

Healing Chemistry of Pepper: The Therapeutic Promise of Piper Species

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ABSTRACT: Aromatic herbs like *Piper* species are aromatic herbs and commonly used as spices. The plants of this genus are utilized in pharmacopoeia all over the world and have a variety of biological activities and consumption rates. Globally, *Piper* species are used in traditional medicine for the treatment of a variety of diseases, including urological issues, liver and skin problems, healing of wounds, stomach issues, fever and inflammation. The *Piper* genus is associated with anti-diabetic, hypolipidemic, cardiovascular and neuroprotective effects, preparation of tea (decoction), infusions, as well as scented baths. Additionally, various plants of the *Piper* species are used to flavor meat dishes, snack items, sauces, and savory foods. Rich oil content is a prominent characteristic of the genus *Piper*, notably in the leaves and fruits. The wealth of essential oils of these plants produces significant anti-inflammatory potential by inhibiting neutrophil chemotaxis and stopping their accumulation at the injury site in the inflammatory process. Additionally, *Piper* species act as natural antimicrobials and strong antioxidants. In comparison to synthetic antioxidants, the phytoconstituents and essential oils of *Piper* species exhibited free radical scavenging potential. The leaves of different *piper* plants are frequently employed in folk medicine to heal toothaches, and the roots are also used to treat gastrointestinal problems and as a diaphoretic for short-term fevers. Based on preclinical in vitro and in vivo research studies, it is believed that the antiproliferative, anti-inflammatory, anticancer, antibacterial and neuroprotective activities of the extracts and bioactive ingredients derived from *Piper* species have key impacts in protection against chronic diseases.

Keywords: Pharmacopoeia, traditional medicine, antioxidants, neuroprotective

INTRODUCTION

One of the oldest and most diverse genera of angiosperms is *Piper L.* (Piperaceae). *Piper* and *Peperomia* are the two major genera of piperaceae family, having more than a thousand species (Sen and Rengaiian, 2021). With 2000 species of herbs, vines and trees, the genus *Piper* is the biggest in the family Piperaceae and is extensively dispersed in the tropical southeast, Central and South America, Central and Western Africa and Oceania. American tropics have the highest concentration of *Piper* species with 1804 species, followed by Southeast Asian tropics (approximately 600 species) and the South Pacific (78 species) (Ulloa et al., 2017).

The plants of this genus are utilized in pharmacopoeia all over the world and have a variety of biological activities and consumption rates (Le et al., 2022). The Piperaceae family of plants is most frequently consumed as food. In many nations, different types of *Pipers* are also utilized in traditional remedies to treat a wide range of illnesses. According to ethnobotanical research published in the literature, the *Piper* genus is associated with medicinal uses such as tea

(decoction), infusions, as well as scented baths (Santhakumari et al., 2003; Wirotasangthong et al., 2008). In conventional medicine, it is mostly used to treat gastrointestinal disorders, pain, inflammation, as a diuretic, anti-hemorrhagic and for hypertension (Lago et al., 2007; Gupta et al., 2015). Rich oil content is a prominent characteristic of the genus *Piper*, notably in the leaves and fruits. It contains essential oils with phytochemicals like aldehydes, ketones, sesquiterpenes, monoterpenes, long-chain alcohol and arylpropanoids. This demonstrates its industrial and commercial potential as well as its application in conventional treatment (Correa et al., 2011).

Any plant species employed to counteract the effects of a certain poison falls under the category of alexoteric plant species (Albiero et al., 2005). According to the literature and studies, members of the genus *Piper* are crucial to preventing these kinds of bites/infections. Piperaceae family with four species exhibiting alexoteric effects (4.76%) is the most commonly used for this purpose (Hakmaoui et al., 2012). Several types of genus *Piper* are esteemed as spices and have been utilized as flavor, color and scent enhancers as well as preservatives for thousands of years (Mgbeahurike et al., 2017). Because extracts or bioactive compounds derived from

extracts act as pharmacological agents with anti-oxidant, anti-microbial, anti-inflammatory, anti-diabetic, hypolipidemic, cardiovascular and neuroprotective effects, the genus *Piper* represents a promising lead in ethnopharmacological research (Salehi et al., 2019; Yadav et al., 2020).

PLANTS WITH MEDICINAL PROPERTIES

Piper nigrum

Piper nigrum L. (*P. nigrum*), known as the “king of spices” because of its enormous market share, is additionally employed to treat fever, cold, colic and digestive disorders in conventional and ayurvedic medicine. It is usually identified as green pepper, white pepper, black pepper, Madagascar pepper, or peppercorn. Black pepper is prepared from *P. nigrum*'s fruits. *P. nigrum* fruits are used to derive black pepper, green peppercorn and white pepper, although all of these are reaped at various periods and processed in different ways. White pepper is prepared by scraping off the outer layer, whereas black pepper is the unripe dried fruit (pericarp). Additionally, it is used to flavor meat dishes, snack items, sauces and savory foods. *P. nigrum* has generally been used to cure cough, asthma, pyrexia and throat infections (Salehi et al., 2019; Suroowan and Mahomoodally, 2016).

Traditional medicinal use of *Piper nigrum* as immunomodulator and anti-inflammatory agent is confirmed from various studies. Oral administration of its extract to healthy animals verifies its effect on lipid metabolism and beneficial modification of gut flora, thus reducing basal/low-grade lipopolysaccharides. The extract is exhibiting prebiotic potential, which could be helpful in the preparation of prebiotic products to ameliorate pathological changes in gut microbiota (Kondapalli et al., 2022). In carrageenan-induced paw edema models, a study clarified the anti-inflammatory activity related to this species, showing a consequential reduction in edema at different doses of ethanolic and hexane extracts (Tasleem et al., 2014). According to a study, the methanolic extract of *P. nigrum* considerably lessened the cholinergic dysfunction triggered by Alzheimer's disease and other forms of neurodegeneration (Ahmed et al., 2013). Among the most significant species in the genus is *Piper longum* (*P. longum*) having blunt and blackish-green fruits, which are used ethno-medically to cure respiratory and gastrointestinal disease, postpartum hemorrhage, epilepsy, diabetes and rheumatoid arthritis (Kumar et al., 2011).

Piper retrofractum

The fruits of *Piper retrofractum* (*P. retrofractum*) are commonly used to treat diarrhea, bronchitis, ulcers, asthma and as digestive, tonic and carminative remedies (Islam et al., 2020). Additionally, a study reported on the multifunctional biological profiles of *P. longum*, *P. retrofractum* and four types of *P. nigrum* (red, white, green and black). A panel of 22 reference microorganisms was used to test the antibacterial and antifungal effects of species and the results revealed strong antioxidant activity and excellent inhibitory effect of white, green, black peppers or *P. retrofractum* against anaerobe species like *F. nucleatum*, *B. fragilis*, *V. paryula*, *P. intermedia* and *A. israelii*. The results also demonstrated moderating

effects of piper spices on the acetylcholinesterase and butyrylcholinesterase enzymes targeted for the treatment of Alzheimer's disease and type 2 diabetes mellitus (amylase, β -glucosidase) (Luca et al., 2021).

Piper aduncum

The herb *Piper aduncum* (*P. aduncum*), also called “skipped pepper”, has a number of applications in traditional medicine, including the treatment of diarrhea, skin boils, wounds and infections (Luyen et al., 2017). Because of its properties as anti-parasitic (de Castro et al., 2015; Villamizar et al., 2017), anti-bacterial and antimicrobial (Gutiérrez et al., 2016; Macedo et al., 2019), insecticidal, and antitumor (Arroyo-Acevedo et al., 2015; Cossolin et al., 2019; Ndjonka et al., 2013), it may be useful in the treatment of infections and malignancies. The *P. aduncum* plant contains a variety of phytochemicals, including phenolics, monoterpenes, sesquiterpenes, and chromene. These bioactive substances help to explain the plants' insecticidal, antibacterial, anti-parasitic, and anticancer activities (Nor and Syukri, 2020).

Piper betle

Apoptosis-induced compounds obtained from plant products have gained popularity in cancer studies since current anti-apoptotic medicines, a number of which are produced from chemicals, frequently fail to inhibit tumor growth and progression. In an investigation using the MTT cell viability assay, acetone decoction of *P. betle* leaves caused 88.7% cytotoxic effects and 11.4% necrosis in the lung tumor cell line (A549). Significant dose-dependent decrease in tumor growth was also observed with the use of ethanolic extract of *P. betle* during the tumor inhibitory assay of B16F10 melanoma in the mice (C57BL/6). s, as concluded from experimental results. In the latest study, Boontha et al. evaluated the antitumor effect of an ethanol extract of betel leaves in human breast carcinoma cells (MCF-7). The study revealed that the infusion demonstrated cytotoxic effects with an IC₅₀ value of 114.3 microgram/ml and a reduction in cell migrations at a 25 microgram/ml concentration (Alam et al., 2012).

Role of *P. betle* on the improvement of cognitive and intellectual capacity was also examined in albino rats with AlCl₃-induced Alzheimer's disease. After treating rats with aqueous betel leaf extract, passive avoidance and Morri's water maze tests showed a decrease in mean escape latency time and increased spatial memory recall. These results were comparable to treatment with rivastigmine in the same subject (Upadhyaya et al., 2019). By performing an in vitro AR (aldose reductase) experiment, Fatmawati and Shimizu determined that the ethanol leaf extract of *Piper betle* can block HRAR (Human Recombinant Aldose Reductase). HRAR is a crucial component in the polyol signal transduction pathway that converts glucose (C₆H₁₂O₆) to sorbitol (C₆H₁₄O₆), preventing aggravation and complexity in diabetes.

The hypocholesterolemic effect of betel leaf extract was also determined in hyperlipidemic rats fed a fatty diet before the experiment. The lipid profile revealed a prominent reduction in all serum lipid parameters after the subjects were treated with the methanolic leaf extract. *P. betle* leaves are

safe, non-poisonous, and are an orally active natural remedy with remarkable potential to protect cardiac structure and function (Savsani et al., 2020), as well as they possess excellent antioxidant properties (Manideep et al., 2019). *P. betle* is also reported to heal ulcers (Bhattacharya et al., 2007), kill bacteria, and treat fertility issues (Hossain et al., 2021). Moreover, betel leaf extractives protect and strengthen the liver (de Castro et al., 2015) and lungs, and also act as an antiasthmatic agent.

Piper crocatum

According to specifically published research, *Piper crocatum* Ruiz and Pav (*P. crocatum*), often known as red betel leaf, is effective in curing dental and periodontal health issues as a natural alternative to antibiotics. This tropical plant was first utilized as an aesthetic plant for a long period of time before its medicinal properties were discovered (Wardhana et al., 2017). It is a naturally occurring substance that may be used to treat tooth decay. The leaf of *P. crocatum* Ruiz and Pav, having multiple bioactive molecules such as essential oils, alkaloids, flavonoids, and polyphenols are effective against *Streptococcus mutans*, a microorganism involved in the development of cavities and tooth decay. In the past, red betel leaves have been used to treat different pathological conditions, including mouth ulcers and toothaches. The antibacterial red betel leaf extract can be used as a mouthwash to eliminate unpleasant mouth odor.

Piper rivinoides

Amongst the ten most prevalent cancers in the world, one is oral squamous cell carcinoma (OSCC). It is the most widespread neck and head cancer affecting people of all nations. There is a wide variety of phytoconstituents in plants of the genus *Piper* with the capacity to be cytotoxic for tumor cells. These plants are employed in traditional medicine to cure tumors. It has been discovered that *Piper rivinoides* (*P. rivinoides*) essential oils extracted from fresh foliage are effective against the SCC9 and SCC25 cell lines. The concentrated fraction of *P. rivinoides*, having principal components (alpha-pinene, beta-pinene, and limonene), showed a higher IC₅₀ compared to the pure essential oils, making it a promising option as an antitumor fusion. These findings will aid the potential discovery of novel medicine to cure OSCC (Machado et al., 2022).

Piper guineense

The plants of the *Piper guineense* plant may help to treat sexual dysfunction induced by lead poisoning. A research study evaluated the antioxidant properties of *Piper guineense* leaf alcoholic extract on the damaged testicular cells caused by lead intoxication in rats. The testosterone and zinc concentrations were dramatically raised following administration of the plant leaf extracts in a dose-dependent fashion. Additionally, the decoction dramatically reduced testicular MDA (malondialdehyde) concentration and considerably increased testicular superoxide dismutase, catalase, and glutathione (GSH) levels, reducing oxidative stress and damage to the cells of the testicles (Nwosu et al., 2022).

Piper cubeba

The tropical medicinal herb *Piper cubeba* (*P. cubeba*) is widespread around the world including Indonesia. According to the reports, *P. cubeba* has a variety of phytochemicals with anti-cancerous, hepato-protective, nephron-protective and anti-leishmanial effects. (Kumar, 2021). It is a potential therapeutic plant. It was discovered that certain *P. cubeba* species have anti-inflammatory properties (Kumar, 2021; Mothana et al., 2016). *P. cubeba* fruit powder was used in a study which demonstrated its antibacterial efficacy against gram (-) *Pseudomonas aeruginosa*, gram (+) *Escherichia coli* and gram (+) *Staphylococcus aureus*. Numerous investigations have revealed that *P. cubeba* possesses strong antioxidant properties, including DPPH scavenging activity of 93.88%, nitric oxide scavenging activity of 89.06% and hydroxyl radical scavenging activity of 87.69% (Choi and Hwang, 2005; Muchandi et al., 2018; Nahak and Sahu, 2011).

Piper sarmentosum

The traditional herb *Piper sarmentosum* (*P. sarmentosum*) is well known for having anti-diabetic effects. It has been used to treat minor illnesses like cough, expectorants, menstrual pain, joint discomfort, waist pain, and chest and tooth pain, as well as to improve urination. An investigation looked at the effects of *P. sarmentosum* extract on the heart tissue and proximal aorta of experimental rats. *P. sarmentosum* extract considerably lowered fasting and urine glucose levels in streptozotocin-induced hyperglycemic rats. According to the findings, *P. sarmentosum* helps diabetic cardiovascular tissues to regain ultrastructural integrity (Thent et al., 2012).

Piper peltatum

A study supported the role of *Piper tuberculatum* (*P. tuberculatum*) essential oils in the treatment of CNS problems. Findings show that *P. tuberculatum* fruit extract has a potential depressive impact and is known to have neuroleptic, anxiolytic, anticonvulsant and hypnotic effects. These effects may be the result of the interaction of monoterpenes in essential oil and the GABAergic system (dos Santos Sales et al., 2022).

Piper retrofractum

Various bioactivities, including antifungal, insecticidal, antibacterial, antileishmanial, antidiabetic, antiobesity and anticancer activity are reported with *Piper retrofractum* (*P. retrofractum*) (Saranya et al., 2017). *P. retrofractum* has been utilized as a medication to treat digestive tract diseases. Cholangio-carcinoma (CCA) has one of the worst prognoses in the world and chemotherapy is essentially worthless in treating it. A study investigated the role of *P. retrofractum* in CCA cells' migration, apoptosis and death processes. *P. retrofractum* considerably inhibited the growth of CCA cells. According to the cell viability experiment, by decreasing the number of cancer cells, colony formation and cell cycle distribution were arrested at the G₀/G₁ phase in KKU-100 cells and the S to G₂/M phase in KKU M452 cells. Furthermore, through boosting ROS production and reducing

mitochondrial activity, *P. retrofractum* impressively boosted late apoptosis and necrosis in both types of cancer cells.

According to the results *P. retrofractum* could be used to treat and prevent CCA. Acute hepatotoxicity from paracetamol in mice was prevented by the ethanol extract of *P. retrofractum*, which also exhibited antioxidant and hepatoprotective properties. The extract exhibited antioxidant potential through DPPH antioxidant free radical and hydroxyl scavenging capabilities. The extract recovered the lower levels of albumin, total proteins and cholesterol (Mahaldar et al., 2020)

Piper capense

Piper capense (*P. capense*) is commonly used in Cameroon to cure cancer, while the shoot of the plant is routinely used in the Comoros Islands to treat diarrhea and cough (Kaou et al., 2010). *P. capense* has historically been used to treat cough, diarrhea, and abdominal pain. Piper species are often proven to exhibit therapeutic and preventative properties against a variety of chronic ailments because they possess antiproliferative, anti-inflammatory, and neuropharmacological properties. Collectively, the studies established with Piper species claim that these plants are potential candidates for the treatment of different chronic diseases. According to other accounts, *P. capense* has historically been used to treat cough, diarrhea, and abdominal pain (Tekwu et al., 2012). Fruits of *P. capense* have carminative, diuretic, stimulant, and vermifuge effects and it can also treat stomach issues, including colic and indigestion, as well as heart and kidney issues if taken as an infusion.

Piper umbellatum, Piper sarmentosum and Piper attenuatum

People belonging to different regions practice the use of different plants, such as *Piper umbellatum* (*P. umbellatum*) for the treatment of pyrexia (Silalahi, 2018). In a study, anti-inflammatory effect and reduced leukocyte migration were reported with the use of dichloromethane extract of *P. umbellatum* leaves on paw edema and carrageenan-induced peritonitis models (Iwamoto et al., 2015). Sundar et al. (2019) identified the anti-inflammatory effect of *Piper sarmentosum* (*P. sermentosum*) due to reduced production of nitric oxide (NO), which is one of the markers in inflammatory pathways. Ethnobotanical studies on *P. saementosum* reported its common use for rheumatism and gout (Sundar et al., 2019).

Piper gaudichaudianum, Piper mikanianum and Piper imperial

The fresh roots of *Piper gaudichaudianum* (*P. gaudichaudianum*) have an anti-inflammatory effect and are commonly used to cure liver disease (Macedo et al., 2019). The leaves of this plant are frequently employed in folk medicine to heal toothaches. *Piper mikanianum* (*P. mikanianum*) is also frequently used to treat ulcers, rheumatism and inflammation. Its roots are also used to treat gastrointestinal problems and are used as a diaphoretic for short-term fevers (Tiwari et al., 2022). The essential oils of *P. mikanianum* and *P. gaudichaudianum* were examined for their

capacity to block neutrophil chemotaxis in vitro when triggered by the *Escherichia coli* lipopolysaccharide. According to these findings, essential oils of both plants have significant anti-inflammatory potential by inhibiting neutrophil chemotaxis and stopping their accumulation at the injury site in the inflammatory process, in a dose-dependent manner. A correlation between the phenolic contents of Piper imperial leaf, flower and wood extracts and their antioxidant, anti-tubercular, and cytotoxic properties has been made. Strong anti-bacterial action was demonstrated by the flower extract against *Mycobacterium tuberculosis*. All of the extracts demonstrated dose-dependent cytotoxic effects on the MCF-7 human breast cancer cell line (Diaz et al., 2012).

Piper truncatum, Piper mollicomum, Piper arboreum, Piper cernuum and Piper cabralanum combination

Some other researchers used three distinct OSCC cell lines, namely SCC4, SCC9, and SCC25, to examine the anticancer effects and selective effectiveness of leaf extracts and semipurified compositions from the *P. truncatum*, *P. mollicomum*, *P. arboreum*, *P. cernuum*, and *P. cabralanum*. It has been discovered that some of these botanicals have potent anticancer effects (IC50 approximately equal to 47 g/mL) and higher selectivity (SI approximately equal to 4.5) compared to periodontal fibroblasts (IC50 approximately equal to 213.0 g/mL), making them potentially useful as chemotherapeutic agents. In acute cytotoxicity studies, this above prepared composition exhibited no hemolytic activity and no detectable harm was reported in mice. Furthermore, the mixture of piper plants showed considerable contribution for creating oral tumor medicine that is more efficacious as well as less harmful (Macedo et al., 2019).

CONCLUSION

Piper species are often proven to exhibit therapeutic and preventative properties against a variety of chronic ailments because they possess antiproliferative, anti-inflammatory, antidiabetic, anticancer, and neuropharmacological properties. Moreover, *piper* species are also used to flavor meat dishes, snack items, sauces and savory foods. Rich oil content is a prominent characteristic of the genus *Piper*, notably in the leaves and fruits and is responsible for antiproliferative, anti-inflammatory properties. Collectively, the studies established with Piper species claim that these plants are potential candidates for the treatment of different chronic diseases.

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