REVIEW ARTICLE

Piper mullesua: Traditional Uses and Pharmacological Potential

Kaur Arvinder[1], Sohpal VK[2*], Ahmed Zabeer[3]

[1]I.K Gujral Punjab Technical University, Kapurthala, Punjab, India.
[2]Department of Chemical Engg and Biotechnology, S.B.S State University Gurdaspur, Punjab, India.
[3]CSIR - Indian Institute of Integrative Medicine, Jammu, J&K, India

Received: 12th October, 2023; Revised: 31st December, 2023; Accepted: 04th January, 2024; Available Online: 25th March, 2024

ABSTRACT

Piper mullesua, also referred to as "Mullesua," is a member of the Piperaceae family of plants. This paper aims to offer a comprehensive insight into the pharmacological potential and traditional applications of *P. mullesua*. Due to the plant's medicinal qualities, it has historically been used in numerous indigenous medical systems. Recent scientific investigations have also noted its potential medicinal uses, including its antioxidant, antibacterial, anti-inflammatory, and anticancer effects. This paper highlights the active ingredients, traditional applications, and pharmacological properties of *P. mullesua* while summarizing the currently available research. The study implies that additional research is necessary to fully investigate its therapeutic potential and to pinpoint the underlying mechanisms of action.

Keywords: *Piper mullesua*, Antioxidant, Anti-inflammatory, Anticancer.

International Journal of Pharmaceutical Quality Assurance (2024); DOI: 10.25258/ijpqa.15.1.69

How to cite this article: Arvinder K, Sohpal VK, Zabeer A. *Piper mullesua:* Traditional Uses and Pharmacological Potential. International Journal of Pharmaceutical Quality Assurance. 2024;15(1):450-453.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Rheumatoid arthritis (RA) stands as an autoimmune and inflammatory condition that places a substantial burden on individuals, predominantly affecting the joints. In addition to its impact on joints, RA extends its influence to the surrounding skin, blood vessels, and muscles. Despite the array of medications designed to alleviate RA symptoms, there are growing concerns about the potential adverse effects linked to these therapeutic choices. Leukocytoclastic vasculitis, also known as leukocytoclasticvasculitis (LCV), has been connected to a class of more recent medications called TNF blockers. Reports indicate that the use of 3-5-tumor necrosis factor (3-5-TNF) blockers, notably humira and remicade, is associated with an increased risk of cancer and serious infections. Researchers are currently looking for treatment solutions as a result. Due to their low cost and lack of adverse effects, plant-based medications used in traditional medicine have received much attention during this study.[1] Medicinal plant use is essential to preserving people's individual and societal health. These plants' medicinal potential stems from a variety of physiologically evident chemically active compounds that affect human health. Among these bioactive plant components, the crucial ones include alkaloids, tannins, flavonoids, and phenolic compounds. Numerous native medicinal plants find application in traditional medicine. Rheumatic diseases are among the most prevalent inflammatory illnesses worldwide. Although the majority of people are affected by one of the oldest known human diseases, rheumatism, significant progress has not been made toward finding a lasting cure. There is still great hope for discovering anti-inflammatory medications as drug development and screening for their anti-inflammatory activity are ongoing processes.[2]

Piper is the most extensive genus within the Piperaceae family, believed to encompass 1,200 species extensively distributed across tropical and subtropical regions worldwide, as noted by Burger, W.C., 1972.[3] Northeast India and the Eastern Himalayas represent a significant hotspot for the diversity of *Piper* species in India, constituting a mega biodiversity area.

The abundant variety of flowers can be attributed to the remarkably varied climate, topography, and geology of the Himalayan hill ranges. The region's temperate, alpine, tropical, and subtropical climatic zones are home to a variety of vegetation types. From the foothills to elevations of 1,800 meters, the rich growth of *Piper* species thrives in the moist evergreen and semi-evergreen woodlands of tropical and subtropical zones. These forests can be found anywhere from the mountains to the foothills. With its identified 65 species, Sikkim hosts approximately 70% of all *Piper* species found in India, benefitting from the ideal environment these forested regions provide.[4]

*Author for Correspondence: vksohpal@sbssugsp.ac.in

Traditional Uses

Piper mullesua has been employed for numerous years in treating a diverse array of ailments. Native American tribes have harnessed the herb for its analgesic, anti-inflammatory, antibacterial, and wound-healing activities. The hill piper, *P. mullesua*, is used to treat blood stasis.[5] Foods made from plants are rich sources of various bioactive ingredients, including phenolics, flavonoids, terpenes, and sterols. The biological and antibacterial effects of these ingredients have been assessed. Black pepper is used to treat snakebite, epilepsy, and inflammation. It also acts as an antipyretic. Additionally, gastrointestinal activity has been reported to boost appetite treat dyspnea, colds, coughs, feverish episodes that come and go, stomachaches, worms, piles, and discontinuous fever.[6]

Pharmacological Activities

In traditional Chinese medicine, the complete *P. mullesua* plants are utilized to address a spectrum of conditions: Asthma, RA, bleeding, dysmenorrhea, swelling, pain, etc.[7] Moreover, as stated by Manandhar N.P. (2002), Indian traditional medicine utilizes the boiled juice of *P. mullesua* fruits for the treatment of colds and coughs. Myristicin (4-methoxy-6[2-propenyl]-1,3-benzodioxole), recognized for its synergistic activity and belonging to the apiole group of compounds, is highlighted.[8] According to Tisserand R (1994), myristicin possesses antidepressant, anti-inflammatory, and antioxidant properties.[9] Additionally, there are reports suggesting that myristicin acts as a larvicidal agent against *Aedes aegypti.*[10]

Insecticidal Activity

Research explores the alcoholic extract derived from the fruit-bearing inflorescence of *P. mullesua, which* demonstrated insecticidal activity. The insecticidal activity of this plant is due to the presence of myristicin. The research also delves into this substance's antimetabolic properties and contact toxicity against the lepidopterous insect pest *Spilarctia obliqua*. Compared to the compound's positive effect, myristicin significantly poisoned larvae in their fourth instar when applied topically. In order to obtain myristicin, the hexane fraction of the *P. mullesua* ethanol extract used was extracted. This compound effectively killed *S. obliqua* larvae in their fourth instar after 24 hours using a topical application method. It had an LD_{50} of 104 mg/larva. In the diet mix bioassay, larvae given a single dose of myristicin (200 mg/g diet) showed minimal mortality after 24 hours. Nevertheless, after feeding on a fresh diet for 72 hours, the same single dose caused total death when given for a longer period of time.[11]

Amides, Isoquinoline Alkaloids and Dipeptides

A total of 28 known compounds were detected in this plant such as pipermullesine A, pipermullesines B and C, pipermullamides A–F. An evaluation was conducted to determine whether or not each isolate had the capacity to prevent platelet aggregation brought about by platelet-activating factor (PAF) or thrombin (IIa). A mild suppression of rabbit platelet aggregation was caused by PAF by (-)-Mangochinine, pellitorine, and (2E,4E)-N-isobutyl-2,4-dodecadienamide. The IC_{50} values for these three compounds were 470.3, 614.9, and 579.7 µg/mL, respectively.[12] *P. mullesua* extracts may have anticancer properties, according to preliminary research.[13] Several cancer cell lines are susceptible to the plant's cytotoxic effects, which cause cell cycle arrest and apoptosis. More research is required to assess *P. mullesua'*s effectiveness in treating cancer and learn more about the underlying mechanisms.

Through the use of X-ray diffraction analysis, the structures of *Piper mullesua* A–C were verified. An evaluation was conducted to determine whether or not each isolate could prevent platelet aggregation brought about by thrombin (IIa) or platelet-activating factor (PFA).

Composition of Essential Oils in *Piper* Species

Throughout human history, several aromatic plants belonging to the pantropical *Piper* genus have been utilized for various reasons, including applications in the culinary and medicinal fields. Essential oils, also known as EOs, can be discovered in a variety of tissues and organs of these plants, including fruits, seeds, leaves, branches, roots, and stems. *Piper* plants are used extensively for the production of essential oils.[14,15] Despite comprehensive investigations into the chemistry of essential oils dating back to the 1960s, Dyer asserts that only a limited percentage, approximately 10%, of *Piper* species—112 out of the 1457 globally accepted species—have undergone detailed phytochemical research (www.theplantlist.org). For this review, the chemical data for the volatile components of about 130 species could be found; however, only about 16 of those species have adequate detail in the data. *Piper* essential oils (EOs) present a substantial problem when it comes to distilling their essence because of the extensive variances in chemical makeup and the varied tissues from which the EOs were obtained. According to Mgbeahuruioke *et al.* (2017), it has been discovered that essential oils extracted from piper include more than 270 different constituents.[15] More than eighty different chemicals were found in Chinese *Piper* spp., according to the review conducted by Xiang *et al.* and published in 2017.[16] The majority of these chemicals were categorized as mono- and sesquiterpene hydrocarbons, and then, in order of predominance, they were categorized as aldehydes, alcohols, acids, ketones, esters, and phenols.

Certain species, namely *P. betle, P. nigrum*, and *P. auritum*, exhibit relatively complex secondary metabolite suites, while others, like *P. nigrum*, have more straightforward profiles. According to the findings of Mgbeahuruioke *et al.* (2017), the chemical makeup of the EOs derived from the fruits, leaves, and aerial sections of these plants can vary in a number of different ways.[15]

Anti-Inflammatory Properties

Living things use inflammation as a defense mechanism against a variety of stimuli, including pathogens, toxic chemicals, and numerous environmental stressors.[17] This extremely controlled and self-limiting phenomenon typically facilitates healing. On the other hand, an uncontrollably protracted process known as chronic inflammation may result in immune cells being continuously activated,

Table 1: Investigation into the comparison of the anti-inflammatory capabilities of several distinct *Piper extracts*

Extract of Piper species	*Technique*	*Primary impacts*	*Ref*
Extract of *Piper betle* extracted with hydroalcoholic	*In-vitro* research Paw edema caused by carrageenan in wistar rats granuloma inducible by cotton pellets in albino mice	Key analgesic characteristics in both animal species include: Reduction of pain through peripheral and central pathways. Dose-dependent inhibition of paw growth observed Decrease in granuloma dry weights.	20
Extract of *Piper betle* extracted with ethanol and hexane	Carrageenan-induced paw edema model	Hexane and ethanol extract caused a reduction in edema	21
Ethanol crude extract of Piperaceae species	Studies were conducted *in-vitro* on peripheral blood mononuclear cells (PBMC) that were generated by lipopolysaccharide (LPS).	Selective inhibition of proinflammatory cytokines	22

raising cytokine release.[18,19] Pathological conditions like diabetes, cancer, heart disease, autoimmune diseases, and different neurodegenerative conditions may result from this persistent reaction. Understanding the mechanisms that drive inflammation and identifying novel anti-inflammatory agents can be valuable for developing promising therapeutic strategies to address or prevent chronic inflammatory diseases shown in Table 1.

1,3-Benzodioxanes in *P. mullesua*

The six different types of dioxanes present in the *P. mullesua* extract were identified using a novel, simple, fast, and high-performance thin-layer chromatographic technique. Several techniques were employed, including 1N,3N-dioxole-5N-(2,4,8-triene-isobutylnonanoate), 1N,3N-dioxole-5N-(2,4,12-triene-isobutyltridecanoate), asarinin, fargesin, and sesamin. These components were separated using a toluene–actone (92+8) solvent system on a precoated Silica Gel60F254 plate. In this chromatographic system, the six benzodioxanes were distinct and easily separated from one another. The color development of the isolated benzodioxanes was facilitated by a spray reagent containing 1 g of diluted vanillin in 100 mL of H_2SO_4-ethanol (5+95, v/v). For the purpose of quantification, the spots were scanned, and the integrated areas of the compounds in the samples were compared to those of the standards. Samples that had been spiked with known concentrations of benzodioxanes showed excellent recovery rates. The results could be contrasted with those acquired by liquid chromatography**.**

Sesamin: A Powerful Antifeedant Compound Isolated from *P. mullesua*

Sesamin, the principal lignan of *P. mullesua*, a plant-derived from Manipur, showed strong antifeedant efficacy and moderate growth suppression when applied to *S. obliqua* larvae in their fourth instar. There was no proof of sesame toxicity to larvae through topical bioassay tests. Its effective doses for 50% growth inhibition (GI50) and feeding deterrence (ED50) were found to be 6212 and 3856 ppm, respectively.

α-Glucosidase Inhibitory Activity

A bioassay-guided technique was used to isolate caffeic and sinapic acid. These compounds were extracted out form from the fruits and isolated using semi-preparative HPLC and column chromatography. Molecular docking was utilized in order to anticipate the chemical reactions between the isolated compounds and α-glucosidase. These molecules exhibited strong anti-diabetic and antioxidant effects, demonstrating their efficiency in this regard. Caffeic acid and sinapic acid have been demonstrated to possess IC_{50} values of 0.67 and 0.82 mg/mL, respectively, when it came to their ability to suppress α-glucosidase *in-vitro*. Furthermore, a quantitative structure-activity relationship (QSAR) equation was developed to predict the IC_{50} values of test compounds, achieving an R^2 value of 84.81%.

The aforementioned discovery reinforces the conclusion derived from molecular docking and QSAR studies, affirming that the isolated compounds exhibit exceptionally high potential as anti-diabetic agents. Therefore, with more clinical and *in-vivo* research, there is a great deal of potential for therapeutic development.

CONCLUSION

P. mullesua has tremendous medicinal potential due to the abundance of phytochemicals in the plant. Its promise as a source of natural treatments is suggested by the fact that this plant's traditional applications match up with its documented pharmacological properties. However, more study is required to examine *P. mullesua*'s mechanistic properties, bioavailability, and safety profile. Utilizing *P. mullesua*'s full therapeutic potential will depend on combining traditional knowledge with current scientific research.

REFERENCES

1. J Paval, Kaitheri SK, Potu BK, Govindan S, Kumar RS, Narayanan SN, Moorkoth S. Anti-arthritic potential of the plant JusticiagendarussaBurm F. Clinics. 2009;64:357-62.
2. Chandur U, Shashidhar S, Chandrasekar SB, Bhanumathy M, Midhun T. Phytochemical evaluation and anti-arthritic activity of root of Saussurealappa. Pharmacologia. 2011;2(9):265-7.
3. Burger WC. Evolutionary trends in the Central American species of Piper (Piperaceae). Brittonia. 1972;24:356-62.
4. Chowdhury U, Tanti B, Rethy P, Gajurel PR. Analysis of genetic diversity of certain species of piper using RAPD-based molecular markers. Applied biochemistry and biotechnology.

2014;174:168-73.

5. Kumar S, Kar A, Beena C, Patel J, Sohil V, Singh R. Antioxidant activities, phenolics, and piperine contents in four Piper species from India. American Journal of Essential Oils and Natural Products. 2021;9(1):24-31.
6. Ashokkumar K, Murugan M, Dhanya MK, Pandian A, Warkentin TD. Phytochemistry and therapeutic potential of black pepper [*Piper nigrum* (L.)] essential oil and piperine: A review. Clinical Phytoscience. 2021;7(1):1-1.
7. Xia MY, Yang J, Zhang PH, Li XN, Luo JF, Long CL, Wang YH. Amides, isoquinoline alkaloids and dipeptides from the aerial parts of *Piper mullesua*. Natural products and bioprospecting. 2018;8:419-30.
8. Manandhar NP, Plants SM. People of Nepal Timber Press Inc. Portland. 2002.
9. Tisserand R, Balacs T. Nutmeg: A review of the toxicology and pharmacology of nutmeg and its essential oil. Int. J. Aromather Winter. 1994;6:28-38.
10. Marston A, Hostettmann K, Msonthi JD. Isolation of antifungal and larvicidal constituents of Diplolophiumbuchanani by centrifugal partition chromatography. Journal of natural products. 1995;58(1):128-30.
11. Srivastava S, Gupta MM, Prajapati V, Tripathi AK, Kumar S. Insecticidal activity of myristicin from *Piper mullesua*. Pharmaceutical biology. 2001;39(3):226-9.
12. Xia MY, Yang J, Zhang PH, Li XN, Luo JF, Long CL, Wang YH. Amides, isoquinoline alkaloids and dipeptides from the aerial parts of *Piper mullesua*. Natural products and bioprospecting. 2018;8:419-30.
13. Smith A, *et al.* Anticancer potential of *Piper mullesua* extracts against various cancer cell lines. Planta Med. 2023;89(1): 32-41.
14. Da Silva JK, Da Trindade R, Alves NS, Figueiredo PL, Maia JG, Setzer WN. Essential oils from neotropical Piper species and their biological activities. International journal of molecular sciences. 2017;18(12):2571.
15. Mgbeahuruike EE, Yrjönen T, Vuorela H, Holm Y. Bioactive compounds from medicinal plants: Focus on Piper species. South African Journal of Botany. 2017;112:54-69.
16. Xiang CP, Han JX, Li XC, Li YH, Zhang Y, Chen L, Qu Y, Hao CY, Li HZ, Yang CR, Zhao SJ. Chemical composition and acetylcholinesterase inhibitory activity of essential oils from Piper species. Journal of Agricultural and Food Chemistry. 2017;65(18):3702-10.
17. Hamdy NA, Gamal-Eldeen AM. New pyridone, thioxopyridine, pyrazolopyridine and pyridine derivatives that modulate inflammatory mediators in stimulated RAW 264.7 murine macrophage. European journal of medicinal chemistry. 2009;44(11):4547-56.
18. Tumer TB, Onder FC, Ipek H, Gungor T, Savranoglu S, Tok TT, Celik A, Ay M. Biological evaluation and molecular docking studies of nitro benzamide derivatives with respect to in vitro anti-inflammatory activity. International immunopharmacology. 2017;43:129-39.
19. Tumer TB, Yılmaz B, Ozleyen A, Kurt B, Tok TT, Taskin KM, Kulabas SS. GR24, a synthetic analog of Strigolactones, alleviates inflammation and promotes Nrf2 cytoprotective response: In vitro and in silico evidences. Computational biology and Chemistry. 2018;76:179-90.
20. Reddy PS, Gupta RK, Reddy SM. Analgesic and anti-inflammatory activity of hydroalcoholic extract of Piper betle leaves in experimental animals. Int. J. Basic Clin. Pharmacol. 2016;5:979-85.
21. Tasleem F, Azhar I, Ali SN, Perveen S, Mahmood ZA. Analgesic and anti-inflammatory activities of Piper nigrum L. Asian Pacific journal of tropical medicine. 2014 Sep 1;7:S461-8.
22. Finato AC, Fraga-Silva TF, Prati AU, de Souza Júnior AA, Mazzeu BF, Felippe LG, Pinto RA, Golim MD, Arruda MS, Furlan M, Venturini J. Crude leaf extracts of Piperaceae species downmodulate inflammatory responses by human monocytes. PloS one. 2018 Jun 20;13(6):e0198682.