biglobosa* was found to be the most effective, reducing the PP by 5.6 mmHg (Imafidon and Igbinaduwa 2010). In contrast, oral administration of a 200 mg/kg *G. kola* ethanol extract led to a more modest reduction in PP by 1.15 mmHg (Olatoye et al. 2023) (Table 3).

3.4 | Clinical Studies

Among the 50 plant species that are traditionally used for hypertension, only 11 species have been subjected to clinical trials (Table 4). BP was the primary outcome in all the studies, with some studies also reporting HR and PP. The most frequently studied species was *N. sativa*, which was the subject of nine trials, followed by *V. vinifera* and *T. cacao*, which were the subjects of four trials each. The remaining plant species, *A. melegueta* (Lawal et al. 2007), *A. graveolens* (Shayani Rad et al. 2022), *C. lanatus* (Sajjad et al. 2020), *C. sativum* (Zeb et al. 2018), *L. usitatissimum* (Rodriguez-Leyva et al. 2013), *P. biglobosa* (Ognatan et al. 2011), *Sesamum indicum* (Miyawaki et al. 2009), and *T. foenum-graecum* (Hadi et al. 2020), have all been the subject of a single clinical trial each (Figure 12).

The most frequently investigated family of seed species was Ranunculaceae ($n = 9$), followed by Vitaceae ($n = 4$). Two studies were conducted for each of the families Apiaceae, Fabaceae, and Malvaceae, whereas only one study was identified for each of the remaining families: Cucurbitaceae, Pedaliaceae, Linaceae, and Zingiberaceae (Figure 13).

The most frequently tested extract in clinical trials was the powdered form ($n = 7$), followed by the essential oil and seed ($n = 5$) and enriched beverages ($n = 2$). A single study was reported for each of aqueous, beverage, fermented, and ligand extract (Figure 14). Blinding was employed in 16 studies, with one, two, and 13 studies utilizing triple blinding, single blinding, and double blinding, respectively. Thirteen studies were randomized trials, whereas 10 studies were placebo-controlled. Two studies featured parallel trials, which were then followed by single-arm ($n = 1$), two-arm ($n = 1$), crossover ($n = 2$), and pilot trials ($n = 1$). Eleven studies included both male and female participants, two studies involved only females, and one study involved only males. The gender distribution of eight studies was not specified.

3.4.1 | Comparisons for SBP

Among the 23 SBP results (Table 4), four were nonquantitative, and three showed minimal changes in SBP, such as an increase of 0.6 mmHg (Moghadam et al. 2013), 0.76 mmHg (Park and Velasquez 2012), and 0.9 mmHg (Hadi et al. 2020). The remaining 20 results were all associated with decreases in SBP, with only one result exceeding 20 mmHg for the seed *A. melegueta*. Ten results indicated increases in SBP ranging from 10 to 12 mmHg; these increases were mainly observed in *N. sativa*, followed by *C. lanatus*, *V. vinifera*, *C. sativum*, and *A. graveolens*.

Comparison of the species' efficacy revealed that *A. melegueta* was the most potent with a reduction in SBP (26.9 mmHg) compared to all other plant species investigated (Lawal et al. 2007). The second highest reduction in SBP was seen with *C. sativum* (reduction of 19 mmHg between Days 0 and 60) (Zeb et al. 2018), followed by *N. sativa* (reduction of 18 mmHg between

TABLE 4 | Seeds tested clinically against hypertension.

Plant species	Extract	Study design/Country/Year	Subjects/Sample size (after withdrawal)/age/gender (M: male and F: female)	Dosage/Duration	Findings			References
					Treatment (T) group [mean difference]	Control (C) group/placebo [mean difference]	Side effects	
<i>Aframomum melegueta</i> K.Schum (Zingiberaceae)	Seeds	NI/ Nigeria/2006	18 healthy, non-smoking, non-alcoholic university students (6 men and 6 women), aged 20–28 years, and 11 hypertensive (5 men and 6 women), aged 35–57 years	Normotensive subjects	In pooled normotensive subjects	NI	NI	Lawal et al. (2007)
				T1: 10 seeds	SBP (mmHg)			
				T2: 15 seeds	Baseline: 113.6 ± 2.0			
				T3: 20 seeds	Lowest: 75.9 ± 1.3			
				Hypertensive subjects	DBP (mmHg)			
				T4: 10 seeds	Baseline: 72.0 ± 1.4			
				T5: 20 seeds	Lowest: 64.4 ± 1.6			
				Administration: Oral	PP (mmHg)			
				Duration: 60 min	Baseline: 41.7 ± 1.4			
				Lowest: 25.6 ± 1.3				
MAP (mmHg)								
Baseline: 85.5 ± 1.6								
Lowest: 75.2 ± 1.5								
HR (mmHg)								
Baseline: 71.6 ± 1.3								
Lowest: 66.5 ± 1.9								
In pooled hypertensive subjects								
				SBP (mmHg)				
				Baseline: 160.70 ± 8.1				
				Lowest: 133.80 ± 6.0				
				DBP (mmHg)				
				Baseline: 99.60 ± 3.8				
				Lowest: 90.40 ± 3.5				
				PP (mmHg)				
				Baseline: 61.10 ± 7.2				
				Lowest: 39.70 ± 4.7				
				MAP (mmHg)				
Baseline: 120.00 ± 4.4								
Lowest: 105.30 ± 3.9								
HR (mmHg)								
Baseline: 76.40 ± 7.19								
Lowest: 69.40 ± 6.82								
<i>Apium graveolens</i> L. (Apiaceae)	Powder	Randomized, triple-blind, placebo-controlled, crossover trial/NI	52 patients	T: 4 capsules containing extract (1.34 g/day)	SBP (mmHg): 141.2 ± 5.91 to 130.0 ± 4.38 [−11.2]	No significant changes were observed	No side-effect was reported	Shayani Rad et al. (2022)
				C: 4 capsules containing placebo (1.34 g/day)	DBP (mmHg): 92.2 ± 5.74 to 84.2 ± 4.87 [−8]			
				Administration: Oral	MABP (mmHg): 108.5 ± 5.76 to 99.5 ± 4.66 [−9]			
				Duration: 4 weeks	PP (mmHg): 49.0 ± 6.21 to 45.8 ± 6.01 [−3.2]			

(Continues)

TABLE 4 | (Continued)

Plant species	Extract	Study design/Country/Year	Subjects/Sample size (after withdrawal)/age/gender (M: male and F: female)	Dosage/Duration	Findings			Side effects	References
					Treatment (T) group [mean difference]	Control (C) group/placebo [mean difference]			
<i>Citrullus lanatus</i> (Thunb.) Matsum. & Nakai (Cucurbitaceae)	Powder	Open labeled, single-arm/NI	16 M and 16 F age 30–60 years hypertensive (Group-A) and normal (Group-B)	Hypertensive subjects T1: 50 g of extract/day	Systolic blood pressure—SBP (mmHg) Males: 147.04 ± 7 to 131.75 ± 7 [−15.29] Females: 136.79 ± 15 to 124.00 ± 7 [−12.79]	Systolic blood pressure—SBP (mmHg) Males: 115.88 ± 4 to 113.50 ± 6 [−2.38] Females: 115.62 ± 5 to 113.00 ± 7 [−2.62]	NI	Sajjad et al. (2020)	
				Normotensive subjects T2: 50 g of extract/day Administration: Oral Duration: 40 days and 1 week of washout	Diastolic blood pressure—DBP (mmHg) Males: 91.38 ± 4 to 83.46 ± 3 [−7.92] Females: 90.50 ± 3 to 80.71 ± 2 [−9.79]	Diastolic blood pressure—DBP (mmHg) Males: 79.67 ± 0.56 to 77.57 ± 4 [−2.01] Females: 79.50 ± 0.75 to 75.63 ± 4 [−3.87]			
<i>Coriandrum sativum</i> L. (Apiaceae)	Powder	Single-blind, randomized, placebo-controlled intervention trial/Pakistan/NI	80 human individual both male and female aged 40–80 years	T1: Garlic powder (2 g/day) T2: Extract (2 g/day) T3: Garlic powder + extract (2 g/day) C: Not fed any supplements Administration: Oral Duration: 60 days	SBP (mmHg) T1 group 0 day: 140 ± 25.2 20 days: 137.14 ± 19.8 40 days: 134.28 ± 14.0 60 days: 134.28 ± 16.2 T2 group 0 day: 140 ± 20.8 20 days: 120 ± 12.9 40 days: 117.14 ± 13.8 60 days: 121.42 ± 13.5 T3 group 0 day: 141.42 ± 21.2 20 days: 133.57 ± 14.9 40 days: 140.71 ± 11.0 60 days: 138.57 ± 10.7 DBP (mmHg) T1 group 0 day: 85.71 ± 14.0 20 days: 85.71 ± 12.1 40 days: 82.85 ± 11.1 60 days: 82.85 ± 11.1 T2 group 0 day: 88.57 ± 9.0 20 days: 84.28 ± 12.7 40 days: 81.42 ± 14.6 60 days: 85.71 ± 11.3 T3 group 0 day: 83.57 ± 11.1 20 days: 82.14 ± 7.0 40 days: 82.14 ± 7.0 60 days: 84.28 ± 5.3	SBP (mmHg) C group 0 day: 137.14 ± 12.5 20 days: 128.57 ± 9.0 40 days: 135.71 ± 18.1 60 days: 132.85 ± 17.0 DBP (mmHg) C group 0 day: 85.71 ± 7.9 20 days: 84.28 ± 7.9 40 days: 85.71 ± 9.8 60 days: 87.14 ± 11.1	NI	Zeb et al. (2018)	

(Continues)

TABLE 4 | (Continued)

Plant species	Extract	Study design/Country/Year	Subjects/sample size (after withdrawal)/age/gender (M: male and F: female)	Findings			Side effects	References
				Dosage/Duration	Treatment (T) group [mean difference]	Control (C) group/placebo [mean difference]		
<i>Linum usitatissimum</i> L. (Linaceae)	Powder	Double-blind, placebo-controlled, randomized trial/NI	110 peripheral artery disease (PAD) patients	T: Fed 1 product/day (bagels, muffins, bars, buns, pasta, tea biscuits) that contained 30 g of extract C: Fed 1 product/day (bagels, muffins, bars, buns, pasta, tea biscuits) that contained 30 g of SBP and 7 mmHg in DBP from extract milled wheat Administration: Oral Duration: 6 months T: 2.5 mL of extract oil C: placebo; 2.5 mL of sunflower oil Administration: Oral Duration: 8 weeks	SBP was ≈ 10 mmHg lower, and DBP was ≈ 7 mmHg lower in the T group compared with C group after 6 months Patients who entered the trial with SBP ≥ 140 mmHg at baseline resulted into a significant reduction of 15 mmHg in SBP and 7 mmHg in DBP from extract ingestion	BP did not change significantly in the placebo group	NI	Rodriguez-Leyva et al. (2013)
<i>Nigella sativa</i> L. (Ranunculaceae)	Seed oil	Double-blind, placebo-controlled/NI	55 patients: 20 M and 35 F (mean age: 59.60 ± 1.42 years)	T: 300 mg of extract (2 capsules/day) C: 300 mg of flour (2 capsules/day) Administration: Oral Duration: 6 weeks	SBP (mmHg) Week 0: 142.50 ± 10.33 Week 3: 136.81 ± 10.08 Week 6: 134.65 ± 10.40 Week 8: 134.13 ± 12.037 DBP (mmHg) Week 0: 87.47 ± 7.15 Week 3: 82.50 ± 6.04 Week 6: 78.90 ± 7.12 Week 8: 78.93 ± 8.15	SBP (mmHg) Week 0: 142.44 ± 11.39 Week 3: 141.70 ± 12.46 Week 6: 138.88 ± 16.86 Week 8: 139.58 ± 15.08 DBP (mmHg) Week 0: 87.09 ± 7.96 Week 3: 86.11 ± 7.26 Week 6: 85.78 ± 8.46 Week 8: 85.98 ± 7.93	No adverse effects were observed in both groups	Shoaei-Hagh et al. (2021)
<i>Nigella sativa</i> L. (Ranunculaceae)	Powder	Double-blind, randomized controlled/NI	76 patients aged ≥ 60 years with hypertension	T: 500 mg of extract (2 capsules/day) after meals C: 500 mg of calcium lactate (2 capsules/day) after meals Administration: Oral Duration: 6 weeks	SBP (mmHg) Before treatment: 160.4 After treatment: 145.8 DBP (mmHg) Before treatment: 78.3 After treatment: 74.4	SBP (mmHg) Before treatment: 160.9 After treatment: 147.53 DBP (mmHg) Before treatment: 79.0 After treatment: 78.2	Reported adverse events include dyspepsia in 6 subjects, nausea in 3 subjects, and constipation in 2 subjects.	Rizka et al. (2017)
<i>Nigella sativa</i> L. (Ranunculaceae)	Powder	Randomized, double-blind trial/Karachi/2006–2007	123 patients aged 18 years or older	T: 500 mg of extract (2 capsules/day) after meals C: 500 mg of calcium lactate (2 capsules/day) after meals Administration: Oral Duration: 6 weeks	SBP (mmHg) 0th week: 128.90 ± 18.37 6th week: 115.39 ± 12.65 DBP (mmHg) 0th week: 81.82 ± 11.24 6th week: 80.87 ± 11.39	SBP (mmHg) 0th week: 122.30 ± 17.76 6th week: 116.97 ± 13.58 DBP (mmHg) 0th week: 80.45 ± 11.48 6th week: 79.12 ± 8.57	No adverse effects were observed.	Qidwai et al. (2009)
<i>Nigella sativa</i> L. (Ranunculaceae)	Aqueous	Randomized, double-blind, placebo-controlled trial/Isfahan/2005	119 healthy male volunteers aged 35–50 years, with mild hypertension	T1: 100 mg of extract (2 capsules/day) T2: 200 mg of extract (2 capsules/day) C: 2 capsules/day Administration: Oral Duration: 8 weeks	The SBP of T1 and T2 was significantly lowered than the baseline level after 4 and 8 weeks of extract administration T1 and T2 groups showed significant when compared with baseline data	No significant change in SBP was observed in placebo group when compared with baseline values The DBP of the C was not significantly changed after 4 and 8 weeks when compared with baseline	NI	Dehkordi and Kamkhah (2008)

(Continues)

TABLE 4 | (Continued)

TABLE 4 | (Continued)

Plant species	Extract	Study design/Country/Year	Subjects/Sample size (after withdrawal)/age/gender (M: male and F: female)	Dosage/Duration	Findings			Side effects	References
					Treatment (T) group [mean difference]	Control (C) group/placebo [mean difference]			
<i>Nigella sativa</i> L. (Ranunculaceae)	Seed	Experimental study/NI	200 patients male and female patients aged 18–60 years/Lahore	T: Standard therapy + 1.5 g of extract once/day C: Only standard therapy only at 0, 6, and 12 weeks Administration : Oral Duration : 12 weeks	SBP (mmHg) 0th week: 139.49 ± 6.337 6th week: 137.87 ± 5.829 12th week: 132.66 ± 5.887 DBP (mmHg) 0th week: 102.32 ± 6.135 6th week: 100.58 ± 6.081 12th week: 95.26 ± 6.594	SBP (mmHg) 0th week: 139.07 ± 6.307 6th week: 138.93 ± 6.961 12th week: 133.37 ± 5.836 DBP (mmHg) 0th week: 102.85 ± 5.844 6th week: 102.75 ± 5.518 12th week: 95.64 ± 6.850	NI	Siddiqui et al. (2022)	
	Oil	Randomized clinical-case control study/Baghdad/2017	24 patients, 15 females and 9 males† aged between 31 and 65 years	Received 10 extract capsules in two divided doses before meals daily (equal to 1 g/day) for 4 weeks C: Received 5 mg ramipril tablet once daily for 4 weeks Administration : Oral Duration : 4 weeks	SBP (mmHg) 0th week: 156 ± 10.84 1st week: 150 ± 6.12 2nd week: 144 ± 4.18 3rd week: 142 ± 4.47 4th week: 138 ± 6.12 DBP (mmHg) 0th week: 95 ± 3.54 1st week: 94 ± 3 2nd week: 92 ± 3.53 3rd week: 90 ± 3.54 4th week: 85 ± 5	SBP (mmHg) 0th week: 167.14 ± 3.23 1st week: 152.14 ± 6.72 2nd week: 146.07 ± 3.5 3rd week: 144.29 ± 3.31 4th week: 137.14 ± 3.51 DBP (mmHg) 0th week: 107 ± 1.52 1st week: 94.29 ± 3.31 2nd week: 90.86 ± 2.28 3rd week: 86.79 ± 1.97 4th week: 83.79 ± 2.89	NI	AL-Jawad et al. (2018)	
<i>Parkia biglobosa</i> Benth. (Fabaceae)	Fermented	NI	200 subjects of both sexes aged between 40 and 50 years/2 different areas of Togo	T1: Consumption of condiments (100 g/day) containing the extract T2: Never consumed this condiment Administration : Oral	SBP or DBP was significantly between the two groups with the values lower for the Bogou group Heart rate was significantly lower in T1 group than in T2 group	NI	NI	Ognatan et al. (2011)	
<i>Sesamum indicum</i> L. (Pedaliaceae)	Sesamin ligand	Double-blind, crossover, placebo-controlled trial/Japan/NI	25 subjects (23 men and 2 women), aged 49.1 ± 1.8 years with mild hypertension	T: 3 capsules twice/day (10 mg wheat germ oil) C: 3 capsules twice/day (only 180 mg wheat germ oil) Administration : Oral Duration : 4 weeks	SBP (mmHg) : 137.6 ± 2.2 to 134.1 ± 1.7 [–3.5] DBP (mmHg) : 87.7 ± 1.3 to 85.8 ± 1.0 [–1.8] In the T group, both SBP and DBP were significantly reduced after administration compared with before administration in period 1. After the 4th week washout, SBP and DBP were slightly increased.	SBP (mmHg) : 135.0 ± 1.8 to 135.1 ± 1.7 [+0.1] DBP (mmHg) : 85.9 ± 1.2 to 86.6 ± 1.2 [+0.7] In the C group, both SBP and DBP were slightly decreased after administration in period 1, but it was not significant. After the washout, BP was slightly increased but decreased after period 2. After administration of placebo in period 2, BP was increased	No side effects were observed	Miyawaki et al. (2009)	

(Continues)

TABLE 4 | (Continued)

Plant species	Extract	Study design/Country/Year	Subjects/Sample size (after withdrawal)/age/gender (M: male and F: female)	Dosage/Duration	Findings			Side effects	References
					Treatment (T) group [mean difference]	Control (C) group/placebo [mean difference]			
<i>Theobroma cacao</i> L. (Malvaceae)	Flavanol-enriched beverage	A pilot, randomized controlled trial/Quebec/2008–2009	44 healthy, pregnant women aged 18–35 years/Quebec/2008–2009	T: Were instructed to consume 40 g of extract within 10 min (high-flavanol) C: Were instructed to consume in the fasting state 40 g of normal chocolate without flavanols within 10 min (low-flavanol) Administration: Oral Duration: 12 weeks	Flow-mediated dilation—FMD (%) 0th week: 11.9 ± 4.7 6th week: 10.8 ± 3.9 12th week: 10.4 ± 3.4 SBP (mmHg) 0th week: 109.4 ± 7.6 6th week: 109.4 ± 7.5 12th week: 108.8 ± 8.9 DBP (mmHg) 0th week: 66.8 ± 6.3 6th week: 68.0 ± 5.0 12th week: 70.5 ± 6.8 MABP (mmHg) 0th week: 81.0 ± 5.9 6th week: 81.8 ± 5.2 12th week: 83.2 ± 7.1	Flow-mediated dilation—FMD (%) 0th week: 13.3 ± 3.8 6th week: 11.4 ± 3.4 12th week: 13.1 ± 3.8 SBP (mmHg) 0th week: 105.9 ± 7.8 6th week: 104.8 ± 6.0 12th week: 106.1 ± 9.7 DBP (mmHg) 0th week: 64.2 ± 6.2 6th week: 65.4 ± 5.9 12th week: 68.2 ± 6.9 MABP (mmHg) 0th week: 78.1 ± 6.5 6th week: 78.5 ± 5.6 12th week: 80.9 ± 7.5		Weight change, digestive, and other signs and symptoms (nausea, abdominal pain, constipation, and headache) were documented	Mogollon et al. (2013)
					SBP (mmHg) T1 group 0th week: 138.0 ± 1.28 8th week: 130.2 ± 1.21 T2 group 0th week: 137.0 ± 1.37 8th week: 130.2 ± 1.28 T3 group 0th week: 136.1 ± 1.11 8th week: 134.5 ± 1.37 DBP (mmHg) T1 group 0th week: 83.5 ± 0.95 8th week: 78.8 ± 0.82 T2 group 0th week: 83.5 ± 1.09 8th week: 80.3 ± 1.04 T3 group 0th week: 82.4 ± 1.13 8th week: 80.8 ± 1.25	NI			
<i>Theobroma cacao</i> L. (Malvaceae)	Flavanol-enriched beverage	Double-blind, controlled, parallel-arm study/Italy/2006–2008	90 elderly individuals without clinical evidence of cognitive dysfunction	T1: Cocoa drinks with high flavanol content once a day in the morning T2: Cocoa drinks with intermediate flavanol content once a day in the morning T3: Cocoa drinks with low flavanol content once a day in the morning Administration: Oral Duration: 8 weeks	SBP (mmHg) T1 group 0th week: 138.0 ± 1.28 8th week: 130.2 ± 1.21 T2 group 0th week: 137.0 ± 1.37 8th week: 130.2 ± 1.28 T3 group 0th week: 136.1 ± 1.11 8th week: 134.5 ± 1.37 DBP (mmHg) T1 group 0th week: 83.5 ± 0.95 8th week: 78.8 ± 0.82 T2 group 0th week: 83.5 ± 1.09 8th week: 80.3 ± 1.04 T3 group 0th week: 82.4 ± 1.13 8th week: 80.8 ± 1.25	NI		No other mild or more severe adverse events reported throughout the trial	Mastroiacovo et al. (2015)
					SBP (mmHg): 11.88 to 11.12 [−0.76] DBP (mmHg): 7.66 to 7.51 [−0.15]	SBP (mmHg): 11.45 to 11.21 [−0.24] DBP (mmHg): 7.59 to 7.66 [+0.07]			
<i>Trigonella foenum-graecum</i> L. (Fabaceae)	Powder	Parallel randomized clinical trial/NI	80 patients aged 30–65 years with type 2 diabetes mellitus (T2DM)	5 g of extract powder mixed with water three times daily between the main meals	SBP (mmHg): 11.88 to 11.12 [−0.76] DBP (mmHg): 7.66 to 7.51 [−0.15]	SBP (mmHg): 11.45 to 11.21 [−0.24] DBP (mmHg): 7.59 to 7.66 [+0.07]		No adverse effects were reported in participants following FS consumption	Hadi et al. (2020)

(Continues)

TABLE 4 | (Continued)

Plant species	Extract	Study design/Country/Year	Subjects/Sample size (after withdrawal)/age/gender (M: male and F: female)	Dosage/Duration	Findings			Side effects	References
					Treatment (T) group [mean difference]	Control (C) group/placebo [mean difference]			
<i>Vitis vinifera</i> L. (Vitaceae)	Seed	Placebo-controlled double-blind trial/Davis/NI	27 adults (age, 25–80 years) with metabolic syndrome	T1: 150 g extract/day T2: 300 g extract/day C: Placebo capsules Administration: Oral Duration: 4 weeks	SBP (mmHg) T1 group 0th week: 134 ± 5 4th week: 123 ± 4 T2 group 0th week: 127 ± 4 4th week: 116 ± 3 DBP (mmHg) T1 group 0th week: 83 ± 3 4th week: 77 ± 2 T2 group 0th week: 78 ± 3 4th week: 71 ± 3	SBP (mmHg) C group 0th week: 123 ± 4 4th week: 121 ± 4 DBP (mmHg) C group 0th week: 74 ± 4 4th week: 70 ± 4	NI	Sivaprakasapillai et al. (2009)	
<i>Vitis vinifera</i> L. (Vitaceae)	Beverage	Randomized, double-blinded, two-arm, parallel, placebo-controlled trial/Chicago/2010–2014	60 subjects, men and women with T: Extract beverage twice/day once in the morning and once in the evening with meals C: Placebo beverage twice/day once in the morning and once in the evening with meals Administration: Oral Duration: 10 weeks		SBP (mmHg) Day-time 0th week: 125.0 6th week: 118.0 10th week: 124.1 Night-time 0th week: 112.9 6th week: 111.5 10th week: 114.3 DBP (mmHg) Day-time 0th week: 83.0 6th week: 79.1 10th week: 81.9 Night-time 0th week: 73.1 6th week: 72.6 10th week: 72.1	SBP (mmHg) Day-time 0th week: 125.6 6th week: 127.0 10th week: 123.7 Night-time 0th week: 113.1 6th week: 111.2 10th week: 114.7 DBP (mmHg) Day-time 0th week: 82.9 6th week: 83.6 10th week: 81.3 Night-time 0th week: 73.1 6th week: 74.7 10th week: 74.8	No adverse effects were reported	Park and Velasquez (2012)	
<i>Vitis vinifera</i> L. (Vitaceae)	Oil	Double-blind clinical trial/NI	70 eligible hyperlipidemic patients aged 30–60 years	T1: Low calorie diet + 20 mL/day refined olive oil (two teaspoons full in the morning and 2 in the afternoon) T2: Low calorie diet + 20 mL/day refined extract (two teaspoons full in the morning and 2 in the afternoon) C: Low calorie diet + no oil Administration: Oral Duration: 6 weeks	Systolic blood pressure (SBP) was significantly decreased after intervention in T1 group Significant differences were also found in mean change of SBP differences among three groups of study The mean of DBP before and after the study were significant between groups	The mean of DBP before and after the study were significant between groups	NI	Kaseb and Biregani (2016)	

(Continues)

TABLE 4 | (Continued)

Plant species	Extract	Study design/Country/Year	Subjects/Sample size (after withdrawal)/age/gender (M: male and F: female)	Dosage/Duration	Findings			References
					Treatment (T) group [mean difference]	Control (C) group/placebo [mean difference]	Side effects	
<i>Vitis vinifera</i> L. (Vitaceae)		Randomized, double-blind, placebo-controlled/Germany/2017	45 healthy subjects (45 male and 35 female) aged between 40 and 70 years with mild elevated blood pressure	T: Two extract tablets (150 mg each) were taken every day orally with sufficient water (one 5–10 min before breakfast and one 5–10 min before lunch) C: Placebo supplementation Administration: Oral Duration: 16 weeks	Mean difference in men			Significant differences between placebo and extract treatment were observed in men after 8 weeks and 16 weeks, leading to a significant decrease in SBP and DBP In women, no superiority of extract on blood pressure reduction when compared with placebo was seen
					SBP (mmHg)			
					4th week: −2.19			
					8th week: −5.36			
					12th week: −3.27			
					16th week: −3.76			
					DBP (mmHg)			
					4th week: −2.15			
					8th week: −3.59			
					12th week: −1.77			
					16th week: −2.98			
					Mean difference in women			
					SBP (mmHg)			
					4th week: 4.76			
					8th week: 0.98			
					12th week: 0.98			
					16th week: 3.73			
					DBP (mmHg)			
					4th week: 2.60			
					8th week: 0.56			
					12th week: 0.22			
					16th week: 0.69			

Abbreviation: NI, not indicated.

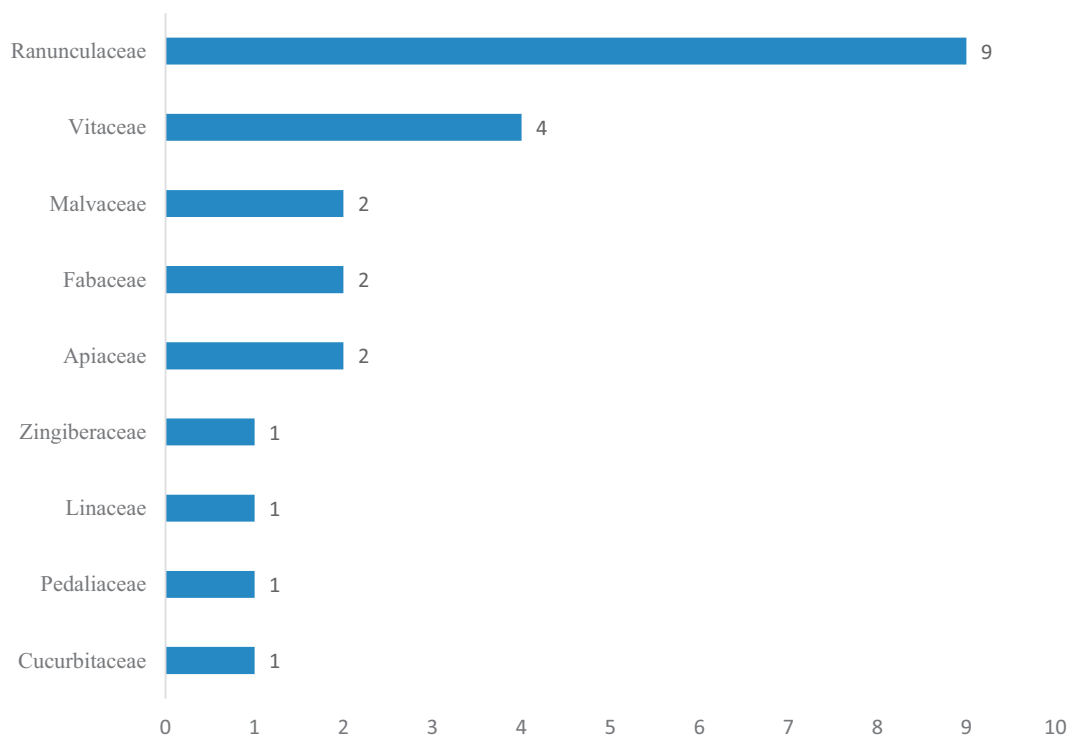


FIGURE 13 | Plant families tested in clinical studies against hypertension.

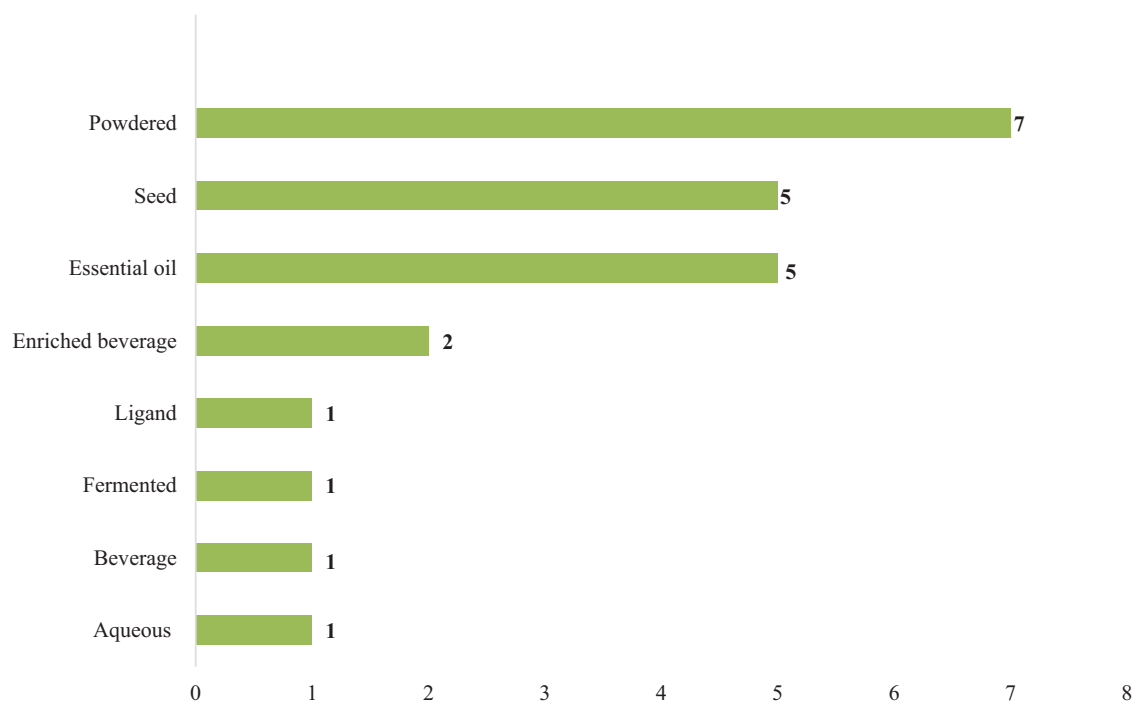


FIGURE 14 | Types of extract tested in clinical studies.

Weeks 0 and 4) (AL-Jawad et al. 2018). In a study conducted on the comparison of changes in SBP in male and female participants treated with *C. lanatus*, it was found that the SBP was reduced by 15.29 mmHg in males and 12.79 mmHg in females, respectively (Sajjad et al. 2020).

Another species that exhibited a significant, albeit lesser, decrease in SBP compared to the previously mentioned species was *N. sativa* (a reduction of 14.6 mmHg) (Rizka et al. 2017), whereas a separate study noted a decrease of 13.51 mmHg (Qidwai et al. 2009). A smaller reduction was reported for *A. graveolens*

(11.2 mmHg) (Shayani Rad et al. 2022), followed by a decrease of 11 mmHg in SBP after administering *V. vinifera* seed extract at doses of 150 and 300 g/day (Sivaprakasapillai et al. 2009). Subsequently, a reduction of 10.69 mmHg in SBP was observed with *N. sativa* (Tavakoli-Rouzbehani et al. 2021). The decreases in SBP reported in the remaining studies were all less than 10 mmHg.

3.4.2 | Comparisons for DBP

Among 19 reports on DBP (Table 3), the most potent reduction in DBP (10 mmHg) was observed for *N. sativa* (AL-Jawad et al. 2018), followed by *C. lanatus* (7.92 and 9.79 mmHg in male and female participants, respectively) (Sajjad et al. 2020), *A. graveolens* (8 mmHg) (Shayani Rad et al. 2022), and *A. melegueta* (7.6 and 9.2 mmHg in normotensive and hypertensive participants, respectively) (Lawal et al. 2007). However, some variations were noticed for *N. sativa* (Tavakoli-Rouzbehani et al. 2021), wherein a reduction of 8.6 mmHg was reported, whereas two other studies with the same plant species demonstrated a decline of 8.49 mmHg (Shoaei-Hagh et al. 2021) and 7.06 mmHg (Siddiqui et al. 2022). The successive reduction in DBP was 6 and 7 mmHg at a dose of 150 and 300 g/day of raw seed extract from Weeks 0 to 4, respectively (Sivaprakasapillai et al. 2009).

3.4.3 | Comparisons for HR, PP, and Mean Arterial Pressure (MAP)

HR was determined in three studies only (Table 3). Lawal et al. (2007) reported a reduction in HR by 7 mmHg after administration of *A. melegueta*, whereas *N. sativa* reduced the HR by 3.12 beats/min (Badar et al. 2017). Another study on *N. sativa* reported that HR decreased by 1 mmHg (Razmpoosh et al. 2021). PP was reported in two studies only. Lawal et al. (2007) reported that *A. melegueta* reduced PP by 21.4 mmHg. *A. graveolens* powdered extract (1.34 g/day) reduced PP by 3.2 mmHg (Shayani Rad et al. 2022). MAP was reported in two studies. In one study, Lawal et al. (2007) reported that oral administration of *A. melegueta* reduced MAP by 14.7 mmHg, whereas MAP of *N. sativa*-treated subjects decreased by 5.74 mmHg (Badar et al. 2017).

3.5 | Compounds

Research into the bioactive compounds derived from plant species has facilitated the development of innovative drugs with distinct mechanisms of action. A selection of these compounds, known for their antihypertensive effects, were identified from clinically tested seed species and subsequently reviewed. These include sesamin and sesamol from *S. indicum*, thymoquinone (TQ) from *N. sativa*, lignan from *L. usitatissimum*, linalool from *C. sativum*, and trigonelline from *T. foenum-graecum*. The chemical structures of these compounds are depicted in Figure 15.

3.5.1 | Sesamin

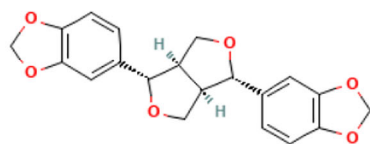
D. Nakano et al. (2002) investigated the mechanism responsible for the antihypertensive effect using deoxycorticosterone

acetate (DOCA)-salt rat hypertensive model. The production of superoxide ($O_2^{\cdot-}$) from the aorta was evaluated in the lucigenin chemiluminescence assay. Hypertensive rats fed with a sesamin-containing diet had significantly lower chemiluminescence signals compared to the control group, which were DOCA-salt rats fed a regular diet. Moreover, a positive correlation was observed between aortic $O_2^{\cdot-}$ production and SBP. In addition, D Nakano et al. (2004) found a significant correlation between sesamin's suppression of BP elevation and its inhibition of excessive superoxide ($O_2^{\cdot-}$) production in the aorta of hypertensive rats. In the DOCA-salt hypertension model, dietary sesamin normalized the increase in the α 1-adrenoceptor-dependent vasoconstrictor response and the decrease in endothelium-dependent vasodilatory response.

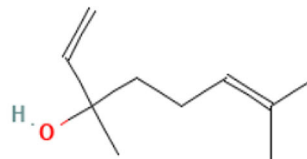
D. Nakano et al. (2008) further investigated sesamin's capacity to inhibit aortic oxidase in DOCA-salt hypertensive rats. They found that sesamin feeding significantly reduced aortic output and markedly suppressed hypertension induced by DOCA salt. DOCA salt application increased aortic mRNA expression of p22phox, gp91phox, Nox1, and Nox4, as well as NADPH oxidase activity. However, sesamin feeding counteracted the increase in NADPH oxidase activity and significantly decreased the rise in Nox1 mRNA expression, gp91phox, and p22phox. Wu et al. (2012) evaluated sesamin's preventive effect against renal endothelial dysfunction and kidney damage in two-kidney, one-clip renovascular hypertensive rats fed a high-fat, high-sucrose diet. Sesamin reduced the expression of p47phox and nitrotyrosine while increasing eNOS protein expression. These results suggest that long-term sesamin therapy ameliorates renal endothelial dysfunction and exerts a renoprotective effect in both the contralateral and clipped kidneys of 2K1C rats fed an HFS diet by decreasing NO oxidative inactivation and enhancing eNOS production.

Furthermore, Noguchi et al. (2001) examined the effects of sesamin, a lignan obtained from sesame oil, on hypertension and thrombosis in stroke-prone spontaneously hypertensive rats (SHR). Their results suggested that long-term sesamin consumption could be beneficial for preventing hypertension due to its reduction of oxidative stress, thrombotic tendency, and BP increase. Similarly, Miyawaki et al. (2009) evaluated the antihypertensive effects of sesamin in humans, finding a significant decrease in blood pressure. Matsumura et al. (2000) studied the influence of sesamin on modified vasodilator and vasoconstrictor responses in aortic rings of rats with induced hypertension via DOCA salt treatment. They found that sesamin feeding considerably delayed the onset of hypertension. Additionally, W.-x. Li et al. (2013) explored the cardioprotective benefits of food-derived sesamin in rats with spontaneous hypertension. These benefits included reduced SBP, increased cardiac total antioxidant capacity, and decreased levels of nitrotyrosine, malondialdehyde content, and transforming growth factor β 1 (TGF- β 1) expression.

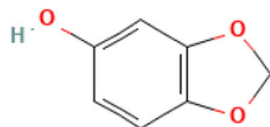
Kong et al. (2009) found that sesamin administration enhanced acetylcholine-induced vasodilation, reduced blood pressure, and augmented NO bioactivity in thoracic aortas. These changes were associated with an increase in eNOS, a decrease in malondialdehyde levels, and a reduction in nitrotyrosine and p47phox protein production. Kong et al. (2015) further explored the



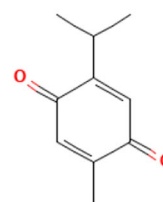
Sesamin
(PubChem CID: 72307)



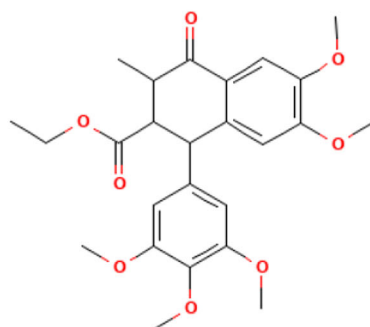
Linalool
(PubChem CID: 6549)



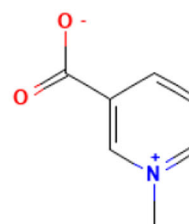
Sesamol
(PubChem CID: 68289)



Thymoquinone
(PubChem CID: 10281)



Lignan
(PubChem CID: 261166)



Trigonelline
(PubChem CID: 5570)

FIGURE 15 | The main antihypertensive compounds identified in clinically tested species.

potential of sesamin to enhance nitric oxide bioactivity in the aortas of SHR. Sesamin treatment in SHRs resulted in improved acetylcholine-induced vascular relaxation, decreased SBP, and increased aortic NO bioactivity. Sesamin therapy caused an increase in P-eNOS and inhibition of eNOS uncoupling, both of which led to improved NO production in the SHR aortas; the latter effect may be due to decreased nitrotyrosine and increased dihydrofolate reductase (DHFR). Additionally, sesamin downregulated p47phox and improved eNOS uncoupling, reducing superoxide anion formation and NO oxidative inactivation. Moreover, sesamin administration significantly decreased the compensatory enhanced T-SOD activity and Cu/Zn-SOD protein expression but had no effect on the levels of GPx or catalase activity.

3.5.2 | Thymoquinone

Khattab and Nagi (2007) examined the effect of TQ supplementation on hypertension and renal dysfunction in nitric oxide-deficient hypertensive rats. They found that co-administration of TQ led to a dose-dependent decrease in the L-NAME-induced rise in SBP. To determine the antihypertensive efficacy of TQ and investigate its mechanism of action, Azzubaidi et al. (2015) carried out a study, which showed that TQ prevented further increases in MAP and reversed established hypertension in the TQ groups. This research confirms the antihypertensive effect of TQ, which is most likely due to angiotensin II receptor blockade rather than ACE inhibition. Zhu et al. (2016) also explored the possibility of TQ reducing monocrotaline-induced (MCT) pulmonary arterial hypertension in rats by preventing pulmonary arterial remodeling. They found that TQ treatment reduced the MCT-induced

increase in pulmonary BP and right ventricular hypertrophy. Furthermore, TQ inhibited the MCT-induced pulmonary arterial remodeling, proliferation of PASMCs, upregulation of matrix metalloproteinase 2 (MMP2), downregulation of the Bax/Bcl-2 ratio, cleavage of caspase-3, and cleavage of PARP. Additionally, TQ blocked the NF- κ B and p38-MAPK activation induced by MCT. It was concluded that TQ inhibits the p38-MAPK/NF- κ B signaling pathway in rats, thereby attenuating MCT-induced pulmonary arterial hypertension.

Furthermore, the hypotensive effect of TQ and its receptor mechanisms in normotensive rats was examined by Azzubaidi et al. (2015). This research supports the conventional use of *N. sativa* L. for hypertension and confirms the dose-dependent hypotensive effect of TQ. The hypotensive mechanism of action of TQ is at least in part stimulation of β -adrenergic receptors, but not vascular muscarinic receptors. Enayatfard et al. (2018) reported that Ang II significantly increased maximal SBP, MAP, and HR compared to the control, whereas losartan significantly and extensively attenuated these effects. TQ and the two higher doses of *N. sativa* (400 and 600 mg/kg) could significantly antagonize the effects of Ang II on MAP and SBP. TQ and extract dose of 600 mg/kg also significantly inhibited Ang II-induced changes in HR. In conclusion, *N. sativa* and its active constituent TQ are beneficial in hypertension, most probably through reducing Ang II-mediated effects on the cardiovascular system. L. Zhang et al. (2022) evaluated the protective effect of TQ against angiotensin II-induced cardiac injury in apolipoprotein E-deficient mice. The results demonstrated that TQ inhibited the increases in serum hs-CRP levels induced by Ang II. In Ang II-treated mice, TQ significantly decreased the elevated levels of tumor necrosis factor alpha (TNF α), IL 1 β , IL 6, collagen I, collagen III, Nox4, and p53. Moreover, TQ inhibited Ang II-induced cardiac injury via suppressing proinflammatory cytokine production, fibrosis, oxidative stress, and apoptosis through inhibition of pERK signaling pathway activation. To sum up, TQ could be a promising therapeutic strategy for Ang II-induced myocardial infarction.

3.5.3 | Sesamol

Hemalatha et al. (2013) conducted an analysis on the antihypertensive and antioxidant properties of sesamol, using uninephrectomized DOCA-salt-induced hypertensive rats. When administered orally at a dose of 50 mg/kg BW, sesamol significantly decreased both systolic and DBP values. It also reduced the activities of hepatic marker enzymes and lipid peroxidation products. Furthermore, the treatment enhanced the body's antioxidant capacity. These findings suggest that sesamol possesses not only antioxidant properties but also antihypertensive attributes.

3.5.4 | Lignan

Park and Velasquez (2012) studied the effects of flaxseed powder with lignan supplementation on body weight, visceral fat, lipid profile, and BP in rats. They observed a significant decrease in BP in the high-fat diet (HFD) with lignan supplementation (HFDL) group compared to HFD group. The results suggest

that lignan supplementation exerts beneficial effects such as reduction of blood pressure, lipid profile improvement, and decrease in body weight and fat accumulation. Sawant and Bodhankar (2016) found that flax lignan concentrate showed an antihypertensive effect via modulation of endogenous enzymes in DOCA salt-induced renal hypertensive rats.

3.5.5 | Linalool

Anjos et al. (2013) conducted a study on the influence of linalool on the cardiovascular systems of both normotensive and hypertensive rats. The results indicate that linalool has the effect of reducing blood pressure, which is likely attributed to its direct impact leading to vasodilation on the vascular smooth muscle.

3.5.6 | Trigonelline

In a study utilizing the streptozotocin-induced neonatal diabetic (nSTZ) rat model, Ghule et al. (2012) explored the potential of trigonelline to mitigate diabetic hypertension nephropathy by inhibiting oxidative stress in the kidney and minimizing renal cell death and fibrosis. Their findings revealed that kidney tissues from the diabetic group exhibited elevated levels of hydroxyproline and diminished activity of antioxidant and membrane-bound enzymes. A 4-week regimen of trigonelline therapy (100 mg/kg/day) significantly improved all assessed biochemical parameters. Histological analyses aligned with these biochemical observations, indicating that trigonelline-treated groups experienced reduced fibrosis and degenerative changes in kidney tissue, suggesting that trigonelline plays a crucial role in mitigating renal damage.

4 | Discussion

A multitude of studies have documented the traditional utilization of edible seeds in the treatment of hypertension. Among these, *N. sativa* has been the most frequently employed seed with promising outcomes in managing hypertension. Furthermore, it has been determined that *A. melegueta* has exhibited the highest efficacy in clinical trials.

Predominantly, the preparation methods most frequently reported for traditional use were decoction and infusion, likely due to their drinkability and reduced preparation time. Infusion involves allowing the material to steep in a solvent such as water or alcohol for a duration, whereas decoction involves boiling the material to extract substances and release aromas. Notably, decoction is more commonly employed in studies examining the biological and therapeutic properties of plant species (Fotakis et al. 2016). However, a significant number of countries lack comprehensive field studies documenting the traditional use of edible seeds for hypertension management. Furthermore, several studies do not offer a thorough description of the preparation methods. Therefore, it is imperative to conduct meticulously documented ethnomedicinal field studies on the traditional use of seed species for hypertension management.

In terms of pharmacological studies, this review presented the analysis of in vitro, in vivo, and clinical investigations. The most examined seed species in vitro was *M. oleifera*. The results were not able to be compared collectively because they were reported as percentage of ACE inhibition and IC₅₀ values. The greater the percentage of ACE inhibition values and the lesser the IC₅₀ values, the more potent activity of plant species was found. Nevertheless, the protein concentrates extract of *H. vulgare* exhibited the greatest percentage of ACE inhibition, and the protein extract of *A. hypogaea* indicated the least IC₅₀ value. The mostly used types of extracts for in vitro studies were protein extract, and it was determined as the most effective extract in comparison with other extracts. The positive controls that were mostly used in in vitro studies were captopril and ramipril. Captopril is an FDA-approved drug that is used as a vital medication for the treatment of hypertension, diabetic nephropathy, and left ventricular dysfunction after myocardial infarction. It mainly acts by blocking the renin–angiotensin–aldosterone system (RAAS) (Marte et al. 2025). Ramipril is a prodrug that enhances the systemic bioavailability of ramiprilat, which is an active inhibitor of ACE (Frampton and Peters 1995). Among six studies that administered captopril and ramipril as drugs, just two studies were comparable because the units of both IC₅₀ values and the drugs were expressed in mg/mL and µg/mL. The others were not comparable because of different units. Thus, it is suggested that further pharmacological studies should focus on captopril and other drugs as medications for a valid comparison.

In vivo studies, *N. sativa* was the most potent in lowering SBP, DBP, MABP, PP, and HR compared to hypertensive controls. Due to its medicinal properties, the use and demand for this plant have dramatically increased as it is currently being marketed and sold in various countries worldwide in the form of soft-gel capsules, seed-derived oil, and nutritional supplements (M. F. Mahomoodally et al. 2022). Some studies measured only ACE as a parameter, whereas some studies measured SBP, DBP, MABP, PP, and HR as parameters along with ACE. As ACE is a dipeptidyl peptidase transmembrane-bound enzyme that plays an important role in BP regulation (Nakas-Icindic et al. 2004). Therefore, it is suggested that ACE should be measured and included with other parameters to get more accurate results. As per the animal model, most studies were conducted on Wistar rats because of their anatomical and physiological similarities with humans. Rats, mice, and humans have around 30,000 genes, and 95% of these genes are present in both rats and humans (Bryda 2013). Apart from this, rats are small in size and require less space and maintenance. Oral administration was mostly preferred against hypertension due to its convenience. In some studies, different doses of extracts along with medications were given to animals, whereas some studies used only the optimum dose to avoid toxicity.

The most studied seed in the clinical trials was *N. sativa*, which showed very good results in reducing high blood pressure. This comes as no surprise as the main part of the plant used for consumption is the seed (M. F. Mahomoodally et al. 2022). A few studies showed some mild side effects, but they were not significant. *N. sativa* was the most effective seed tested in the clinical and in vivo studies, highlighting the need for further research on this plant for its therapeutic potential in humans. This review found that the most common extract used for the

clinical trials was the powdered extract. This is probably due to its availability and ease of administration. Double blinding was the most common study design employed in the clinical trials reviewed. This helps reduce bias and strengthens the validity of the study (Day and Altman 2000).

In the analysis of compounds derived from clinically tested seeds, sesamin from *S. indicum* was the most frequently examined, followed by TQ from *N. sativa*. The predominant animal model employed was the DOCA-induced hypertensive rat. The DOCA-salt model has been extensively used for many years. In rats or mice, DOCA, a mineralocorticoid, induces hypertension when paired with uninephrectomy and a high-salt diet (Mortensen 2014). Sesamin administration to these animals has shown a reduction in reactive oxygen species (ROS) increases, including Nox1 mRNA expression, gp91phox, and p22phox. These ROS are known contributors to hypertension in the cardiovascular system. The regulation of NADPH oxidases (NOXes) in the cardiovascular system is influenced by various prohypertensive and inflammatory agents such as angiotensin II (Ang II), endothelin-1 (ET-1), aldosterone, salt, growth factors (VEGF and epidermal growth factor, respectively), and TNF (Griendling et al. 2021) (Figure 16).

Pharmacological profile of TQ is very complex and diverse, which includes antibacterial, antihistamine, antioxidant, immunomodulator, and anticancer activities. The effects of TQ on immunomodulation, oxidative stress, and various types of cancers have been reviewed extensively. In addition, the role of TQ in the immune system activation through the modulation of various inflammatory mediators has also been reviewed exhaustively (M. F. Mahomoodally et al. 2022). Similarly, the role of TQ and its mechanism of action in hypertension have also been studied. MMP2 is a gene that codes for matrix metalloproteinase 2 enzyme. This enzyme causes angiotensin II-induced hypertension under the transcriptional control of MMP-7 and TACE. The inhibition of MMP-7 and TACE prevents the induction of hypertension, heart failure, and fibrosis by Ang II. In the downstream signaling cascade of MMP-7 and TACE, there is a bifurcation where Ang II-induced hypertrophy and fibrosis occur independent of the MMP-2 gene expression and the resulting hypertension (Odenbach et al. 2011) (Figure 17). TQ inhibits the Ang II-induced upregulation of MMP2 and ultimately blocks hypertension.

Furthermore, TQ was found to inhibit the p38-MAPK/NF-κB signaling pathway. Notably, the p38-MAPK signaling pathway regulates numerous pathologic conditions, with a particular significance in myocardial ischemia-reperfusion. MAPK stimulation results in reduced cardiac efficiency and increased I/R-induced myocardial injury (Sahu and Rawal 2024). As shown in Figure 18, administration of natural products can effectively regulate c-JNK/p38-MAPK dysregulation, thereby managing hypertension.

5 | Conclusion

This review is a pioneering effort to catalogue the traditionally utilized edible seeds for combating hypertension globally. It also elucidates the efficacy of seeds in managing hypertension by consolidating and analyzing in vitro, in vivo, and clinical studies. Notably, *N. sativa* demonstrated the most pronounced activity

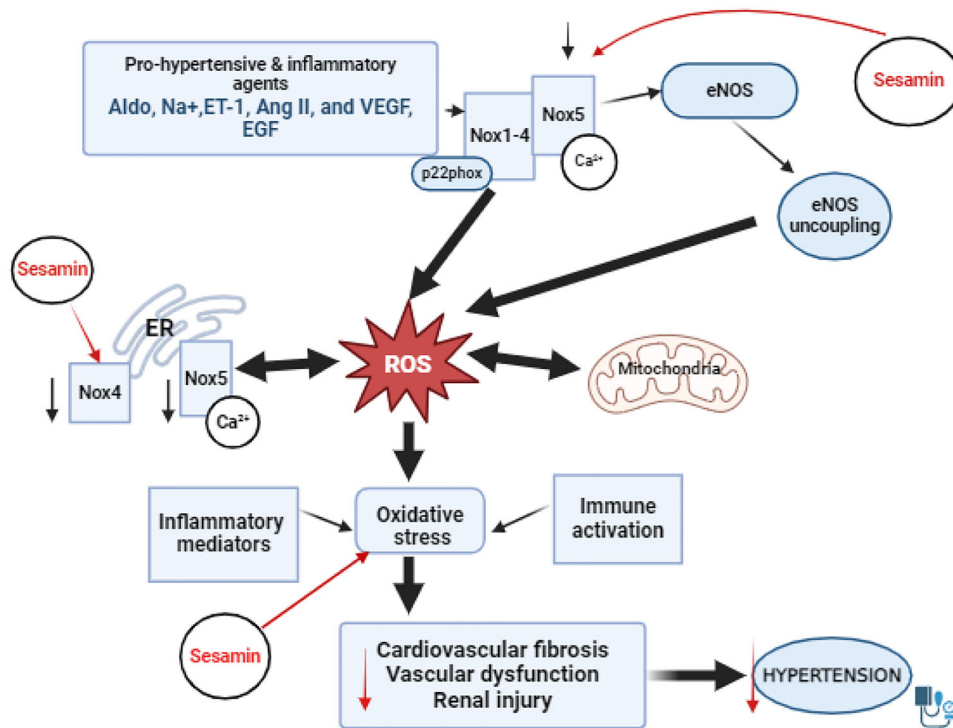


FIGURE 16 | Sesamin inhibiting ROS. ROS, reactive oxygen species.

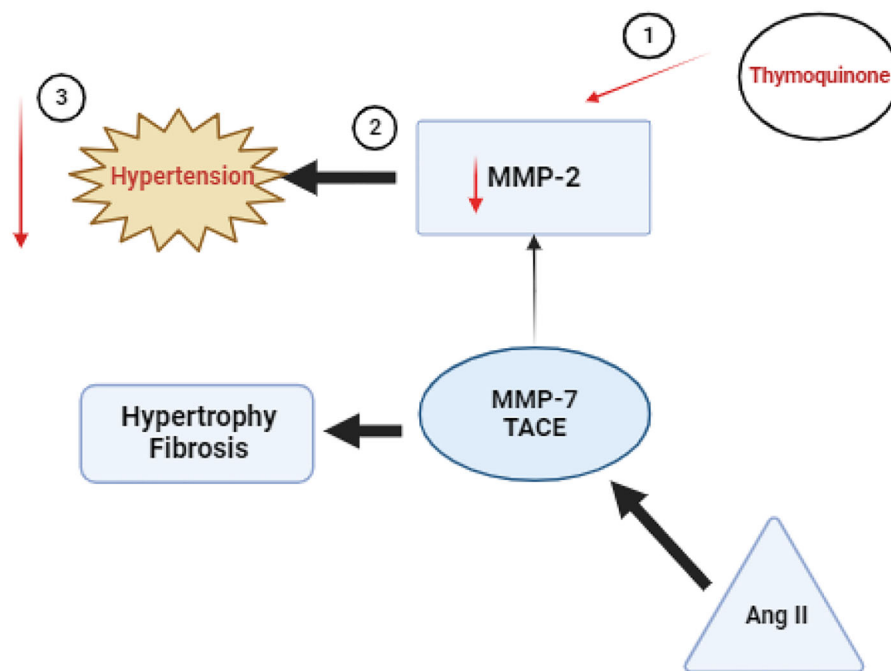


FIGURE 17 | TQ inhibiting metalloproteinase signaling in Ang II-induced cardiovascular disease. MMP, matrix metalloproteinase.

against hypertension, with clinical studies evidencing the most significant reduction in SBP, DBP, MABP, PP, and HR. Among the bioactive compounds derived from clinically tested seeds, sesamin (from *S. indicum*) and TQ (from *N. sativa*) exhibited notable antihypertensive effects. The predominant mechanisms of action included Nox1 mRNA expression, gp91phox, p22phox, MMP-7, TACE, and p38-MAPK/NF- κ B signaling. These insights

offer a foundational scientific dataset for ensuing pharmacological interventions for hypertension management. Future research should prioritize addressing the identified research gaps, notably the exploration of the primary bioactive compounds of these seed species and associated clinical studies. It is envisaged that this review will pave the way for innovative research avenues to mitigate the global hypertension burden. Although seeds possess

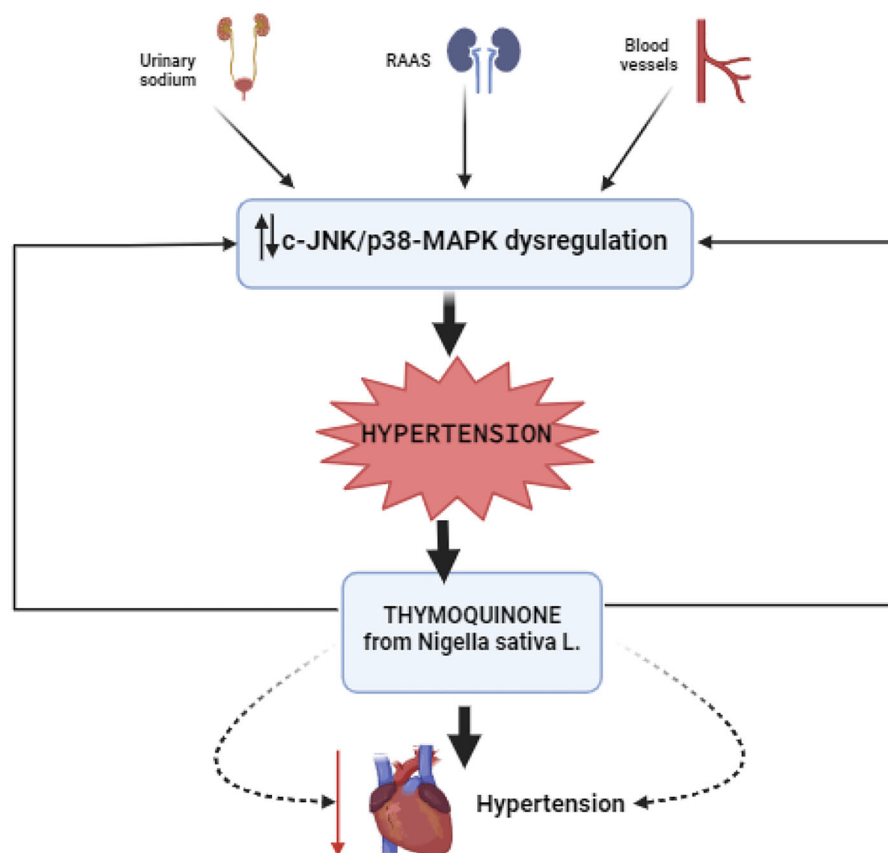


FIGURE 18 | TQ regulating the p38-MAPK pathway. p38-MAPK, p38 mitogen-activated protein kinases.

numerous medicinal attributes due to their rich bioactive compounds, they are often overshadowed by fruits, flowers, and leaves in terms of consumption and recognition. In conclusion, these underutilized plant components harbor a plethora of therapeutic potentials and warrant further exploration by the scientific realm for biopharmaceutical development.

Author Contributions

Jinmin Shi: investigation, methodology, formal analysis, writing – original draft, writing – review and editing. **Ruttun Bushra Umme Zainab:** investigation, methodology, formal analysis, writing – original draft, writing – review and editing. **Ahmed Abduljalal Abduljabbar:** investigation, methodology, data analysis, visualization, writing – original draft, writing – review and editing. **Katharigatta N. Venugopala:** investigation, methodology, writing – review and editing. **Mohamad Fawzi Mahomoodally:** investigation, methodology, formal analysis, writing – original draft, writing – review and editing. **Gokhan Zengin:** investigation, data analysis, supervision, writing – review and editing. **Xuebo Hu:** investigation, data analysis, supervision, writing – review and editing. **Sakina Yagi:** investigation, methodology, data analysis, writing – original draft, writing – review and editing. **Meng-Yao Li:** investigation, data analysis, supervision, writing – review and editing.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Aboua, S. C. M. J., T. Houèchégnon, B. N. K. Sourou, A. A. Wédjangnon, G. Azongnidé, and C. A. I. N. Ouinsavi. 2024. “Diversity of Plant Species With Ethnomedicinal Potential for Treating Arterial Hypertension and Gastric Ulcers, Two Chronic Diseases: An Ethnobotanical Assessment

- in Benin." *Ethnobotany Research and Applications* 29: 1–22. <https://ethnobotanyjournal.org/index.php/era/article/view/5801>.
- Abu-Irmaileh, B. E., and F. U. Afifi. 2003. "Herbal Medicine in Jordan With Special Emphasis on Commonly Used Herbs." *Journal of Ethnopharmacology* 89, no. 2: 193–197. [https://doi.org/10.1016/S0378-8741\(03\)00283-6](https://doi.org/10.1016/S0378-8741(03)00283-6).
- Acho, M. A., R. O. Olasehinde, and R. O. Arise. 2023. "Antioxidant and Antihypertensive Properties of Neem Seed Protein Hydrolysates: The Effects of Hydrolytic Enzyme Type and Peptide Size." *International Journal of Peptide Research and Therapeutics* 29, no. 3: 47. <https://doi.org/10.1007/s10989-023-10526-1>.
- Adefegha, S. A., G. Oboh, O. M. Adefegha, and T. Henle. 2016. "Alligator Pepper/Grain of Paradise (*Aframomum melegueta*) Modulates Angiotensin-I Converting Enzyme Activity, Lipid Profile and Oxidative Imbalances in a Rat Model of Hypercholesterolemia." *Pathophysiology* 23, no. 3: 191–202. <https://doi.org/10.1016/j.pathophys.2016.05.005>.
- Ademiluyi, A. O., and G. Oboh. 2012. "Phenolic-Rich Extracts From Selected Tropical Underutilized Legumes Inhibit α -Amylase, α -Glucosidase, and Angiotensin I Converting Enzyme In Vitro." *Journal of Basic and Clinical Physiology and Pharmacology* 23, no. 1: 17–25. <https://doi.org/10.1515/jbcp-2011-0005>.
- Aderinola, T. A., T. N. Fagbemi, V. N. Enujiugha, A. M. Alashi, and R. E. Aluko. 2018. "Amino Acid Composition and Antioxidant Properties of *Moringa oleifera* Seed Protein Isolate and Enzymatic Hydrolysates." *Heliyon* 4, no. 10: e00877. <https://doi.org/10.1016/j.heliyon.2018.e00877>.
- Aderinola, T. A., T. N. Fagbemi, V. N. Enujiugha, A. M. Alashi, and R. E. Aluko. 2019. "In Vitro Antihypertensive and Antioxidative Properties of Alcalase-Derived *Moringa oleifera* Seed Globulin Hydrolysate and Its Membrane Fractions." *Journal of Food Processing and Preservation* 43, no. 2: e13862. <https://doi.org/10.1111/jfpp.13862>.
- Agunu, A., B. A. Lawal, and A. A. Akande. 2017. "A Survey of Plants Used in Treatment of Hypertension and Diabetes Mellitus in Ilorin, Kwara State, Nigeria." *Nigerian Journal of Pharmaceutical Research* 13, no. 1: 27–35.
- Ahad, A., M. Raish, Y. A. B. Jordan, M. A. Alam, A. M. Al-Mohizea, and F. I. Al-Jenoobi. 2020. "Potential Pharmacodynamic and Pharmacokinetic Interactions of *Nigella sativa* and *Trigonella foenum-graecum* With Losartan in L-NAME Induced Hypertensive Rats." *Saudi Journal of Biological Sciences* 27, no. 10: 2544–2550.
- Ahmed-Farid, O., A. M. Abdelrazek, H. Elwakel, and M. M. Mohamed. 2023. "*Hordeum vulgare* Ethanolic Extract Mitigates High Salt-Induced Cerebellum Damage via Attenuation of Oxidative Stress, Neuroinflammation, and Neurochemical Alterations in Hypertensive Rats." *Metabolic Brain Disease* 38, no. 7: 2427–2442.
- Airaodion, A. I., and E. O. Ogbuagu. 2020. "Ameliorative Effect of *Parkia biglobosa* (African Locust Bean) Against Egg-Yolk Induced Hypertension." *Hypertension* 17: 18.
- Akin-Osanaiye, B., O. Adeniran, and A. Aderemi. 2015. "Auspicious Antimicrobial Potentials of Ethanol Extracts of Stem and Root of *Cnidioscolus aconitifolius*." *International Journal of Medicinal Plants and Natural Products* 1, no. 1: 15–19.
- Alachkar, A., A. Jaddouh, M. S. Elsheikh, A. R. Bilia, and F. F. Vincieri. 2011. "Traditional Medicine in Syria: Folk Medicine in Aleppo Governorate." *Natural Product Communications* 6, no. 1: 79–84. <https://doi.org/10.1177/1934578x1100600119>.
- Ali, I. H. M., Q. H. Abdullah, and O. A. M. Al-Habib. 2020. "*Nigella sativa* Aqueous and Hydro-Methanol Extracts Act as a Novel Blocker for Angiotensin II Receptor Type I." *Duhok Medical Journal* 14, no. 2: 73–85.
- AL-Jawad, F. H., H. Hashim, Z. Al-Attar, and A. H. Al-Ani. 2018. "Changing the Lipid Profile and Renal Functions by *Allium sativum*, *Nigella sativa* and *Hibiscus sabdariffa* in Essential Hypertensive Patients." *World Journal of Pharmacy and Pharmaceutical Sciences* 4: 125–134.
- Amaechina, F. C., A. P. Uchendu, C. I. Oboh, N. I. Agokei, and C. J. Eboka. 2017. "Preliminary Comparative Effect of the Aqueous Extract of *Persea americana* Seeds on the Blood Pressure of Normotensive Rabbits and Rats." *Blood Pressure* 11: 12.
- Amel, B. 2013. "Traditional Treatment of High Blood Pressure and Diabetes in Souk Ahras District." *Journal of Pharmacognosy and Phytotherapy* 5, no. 1: 12–20.
- Amir Masoud, J.-N., R. Negin, E. Melika, et al. 2024. "A Review of the Dual Role of MicroRNA-21 in Cardiovascular Diseases: Risk Factor or a Potential Therapeutic Target." *Current Molecular Pharmacology* 17: 1–18. <https://doi.org/10.2174/0118761429287057240116040703>.
- Anaka, O. N., R. I. Ozolua, and S. O. Okpo. 2009. "Effect of the Aqueous Seed Extract of *Persea americana* Mill (Lauraceae) on the Blood Pressure of Sprague-Dawley Rats." *African Journal of Pharmacy and Pharmacology* 3, no. 10: 485–490.
- Anjos, P. J., A. O. Lima, P. S. Cunha, et al. 2013. "Cardiovascular Effects Induced by Linalool in Normotensive and Hypertensive Rats." *Zeitschrift Für Naturforschung C* 68, no. 5–6: 181–190.
- Apedjinou, K. M. B., S. C. J. Sanvee, K. M. Dossou-Yovo, et al. 2023. "Cardiovascular Effect of the Fermented Seeds of *Parkia biglobosa* on Rabbits *Oryctolagus cuniculus*." *European Journal of Medicinal Plants* 34, no. 7: 47–53.
- Arise, R. O., M. A. Acho, A. A. Yekeen, et al. 2019. "Kinetics of Angiotensin-I Converting Enzyme Inhibition and Antioxidative Properties of *Azadirachta indica* Seed Protein Hydrolysates." *Heliyon* 5, no. 5: e01747. <https://doi.org/10.1016/j.heliyon.2019.e01747>.
- Asafo-Agyei, T., Y. Appau, K. B. Barimah, and A. Asase. 2023. "Medicinal Plants Used for Management of Diabetes and Hypertension in Ghana." *Heliyon* 9, no. 12: e22977. <https://doi.org/10.1016/j.heliyon.2023.e22977>.
- Atawodi, S. E.-O., O. D. Olowoniya, and M. A. Daikwo. 2014. "Ethnobotanical Survey of Some Plants Used for the Management of Hypertension in the Igala Speaking Area of Kogi State, Nigeria." *Annual Research & Review in Biology* 4, no. 24: 4535–4543. <https://doi.org/10.9734/ARRB/2014/8633>.
- Ayub, M., G. M. Shah, M. Irfan, F. Ullah, and A. Ullah. 2023. "Ethnomedicinal Study of the Flora of Sella Pattay Valley, District Malakand, Khyber Pakhtunkhwa, Pakistan." *Ethnobotany Research and Applications* 26: 1–17. <https://ethnobotanyjournal.org/index.php/era/article/view/5203>.
- Azzubaidi, M. S., N. M. Noor, and H. A. Mizher. 2015. "Antihypertensive and Antihyperlipidemic Activities of Thymoquinone in L-Name Hypertensive Rats." *Journal of Hypertension* 33: e7–e8. <https://doi.org/10.1097/01.hjh.0000469745.96124.18>.
- Badar, A., H. Kaatabi, A. Bamosa, et al. 2017. "Effect of *Nigella sativa* Supplementation Over a One-Year Period on Lipid Levels, Blood Pressure and Heart Rate in Type-2 Diabetic Patients Receiving Oral Hypoglycemic Agents: Nonrandomized Clinical Trial." *Annals of Saudi Medicine* 37, no. 1: 56–63. <https://doi.org/10.5144/0256-4947.2017.56>.
- Badavi, M., F. Z. Mehrgerdi, A. Sarkaki, M. Naseri, and M. Dianat. 2008. "Effect of Grape Seed Extract on Lead Induced Hypertension and Heart Rate in Rat." *Pakistan Journal of Biological Sciences* 11, no. 6: 882–887.
- Baharvand-Ahmadi, B., and M. Asadi-Samani. 2016. "A Mini-Review on the Most Important Effective Medicinal Plants to Treat Hypertension in Ethnobotanical Evidence of Iran." *Journal of Nephrotharmacology* 6, no. 1: 3–8.
- Balaraman, R., S. Dangwal, and M. Mohan. 2006. "Antihypertensive Effect of *Trigonella foenum-graecum*. Seeds in Experimentally Induced Hypertension in Rats." *Pharmaceutical Biology* 44, no. 8: 568–575. <https://doi.org/10.1080/13880200600896538>.
- Berzou, S., D. Krouf, N. Taleb-Dida, and A. Guenzet. 2020. "Flaxseeds (*L. usitatissimum*) Attenuates Blood Pressure, Acetylcholinesterase Activity and Oxidative Stress in Ouabain-Induced Hypertension in Normal Wistar Rats." *Nutrition & Food Science* 50, no. 4: 725–737. <https://doi.org/10.1108/NFS-05-2019-0157>.
- Bin Jordan, Y. A., A. Ahad, M. Raish, M. A. Alam, A. M. Al-Mohizea, and F. I. Al-Jenoobi. 2021. "Effects of Garden Cress, Fenugreek and Black

- Seed on the Pharmacodynamics of Metoprolol: An Herb-Drug Interaction Study in Rats With Hypertension." *Pharmaceutical Biology* 59, no. 1: 1086–1095. <https://doi.org/10.1080/13880209.2021.1961817>.
- Bryda, E. C. 2013. "The Mighty Mouse: The Impact of Rodents on Advances in Biomedical Research." *Missouri Medicine* 110, no. 3: 207–211.
- Campos, K. E. d., A. P. C. Balbi, and M. J. Q. D. F. Alves. 2009. "Diuretic and Hipotensive Activity of Aqueous Extract of Parsley Seeds (*Petroselinum sativum* Hoffm.) in Rats." *Revista Brasileira De Farmacognosia* 19: 41–45.
- Castillo-España, P., A. Cisneros-Estrada, M. Garduño-Ramírez, O. Hernández-Abreu, R. Ramírez, and S. Estrada-Soto. 2009. "Preliminary Ethnopharmacological Survey of Plants Used in Mexico for the Treatment of Hypertension." *Pharmacognosy Reviews* 3, no. 5: 41–65.
- Ceuterick, M., I. Vandebroek, and A. Pieroni. 2011. "Resilience of Andean Urban Ethnobotanics: A Comparison of Medicinal Plant Use Among Bolivian and Peruvian Migrants in the United Kingdom and in Their Countries of Origin." *Journal of Ethnopharmacology* 136, no. 1: 27–54. <https://doi.org/10.1016/j.jep.2011.03.038>.
- Chandrasekar, R., and B. Sivagami. 2021. "Edible Seeds Medicinal Value, Therapeutic Applications and Functional Properties: A Review." *International Journal of Pharmacy and Pharmaceutical Science* 13: 11–18.
- Chaudhary, S. K., P. K. Mukherjee, N. K. Nema, S. Bhadra, and B. Saha. 2012. "ACE Inhibitor Activity of Standardized Extract and Fractions of *Terminalia bellerica*." *Oriental Pharmacy and Experimental Medicine* 12: 273–277.
- Chermat, S., and R. Gharzouli. 2015. "Ethnobotanical Study of Medicinal Flora in the North East of Algeria-An Empirical Knowledge in Djebel Zdimm (Setif)." *Journal of Material Sciences and Engineering* 5: 50–59.
- Chima, U., E. Ofodile, and M. Okorie. 2013. "A Survey of Plants Used in the Treatment of Ante-Natal and Post-Natal Disorders in Nneochi Local Government Area of Abia State, Nigeria." *Greener Journal of Biological Sciences* 3, no. 6: 229–237.
- Coronado-Cáceres, L. J., B. Hernández-Ledesma, L. Mojica, et al. 2021. "Cocoa (*Theobroma cacao* L.) Seed-Derived Peptides Reduce Blood Pressure by Interacting With the Catalytic Site of the Angiotensin-Converting Enzyme." *Foods* 10, no. 10: 2340.
- Das, S., and B. De. 2013. "Evaluation Du Potentiel Inhibiteur de L'enzyme de Conversion de L'angiotensine I (ECA) Dans Certains Fruits Indigènes Sous-Utilisés Du Bengale Occidental, à L'aide D'un Modèle In Vitro." *Fruits* 68, no. 6: 499–506. <https://doi.org/10.1051/fruits/2013092>.
- Day, S. J., and D. G. Altman. 2000. "Blinding in Clinical Trials and Other Studies." *BMJ* 321, no. 7259: 504. <https://doi.org/10.1136/bmj.321.7259.504>.
- Dehkordi, F. R., and A. F. Kamkhah. 2008. "Antihypertensive Effect of *Nigella sativa* Seed Extract in Patients With Mild Hypertension." *Fundamental & Clinical Pharmacology* 22, no. 4: 447–452. <https://doi.org/10.1111/j.1472-8206.2008.00607.x>.
- Di Stasi, L. C., G. P. Oliveira, M. A. Carvalhaes, et al. 2002. "Medicinal Plants Popularly Used in the Brazilian Tropical Atlantic Forest." *Fitoterapia* 73, no. 1: 69–91. [https://doi.org/10.1016/S0367-326X\(01\)00362-8](https://doi.org/10.1016/S0367-326X(01)00362-8).
- Eddouks, M., M. Maghrani, A. Lemhadri, M. L. Ouahidi, and H. Jouad. 2002. "Ethnopharmacological Survey of Medicinal Plants Used for the Treatment of Diabetes Mellitus, Hypertension and Cardiac Diseases in the South-East Region of Morocco (Tafilalet)." *Journal of Ethnopharmacology* 82, no. 2: 97–103. [https://doi.org/10.1016/S0378-8741\(02\)00164-2](https://doi.org/10.1016/S0378-8741(02)00164-2).
- Ekpo, B. A., D. N. Bala, E. E. Essien, and S. A. Adesanya. 2008. "Ethnobotanical Survey of Akwa Ibom State of Nigeria." *Journal of Ethnopharmacology* 115, no. 3: 387–408.
- El Abbouyi, P. A., N. F. Ansari, P. S. E. Khyari, and H. Loukili. 2014. "Inventory of Medicinal Plants Prescribed by Traditional Healers in El Jadida City and Suburbs (Morocco)." *International Journal of Green Pharmacy (IJGP)* 8, no. 4: 242–251.
- Enayatfard, L., R. Mohebbati, S. Niazmand, M. Hosseini, and M. N. Shafei. 2018. "The Standardized Extract of *Nigella sativa* and Its Major Ingredient, Thymoquinone, Ameliorates Angiotensin II-Induced Hypertension in Rats." *Journal of Basic and Clinical Physiology and Pharmacology* 30, no. 1: 51–58.
- Eriz, G., V. Sanhueza, M. Roeckel, and K. Fernández. 2011. "Inhibition of the Angiotensin-Converting Enzyme by Grape Seed and Skin Proanthocyanidins Extracted From *Vitis vinifera* L. cv. País." *LWT—Food Science and Technology* 44, no. 4: 860–865.
- Esakkimuthu, S., S. Mutheeswaran, S. Arvinth, M. G. Paulraj, P. Pandikumar, and S. Ignacimuthu. 2016. "Quantitative Ethnomedicinal Survey of Medicinal Plants Given for Cardiometabolic Diseases by the Non-Institutionally Trained Siddha Practitioners of Tiruvallur District, Tamil Nadu, India." *Journal of Ethnopharmacology* 186: 329–342.
- Fang, T., J. Xiao, Y. Zhang, H. Hu, Y. Zhu, and Y. Cheng. 2021. "Combined With Interventional Therapy, Immunotherapy Can Create a New Outlook for Tumor Treatment." *Quantitative Imaging in Medicine and Surgery* 11, no. 6: 2837–2860. <https://qims.amegroups.org/article/view/65075>.
- FDA. 2021. *High Blood Pressure*. FDA. <https://www.fda.gov/consumers/womens-health-topics/high-blood-pressure..>
- Fotakis, C., D. Tsigirmani, T. Tsiaka, et al. 2016. "Metabolic and Antioxidant Profiles of Herbal Infusions and Decoctions." *Food Chemistry* 211: 963–971.
- Frampton, J. E., and D. H. Peters. 1995. "Ramipril: An Updated Review of Its Therapeutic Use in Essential Hypertension and Heart Failure." *Drugs* 49: 440–466.
- Gangopadhyay, N., K. Wynne, P. O'Connor, et al. 2016. "In Silico and In Vitro Analyses of the Angiotensin-I Converting Enzyme Inhibitory Activity of Hydrolysates Generated From Crude Barley (*Hordeum vulgare*) Protein Concentrates." *Food Chemistry* 203: 367–374.
- Gbolade, A. 2012. "Ethnobotanical Study of Plants Used in Treating Hypertension in Edo State of Nigeria." *Journal of Ethnopharmacology* 144, no. 1: 1–10.
- Ghule, A. E., S. S. Jadhav, and S. L. Bodhankar. 2012. "Trigonelline Ameliorates Diabetic Hypertensive Nephropathy by Suppression of Oxidative Stress in Kidney and Reduction in Renal Cell Apoptosis and Fibrosis in Streptozotocin Induced Neonatal Diabetic (nSTZ) Rats." *International Immunopharmacology* 14, no. 4: 740–748.
- Girardi, C., J. F. Butaud, C. Ollier, et al. 2015. "Herbal Medicine in the Marquesas Islands." *Journal of Ethnopharmacology* 161: 200–213.
- Gokhale, S., and A. N. Sahu. 2016. "Effect of Aqueous Extract of Defatted Flaxseeds (*Linum usitatissimum* Linn) on Fructose-Induced Hypertension in Rats by Inhibiting Angiotensin-Converting Enzyme (ACE)." *IOSR Journal of Pharmacy and Biological Sciences* 11, no. 6: 53–58.
- Griendling, K. K., L. L. Camargo, F. J. Rios, R. Alves-Lopes, A. C. Montezano, and R. M. Touyz. 2021. "Oxidative Stress and Hypertension." *Circulation Research* 128, no. 7: 993–1020.
- Güzel, Y., M. Güzelşemme, and M. Miski. 2015. "Ethnobotany of Medicinal Plants Used in Antakya: A Multicultural District in Hatay Province of Turkey." *Journal of Ethnopharmacology* 174: 118–152.
- Guzmán-Gerónimo, R. I., T. M. Alarcón-Zavaleta, R. M. Oliart-Ros, J. E. Meza-Alvarado, S. Herrera-Meza, and J. L. Chávez-Servia. 2017. "Blue Maize Extract Improves Blood Pressure, Lipid Profiles, and Adipose Tissue in High-Sucrose Diet-Induced Metabolic Syndrome in Rats." *Journal of Medicinal Food* 20, no. 2: 110–115.
- Hadi, A., A. Arab, H. Hajianfar, et al. 2020. "The Effect of Fenugreek Seed Supplementation on Serum Irisin Levels, Blood Pressure, and Liver and Kidney Function in Patients With Type 2 Diabetes Mellitus: A Parallel Randomized Clinical Trial." *Complementary Therapies in Medicine* 49: 102315.
- Haouari, M., S. el Makaoui, M. Jnah, and A. Haddaouy. 2018. "A Survey of Medicinal Plants Used by Herbalists in Taza (Northern Morocco)

- to Manage Various Ailments.” *Journal of Materials and Environmental Science* 9: 1875–1888. <https://doi.org/10.26872/jmes.2018.9.6.207>.
- Hassaine, S., A. Saïdi, and O. A. Belhadj. 2019. “Ethnobotanical Study of Medicinal Plants Used in the Treatment of High Blood Pressure in the Region of Tlemcen (Northwestern Algeria).” *Journal of Pharmacy & Pharmacognosy Research* 7, no. 1: 1–11.
- Hemalatha, G., K. V. Pugalandi, and R. Saravanan. 2013. “Modulatory Effect of Sesamol on DOCA-Salt-Induced Oxidative Stress in Uninephrectomized Hypertensive Rats.” *Molecular and Cellular Biochemistry* 379: 255–265.
- Hivrale, V., and P. Lomate. 2013. “Angiotensin-Converting Enzyme Inhibitory Potential of Harmaline Isolated From *Peganum harmala* L. Seeds.” *Journal of Herbs, Spices & Medicinal Plants* 19: 48–53. <https://doi.org/10.1080/10496475.2012.736925>.
- Huang, W.-H., J. Sun, H. He, H.-W. Dong, and J.-T. Li. 2011. “Antihypertensive Effect of Corn Peptides, Produced by a Continuous Production in Enzymatic Membrane Reactor, in Spontaneously Hypertensive Rats.” *Food Chemistry* 128, no. 4: 968–973. <https://doi.org/10.1016/j.foodchem.2011.03.127>.
- Imafidon, K. E., and P. Igbinauwa. 2010. “The Effect of Aqueous Extract of *P. americana* Mill.(Avocado) Seeds on Blood Pressures and Electrolytes in Hypertensive Rats.” *Biosciences, Biotechnology Research Asia* 7, no. 1: 134–136.
- Ishtiaq Ch, D. M., A. Mumtaz, T. Hussain, and A. Ghani. 2012. “Medicinal Plant Diversity in the Flora of Leepa Valley, Muzaffarabad (AJK), Pakistan.” *African Journal of Biotechnology* 11: 3087–3098. <https://doi.org/10.5897/AJB11.2711>.
- Jaarin, K., W. D. Foong, M. H. Yeoh, et al. 2015. “Mechanisms of the Antihypertensive Effects of *Nigella sativa* Oil in L-NAME-Induced Hypertensive Rats.” *Clinics* 70: 751–757.
- Javaid, B., N. Majeed, F. Deebea, et al. 2021. “Anti-Trypsin and Antihypertensive Activity of Protein Extracts From *Nigella sativa* Seeds.” *Pakistan Journal of Agricultural Sciences* 58, no. 4: 1237–1243.
- Jouad, H., M. Haloui, H. Rhiaoui, J. El Hilaly, and M. Eddouks. 2001. “Ethnobotanical Survey of Medicinal Plants Used for the Treatment of Diabetes, Cardiac and Renal Diseases in the North Centre Region of Morocco (Fez–Boulemane).” *Journal of Ethnopharmacology* 77, no. 2–3: 175–182.
- Kajal, P. B., and N. K. Ramanlal. 2023. “Spectroscopic and Chromatographic Estimation of some Sartans and Their Combinations With Thiazide Diuretics: A Review.” *Current Pharmaceutical Analysis* 19, no. 8: 610–628. <https://doi.org/10.2174/0115734129255763230927115653>.
- Kalaivani, P., R. B. Saranya, G. Ramakrishnan, et al. 2013. “Cuminum Cyminum, a Dietary Spice, Attenuates Hypertension via Endothelial Nitric Oxide Synthase and NO Pathway in Renovascular Hypertensive Rats.” *Clinical and Experimental Hypertension* 35, no. 7: 534–542.
- Kaseb, F., and A. N. Biregani. 2016. “Effects of Olive Oil and Grape Seed Oil on Lipid Profile and Blood Pressure in Patients With Hyperlipidemia: a Randomized Clinical Trial.” *Food and Nutrition Sciences* 7, no. 08: 682–688.
- Khatib, O., and M. El-Guindy. 2005. *Clinical Guidelines for the Management of Hypertension*. EMRO Technical Publications Series 29. World Health Organization.
- Khattab, M. M., and M. N. Nagi. 2007. “Thymoquinone Supplementation Attenuates Hypertension and Renal Damage in Nitric Oxide Deficient Hypertensive Rats.” *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives* 21, no. 5: 410–414.
- Kim, H., and M.-J. Song. 2011. “Analysis and Recordings of Orally Transmitted Knowledge About Medicinal Plants in the Southern Mountainous Region of Korea.” *Journal of Ethnopharmacology* 134, no. 3: 676–696.
- Komolafe, K., A. C. Akinmoladun, T. R. Komolafe, et al. 2018. “Angiotensin-1-Converting Enzyme Inhibition, Antioxidant Activity, and Modulation of Cerebral Na⁺/K⁺ ATPase by Free Phenolics of African Locust Bean (*Parkia biglobosa*).” *Health Science Reports* 1, no. 1: e17.
- Kong, X., W. Li, L.-Q. Guo, et al. 2015. “Sesamin Enhances Nitric Oxide Bioactivity in Aortas of Spontaneously Hypertensive Rats.” *Therapeutic Advances in Cardiovascular Disease* 9, no. 5: 314–324.
- Kong, X., J.-R. Yang, L.-Q. Guo, et al. 2009. “Sesamin Improves Endothelial Dysfunction in Renovascular Hypertensive Rats Fed With a High-Fat, High-Sucrose Diet.” *European Journal of Pharmacology* 620, no. 1–3: 84–89.
- KouassiN’dri, K., S. Nene-Bi, O. Zahoui, and F. Traoré. 2015. “Phytochemical and Toxicological Studies of an Extract of the Seeds of *Picralima Nitida* Stapf (Apocynaceae) and Its Pharmacological Effects on the Blood Pressure of Rabbit.” *Journal of Biology and Life Science* 6, no. 1: 1–13.
- Lagnika, L., R. Djehoue, H. Yedomonhan, and A. Sanni. 2016. “Ethnobotanical Survey of Medicinal Plants Used in Malaria Management in South Benin.” *Journal of Medicinal Plants Research* 10, no. 41: 748–756.
- Lawal, B., A. Aderibigbe, G. Essiet, and A. Essien. 2007. “Hypotensive and Antihypertensive Effects of *Aframomum melegueta* Seeds in Humans.” *International Journal of Pharmacology* 3: 311–318.
- Leporatti, M., and L. Corradi. 2001. “Ethnopharmacobotanical Remarks on the Province of Chieti Town (Abruzzo, Central Italy).” *Journal of Ethnopharmacology* 74, no. 1: 17–40.
- Li, C.-C., Y.-C. Lee, H.-Y. Lo, Y.-W. Huang, C.-Y. Hsiang, and T.-Y. Ho. 2019. “Antihypertensive Effects of Corn Silk Extract and Its Novel Bioactive Constituent in Spontaneously Hypertensive Rats: The Involvement of Angiotensin-Converting Enzyme Inhibition.” *Molecules (Basel, Switzerland)* 24, no. 10: 1886.
- Li, D., T. Zhao, X. Gong, Y. Ahemaiti, L. Wei, and S. Hu. 2024. “Sudden Hemoptysis Originating From Spontaneous Right Bronchial Artery Bleeding During Arterial Duct Closure in an Adult Patient With Chronic Myeloid Leukemia.” *Medicine Advances* 2, no. 2: 195–198. <https://doi.org/10.1002/med4.60>.
- Li, G. H., G. W. Le, H. Liu, and Y. H. Shi. 2005. “Mung-Bean Protein Hydrolysates Obtained With Alcalase Exhibit Angiotensin I-Converting Enzyme Inhibitory Activity.” *Food Science and Technology International* 11, no. 4: 281–287.
- Li, G.-H., H. Liu, Y.-H. Shi, and G.-W. Le. 2005. “Direct Spectrophotometric Measurement of Angiotensin I-Converting Enzyme Inhibitory Activity for Screening Bioactive Peptides.” *Journal of Pharmaceutical and Biomedical Analysis* 37, no. 2: 219–224.
- Li, G.-H., Y.-H. Shi, H. Liu, and G.-W. Le. 2006. “Antihypertensive Effect of Alcalase Generated Mung Bean Protein Hydrolysates in Spontaneously Hypertensive Rats.” *European Food Research and Technology* 222: 733–736.
- Li, G. H., J. Z. Wan, G. W. Le, and Y. H. Shi. 2006. “Novel Angiotensin I-Converting Enzyme Inhibitory Peptides Isolated From Alcalase Hydrolysate of Mung Bean Protein.” *Journal of Peptide Science: An Official Publication of the European Peptide Society* 12, no. 8: 509–514.
- Li, M.-Y., A. Gu, J. Li, et al. 2025. “Exploring Food and Medicine Homology: Potential Implications for Cancer Treatment Innovations.” *Acta Materia Medica* 4, no. 2: 200–206. <https://doi.org/10.15212/amm-2025-0003>.
- Li, M.-Y., Q. Zhang, J. Li, and G. Zengin. 2025. “Food and Medicine Homology in Cancer Treatment: Traditional Thoughts Collide With Scientific Evidence.” *Food & Medicine Homology* 2, no. 3: 9420120. <https://doi.org/10.26599/FMH.2025.9420120>.
- Li, W.-X., X. Kong, J.-X. Zhang, and J.-R. Yang. 2013. “Long-Term Intake of Sesamin Improves Left Ventricular Remodelling in Spontaneously Hypertensive Rats.” *Food & Function* 4, no. 3: 453–460.
- Liu, W., G. Wei, R. He, Y. Tian, A. Huang, and X. Wang. 2023. “Health-Promoting Activities of *Moringa oleifera* Lam. Seeds Protein Hydrolysates and Its Ultra-Filtered Peptide Fractions.” *Food Chemistry Advances* 2: 100324.

- Lyousse, B., M. Bakour, K. Cherkaoui-Tangi, J. El-Hilaly, and C. Hano. 2023. "Ethnobotanical Survey and Pharmacological Screening of Medicinal Plants Used as Antihypertensive in Sefrou Province (Middle-North of Morocco): Benefits and Challenges." *Frontiers in Bioscience-Scholar* 15, no. 1: 4.
- Madani, S., S. Djamel, H. Noui, and B. Amel. 2012. "Ethnobotanical Study of Therapeutic Plants Used to Treat Arterial Hypertension in the Hodna Region of Algeria." *Global Journal of Research on Medicinal Plants & Indigenous Medicine* 1, no. 9: 411–417.
- Mahomoodally, F., S. Suroowan, and U. Sreekeessoon. 2018. "Adverse Reactions of Herbal Medicine—A Quantitative Assessment of Severity in Mauritius." *Journal of Herbal Medicine* 12: 49–65.
- Mahomoodally, M. F., M. Z. Aumeeruddy, L. J. Legoabe, D. Montesano, and G. Zengin. 2022. "Nigella sativa L. and Its Active Compound Thymoquinone in the Clinical Management of Diabetes: A Systematic Review." *International Journal of Molecular Sciences* 23, no. 20: 12111.
- Malik, K., M. Ahmad, R. W. Bussmann, et al. 2018. "Ethnobotany of Anti-Hypertensive Plants Used in Northern Pakistan." *Frontiers in Pharmacology* 9: 789.
- Mansurah, A. A., N. T. Chioma, M. Ismaila, S. A. Abdulmalik, C. Williams, and A. Wudil. 2015. "Partial-Purification and Characterization of Angiotensin Converting Enzyme Inhibitory Proteins From the Leaves and Seeds of *Moringa oleifera*." *International Journal of Biochemistry Research & Review* 5, no. 1: 39–48.
- Marpaung, J., M. F. G. Siregar, M. Sitepu, and A. Bachtar. 2020. "Black Cumin (*Nigella sativa*) Effect on Blood Pressure, Mean Arterial Pressure, Proteinuria in Preeclamptic Model Rats." *International Journal of Current Pharmaceutical Research* 12: 127–133.
- Marte, F., P. Sankar, P. Patel, and M. Cassagnol. 2025. "Captopril." In *StatPearls*. StatPearls Publishing LLC.
- Mastroiaco, D., C. Kwik-Urbe, D. Grassi, et al. 2015. "Cocoa Flavanol Consumption Improves Cognitive Function, Blood Pressure Control, and Metabolic Profile in Elderly Subjects: The Cocoa, Cognition, and Aging (CoCoA) Study—A Randomized Controlled Trial." *American Journal of Clinical Nutrition* 101, no. 3: 538–548.
- Matsumura, Y., S. Kita, R. Ohgushi, and T. Okui. 2000. "Effects of Sesamin on Altered Vascular Reactivity in Aortic Rings of Deoxycorticosterone Acetate-Salt-Induced Hypertensive Rat." *Biological & Pharmaceutical Bulletin* 23, no. 9: 1041–1045. <https://doi.org/10.1248/bpb.23.1041>.
- Meresa, A., N. Fekadu, S. Degu, A. Tadele, and B. Geleta. 2017. "An Ethno Botanical Review on Medicinal Plants Used for the Management of Hypertension." *Clinical and Experimental Pharmacology* 7: 2–16.
- Mills, G., A. Badeghiesh, E. Suarathana, H. Baghlaf, and M. H. Dahan. 2020. "Polycystic Ovary Syndrome as an Independent Risk Factor for Gestational Diabetes and Hypertensive Disorders of Pregnancy: A Population-Based Study on 9.1 Million Pregnancies." *Human Reproduction* 35, no. 7: 1666–1674.
- Miyawaki, T., H. Aono, Y. Toyoda-Ono, H. Maeda, Y. Kiso, and K. Moriyama. 2009. "Antihypertensive Effects of Sesamin in Humans." *Journal of Nutritional Science and Vitaminology* 55, no. 1: 87–91.
- Moghadam, M. H., M. Imenshahidi, and S. A. Mohajeri. 2013. "Antihypertensive Effect of Celery Seed on Rat Blood Pressure in Chronic Administration." *Journal of Medicinal Food* 16, no. 6: 558–563.
- Mortensen, R. M. 2014. "Hypertension." In *Pathobiology of Human Disease*, edited by L. M. McManus, and R. N. Mitchell, 2958–2969. Academic Press.
- Mogollon, J. A., E. Bujold, S. Lemieux, et al. 2013. "Blood Pressure and Endothelial Function in Healthy, Pregnant Women After Acute and Daily Consumption of Flavanol-Rich Chocolate: A Pilot, Randomized Controlled Trial." *Nutrition Journal* 12, no. 1: 41.
- Naiho, A., and A. Ugwu. 2011. "Blood Pressure Reducing Effect of Garcinia Kola in Wistar Rats." *African Journal of Tropical Medicine and Biomedical Research* 2, no. 1: 61–107.
- Nakano, D., C. Itoh, M. Takaoka, Y. Kiso, T. Tanaka, and Y. Matsumura. 2002. "Antihypertensive Effect of Sesamin. IV. Inhibition of Vascular Superoxide Production by Sesamin." *Biological and Pharmaceutical Bulletin* 25, no. 9: 1247–1249.
- Nakano, D., D. Kurumazuka, Y. Nagai, A. Nishiyama, Y. Kiso, and Y. Matsumura. 2008. "Dietary Sesamin Suppresses Aortic NADPH Oxidase in DOCA Salt Hypertensive Rats." *Clinical & Experimental Pharmacology & Physiology* 35, no. 3: 324–326.
- Nakano, D., M. Takaoka, Y. Kiso, and Y. Matsumura. 2004. "Antihypertensive Effect of Sesamin." *Vascular Disease Prevention* 1, no. 3: 233–241.
- Nakas-Icindic, E., A. Zaciragic, A. Hadzovic, and N. Avdagic. 2004. "Endothelin in Health and Disease." *Bosnian Journal of Basic Medical Sciences* 4, no. 3: 31–34.
- Neamsuvan, O., P. Komonhiran, and K. Boonming. 2018. "Medicinal Plants Used for Hypertension Treatment by Folk Healers in Songkhla Province, Thailand." *Journal of Ethnopharmacology* 214: 58–70. <https://doi.org/10.1016/j.jep.2017.11.032>.
- Noguchi, T., K. Ikeda, Y. Sasaki, et al. 2001. "Effects of Vitamin E and Sesamin on Hypertension and Cerebral Thrombogenesis in Stroke-Prone Spontaneously Hypertensive Rats." *Hypertension Research* 24, no. 6: 735–742. <https://doi.org/10.1291/hypres.24.735>.
- Oboh, G., A. O. Ademosun, A. O. Ademiluyi, O. S. Omojokun, E. E. Nwanna, and K. O. Longe. 2014. "In Vitro Studies on the Antioxidant Property and Inhibition of α -Amylase, α -Glucosidase, and Angiotensin I-Converting Enzyme by Polyphenol-Rich Extracts From Cocoa (*Theobroma cacao*) Bean." *Pathology Research International* 2014, no. 1: 549287. <https://doi.org/10.1155/2014/549287>.
- Odenbach, J., X. Wang, S. Cooper, et al. 2011. "MMP-2 Mediates Angiotensin II-Induced Hypertension under the Transcriptional Control of MMP-7 and TACE." *Hypertension* 57, no. 1: 123–130.
- Odubango, V. O., T. A. Olasehinde, S. I. Oyeleye, G. Oboh, and A. A. Boligon. 2018. "Seed Extracts From *Myristica fragrans* (Nutmeg) and *Moringa oleifera* (Drumstick Tree) Inhibits Enzymes Relevant to Erectile Dysfunction and Metal-Induced Oxidative Damage in Rats' Penile Tissues." *Journal of Food Biochemistry* 42, no. 1: e12452.
- Ofori, D. A., B. D. Obiri, A. Gyimah, K. A. Adam, S. O. Jimoh, and R. Jamnadass. 2012. "Ethnobotany, Propagation and Conservation of Medicinal Plants in Ghana." *Ghana Journal of Forestry* 28: 29–38.
- Ognatan, K., K. Adi, C. Lamboni, et al. 2011. "Effect of Dietary Intake of Fermented Seeds of *Parkia biglobosa* (Jacq) Benth (African Locust Bean) on Hypertension in Bogou and Goumou-Kope Areas of Togo." *Tropical Journal of Pharmaceutical Research* 10, no. 5: 603–609.
- Okullo, J., F. Omujal, C. Bigirimana, et al. 2014. "Ethno-Medicinal Uses of Selected Indigenous Fruit Trees From the Lake Victoria Basin Districts in Uganda." *Journal of Medicinal Plants* 2, no. 1: 78–88.
- Olatoye, F. J., A. J. Akindele, O. E. Balogun, O. Awodele, and A. A. Adejare. 2023. "Antihypertensive Effect of Kolaviron, a Bioflavonoid From Garcinia Kola, in L-NAME Induced Hypertension in Rats." *Natural Product Communications* 18, no. 3: 1–10.
- Olçay, B., and Ş. Kültür. 2020. "Medicinal Plants Used in Traditional Treatment of Hypertension in Turkey." *International Journal of Scientific and Technology Research* 6, no. 3: 80–95.
- Olorunnisola, O., A. Adetutu, and A. Afolayan. 2015. "An Inventory of Plants Commonly Used in the Treatment of Some Disease Conditions in Ogbomoso, South West, Nigeria." *Journal of Ethnopharmacology* 161: 60–68.
- Olowokudejo, J., A. Kadiri, and V. Travi. 2008. "An Ethnobotanical Survey of Herbal Markets and Medicinal Plants in Lagos State of Nigeria." *Ethnobotanical Leaflets* 2008: 116.
- Olusola, A. O., and O. E. Ekun. 2018. "Arachis Hypogaea Seed Protein Hydrolysates Demonstrate α -Amylase-Inhibitory and Antioxidant Prop-

- erties In-Vitro.” *Journal of Emerging Trends in Engineering and Applied Sciences* 9, no. 4: 150–159.
- Omodamiro, O., O. Ajah, C. Ewa-Ibe, and M. Jimoh. 2021. “Avocado Pear (*Persea americana*) Seed Ameliorated Altration in some Hypertension Associated Biochemical Indices in Male Wistar Rats.” *Journal of Pharmaceutical Sciences and Research* 13, no. 3: 138–142.
- Oppong Bekoe, E., I. Akwo Kretchy, J. Adusei Sarkodie, et al. 2017. “Ethnomedicinal Survey of Plants Used for the Management of Hypertension Sold in the Makola Market, Accra, Ghana.” *European Journal of Medicinal Plants* 19, no. 3: 1–9. <https://doi.org/10.9734/EJMP/2017/32342>.
- Oyeleye, S. I., T. A. Olasehinde, A. O. Ademosun, A. J. Akinyemi, and G. Oboh. 2019. “Horseradish (*Moringa oleifera*) Seed and Leaf Inclusive Diets Modulates Activities of Enzymes Linked With Hypertension, and Lipid Metabolites in High-Fat Fed Rats.” *PharmaNutrition* 7: 100141.
- Park, J. B., and M. T. Velasquez. 2012. “Potential Effects of Lignan-Enriched Flaxseed Powder on Bodyweight, Visceral Fat, Lipid Profile, and Blood Pressure in Rats.” *Fitoterapia* 83, no. 5: 941–946.
- Pihlanto, A., T. Johansson, and S. Mäkinen. 2012. “Inhibition of Angiotensin I-Converting Enzyme and Lipid Peroxidation by Fermented Rapeseed and Flaxseed Meal.” *Engineering in Life Sciences* 12, no. 4: 450–456.
- Pinheiro, A. C. S., A. A. Pais, A. C. B. Tardivo, and M. Alves. 2011. “Efeito Do Extrato Aquoso de Cabelo de Milho (*Zea mays* L.) Sobre a Excreção Renal de Água e Eletrólitos e Pressão Arterial em Ratos Wistar Anestesiados.” *Revista Brasileira De Plantas Mediciniais* 13: 375–381.
- Popoola, J. O., and O. O. Obembe. 2013. “Local Knowledge, Use Pattern and Geographical Distribution of *Moringa oleifera* Lam.(Moringaceae) in Nigeria.” *Journal of Ethnopharmacology* 150, no. 2: 682–691.
- Priyono, Q. A. P., P. A. Yusniasari, M. R. T. Alifiansyah, et al. 2024. “Ethnomedical Potentials, Phytochemicals, and Medicinal Profile of *Alpinia galanga* L.: A Comprehensive Review.” *BIO Integration* 5, no. 1: 1–9. <https://doi.org/10.15212/bioi-2024-0032>.
- Qidwai, W., H. B. Hamza, R. Qureshi, and A. Gilani. 2009. “Effectiveness, Safety, and Tolerability of Powdered *Nigella sativa* (Kalonji) Seed in Capsules on Serum Lipid Levels, Blood Sugar, Blood Pressure, and Body Weight in Adults: Results of a Randomized, Double-Blind Controlled Trial.” *Journal of Alternative and Complementary Medicine* 15, no. 6: 639–644.
- Quist, E. E., R. D. Phillips, and F. K. Saalia. 2009. “Angiotensin Converting Enzyme Inhibitory Activity of Proteolytic Digests of Peanut (*Arachis hypogaea* L.) Flour.” *LWT—Food Science and Technology* 42, no. 3: 694–699.
- Ra, J.-E., S.-Y. Woo, H. Jin, et al. 2020. “Evaluation of Antihypertensive Polyphenols of Barley (*Hordeum vulgare* L.) Seedlings via Their Effects on Angiotensin-Converting Enzyme (ACE) Inhibition.” *Applied Biological Chemistry* 63: 1–9.
- Rahma, H., I. Indrawan, M. Nooryanto, and K. Keman. 2017. “Effect of a Black Cumin (*Nigella sativa*) Ethanol Extract on Placental Angiotensin II Type 1-Receptor Autoantibody (AT1-AA) Serum Levels and Endothelin-1 (ET-1) Expression in a Preeclampsia Mouse Model.” *Journal of Taibah University Medical Sciences* 12, no. 6: 528–533.
- Randriamboavonjy, J. I., G. Loirand, N. Vaillant, et al. 2016. “Cardiac Protective Effects of *Moringa oleifera* Seeds in Spontaneous Hypertensive Rats.” *American Journal of Hypertension* 29, no. 7: 873–881.
- Razmpoosh, E., S. Safi, A. Nadjarzadeh, et al. 2021. “The Effect of *Nigella sativa* Supplementation on Cardiovascular Risk Factors in Obese and Overweight Women: A Crossover, Double-Blind, Placebo-Controlled Randomized Clinical Trial.” *European Journal of Nutrition* 60: 1863–1874.
- Ried, K., and P. Fakler. 2014. “Potential of Garlic (*Allium sativum*) in Lowering High Blood Pressure: Mechanisms of Action and Clinical Relevance.” *Integrated Blood Pressure Control* 7: 71–82.
- Rizka, A., S. Setiati, A. Lydia, and E. Dewiasty. 2017. “Effect of *Nigella sativa* Seed Extract for Hypertension in Elderly: A Double-Blind, Randomized Controlled Trial.” *Acta Medica Indonesiana* 49, no. 4: 307–307.
- Rodriguez-Leyva, D., W. Weighell, A. L. Edel, et al. 2013. “Potent Antihypertensive Action of Dietary Flaxseed in Hypertensive Patients.” *Hypertension* 62, no. 6: 1081–1089.
- Sadeghi, Z., K. Kuhestani, V. Abdollahi, and A. Mahmood. 2014. “Ethnopharmacological Studies of Indigenous Medicinal Plants of Saravan Region, Baluchistan, Iran.” *Journal of Ethnopharmacology* 153, no. 1: 111–118.
- Sahu, R., and R. K. Rawal. 2024. “Modulation of the c-JNK/p38-MAPK Signaling Pathway: Investigating the Therapeutic Potential of Natural Products in Hypertension.” *Phytomedicine Plus* 4: 100564.
- Sajjad, S., B. Israr, F. Ali, and I. Pasha. 2020. “Investigating the Effect of Phytochemicals Rich Watermelon Seeds Against Hypertension.” *Pakistan Journal of Agricultural Sciences* 57, no. 4: 1157–1164.
- Saleem, Z., H. Saeed, Z. A. Khan, et al. 2019. “Association of Hypertension and Dyslipidaemia With Increasing Obesity in Patients With Type 2 Diabetes Mellitus.” *Brazilian Journal of Pharmaceutical Sciences* 55: e18136.
- Saqib, F., M. Wahid, A. A. Al-Huqail, et al. 2022. “Metabolomics Based Mechanistic Insights to Vasorelaxant and Cardioprotective Effect of Ethanolic Extract of *Citrullus lanatus* (Thunb.) Matsum. & Nakai. Seeds in Isoproterenol Induced Myocardial Infraction.” *Phytomedicine* 100: 154069.
- Sawant, S. H., and S. L. Bodhankar. 2016. “Flax Lignan Concentrate Reverses Alterations in Blood Pressure, Left Ventricular Functions, Lipid Profile and Antioxidant Status in DOCA-Salt Induced Renal Hypertension in Rats.” *Renal Failure* 38, no. 3: 411–423.
- Schön, C., P. Allegrini, K. Engelhart-Jentzsch, A. Riva, and G. Petrangolini. 2021. “Grape Seed Extract Positively Modulates Blood Pressure and Perceived Stress: A Randomized, Double-Blind, Placebo-Controlled Study in Healthy Volunteers.” *Nutrients* 13, no. 2: 654.
- Semenya, S. S., and M. J. Potgieter. 2013. “Ethnobotanical Survey of Medicinal Plants Used by Bapedi Traditional Healers to Treat Erectile Dysfunction in the Limpopo Province, South Africa.” *Journal of Medicinal Plants Research* 7, no. 7: 349–357.
- Serra, C. P., S. D. F. Côrtes, J. A. Lombardi, A. B. de Oliveira, and F. C. Braga. 2005. “Validation of a Colorimetric Assay for the In Vitro Screening of Inhibitors of Angiotensin-Converting Enzyme (ACE) From Plant Extracts.” *Phytomedicine* 12, no. 6–7: 424–432.
- Sezik, E., E. Yesilada, H. Shadidoyatov, et al. 2004. “Folk Medicine in Uzbekistan: I. Toshkent, Djizzax, and Samarqand Provinces.” *Journal of Ethnopharmacology* 92, no. 2–3: 197–207.
- Shayani Rad, M., M. Moohebati, and S. A. Mohajeri. 2022. “Effect of Celery (*Apium graveolens*) Seed Extract on Hypertension: a Randomized, Triple-Blind, Placebo-Controlled, Cross-Over, Clinical Trial.” *Phytotherapy Research* 36, no. 7: 2889–2907.
- Shoaei-Hagh, P., F. Kamelan Kafi, S. Najafi, et al. 2021. “A Randomized, Double-Blind, Placebo-Controlled, Clinical Trial to Evaluate the Benefits of *Nigella sativa* Seeds Oil in Reducing Cardiovascular Risks in Hypertensive Patients.” *Phytotherapy Research* 35, no. 8: 4388–4400.
- Siddiqui, A. H., N. Khan, S. Naseer, et al. 2022. “Anti-Hypertensive Effect of *Nigella sativa* Seeds in Patients With Hypertension.” *Pakistan Journal of Medical & Health Sciences* 16, no. 02: 86–86.
- Sium Demoz, M., K. Patrick Gachoki, K. Joseph Mungai, and B. Girmay Negusse. 2015. “Ethnobotanical Survey and Preliminary Phytochemical Studies of Plants Traditionally Used for Diabetes in Eritrea.” *European Journal of Medicinal Plants* 9, no. 2: 1–11. <https://doi.org/10.9734/EJMP/2015/18777>.

- Sivaprakasapillai, B., I. Edirisinghe, J. Randolph, F. Steinberg, and T. Kappagoda. 2009. "Effect of Grape Seed Extract on Blood Pressure in Subjects With the Metabolic Syndrome." *Metabolism* 58, no. 12: 1743–1746.
- Sudheendra, A. T., R. Shenoy, and A. D. Taranalli. 2009. "Evaluation of Saponin Rich Fraction of *Trigonella foenum graecum* for Antihypertensive Activity." *PharmacologyOnLine* 1: 1229–1233.
- Tahraoui, A., J. El-Hilaly, Z. Israili, and B. Lyoussi. 2007. "Ethnopharmacological Survey of Plants Used in the Traditional Treatment of Hypertension and Diabetes in South-Eastern Morocco (Errachidia Province)." *Journal of Ethnopharmacology* 110, no. 1: 105–117.
- Takamiya, D., H. Takahashi, A. Nakamura, Y. Xia, and T. Kuda. 2023. "Effect of *Lactiplantibacillus plantarum* Fermentation on the In-Vitro Antioxidant and Angiotensin I-Converting Enzyme-Inhibitory Properties of Turmeric, Coriander, Cumin, and Red Chili Pepper Suspensions." *Biocatalysis and Agricultural Biotechnology* 47: 102610.
- Taşar, N., Ö. Şehirli, Ö. Yiğiner, et al. 2012. "Protective Effects of *Nigella sativa* Against Hypertension-Induced Oxidative Stress and Cardiovascular Dysfunction in Rats." *Marmara Pharmaceutical Journal* 16, no. 2: 141–149.
- Tavakoli-Rouzbehani, O. M., M. Abbasnezhad, S. Kheirouri, and M. Alizadeh. 2021. "Effects of *Nigella sativa* Oil Supplementation on Selected Metabolic Parameters and Anthropometric Indices in Patients With Coronary Artery Disease: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial." *Phytotherapy Research* 35, no. 7: 3988–3999.
- Traore, M. S., A. Camara, M. A. Balde, et al. 2022. "Ethnobotanical Survey of Medicinal Plants Used to Manage Hypertension in the Republic of Guinea." *Journal of Pharmacy & Pharmacognosy Research* 10, no. 5: 938–951.
- Viernes, L., R. Garcia, M. Torio, and M. Angelia. 2012. "Antihypertensive Peptides From Vicilin, the Major Storage Protein of Mung Bean (*Vigna radiata* (L.) R. Wilczek)." *Journal of Biological Sciences* 12: 393–399.
- Vitalini, S., C. Puricelli, I. Mikerezi, and M. Iriti. 2015. "Plants, People and Traditions: Ethnobotanical Survey in the Lombard Stelvio National Park and Neighbouring Areas (Central Alps, Italy)." *Journal of Ethnopharmacology* 173: 435–458.
- Wen, S., J. Wang, Z. Huang, Y. Huang, F. Wang, and B. Zhang. 2024. "Scoring System Related to Retrograde Percutaneous Coronary Intervention for Coronary Chronic Total Occlusion." *Medicine Advances* 2, no. 1: 20–28. <https://doi.org/10.1002/med4.54>.
- WHO. 2023. *Hypertension*. WHO. <https://www.who.int/news-room/fact-sheets/detail/hypertension>.
- Wongngam, W., A. Hamzeh, F. Tian, S. Roytrakul, and J. Yongsawatdigul. 2023. "Purification and Molecular Docking of Angiotensin Converting Enzyme-Inhibitory Peptides Derived From Corn Gluten Meal Hydrolysate and From In Silico Gastrointestinal Digestion." *Process Biochemistry* 129: 113–120.
- Wu, X.-Q., X. Kong, Y. Zhou, K. Huang, J.-R. Yang, and X.-L. Li. 2012. "Sesamin Exerts Renoprotective Effects by Enhancing NO Bioactivity in Renovascular Hypertensive Rats Fed With High-Fat-Sucrose Diet." *European Journal of Pharmacology* 683, no. 1–3: 231–237.
- Yang, Y., G. Tao, P. Liu, and J. Liu. 2007. "Peptide With Angiotensin I-Converting Enzyme Inhibitory Activity From Hydrolyzed Corn Gluten Meal." *Journal of Agricultural and Food Chemistry* 55, no. 19: 7891–7895.
- Zeb, F., M. Safdar, S. Fatima, et al. 2018. "Supplementation of Garlic and Coriander Seed Powder: Impact on Body Mass Index, Lipid Profile and Blood Pressure of Hyperlipidemic Patients." *Pakistan Journal of Pharmaceutical Sciences* 31, no. 5: 1935–1941.
- Zeggwagh, N., J. Michel, and M. Eddouks. 2007. "Cardiovascular Effect of *Capparis spinosa* Aqueous Extract. Part VI: In Vitro Vasorelaxant Effect." *American Journal of Pharmacology and Toxicology* 2, no. 3: 135–139.
- Zhang, L., H. Zhang, J. Ma, Y. Wang, Z. Pei, and H. Ding. 2022. "Effects of Thymoquinone Against Angiotensin II-Induced Cardiac Damage in Apolipoprotein E-Deficient Mice." *International Journal of Molecular Medicine* 49, no. 5: 63.
- Zhang, T.-T., Q.-L. Cai, Z.-Y. Gu, and T.-Y. Song. 2024. "Novel ACE-Inhibiting Peptides From Soybean Protein Hydrolysates by Peptidomics Combined With In Silico Analysis and Their Inhibitory Effects on Proliferation and Migration of Ang II-Induced VSMCs." *Food & Medicine Homology* 1, no. 2: 9420023. <https://doi.org/10.26599/FMH.2024.9420023>.
- Zheng, H., H. Li, L. Kong, et al. 2023. "Association of Dietary Patterns With Cognitive Function in Older People: Results From the Chinese Longitudinal Healthy Longevity Survey." *Medicine Advances* 1, no. 3: 246–259. <https://doi.org/10.1002/med4.35>.
- Zheng, R.-L., J. Wang, S.-Y. Liu, Z.-P. Sun, L.-Y. Zhao, and G.-T. Chen. 2024. "Screening and Extraction Process Optimization for Potential α -Glucosidase Inhibitors From Quinoa Seeds." *Food & Medicine Homology* 1, no. 1: 9420004. <https://doi.org/10.26599/FMH.2024.9420004>.
- Zhu, N., X. Zhao, Y. Xiang, et al. 2016. "Thymoquinone Attenuates Monocrotaline-Induced Pulmonary Artery Hypertension via Inhibiting Pulmonary Arterial Remodeling in Rats." *International Journal of Cardiology* 221: 587–596.