Psidium Guajava Linn: A Revised Study of the Folklore Activity and Therapeutic Action Emphasizing on Its Anti-Hypertensive Potentiality

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ABSTRACT

The creation of new bioactive compounds derived from ethno-medicine is becoming increasingly popular. Historically, different parts of guava (Psidium guajava Linn.) are used to treat a wide range of diseases. Extensive in vitro and in vivo pharmacological research has demonstrated the potential of leaf extracts for the co-treatment of numerous high-prevalence diseases, supporting the use of traditional medicine in the treatment of conditions such as diabetes, cardiovascular disease, cancer, and parasitic infections. Additionally, the bioactive composition of the leaves and several phytochemical subclasses and compounds have been linked to the biological activity of the plant. The phenolic compounds in guava leaf are associated with glucose regulation. An attempt has been made with an objective to compile and enlist the information from in vitro and in vivo studies reported on guava leaves over the past decade in order to inform future research into the findings of bioactive components.

Keywords: *Psidium guajava*, antihypertensive activity, pharmacology, phytochemical.

1. INTRODUCTION

Plant-based therapeutic agents have now been evolved as influential alternatives in place of conventional synthetic drugs for the management and treatment of wide range of aliments. Market share of phytomedicines/ phytochemical products is go on increasing day by day with investigation on novel therapeutic approaches for their improved delivery. whereas phytochemical constituents from many plant parts have been isolated and being

used in several formulation developments, uncountable number of plants (having folkloric therapeutic history) are still remain unexplored.

At present, growing number of countries throughout the globe are witnessing an increased prevalence of hypertension (elevated blood pressure), which has also been a significant cause of cardiovascular disease (CVD) and associated medical complications [1]. Research has shown that the renin-angiotensin system is responsible for a significant portion of the management of blood pressure, especially in the elderly [2]. If the angiotensin-converting enzyme (ACE) is present and functional, the angiotensin I and the vasodilator bradykinin will most likely be converted to angiotensin II, which will then be released. ACE antagonists, thus are the type of drugs that are primarily employed to lower blood pressure levels by blocking the mechanism. Hypertension has also been found as one of the prime culprits for the development and progression of type 2 diabetes (Type II DM). In turn, Type II DM is further related to obesity, renal disorder and several other health problems. Now, several studies have also claimed a strong relationship between high blood pressure and an increased risk of getting gout [3, 4]. An increase in uric acid levels, in conjunction with obesity, are the risk factors that may contribute to the progression of gout. Having high blood pressure and having high uric acid levels are two of the most prevalent variables in the gout development [5, 6]. Thus, we may overall conclude that hypertension has the potential to have a significant negative influence on people's overall quality of life, especially in elderly people.

For the management of hypertension, ACE inhibitors have been the drug of choice over the years. But, now it has been an accepted fact that long-term use of synthetic ACE inhibitors is associated with numbers of undesirable side-effects, which compels the formulation scientists for large scale investigation on traditional plant-based therapeutics. The photochemical components found in plant extracts, according to previous research, have shown the capacity to serve as effective ACE inhibitors *in vitro* [7, 8].

Psidium guajava (Family: Myrtaceae) is a widely available plant in India having many reported medicinal properties. Fruit of the plant has been recognized as a potent source of important phytoconstituents and have been used to cure a wide range of diseases including hypertension [9]. The leaves and bark of the *P. guajava* also have a long history of medical usage [10, 11]. The present review covers the various reported medicinal activity of *P. guajava* with a special emphasis on its anti-hypertensive potential. Such updated reports on recent research works on the antihypertensive property of *P. Guajava* have not been documented so far. The review would therefore be an important piece of article for budding investigators of pharma and medicine fraternity to carry out further research on novel formulation design, drug repurposing and pre-clinical investigations on *Psidium guajava* to establish it as potential antihypertensive agent in clinical settings.

2. DISTRIBUTION AND OTHER CHARACTRISTICS

Psidium guajava is a well-known tropical fruit tree in India, which is also known as Guava. The plant includes under phylum: Magnoliophyta and class: Magnoliopsida. There are around 3,800 species under the genus *Psidium*. All of the plant's components have

been utilized in traditional medicine for centuries. In India, it is popularly referred to as Pijuli in Odisha, Pyara in West Bengal, Pungton in Manipur, Koyya in Tamil Nadu and Amrood in Uttar Pradesh. The resilience of the plant to a range of soil conditions makes it a popular choice in tropical settings. A total of 192,850 tons of Guava are gathered in Mexico each year on about 36,000 acres of land [12]. Due to its high nutritional value, low cost, along with broad availability, it is sometimes referred to as "the poor man's apple" in tropical and subtropical climates.

2.1 Plant description

2.1.1. Whole Plant

On its typically twisted stems, opposing leaflets with short petioles ranging in length from 3 cm - 16 cm may be observed. The leaves are big and bright green, with distinct veins. The beautiful white flowers on this shrub have curled petals. Insects pollinate the four to six petal flowers, which have yellow anthers. They vary in size from microscopic to bigger, with lengths ranging from 3 to 6 inches. When fully developed, it takes on the form of a pear and becomes golden in color. The seeds are golden, but the pulp is somewhat darker. The seeds are so little that they can be readily consumed.

2.1.2. Bark

Bark of the plant has been employed as an astringent in many countries like Panama, Bolivia, Venezuela to treat wounds, ulcers, diarrhea, dysentery, and skin disorders. The decoction has also the traditional history of use as a poultice to treat postpartum placental evacuation, skin infections, vaginal bleeding wounds, fever, and respiratory problems [13].

2.1.3. Roots

Literature shows that roots of *P. guajava* has the application as a decoction in West Africa for diarrhea, coughs, dysentery-related stomach pains, and gastrointestinal problems such as digestion problems along with constipation. The roots are also incorporated as an astringent in the Philippines, Fiji, and South Africa for sores, wounds, and ulcers [14].

2.1.4. Leaves

Leaves of *P. guajava* is often used in India to treat rheumatoid arthritis (RA), as well as fever and muscle cramps. In the United States, poultices and decoctions made from the leaves are used to heal wounds, ulcers, and toothaches. Guava tea may help with asthma, bronchitis, and coughing [14].

Table 1. Taxonomical Classification of *P. Guajava* Plant

Kingdom	**Plantae**
Order	Myrtales
Family	Myrtaceae
Subfamily	Myrtoideae
Genus	*Psidium*

Species	*Guajava*
Binomial name	*Psidium guajava* Linn

2.2 Nutritional Value

Guavas have earned the title of "super fruit" owing to the high concentrations of nutrients contained in them, including high levels of fibers plus Vitamin- A, Vitamin- C, folic acid, and trace quantities of minerals such as potassium, copper, and manganese, among others. One fruit of guava contains four times vitamin C when compared to an orange, as well as a wide variety of other nutrients and antioxidants that are beneficial to human health. However, there is a remarkable difference in the nutritional content of various Guava types [15].

Table 2. Nutritional content of Guava fruit

Sr. No	Nutrient	Quantity
1	Moisture	2.8-5.5g
2	Crude Fiber	0.9-1.0 g
3	Protein	0.1-0.5 mg
4	Fat	0.43-0.7 mg
5	Thiamine	0.03-0.04 mg
6	Niacin	40 I.U
7	Vitamin	36-50 mg
8	Carotene	0.046 mg

2.3 Traditional uses

P. Guajava has been widely employed for centuries in the tribal drug system [16]. Traditional treatments were offered for a broad range of conditions, including wounds, boils, skin problems, and soft tissue illnesses. The laxative properties of the plant may be found in all of its components, including the fruit and leaves. Aside from that, it has been demonstrated to have anti-amoebic and anti-malarial properties as well as anti-tumor characteristics. The anti-hyperglycemic benefits of the plant *P. Guajava* has also been documented from many years [16-18]. Various traditional uses of *P. Guajava* across different countries has been depicted in **Table 2.**

Table 3. Traditional uses of *P. Guajava* Linn across various countries

Country	Uses
India	cerebral ailments, childbirth, chorea, convulsions, epilepsy, nephritis
Mexico	diarrhea, itch, scabies, stomachache, swelling, ulcer, worms, wounds
Peru	cough, diarrhea, digestive problems, dysentery, edema, gout, hemorrhages, gastroenteritis, gastritis, lung problems, PMS, shock, vaginal discharge, vertigo, vomiting, worms
Ghana	coughs, diarrhea, dysentery, toothache
Malaya	dermatosis, diarrhea, epilepsy, hysteria, menstrual disorders
Trinidad	bacterial infections, blood cleansing, diarrhea, dysentery

3. PHYSICOCHEMICAL CHARACTERIZATION

According to one observation, a powder of *P. guajava* leaves has 1.0 percent moisture and 2.80 percent ash. It has a larger proportion of organic components than the plant's ash value, suggesting that the plant has fewer inorganic components. It serves as a powerful energy source since it is low in protein and fat but rich in carbohydrates [19]. *P. guajava* powder also includes essential trace elements like iron, manganese, and zinc. The heavy metals found in the powder leaves samples were within their tolerated limits [20]. The leafy hydro-ethanolic extract of *P. guajava* contains saponins, alkaloids, tannins, cardiac-glycosides, as well as terpenoids, flavonoids, and sterols; according to a phytochemical study [21].

3.1. Phytochemical analysis

Additionally, guava is rich in alkaloids, glycosides, steroids, and flavonoids, as well as in saponins and saponin glycosides. Lutein and zeaxanthine are abundant in guava, making it an excellent source of antioxidants and vitamins [22]**.** In addition to copanene, farnesene, humelene, the alkaloids ursolic, crategolic, along with guayavolic acids, nerolidol etc. are also present in guava. Red-orange guavas contain more retinoid-rich polyphenols, carotenes, and provitamin-A than yellow-green guavas. Other components include polyphenols and carotenoids such as gallocatechin, guaijaverin, leucocyanin, amritoside etc. **[23-25]**. Cineol, tannins, and triterpenes are thought to be present in the essential oil collected from the leaves of *P. guajava*. The bark of the guava tree has a high concentration of tannin (11-27%), making it suitable for tanning and dyeing.

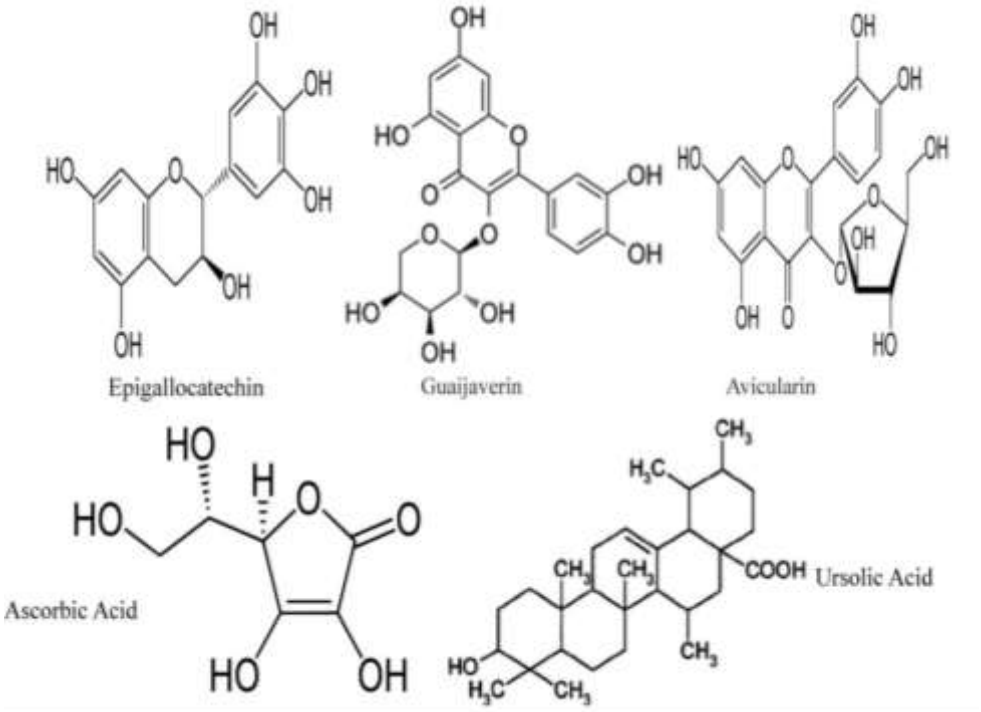

Figure 1. Predominant phytoconstituent in *P. guajava*

Along with lesser calories, the greater energy and highest water content has been found in guava fruit, making it an excellent choice for diabetics. The fruit has a high content of nutrients such as vitamins A and Vitamin C, as well as the B vitamins (thiamine and riboflavin), niacin, and manganese, among others. A significant amount of carbonyl molecules [26-27] are present to provide a unique fruity fragrance. In immature fruit, there is a risk of higher tannic acid concentrations. The depletion and destruction of ascorbic acid, which is the major component of the fruit peel, occurs throughout the canning and processing process. Active chemicals found in the fruits of P. guajava include glucuronic acid, arjunolic acid, and ursolic acid. In addition to gallic acid, quercetin, and triterpenoids [28-29], guava leaves contain a significant quantity of polyphenols, which have been associated with a range of health advantages. Additionally, guava leaves contain sitosterol (vitamin E), brahmic acid (vitamin B_2), and polyphenolics such as gallic and ferulic acids (vitamin C). Carbohydrate molecules, namely carbonyl molecules, are responsible for the fruit's rich, pleasant aroma. Guava is also high in the antioxidant guajadial [30, 31]. The bark contains 12 % to 30 % tannin, resin, and calcium oxalate crystals. The bark portion is abundant in resin and calcium oxalate crystals. Tannin may be found in the roots of the plant as well as in the leaves. Among other compounds, roots include leukocyanidins, gallic acid, and sterols. Several studies have shown that the presence of quercetin in guava leaves may be responsible for its spasmolytic action. There has been enough evidence to suggest that guava is beneficial in the treatment of *E. coli* or *S. aureus* toxin-induced diarrhea [30,31]. The molecule present in guava; heme oxygenase-1, is responsible for suppressing histamine production while simultaneously producing nitric acid. This substance can also alter the function of the protein heme oxygenase-1 [32].

4. THERAPEUTIC PROPERTIES OF *P. GUAJAVA*

4.1. Inhibition of microbes/ bacteria

Guava leaf extract exhibits repulsive action towards the growth of the bacterium *Staphylococcus aureus*. The antibacterial activities of methanol leaf and bark extracts of the plant have been reported. This prevents the bacteria Bacillus and Salmonella from multiplying. Guava methanol extract has been shown to destroy bacteria. Its active flavonoids are useful in the prevention of plaque formation. The anti-coughing properties of guava leaf extract are well-known in the medical community. Bacterial growth is suppressed by leaf extracts in several solvents, including water, chloroform, and methanol. Bacteria such as Salmonella and *Staphylococcus aureus* have been proven to be destroyed by guava oil. Gallic acid with cyanidin 3-glucoside [33-34] are also found; both of these compounds are antioxidants. The presence of these compounds contributes to the improved flavor of guava. Comparisons were made between *P. guajava* alcohol fruit extracts *Vs. Ananas comosus* and *Malus domestica* fruit extracts to determine their efficacy. The microbes under investigation included *E. faecalis, flexineri, E. cloacae, enterotoxigenic E. coli, enteroaggregative E. coli,* and *S. aureus*, where the *P. guajava* fruit extract showed preferential antimicrobial activity than the other two tested plant extracts [35].

4.2. Inflammation-fighting properties

Anti-germ and anti-thymic effects of guava extract in ethyl acetate have been shown. Guava may be used to treat skin irritation as an anti-inflammatory agent**.** Guava extract in ethanol suppresses the production of nitric oxide, which in turn lowers E_2 expression. As a result, TNF- and IL-4 mRNA synthesis gets terminated, which makes the antigen ineffective, and IB- starts to malfunction. The guava fruit contains a lot of benzophenone and flavonoids, which are two significant anti-inflammatory components. These molecules suppress histamine synthesis, causing nitric acid to be produced [36].

4.3. Antioxidant activity

Antioxidants and anti-proliferative components of guava are crucial for reducing free radical activity in addition to safeguarding cells. Chemical antioxidants minimize oxidative stress by slowing the oxidation process. Many diseases, including cancer, are thought to be triggered by free radicals, which cause cell damage. Various phytochemicals present in guava are beneficial to human health when it comes to diabetes, obesity, and high blood pressure *via* reduction of free radicals. Pink guavas have been found to be rich in antioxidants [37]. Guavas contain a lot of essential vitamins, minerals and anti-oxidants. Among the several available anti-oxidants, proportion of ascorbic acid and quercetin A are higher in guava. According to a study by Arima Et al., guava has shown preferential antioxidant and radioprotective properties *in vitro and in vivo* [38].

4.4. Anti-diarrheal activity

It is possible to extract both quercetin-3-arabinoside and quercetin from guava leaves, which have predominant anti-diarrheal property. The leaves of this plant also contain a morphine-like chemical. Quercetin reduces calcium-induced intestinal spasms. The ileum is affected by quercetin. The spasmolytic action of guava leaf is mostly due to the flavonoid quercetin. Guava leaves are used in the treatment of diarrhea caused by *E. coli* and *S. aureus* toxin. In 2008, Ojewole et al examined the anti-diarrheal properties of guava leaf extract in water-induced diarrhea. This extract greatly prevented rats and mice from diarrhea. In ethanolic extracts, guava has also shown substantial antidiarrheal and antidiabetic properties [39, 40].

4.5. Anti neoplasmic Activity

Kawakami et al. investigated anti-proliferative efficacy of guava leaf extract using a human colon cancer cell line. The scientists concluded that infusing the extract with quercetin and quercetin glycosides slowed the proliferation of cancer cells [41]. Additionally, three distinct cancer cell lines were tested using various extracts: cervical cancer (HeLa), breast cancer (MDA-MB-231), and osteosarcoma (MG-63). Although none of the extracts decreased HeLa cell multiplication, they showed potential effects in MDA-MB-231 and MG-63 cells, with the ether extract being the most efficient, followed by the methanol and water extracts. Guava terpenes have been demonstrated to suppress the growth of nine human cancer cell lines: leukaemia (K-562), breast (MCF-7), resistant ovarian (NCI/ADR-RES), lung (NCI-H460), melanoma (UACC-62), prostate (PC-3), and

colon (HT-29) (786-0) cancer [42]. Additionally, it was shown that guava leaf essential oil inhibited the growth of human oral epidermal carcinoma (KB) and murine leukaemia (P388) cell lines **[43].**

4.6. Immuno modulatory activity

On mice macrophages (RAW264.7) cells, guava leaf extract (fermented) showed preferential immunomodulatory activity [39,40]. According to Jang and colleagues, phenolic content of guava influenced prostaglandin E_2 synthesis. When Kaileh et al. observed that nuclear factor-B was unable to bind to DNA in murine fibrosarcoma (L929sA) and two breast cancer cell lines (MDA-MB231 and MCF7), they hypothesized that nuclear factor-B suppression may occur at the transcriptional level. Guava tree leaves may offer anti-inflammatory and immune-boosting qualities. Because there are only two hypothesized mechanisms for NF-B downregulation [44] further study is required to justify immunomodulatory potential of *P. guajava.*

4.7. For Endocrine and Metabolic Diseases

According to one study, the extract of Guava lowers the formation of advanced glycation end products *in vitro*. In an albumin/glucose model system, aqueous guava leaf extract inhibited amadori products. Gallic acid, catechin, and quercetin all inhibited the enzyme more than 80% of the time, although ferulic acid had no impact. Flavonoid compounds were shown to have substantial inhibitory effects on sucrase, maltase, amylase, and glucosidase in another investigation [44]. This plant included quercetin, kaempferol, guaijaverin, avicularin, myricetin, and hyperin, among other phytochemicals. In addition, Deguchi and Miyazaki demonstrated that guava polymerized polyphenol inhibited -glucosidase enzyme activity *in vitro*. An ethanol extract from guava leaves is considered effective in the future battle against human obesity since it decreases levels of adipogenic transcription factors and indicators, inhibiting adipocyte production in pre-adipocyte cell lines (3T3-L1). The ability of cells from insulin-resistant mice (FL83B) Wickmannin was shown to be required for glucose absorption in L6 myoblasts and myotubes. The leaves of the guava tree have also been demonstrated to inhibit aldose reductase activity and enhance the cellular synthesis of different proteins, including insulin receptors and glucose absorption [45].

4.8. Diseases of the Circulatory System

The loss of endothelial cells, which results in atherosclerosis, has been linked to cardiovascular disease. In vitro, flowering guava leaves showed a protective effect on bovine aortal endothelial cells by delaying low-density lipoprotein oxidation and reducing oxidized low-density lipoprotein cytotoxicity [46]. The capacity to sustain cell viability, minimize reactive oxygen species generation, and release and regulate NF B expression were all seen in human umbilical vein endothelial cells. Flowering Guava leaf extracts in plasma suppressed antithrombin III activity and decreased thrombin clotting time, which proved their capacity to prevent cardiovascular disorders [47].

4.9. Skin Disorder

The plant leaves may be used to treat atopic dermatitis and itching. Eczema symptoms result in fewer skin lesions and lower blood immunoglobin E levels. Wound healing study showed the reconstruction of epithelium using connective tissue-containing leaves, and irritation was also maintained to a minimum [48]. When evaluated against an active cutaneous allergy reaction, guava leaf extract demonstrated anti-anaphylactic properties in rats [49].

4.10. Diseases of the Gastro-intestinal System

Guava leaves have been found to prevent gastrointestinal lesions, decrease gastric secretion volume to check stomach ulcers [50]. Flavonoids found in the leaves that protect mucosa have been linked to anti-ulcer effects. Guava leaf extract provided protection, decreased intestinal transit, and delayed stomach emptying [50]. Guava has also been demonstrated to have hepatoprotective benefits in rats with acute liver injury, as shown by a steep decrease in blood hepatic enzyme markers and histological abnormalities. Leaf decoction seems to be a more effective method of getting the chemicals responsible for hepatoprotective activity.

4.11. Antihypertensive Activity of Psidium guajava

Controlling high blood pressure is the key to reduce stroke and coronary heart disease. According various epidemiological research, guava fruit may help to prevent cardiovascular disease because of the important photochemical they contain. Phosphate antioxidants present in the fruit may also have a function in protecting the body from free radical damage [51,52].

It was later discovered by Sarah et al. that teenagers with high blood pressure benefitted more from their unique eating habits including abundant in fruits and vegetables. Fruit consumption has been linked to lower rates of hypertension in epidemiological studies. Peroxynitrite-mediated damage may be protected against carotenoids, which have been found to lower coronary artery disease risk. Study of a bioflavonoid, phenolic acid, and anthocyanin-rich purple passion fruit peel extract showed satisfactory activity in both SHRs and humans [53]. As a consequence of these findings, the extract has the potential to be used as a safe treatment for hypertension. An aqueous extract of barberry may be utilized to treat hypertension since it has beneficial effects on the circulatory system [54]**.** A grapefruit-pummelo cross (a high-flavonoid sweetie juice) was substantially more beneficial to Stage I hypertension patients than low-flavonoid sweetie juice, as shown by [55]. In lieu of these studies, scientists have been investigating natural enzyme inhibitors present in guava because of its long folkoric history, safety, and low cost. Preliminary research done by Reshef et al 2005 has revealed that guava leaf extracts may reduce inflammation in rats, as well as lower blood pressure [55]**.**

It was found that leaves extract of plant contained flavoring compounds like quercetin and catechins. Quercetin came in second, followed by catechins and luteolin in third and

fourth place, respectively. Also found in the extract were the phenolic acids caffeic acid, chlorogenic acid, and gallic acid; caffeic acid was the most prevalent, followed by chlorogenic acid [56]**.** Gout and hypertension have been shown to benefit from the antioxidant qualities of the guava extracts, which are rich in flavonoids and phenolic acids [57-59]. An important treatment technique for treating hyperuricemia and gouty arthritis is to reduce oxidative stress in the blood vessels by suppressing XO. Hyperuricemia caused by XO can be mitigated with the use of polyphenolics derived from guava.

5. RECENT RESEARCH WORK ON GUAVA AS A ANYI-HYPERTENSIVE DRUG

Several recent studies across the globe have documented the anti-hypertensive effect of guava. Though many studies are highly limited to *in vivo* animal testing, but few studies are there on the patients also. In a study, when patients were given extracts from six distinct types of guava leaf, it was discovered that their diastolic blood pressure, kidney function indicators, nitric oxide production and expression of the renal ACE gene, all decreased as a result of the treatment [60]. It poses no significant scientific difference in the activity of extracts from multiple unique types of guava leaf employed in this experiment ($p>0.05$), indicating that they were not statistically different from one another. It is highly expected from the study that guava leaves extract would be beneficial in the treatment and control of high blood pressure [60].

Irondi and colleagues [61] investigated the effect of guava leaves extract in the treatment of inflammation and high blood pressure. Results showed reasonable anti-hypertensive effect of guava leaves extract. Phenolic extracts of fruits and leaves from different species of guava were shown to have equal antihypertensive and antioxidant effects, according to the research data. In another study, many guava species (largely white, tiny white, stripped, and pink) were investigated *in vitro* to assess their antihypertensive and antioxidative effects. The pink guava type was shown to have the greatest quantities of ACE inhibitory and antioxidant capabilities. Among the phyoconstituents, pectin, catechin, eugenol, and carvacrol extracts were reported in higher concentrations in pink guava type [61]. High concentration of polyphenolic chemicals in pink guava extract might be responsible for their predominant antihypertensive and antioxidant property.

Kumari S and colleagues tested the antihypertensive potential of guava extract in laboratory animal model. However, weight loss was seen only in group B animals and not in group A, even though fasting plasma glucose, total cholesterol, and triglycerides were remarkably greater ($p<0.05$) in the latter group. A significant difference ($p<0.05$) was detected between group B and the control group in terms of fasting plasma glucose, total cholesterol, and triglycerides. The blood pressure of animals in the group B were much lower than those of group A ($p< 0.05$). According to the results, the pulp of guavas, and not the peel, has lesser quantities of total cholesterol, triglycerides, and low-density lipoprotein cholesterol in the bloodstream, which would be helpful in improving cardiovascular health [61]**.**

Four guava fruit and leaf extracts were investigated in vitro for their antihypertensive and antioxidant properties (large white, tiny white, stripped and pink). Consequently, guava fruit and leaves were subjected to a methanol/1 M HCl (20:1) extraction. Angiotensin I converting enzyme (ACE) inhibitory effect, total phenol and flavonoid content, reducing property, radicals (DPPH, ABTS•+, hydroxyl and nitric oxide) scavenging ability, Fe2+ chelating ability, and inhibition of Fe2+ and Sodium nitroprusside (SNP)-induced lipid peroxidation reactions were then evaluated (in vitro). All extracts significantly decreased ($P \leq 0.05$) ACE activity, neutralized radicals (DPPH, ABTS•+, nitric oxide, and hydroxyl), chelated Fe2+, and inhibited Fe2+- and SNP-induced lipid per oxidation in rat heart (in vitro). However, the pink guava had the highest levels of ACE inhibitor and antioxidant properties. The ACE-inhibiting activities and antioxidant capacities of guava extracts, which correlate strongly with their phenolic content, may significantly contribute to the antihypertensive properties reported in conventional medicine.

Another study assessed the effect of pink guava puree supplementation on the kidney and liver functions of rats with spontaneously hypertensive rat (SHR). Twenty-four male SHR were divided into four different groups such as control (distilled water), low dose (0.5 g/kg body weight), medium dose (1.0 g/kg body weight), and high dose (2.0 g/kg body weight). At the conclusion of the trial, rats were fasted for 12 to 14 hours, euthanized under ether anesthesia, and blood samples were obtained from their portal vein or posterior vena cava. Compared to CG, the specific activities of glutathione peroxidase (GPx) in LDG, MDG, and HDG were significantly greater. The activities of glutathione reductase (GR) changed significantly between treated groups [LDG (132.511.8 U/l), MDG (141.516.4 U/l, and HDG (148.813.2 U/l versus CG (126.114.2 U/l)]. The liver function tests for total antioxidant status (TAS), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and -glutamyl transpeptidase (GGT) revealed statistically significant differences between the treatment and control groups. This study concludes that supplementation with pink guava puree increased SHR enzyme activity in the bloodstream and thus could be used as an effective antihypertensive agent [62].

The effects of guava fruit on blood pressure and blood lipids in patients with hypertension were examined in a randomised, single-blind, controlled experiment. 72 patients were randomly assigned to a soluble fibre and potassium-rich diet consisting of 0.5-1 kg of guava per day (group A), while 73 patients were randomly assigned to their usual diet (group B), with equal salt, fat, cholesterol, coffee, and alcohol intakes. In both groups, male gender, average age, and average body weight were comparable, as were risk factors, average blood pressure, average serum sodium, potassium, calcium, magnesium, triglycerides, cholesterol, and HDL-cholesterol. After four weeks of potassium supplementation and sodium restriction, patients in group A showed a net decrease in systolic and diastolic blood pressure of 7.5/8.5 mmHg compared to those in group B. Increased intake of soluble dietary fibre (47.8 +/- 11.5 vs. 9.5 +/- 0.85 g/day) was

associated with a significant decrease in serum total cholesterol (7.9 %) and triglycerides (7.0 %), as well as an insignificant increase in HDL-cholesterol (4.6 %) and a slight increase in the ratio of total cholesterol/HDL-cholesterol in group A patients compared to group B. Due to the high potassium and soluble fibre content of guava fruit, greater consumption might result in a significant decrease in blood pressure and blood lipids without changing HDL-cholesterol levels [63].

6. TOXICITY STUDIES OF *P. GUAJAVA*

The acute toxicity of a water extract from *P. guajava* leaves was examined in Wistar rats that had been exposed to *Salmonella typhi* in the laboratory. In the study, rats were administered the test extract at a dose of 10-30 mg/100 g twelve hours after being infected with *Salmonella typhi*, and they recovered in 7 days. During/after the study, no discernible negative effects were reported in the tested animals. The antibiotic chloramphenicol was used as a standard drug for comparison **[62].**Two weeks after receiving the aqueous leaf extract of *P. guajava* orally, the researchers observed a good response in the rats. Two weeks after the seventh and fourteenth injections of the ethanol solution, three rats from each group were subjected to blood tests to determine their serum liver enzyme levels (including serum aspartate aminotransferase, serum alanine aminotransferase, and serum alkaline phosphatase). According to the LD_{50} analysis, there have been no documented fatalities till 5000 mg/kg oral dose. It was also observed that the extract showed no significant changes in the enzyme activity assessed 7 days after oral administration as compared to control groups. The oral administration of the extract at a daily dosage of up to 500mg/kg for two weeks in all three groups resulted in no statistically significant changes in enzyme activity ($P<0.05$). Thus, the study overall showed that the aqueous extract of *P. guajava* leaf is purely non-toxic and safe within the tested concentrations and thus can be effectively explored for future clinical applications [64].

7. CLINICAL TRIALS

Though clinical studies on the guava are quite less in number, but few clinical reports have documented the effective application of guava in ameliorating blood pressure, lipid levels and to improve cardiovascular health. In a in a randomized, single-blinded clinical study, therapeutic impact of fruit consumption on high blood pressure and lipid levels was investigated [65]. An 8 percent decrease in total cholesterol was seen in the trial subjects after 12 weeks of fruit-eating, as was an 8 percent reduction in triglycerides, and an 8 percent rise in HDL cholesterol was also observed after the same period. The study showed that guava fruit consumption has been shown to decrease hypertension and lipid levels while not affecting HDL cholesterol levels. High potassium and soluble fiber content of the fruit might be responsible for such beneficial effects, as concluded by the research group [65]. The study revealed the cardiovascular benefits of yam bean (Pachyrhizus erosus, L.) and guava (Psidium guajava, L.) juices by examining the acute cardiovascular effects of these liquids on healthy volunteers. The potential contributions of dietary nitrates to their effects were also investigated. We show for the first time that yam bean root juice and guava fruit juice inhibit collagen-induced ex vivo platelet

aggregation in healthy individuals. It was determined that the effect of yam bean root juice was connected to dietary nitrate, but not guava fruit juice. Following administration of yam bean root juice, systemic nitrate is converted to nitrite and then to NO, which may inhibit platelet responses to collagen stimulation. The juices of yam bean root and guava fruit are extremely beneficial for cardiovascular health [66]**.**

8. CONCLUSION

Recent decades have witnessed an explosion of research in the therapeutic applications of phytochemicals discovered from a wide variety of plant parts. Investigations on herbal medicines for the prevention/treatment of different diseases is on high note; especially such diseases, for which conventional allopathic synthetic drug therapy has not able to find satisfactory outcome. *P. guajava*, a widely available medicinal plant throughout India has number of therapeutic applications from ancient times, however, it still remains highly ignored in current medicine practice. Human study has shown that phytochemicals such as quercetin, guaiaverin, flavonoids, and galactose-specific lecithins, present in *P. guajava* offer potential health advantages. In tests conducted on mice/rat and other laboratory animals, as well as on humans, the researchers found no indication of toxicity in either the leaf or the fruit of *P. guajava*, which is an encouraging outcome to carry out further research. Further studies into the pharmacodynamics and kinetics, in addition to adequate standardization and clinical trials would pave the path to establish *P. guajava* in clinical practice in future days.

Conflict of interest

The authors of the manuscript has no conflict of interest to declare.

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