



PHARMACOLOGICAL ACTIVITY OF *PUNICA GRANATUM* (POMEGRANATE) LEAVES ON HYPERTENSION: A REVIEW

Rushikesh P. Varankar*, Rakesh Kumar Turkar, Rajesh Mujariya, Manjeet Singh

Institute of Pharmaceutical Science & Research, Balaghat (M.P.)

Abstract

Hypertension is one of the most common cardiovascular disorders worldwide and is considered a major risk factor for stroke, myocardial infarction, heart failure, and renal diseases. Despite the availability of numerous antihypertensive agents, long-term therapy is often associated with adverse effects and poor patient compliance. Medicinal plants have gained increasing attention as alternative therapeutic agents because of their safety, affordability, and pharmacological effectiveness. *Punica granatum*, commonly known as pomegranate, is a medicinal plant widely used in traditional medicine systems for the treatment of various ailments. Although the fruit, peel, and seeds of *Punica granatum* have been extensively studied, the leaves also possess significant pharmacological activities due to the presence of bioactive phytoconstituents such as flavonoids, tannins, alkaloids, phenolic compounds, and glycosides. Recent studies have demonstrated that pomegranate leaves exhibit antioxidant, anti-inflammatory, vasodilatory, cardioprotective, and antihypertensive activities. The antihypertensive effect is mainly attributed to the reduction of oxidative stress, inhibition of angiotensin-converting enzyme, improvement of endothelial function, and modulation of lipid metabolism. This review summarizes the phytochemistry, pharmacological activities, possible mechanisms, and therapeutic potential of *Punica granatum* leaves in the management of hypertension.

Keywords

Punica granatum, Pomegranate leaves, Hypertension, Antioxidant activity, Antihypertensive activity, Medicinal plants.

Introduction

Hypertension is a chronic and progressive cardiovascular disorder characterized by a sustained elevation in arterial blood pressure above the normal physiological range (Hall *et al.*, 2012). It is considered one of the most prevalent non-communicable diseases worldwide and represents a major public health concern due to its association with increased morbidity and mortality. According to global health reports, millions of individuals suffer from hypertension, and the prevalence continues to rise because of rapid urbanization, unhealthy lifestyles, stress, aging populations, and dietary changes (Saxena *et al.*, 2018). Persistent elevation of blood pressure exerts excessive force on blood vessel walls, resulting in vascular damage and impaired

circulation. If left untreated or poorly controlled, hypertension may lead to severe complications such as stroke, myocardial infarction, congestive heart failure, atherosclerosis, kidney failure, and other cardiovascular disorders. Because hypertension often remains asymptomatic during its early stages, it is commonly referred to as a “silent killer.”

Several risk factors contribute to the development and progression of hypertension. Lifestyle-related factors such as obesity, excessive salt intake, consumption of fatty foods, smoking, alcohol intake, lack of physical activity, and chronic psychological stress significantly increase the risk of elevated blood pressure (Mayet and Hughes, 2003). In addition, genetic predisposition, advancing age, diabetes mellitus, renal diseases, endocrine disorders, and oxidative stress also play important roles in the pathogenesis of hypertension. The condition is associated with disturbances in vascular homeostasis, endothelial dysfunction, activation of the renin-angiotensin-aldosterone system (RAAS), increased sympathetic nervous activity, and excessive production of reactive oxygen species (ROS). These factors collectively contribute to vasoconstriction, inflammation, and increased peripheral vascular resistance, ultimately resulting in elevated blood pressure. Various classes of synthetic antihypertensive drugs including diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and vasodilators are widely prescribed for the management of hypertension (Oparil *et al.*, 2003). Although these drugs are effective in controlling blood pressure, their long-term use is often associated with several adverse effects such as dizziness, headache, fatigue, electrolyte imbalance, cough, hypotension, gastrointestinal disturbances, renal dysfunction, and metabolic abnormalities. In some cases, patients may also experience poor compliance due to the requirement for prolonged therapy and multiple drug administration. These limitations have encouraged researchers to explore safer and more effective alternative therapies from natural sources.

Medicinal plants have been utilized since ancient times in traditional systems of medicine for the prevention and treatment of various diseases, including cardiovascular disorders (Rastogi *et al.*, 2016). Herbal medicines are widely accepted because of their therapeutic effectiveness, lower incidence of adverse effects, affordability, and easy availability. Numerous medicinal plants contain bioactive phytoconstituents such as flavonoids, alkaloids, tannins, glycosides, terpenoids, and phenolic compounds that exhibit antioxidant, anti-inflammatory, cardioprotective, vasodilatory, and antihypertensive properties (Shaito *et al.*, 2020). In recent years, scientific interest in herbal antihypertensive agents has increased significantly due to their potential to manage hypertension through multiple mechanisms with improved safety profiles (Anwar *et al.*, 2016).

Among the various medicinal plants, *Punica granatum*, commonly known as pomegranate, has gained considerable attention for its diverse pharmacological properties (Jacinto, 2018). *Punica granatum* belongs to the family Lythraceae and is widely cultivated in tropical and subtropical regions throughout the world (Saeed *et al.*, 2018). Different parts of the plant including fruits, peels, seeds, bark, flowers, and leaves have been extensively used in traditional medicine for the treatment of several ailments such as diarrhea, dysentery, diabetes, inflammation, infections, and cardiovascular diseases (Puneeth and Chandra, 2020). The plant is rich in valuable phytoconstituents including flavonoids, polyphenols, tannins, alkaloids, anthocyanins, glycosides, ellagic acid, gallic acid, and punicalagin, which are responsible for its therapeutic activities.

Although the fruit and peel of *Punica granatum* have been widely investigated for their medicinal properties, the leaves also possess significant pharmacological potential. Pomegranate leaves contain a variety of phenolic compounds and antioxidants that help reduce oxidative stress and inflammation, both of which are major contributors to hypertension and cardiovascular damage (Holland and Bar-Ya'akov, 2018). Experimental studies have demonstrated that leaf extracts exhibit antioxidant, anti-inflammatory, antimicrobial, antidiabetic, cardioprotective, hypolipidemic, and vasodilatory activities. The antihypertensive activity of *Punica granatum* leaves is mainly attributed to their ability to scavenge free radicals, improve endothelial function, enhance nitric oxide production, inhibit angiotensin-converting

enzyme activity, and reduce lipid peroxidation. These mechanisms collectively contribute to lowering blood pressure and protecting cardiovascular tissues from damage.

Therefore, the present review aims to provide a comprehensive overview of the pharmacological activity of *Punica granatum* leaves in the management of hypertension. The review discusses the phytochemical constituents, pharmacological properties, possible mechanisms of antihypertensive action, and therapeutic significance of pomegranate leaves as a promising natural remedy for cardiovascular disorders.

Phytochemical Constituents of *Punica granatum* Leaves

Punica granatum leaves contain numerous bioactive compounds responsible for their therapeutic activities. The major phytoconstituents present in the leaves include flavonoids, tannins, polyphenols, alkaloids, glycosides, saponins, terpenoids, and other phenolic compounds. Important phytochemicals such as ellagic acid, gallic acid, and punicalagin are also found in the leaves (Ranjha *et al.*, 2023). These constituents possess strong antioxidant and free radical scavenging properties that contribute significantly to cardioprotective and antihypertensive activities.

These phytochemicals possess strong antioxidant and free radical scavenging properties that contribute to cardioprotective and antihypertensive activities (Machado *et al.*, 2023).

Hypertension

Hypertension is a chronic cardiovascular disorder characterized by a persistent elevation in arterial blood pressure beyond the normal physiological limit. Clinically, hypertension is generally defined as a sustained systolic blood pressure greater than 140 mmHg and diastolic blood pressure greater than 90 mmHg (Poulter *et al.*, 2015). It is considered one of the most important risk factors for cardiovascular diseases and is associated with high rates of morbidity and mortality worldwide. Hypertension affects millions of people globally and contributes significantly to serious complications such as stroke, myocardial infarction, heart failure, kidney damage, peripheral vascular disease, and visual impairment (Hall and Hall, 2018). The condition is often asymptomatic during its early stages and therefore is commonly referred to as a “silent killer.”

Hypertension is broadly classified into two major categories: primary (essential) hypertension and secondary hypertension. Primary hypertension accounts for nearly 90–95% of all hypertension cases and develops gradually without any identifiable underlying cause (Augustyniak *et al.*, 2002). It is mainly associated with genetic, environmental, and lifestyle-related factors. Secondary hypertension, on the other hand, occurs due to identifiable medical conditions such as renal diseases, endocrine disorders, cardiovascular abnormalities, or drug-induced causes. Early diagnosis and proper management of hypertension are essential to prevent long-term cardiovascular complications and improve quality of life (Fujita, 2014).

Causes of Hypertension

The development of hypertension is influenced by multiple genetic, physiological, environmental, and lifestyle-related factors (Kokubo *et al.*, 2019). Genetic predisposition plays an important role, as individuals with a family history of hypertension are at greater risk of developing the condition. Obesity and overweight are major contributing factors because excessive body fat increases cardiac workload and peripheral vascular resistance (Korner, 2007). Dietary habits such as excessive intake of sodium-rich foods, high-fat diets, and low consumption of fruits and vegetables are also strongly associated with elevated blood pressure.

Psychological stress, anxiety, and emotional disturbances stimulate sympathetic nervous system activity, leading to increased secretion of stress hormones such as adrenaline and cortisol, which elevate blood pressure. Lifestyle factors including smoking, alcohol consumption, physical inactivity, and sedentary habits further increase the risk of hypertension by damaging blood vessels and impairing cardiovascular function (Fatma *et al.*, 2024). Advancing age is another important factor, as aging is associated with reduced elasticity of blood vessels and increased arterial stiffness.

Several pathological conditions also contribute to hypertension, including diabetes mellitus, chronic kidney disease, thyroid dysfunction, adrenal gland disorders, and hormonal imbalance. Excessive production of

reactive oxygen species and oxidative stress may damage vascular endothelial cells, resulting in impaired vasodilation and increased vascular resistance (Zheng *et al.*, 2014). In addition, certain medications such as corticosteroids, oral contraceptives, and nonsteroidal anti-inflammatory drugs may induce secondary hypertension in susceptible individuals.

Pathophysiology of Hypertension

The pathophysiology of hypertension is complex and involves the interaction of multiple physiological mechanisms that regulate vascular tone and blood pressure (Flynn and Bakris, 2014). One of the major factors responsible for hypertension is increased peripheral vascular resistance due to narrowing or constriction of blood vessels. Endothelial dysfunction plays a critical role in this process. Under normal physiological conditions, endothelial cells produce nitric oxide, a potent vasodilator that helps maintain vascular relaxation and blood flow. However, in hypertension, endothelial dysfunction reduces nitric oxide availability, resulting in vasoconstriction and elevated blood pressure.

Oxidative stress is another major contributor to the development of hypertension (Guzik and Touyz, 2017). Excessive generation of reactive oxygen species damages vascular tissues and promotes inflammation, lipid peroxidation, and endothelial injury. Reactive oxygen species also inactivate nitric oxide, further impairing vasodilation. Chronic inflammation within blood vessels contributes to vascular remodeling and stiffness, which increase peripheral resistance and blood pressure.

Activation of the renin-angiotensin-aldosterone system (RAAS) also plays an important role in hypertension (Yuan *et al.*, 2015). Renin released from the kidneys converts angiotensinogen into angiotensin I, which is further converted into angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II is a powerful vasoconstrictor that increases blood pressure by narrowing blood vessels and stimulating aldosterone secretion. Aldosterone promotes sodium and water retention, resulting in increased blood volume and elevated blood pressure. Enhanced sympathetic nervous system activity additionally contributes to increased heart rate, vasoconstriction, and cardiac output. Collectively, these mechanisms lead to sustained elevation of arterial blood pressure and progressive cardiovascular damage.

Pharmacological Activities of *Punica granatum* Leaves

Punica granatum leaves possess a wide range of pharmacological activities due to the presence of various bioactive phytoconstituents such as flavonoids, polyphenols, tannins, alkaloids, glycosides, terpenoids, and phenolic compounds (Machado *et al.*, 2023). These phytochemicals exhibit significant therapeutic effects and contribute to the medicinal value of the plant. Among the important pharmacological activities of *Punica granatum* leaves are antioxidant, anti-inflammatory, cardioprotective, vasodilatory, and antihypertensive activities, which are particularly beneficial in the management of cardiovascular diseases and hypertension.

Antioxidant Activity

Punica granatum leaves exhibit strong antioxidant activity mainly due to the presence of polyphenols, flavonoids, tannins, and phenolic acids such as gallic acid and ellagic acid (Fellah *et al.*, 2018). These compounds possess free radical scavenging properties and protect cells from oxidative damage caused by reactive oxygen species. Oxidative stress plays a major role in the pathogenesis of hypertension and cardiovascular disorders by damaging endothelial cells and promoting inflammation. Antioxidants present in pomegranate leaves neutralize reactive oxygen species, reduce lipid peroxidation, and improve antioxidant defense systems within the body. This protective effect helps maintain vascular integrity and reduces the risk of hypertension-related complications.

Anti-inflammatory Activity

The leaves of *Punica granatum* possess significant anti-inflammatory properties that contribute to cardiovascular protection. Inflammation is closely associated with the progression of hypertension and vascular dysfunction. Bioactive compounds present in pomegranate leaves inhibit the production and release of inflammatory mediators such as prostaglandins, cytokines, tumor necrosis factor-alpha, and interleukins (Bekir *et al.*, 2013). The suppression of inflammatory pathways helps reduce vascular inflammation and

endothelial damage. In addition, flavonoids and tannins present in the leaves stabilize cell membranes and inhibit inflammatory enzyme activity, thereby protecting blood vessels from injury and reducing cardiovascular risk.

Cardioprotective Activity

Punica granatum leaves exhibit cardioprotective activity by protecting the heart and blood vessels against oxidative and inflammatory damage (Niewiadomska *et al.*, 2023). The antioxidant compounds present in the leaves reduce lipid peroxidation and prevent oxidative stress-induced injury to cardiac tissues. The leaves also improve endothelial function, enhance blood circulation, and maintain vascular elasticity. Reduction in serum cholesterol and triglyceride levels further contributes to cardiovascular protection by preventing atherosclerosis and plaque formation in blood vessels. Experimental studies have shown that pomegranate leaf extracts can improve cardiac function and reduce the risk of cardiovascular diseases associated with hypertension.

Vasodilatory Activity

The vasodilatory activity of *Punica granatum* leaves plays a crucial role in lowering blood pressure. Bioactive constituents present in the leaves stimulate the production and availability of nitric oxide, which is an important vasodilator produced by endothelial cells. Nitric oxide relaxes vascular smooth muscles and promotes widening of blood vessels, thereby improving blood flow and reducing vascular resistance (Wang *et al.*, 2018). The vasodilatory effect helps decrease systolic and diastolic blood pressure and reduces the workload on the heart. This mechanism significantly contributes to the antihypertensive potential of pomegranate leaves.

Antihypertensive Activity

Several experimental and pharmacological studies have demonstrated the antihypertensive activity of *Punica granatum* leaf extracts (Monir *et al.*, 2020). Ethanolic and hydroalcoholic extracts of the leaves have shown significant reduction in both systolic and diastolic blood pressure in experimental animal models. The antihypertensive effect is mainly attributed to antioxidant activity, vasodilation, inhibition of angiotensin-converting enzyme activity, and improvement of endothelial function. Reduction of oxidative stress and vascular inflammation further contributes to lowering blood pressure and preventing cardiovascular complications. In addition, the hypolipidemic effect of pomegranate leaves reduces serum lipid levels and improves overall cardiovascular health, making the plant a promising natural remedy for hypertension management.

Mechanism of Antihypertensive Activity

The antihypertensive activity of *Punica granatum* leaves occurs through multiple pharmacological mechanisms that collectively contribute to blood pressure reduction and cardiovascular protection. The presence of bioactive compounds such as flavonoids, tannins, polyphenols, and phenolic acids plays an important role in modulating oxidative stress, vascular tone, endothelial function, and lipid metabolism. These mechanisms help improve cardiovascular function and prevent the progression of hypertension-related complications.

Antioxidant Mechanism

One of the major mechanisms responsible for the antihypertensive activity of *Punica granatum* leaves is their antioxidant property. Flavonoids and phenolic compounds present in the leaves scavenge reactive oxygen species and reduce oxidative stress within vascular tissues (Mayasankaravalli *et al.*, 2020). Excessive oxidative stress damages endothelial cells and decreases nitric oxide availability, leading to vasoconstriction and elevated blood pressure. By neutralizing free radicals and improving antioxidant defense systems, pomegranate leaves help restore endothelial function and promote vascular relaxation, thereby lowering blood pressure.

ACE Inhibition

Punica granatum leaf extracts may exert antihypertensive effects through inhibition of angiotensin-converting enzyme (ACE) (Ali *et al.*, 2023). ACE is responsible for converting angiotensin I into angiotensin II, a potent vasoconstrictor that increases blood pressure and stimulates aldosterone secretion. Inhibition of ACE reduces the formation of angiotensin II, leading to relaxation of blood vessels and decreased sodium and water retention. As a result, blood pressure is effectively lowered and cardiovascular stress is reduced.

Nitric Oxide Enhancement

Nitric oxide plays an essential role in maintaining vascular homeostasis and regulating blood vessel relaxation. Bioactive constituents of *Punica granatum* leaves enhance nitric oxide production and availability within endothelial cells. Increased nitric oxide levels promote vasodilation by relaxing vascular smooth muscles and improving blood circulation. This mechanism decreases peripheral vascular resistance and contributes significantly to blood pressure reduction. Enhanced nitric oxide activity also protects blood vessels from endothelial dysfunction and oxidative injury.

Lipid Lowering Effect

Punica granatum leaves also exhibit hypolipidemic activity, which contributes indirectly to their antihypertensive effects (El-Hadary *et al.*, 2019). Elevated serum cholesterol and triglyceride levels are major risk factors for atherosclerosis and cardiovascular diseases. The leaves help reduce total cholesterol, low-density lipoprotein (LDL), and triglyceride levels while improving high-density lipoprotein (HDL) levels. Reduction in lipid accumulation prevents narrowing and hardening of blood vessels, improves blood circulation, and decreases cardiovascular risk associated with hypertension.

Advantages of Herbal Antihypertensive Therapy

Herbal antihypertensive therapy has gained considerable importance in recent years because of its therapeutic effectiveness, better safety profile, and reduced incidence of adverse effects compared to conventional synthetic medications (Shabana *et al.*, 2024). Synthetic antihypertensive drugs, although effective in controlling blood pressure, are often associated with several side effects such as dizziness, fatigue, electrolyte imbalance, cough, gastrointestinal disturbances, renal dysfunction, and metabolic complications during long-term use. In contrast, herbal medicines are generally considered safer and better tolerated by patients, making them more suitable for prolonged therapy in chronic conditions like hypertension.

One of the major advantages of herbal antihypertensive therapy is the presence of multiple bioactive phytoconstituents that act through different mechanisms to control blood pressure and improve cardiovascular health (Jough *et al.*, 2021). Medicinal plants contain compounds such as flavonoids, alkaloids, tannins, glycosides, terpenoids, and phenolic compounds that exhibit antioxidant, anti-inflammatory, vasodilatory, cardioprotective, and hypolipidemic activities. These combined therapeutic actions not only help reduce blood pressure but also protect against complications associated with hypertension, including atherosclerosis, endothelial dysfunction, oxidative stress, and cardiac damage.

Herbal medicines are also considered cost-effective and easily accessible, especially in developing countries where a large proportion of the population depends on traditional systems of medicine for primary healthcare. The natural origin and wide availability of medicinal plants make herbal therapy an economical alternative to expensive synthetic drugs. Furthermore, herbal remedies are often culturally accepted and have been used traditionally for centuries, which enhances patient trust and compliance during treatment.

Another important advantage of herbal antihypertensive therapy is improved patient compliance due to fewer side effects and better tolerability. Many medicinal plants provide gradual and sustained therapeutic effects without causing significant toxicity. Herbal formulations may also reduce the need for multiple drug therapy because of their multifunctional pharmacological properties (Lachovicz *et al.*, 2025). In addition, several medicinal plants exhibit synergistic effects when used in combination with conventional antihypertensive drugs, thereby enhancing therapeutic outcomes and reducing required dosages of synthetic medications.

Medicinal plants such as *Punica granatum* possess potent antioxidant and free radical scavenging properties that help reduce oxidative stress, which is one of the major contributors to hypertension and cardiovascular disorders (Mokgalaboni *et al.*, 2023). The anti-inflammatory and lipid-lowering effects of herbal medicines further contribute to vascular protection and improved endothelial function. Therefore, herbal antihypertensive therapy represents a promising and holistic approach for the prevention and management of hypertension and associated cardiovascular diseases.

Limitations and Future Perspectives

Despite the promising pharmacological and antihypertensive activities of *Punica granatum* leaves, several limitations still exist regarding their therapeutic application and scientific validation. Most of the available studies on the antihypertensive activity of pomegranate leaves have been conducted using experimental animal models or in vitro methods, while well-designed clinical studies in human subjects remain limited. Therefore, additional clinical investigations are necessary to establish the efficacy, safety, and therapeutic reliability of *Punica granatum* leaves in the management of hypertension in humans.

Another major limitation is the lack of standardization of herbal extracts and formulations. Variations in geographical location, climatic conditions, harvesting time, extraction methods, and storage conditions may influence the phytochemical composition and therapeutic potency of the plant. As a result, achieving consistent quality, efficacy, and reproducibility in herbal preparations becomes challenging. Standardization of extraction procedures and identification of active phytoconstituents are essential for the development of reliable herbal antihypertensive formulations.

Although *Punica granatum* leaves contain numerous bioactive compounds, the exact mechanisms responsible for their antihypertensive activity have not been fully elucidated. Further research is required to identify the specific phytochemicals involved and understand their molecular targets and pharmacological pathways (Benchagra *et al.*, 2021). Detailed investigations on mechanisms such as angiotensin-converting enzyme inhibition, nitric oxide modulation, antioxidant activity, endothelial protection, and calcium channel regulation may provide better insight into their therapeutic potential.

Toxicological and safety evaluations are also necessary before the widespread therapeutic use of *Punica granatum* leaf extracts. Long-term toxicity studies, dose optimization, pharmacokinetic analysis, and herb-drug interaction studies should be conducted to ensure safe clinical application. Since many hypertensive patients are already receiving conventional medications, understanding possible interactions between herbal products and synthetic drugs is essential to avoid adverse effects or therapeutic failure (Akbari *et al.*, 2022).

Future research should focus on advanced pharmaceutical approaches for the formulation and delivery of *Punica granatum* leaf extracts. Novel drug delivery systems such as nanoparticles, liposomes, phytosomes, and nanoemulsions may improve bioavailability, stability, and therapeutic efficacy of the active constituents. In addition, large-scale randomized clinical trials are needed to validate the antihypertensive efficacy and long-term safety of pomegranate leaf preparations. Exploration of synergistic combinations of *Punica granatum* leaves with other medicinal plants may also provide enhanced therapeutic benefits in cardiovascular disease management.

Conclusion

Punica granatum leaves possess significant pharmacological activities including antioxidant, anti-inflammatory, cardioprotective, vasodilatory, and antihypertensive effects. The presence of flavonoids, tannins, and phenolic compounds contributes to their therapeutic potential in hypertension management. Experimental studies indicate that pomegranate leaves can reduce oxidative stress, improve endothelial function, and lower blood pressure through multiple mechanisms. Therefore, *Punica granatum* leaves may serve as a promising natural source for the development of herbal antihypertensive formulations. However, further clinical and pharmacological studies are necessary to establish their efficacy and safety in humans.

References

- Hall JE, Granger JP, do Carmo JM, da Silva AA, Dubinion J, George E, Hamza S, Speed J, Hall ME. Hypertension: physiology and pathophysiology. *Comprehensive Physiology*. 2012 Oct 1;2(4):2393-442.
- Saxena T, Ali AO, Saxena M. Pathophysiology of essential hypertension: an update. *Expert review of cardiovascular therapy*. 2018 Dec 2;16(12):879-87.
- Mayet J, Hughes A. Cardiac and vascular pathophysiology in hypertension. *Heart*. 2003 Sep 1;89(9):1104-9.
- Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. *Annals of internal medicine*. 2003 Nov 4;139(9):761-76.
- Rastogi S, Pandey MM, Rawat AK. Traditional herbs: a remedy for cardiovascular disorders. *Phytomedicine*. 2016 Oct 15;23(11):1082-9.
- Shaito A, Thuan DT, Phu HT, Nguyen TH, Hasan H, Halabi S, Abdelhady S, Nasrallah GK, Eid AH, Pintus G. Herbal medicine for cardiovascular diseases: efficacy, mechanisms, and safety. *Frontiers in pharmacology*. 2020 Apr 7;11:422.
- Anwar MA, Al Disi SS, Eid AH. Anti-hypertensive herbs and their mechanisms of action: part II. *Frontiers in pharmacology*. 2016 Mar 8;7:172328.
- Jacinto AM. Review of the phytochemical, pharmacological and toxicological properties of *Punica granatum L.*(Lythraceae) Plant. *International Journal of Food Science and Agriculture*. 2018 Mar 29;2(3).
- Saeed M, Naveed M, BiBi J, Kamboh AA, Arain MA, Shah QA, Alagawany M, El-Hack ME, Abdel-Latif MA, Yattoo MI, Tiwari R. The promising pharmacological effects and therapeutic/medicinal applications of *Punica granatum L.*(Pomegranate) as a functional food in humans and animals. *Recent patents on inflammation & allergy drug discovery*. 2018 May 1;12(1):24-38.
- Puneeth HR, Chandra SS. A review on potential therapeutic properties of Pomegranate (*Punica granatum L.*). *Plant Sci. Today*. 2020 Jan 1;7(1):9-16.
- Holland D, Bar-Ya'akov I. Pomegranate (*Punica granatum L.*) breeding. In *Advances in Plant Breeding Strategies: Fruits: Volume 3* 2018 Jul 19 (pp. 601-647). Cham: Springer International Publishing.
- Ranjha MM, Shafique B, Wang L, Irfan S, Safdar MN, Murtaza MA, Nadeem M, Mahmood S, Mueen-ud-Din G, Nadeem HR. A comprehensive review on phytochemistry, bioactivity and medicinal value of bioactive compounds of pomegranate (*Punica granatum*). *Advances in Traditional Medicine*. 2023 Mar;23(1):37-57.
- Machado JC, Ferreira MR, Soares LA. *Punica granatum* leaves as a source of active compounds: A review of biological activities, bioactive compounds, food, and technological application. *Food bioscience*. 2023 Feb 1;51:102220.
- Poulter NR, Prabhakaran D & Caulfield M. Hypertension. *Lancet* 386, 801–812 (2015).
- Hall ME & Hall JE. Pathogenesis of Hypertension. *Hypertension: A Companion to Braunwald's Heart Disease* 33–51 (2018).
- Augustyniak RA, Tuncel M, Zhang W, Toto RD & Victor RG Sympathetic overactivity as a cause of hypertension in chronic renal failure. *J. Hypertens* 20, 3–9 (2002).
- Fujita T. Mechanism of Salt-Sensitive Hypertension: Focus on Adrenal and Sympathetic Nervous Systems. *J. Am. Soc. Nephrol* 25, 1148–1155 (2014).

- Kokubo Y, Padmanabhan S, Iwashima Y, Yamagishi K, Goto A. Gene and environmental interactions according to the components of lifestyle modifications in hypertension guidelines. *Environmental Health and Preventive Medicine*. 2019 Dec;24(1):19.
- Korner PI. *Essential hypertension and its causes: neural and non-neural mechanisms*. Oxford University Press; 2007 May 11.
- Fatma H, Srivastava P, Johri P, Rajput MS, Syed S, Trivedi M. Hypertension and Cardiovascular Problems-An Outlook Associated with Adolescents' Lifestyles. In *Lifestyle Diseases in Adolescents: Diseases, Disorders, and Preventive Measures* 2024 Jul 23 (pp. 88-107).
- Zheng Z, Li Y, Cai Y. Estimation of hypertension risk from lifestyle factors and health profile: a case study. *The Scientific World Journal*. 2014;2014(1):761486.
- Flynn C, Bakris GL. Pathophysiology of hypertension. *Metabolism of Human Diseases: Organ Physiology and Pathophysiology*. 2014 Jun 2:339.
- Guzik TJ, Touyz RM. Oxidative stress, inflammation, and vascular aging in hypertension. *Hypertension*. 2017 Oct;70(4):660-7.
- Yuan YM, Luo L, Guo Z, Yang M, Ye RS, Luo C. Activation of renin–angiotensin–aldosterone system (RAAS) in the lung of smoking-induced pulmonary arterial hypertension (PAH) rats. *Journal of the Renin-Angiotensin-Aldosterone System*. 2015 Jun;16(2):249-53.
- Machado JC, Ferreira MR, Soares LA. *Punica granatum* leaves as a source of active compounds: A review of biological activities, bioactive compounds, food, and technological application. *Food bioscience*. 2023 Feb 1;51:102220.
- Fellah B, Bannour M, Rocchetti G, Lucini L, Ferchichi A. Phenolic profiling and antioxidant capacity in flowers, leaves and peels of Tunisian cultivars of *Punica granatum* L. *Journal of food science and technology*. 2018 Sep;55(9):3606-15.
- Bekir J, Mars M, Souchard JP, Bouajila J. Assessment of antioxidant, anti-inflammatory, anti-cholinesterase and cytotoxic activities of pomegranate (*Punica granatum*) leaves. *Food and chemical toxicology*. 2013 May 1;55:470-5.
- Niewiadomska J, Kasztura M, Janus I, Chelmecka E, Stygar DM, Frydrychowski P, Wojdyło A, Noszczyk-Nowak A. *Punica granatum* L. Extract shows cardioprotective effects measured by oxidative stress markers and biomarkers of heart failure in an animal model of metabolic syndrome. *Antioxidants*. 2023 May 25;12(6):1152.
- Wang D, Ozen C, Abu-Reidah IM, Chigurupati S, Patra JK, Horbanczuk JO, Jozwik A, Tzvetkov NT, Uhrin P, Atanasov AG. Vasculoprotective effects of pomegranate (*Punica granatum* L.). *Frontiers in pharmacology*. 2018 May 24;9:544.
- Monir R, Elkarim AS, Shalaby MF, Zaki AA, Shabana S. Anti-Hypertensive Activity of *Punica granatum* peels Ethyl Acetate Extract on Fludrocortisone Induced Hypertension in Wistar Rats. *Pharmacognosy Journal*. 2020 Sep 1;12(5).
- Mayasankaravalli C, Deepika K, Lydia DE, Agada R, Thagriki D, Govindasamy C, Chinnadurai V, Gatar OM, Khusro A, Kim YO, Kim HJ. Profiling the phyto-constituents of *Punica granatum* fruits peel extract and accessing its in-vitro antioxidant, anti-diabetic, anti-obesity, and angiotensin-converting enzyme inhibitory properties. *Saudi Journal of Biological Sciences*. 2020 Dec 1;27(12):3228-34.
- Ali MY, Jannat S, Chang MS. Discovery of potent angiotensin-converting enzyme inhibitors in pomegranate as a treatment for hypertension. *Journal of Agricultural and Food Chemistry*. 2023 Jun 29;71(30):11476-90.

- El-Hadary AE, Ramadan MF. Phenolic profiles, antihyperglycemic, antihyperlipidemic, and antioxidant properties of pomegranate (*Punica granatum*) peel extract. *Journal of food biochemistry*. 2019 Apr;43(4):e12803.
- Shabana S, Shalaby MF, Zaki AA, Elhaggar RS. Pharmacological activity of Pomegranate peels ethyl acetate extract: antihypertensive potential. *Journal of Pharmaceutical Sciences and Drug Manufacturing-Misr University for Science and Technology*. 2024 Jun 1;1(2):93-7.
- Jough, S.S., Saini, R.K. and Parveen, A., 2021. A Comprehensive Study on Anti-hypertensive properties of *Punica granatum* (Pomegranate), *Cynara scolymus* (Artichoke), *Coscinium fenestratum* (Yellow vine) in Phytopharmacological, Molecular Biology Researches. *Asian Journal of Research in Pharmaceutical Science*, 11(2), pp.126-132.
- Lachovicz R, Ferro-Lebres V, Almeida-de-Souza J, Pereira JA. Efficacy of Olive Leaf Extract in Improving Blood Pressure in Pre-Hypertensive and Hypertensive Individuals: A Systematic Review and Meta-Analysis. *Phytotherapy Research*. 2025;39(6):2863-74.
- Mokgalaboni K, Dlamini S, Phoswa WN, Modjadji P, Lebelo SL. The impact of *Punica granatum* Linn and its derivatives on oxidative stress, inflammation, and endothelial function in diabetes mellitus: Evidence from preclinical and clinical studies. *Antioxidants*. 2023 Aug 4;12(8):1566.
- Benchagra L, Berrougui H, Islam MO, Ramchoun M, Boulbaroud S, Hajjaji A, Fulop T, Ferretti G, Khalil A. Antioxidant effect of moroccan pomegranate (*Punica granatum* L. sefri variety) extracts rich in punicalagin against the oxidative stress process. *Foods*. 2021 Sep 18;10(9):2219.
- Akbari B, Baghaei-Yazdi N, Bahmaie M, Mahdavi Abhari F. The role of plant-derived natural antioxidants in reduction of oxidative stress. *BioFactors*. 2022 May;48(3):611-33.

