

PHARMACOLOGY AND PHARMACY

ETHNOPHARMACOLOGICAL CHARACTERISTICS OF PIPER BETLE FROM INDONESIAN-ASIAN REGION AND PROSPECTS OF ITS USE IN BIOMEDICAL PURPOSES

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RESUME

Rationale. Piper betle of the family of Piperaceae, (*P. betle*) is a liana growing in the tropics of the Indonesian-Asian region, has long been actively used in folk medicine as a source of remedies for a variety of health problems. At the same time, the methods and purposes of using *P. betle* in folk medicine vary from region to region, and the effectiveness of its impact on human remains fully underestimated.

The aim of the study. To systematize and analyze modern literature data on the pharmacological potential of the medicinal plant Piper betle, growing in the countries of Madagascar, India, Bali and China of the Indonesian-Asian region.

Materials and methods. The search and analysis of data were carried out in international and regional databases (PubMed, Scopus, Web of Science, Science Direct, and Google Scholar) for the period from 1996 to 2025.

Results. The analysis of scientific literature data showed that the target fragment of metabolome (TFM) of *Peper betle* is characterized by a complex composition of biologically active compounds (BAS), which varies significantly from region to region. BAS of the TFM of this plant are responsible for various types of pharmacological activity, which justifies its use in traditional medicine and growing interest to the medical scientific community. It was found that within the range of *P. betle* growth, the chemical composition of TFM varies in terms of the content of alkaloids, terpenes, phenolic compounds, including flavonoids and volatile components.

Conclusion. *P. betle* is a promising object for further research in the field of phytopharmacology and reproductive medicine. Obviously, in-depth preclinical and clinical studies are needed to confirm the identified effects based on literature sources. At the same time, the collected literature data can contribute to future research in the field of pharmacology in order to create new promising drugs.

Keywords: Piper betle, ethnobotany, phytochemistry, chemical composition, biological activity, traditional medicine

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ЭТНОФАРМАКОЛОГИЧЕСКИЕ ХАРАКТЕРИСТИКИ *PIPER BETLE* ИЗ ИНДОНЕЗИЙСКО-АЗИАТСКОГО РЕГИОНА И ПЕРСПЕКТИВЫ ЕГО ИСПОЛЬЗОВАНИЯ В БИМЕДИЦИНСКИХ ЦЕЛЯХ

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РЕЗЮМЕ

Обоснование. *Piper betle* семейства перечных Piperaceae, (*P. betle*) — лиана, произрастающая в тропиках Индонезийско-Азиатского региона, издавна активно используется в народной медицине в качестве источника средств для решения самых различных проблем со здоровьем. Вместе с тем, способы и цели использования *P. betle* в народной медицине различаются от региона к региону, а эффективность его воздействия на человека остается недооцененной в полной мере.

Цель исследования. Систематизировать и проанализировать современные литературные данные о фармакологическом потенциале лекарственного растения *Piper betle*, произрастающего в странах Индонезийско-Азиатского региона: Мадагаскар, Индия, Бали и Китай.

Материалы и методы. Поиск и анализ данных проводился в международных и региональных базах данных (PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar) за период с 1996 по 2025 гг.

Результаты. В ходе анализа научных литературных данных было показано, что целевой фрагмент метаболома (ЦФМ) *Peper betle* характеризуется сложным составом биологически активных веществ (БАВ), который существенно варьирует от региона к региону. БАВ ЦФМ этого растения отвечают за различные виды фармакологической активности, что оправдывает его применение в традиционной медицине и вызывает растущий интерес со стороны медицинского научного сообщества. Установлено, что в пределах ареала произрастания *P. betle* отличается вариабельностью химического состава ЦФМ по содержанию алкалоидов, терпенов, фенольных соединений, в том числе флавоноидов и летучих компонентов.

Заключение. *P. betle* представляет собой перспективный объект для дальнейших исследований в области фитофармакологии и репродуктивной медицины. Очевидно, для подтверждения выявленных эффектов на основе литературных источников необходимы углубленные доклинические и клинические исследования. Вместе с тем, собранные литературные данные могут способствовать проведению будущих исследований в области фармакологии с целью создания новых перспективных лекарственных средств.

Ключевые слова: *Piper betle*, этноботаника, фитохимия, химический состав, биологическая активность, традиционная медицина

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INTRODUCTION

The emergence of substantial evidence supporting the successful therapeutic use of *Piper betle* (*P. betle*) in the central and eastern regions of Malaysia has recently sparked significant scientific and practical interest in the plant [1]. In the wild, this species is primarily distributed across South and Southeast Asia, including India, Sri Lanka, Bangladesh, Malaysia, Indonesia, Myanmar, the Philippines, and parts of China. It is also found on Pacific islands such as Fiji, Micronesia, and the Solomon Islands [2]. Furthermore, it is widely cultivated for commercial purposes in India, Thailand, Sri Lanka, Taiwan, and many other tropical regions of South and Southeast Asia, Africa, and Madagascar, where it serves as both a food product and a source of raw material for the pharmaceutical industry.

P. betle is notable for being referred to as the “green gold of India,” as an estimated 20 million people depend on this plant for their livelihood through the cultivation, processing, and trade of its leaves [3]. *P. betle* leaves are deeply embedded in the culture of the Hindu people, where they are widely used in various social, cultural, and religious ceremonies. Since ancient times, *P. betle* has been utilized in numerous traditional medical systems, including Indian Ayurvedic medicine, Traditional Chinese Medicine, and the folk medicine of the West Indies and Latin America. In Ayurveda, the juice extracted from the leaves is used, often as an auxiliary component in combination with other medicinal plants [4]. In traditional medicine, *P. betle* leaves are employed to treat a variety of ailments, such as colds, bronchial asthma, coughs, stomach pain, rheumatism, and inflammatory conditions including boils, halitosis, constipation, conjunctivitis, oral diseases, abscesses, wounds, and cuts [5].

Recently, particular interest has been drawn to the biological activity of the chemical compounds found in medicinal plants, which belong to diverse classes such as alkaloids, various glycosides, phenolic compounds (including flavonoids and tannins), terpenes, and oligosaccharides [6]. The broad spectrum of chemical compounds in *P. betle*, including chavicol, chavibetol, hydroxychavicol, eugenol, estragole, methyleugenol, hydroxycatechin, α -pinene, caryophyllene, β -pinene, 1,8-cineole, among others, is largely determined by specific growth conditions, soil type, and the geographical characteristics of the plant's habitat. In this review, we have analyzed information on the target metabolome fragments (TMFs) of *P. betle* growing in different parts of the Indonesian–Asian region and evaluated data on its pharmacological activity, which establishes it as one of the most important representatives of the region's ethnomedicine. At the same time, considering the vast untapped potential for the practical use of *P. betle* as a medicinal agent, we have focused on a comprehensive examination of current research pertaining to its application in maintaining human health.

Maintaining reproductive health in both women and men is a critically important component of overall human health, as fertility and hormonal balance disorders are becoming increasingly prevalent among the reproductive-age population in many countries. The traditional use of *P. betle* by the peoples of various regions to enhance sexual activity and fertility suggests its potential role in supporting reproductive health. Given that the biologically active compounds (BACs) of *P. betle*, characterized by their multifunctional action, can influence both inflammatory and hormonal processes directly involved in the regulation of reproductive function, systematizing this modern scientific data will allow for an assessment of the plant's possible role in regulating human and animal reproductive function.

Thus, this article presents a review of recent research on the biological activity of various morphological parts of *P. betle* from four different areas of the Indonesian–Asian region, describing the cause-and-effect relationship between the traditional use of this plant by the inhabitants of these regions and the potential improvement of their health.

THE AIM OF THE STUDY

To systematize and analyze current literature data on the pharmacological potential of the medicinal plant *Piper betle* growing in Madagascar, India, Bali, and China within the Indonesian–Asian region.

MATERIALS AND METHODS

The literature search and data analysis were conducted using international and regional databases (PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar) for the period from 1996 to 2025.

RESULTS

Growth conditions of *P. betle* in the wild and under cultivation

P. betle grows in tropical and subtropical climate regions. The plant thrives at a consistent temperature range of 15 to 30 °C and under relatively high air humidity [7]. Temperatures below 10 °C can threaten its growth and, ultimately, its survival. Thus, the plant's natural distribution range is limited by its thermal and water requirements. Since *P. betle* requires diffused light rather than direct sunlight for active growth, it prefers the understory of tropical forests, beneath the canopy of tall trees. Prolonged exposure to sunlight can lead to water and heat stress, negatively affecting plant development [7]. For optimal growth, the plant requires well-drained soil rich in organic matter. A soil pH in the range of 5.5 to 6.5 is considered

optimal [8]. Conditions that deviate from these norms can lead to nutritional problems and a decline in plant health.

The optimal conditions for cultivating *P. betle* are highlands, particularly with fertile sandy, sandy-clay, or sandy-loam soils that have a good drainage system and a pH range of 5.6–8.2. Consequently, saline and alkaline soils, where waterlogging is an issue, are unsuitable. The plant requires approximately 2,250–4,750 mm of rainfall, relative humidity of 40–80 %, and a temperature range of 15–40 °C, all of which are considered suitable. Under cultivation, regular, abundant watering every 3–4 days is necessary; however, it is crucial to avoid waterlogging. Regular misting with water is beneficial for increasing ambient humidity [7]. On farms, *P. betle* is propagated by stem cuttings, with the necessary support for the vine to grow vertically. One year after planting the cutting, the leaves can already be harvested as raw material for practical use, and harvesting from a single plant can continue for several years [9].

Biologically active compounds of the target metabolome fragment of *Piper betle* from different regions

Piper betle, known as “pan” in Hindi, holds significant importance in both the cultural life and medicine of India. It is widely cultivated and consumed throughout the country, playing an important role in various religious ceremonies. Numerous studies have demonstrated the extensive phytochemical diversity of *P. betle*, which is influenced by the climatic conditions of its growing region, including soil composition, air humidity, and rainfall. The content of biologically active compounds (BACs) also depends on the harvest time of the betel leaves in a given region, the species diversity of other plants growing in the betel pepper’s habitat, and the type of agrochemical practices in the region [10]. Interestingly, the composition of *P. betle* from the Indian region includes compounds from the phenol and terpene classes. Terpenoids and their derivatives are particularly prevalent, including cadinene, 1,8-cineole, chavicol, chavibetol, safrole, camphene, limonene, caryophyllene, pinene, carvacrol, allylpyrocatechol, and eugenol [11]. Aqueous and methanolic extracts of *P. betle* from the Indian region have been found to contain alkaloids, flavonoids, tannins, steroids, glycosides, saponins, and terpenoids [12]. Extracts of *P. betle* leaves from Sri Lanka have been shown to contain the sesquiterpenes cadinene and caryophyllene, as well as safrole (52.7 %), eugenyl acetate (5.8 %), allylpyrocatechol diacetate (15.4 %), and eugenol (6.4 %) [13]. The predominant chemical constituents of *P. betle* in the Indian region include hydroxychavicol, known for its antibacterial and antioxidant properties, piperitenone, and chavibetol acetate (a phenolic compound), which exhibit significant antimicrobial and antifungal activity against 10 gram-positive and 12 gram-negative strains, as well as a fungal strain, *Candida tropicalis* [14].

P. betle is a medicinal plant valued in Asia and used as an important source of biologically active chemical compounds such as hydroxychavicol, flavonoids, eugenol, chavibetol, and naturally occurring nitrogenous compounds. The authors of one publication assert that various bioactive compounds, including tannins, flavonoids (quercetin), eugenol, hydroxychavicol, and chavibetol, possess antibacterial, antifungal (against *Aspergillus niger* and *Candida albicans*), antioxidant, antidiabetic, and anticancer properties [15]. The antimicrobial activity of phenolic compounds such as hydroxychavicol and eugenol has been studied against a range of microorganisms, including gram-negative *Escherichia coli* and *Pseudomonas aeruginosa*, gram-positive *Staphylococcus aureus*, and *Candida albicans* [16]. The presence of volatile compounds, among which limonene, linalool, and methylchavicol are of greatest interest, accounts for the characteristic aroma of *P. betle* [17]. Flavonoids, including quercetin and kaempferol, have demonstrated pronounced antioxidant and anti-inflammatory properties [18]. In addition to the aforementioned classes of compounds, *P. betle* from the Asian region also contains terpenes and amino acids [19].

The use of *P. betle* since ancient times has formed the basis of many cultural and medical traditions in various regions of the island of Bali. Balinese *P. betle* is characterized by a high content of phenolic compounds and essential oils, particularly safrole, chavibetol, and eugenol, as well as flavonoids, tannins, and hydroxychavicol. Due to this composition, *P. betle* extracts from Bali exhibit pronounced antioxidant activity, manifested in their ability to neutralize free radicals, prevent oxidative cell damage, and reduce oxidative stress levels. This is particularly important for protecting reproductive cells and other biological structures from damage [20]. The phenolic compounds, including hydroxychavicol and eugenol, abundant in *P. betle* in Bali, demonstrate strong antibacterial activity against specific pathogens, inhibiting the growth of both gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* bacteria and disrupting biofilm formation [21]. Volatile compounds, especially limonene, linalool, and methylchavicol, contribute to the characteristic aroma of Balinese *P. betle* [22].

Extracts of *P. betle* leaves growing in the southern regions of China possess a complex phytochemical composition, including bioactive compounds such as hydroxychavicol, eugenol, chavibetol, flavonoids (e.g., quercetin and apigenin), and tannins. Hydroxychavicol and eugenol exhibit pronounced *in vitro* antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*, as well as antioxidant activity, confirmed by DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) assays. These phenolic compounds are also abundant in Chinese *P. betle* [23]. Volatile compounds, with linalool and β -caryophyllene as the major constituents

identified in Chinese studies, impart the characteristic aroma to Chinese *P. betle* [24]. Flavonoids such as quercetin and kaempferol have been detected in Chinese *P. betle*, and their antioxidant and anti-inflammatory potential has been extensively studied [25].

Biological activity of compounds derived from *Piper betle*

P. betle, a plant widely used in traditional Asian medicine, possesses an impressive diversity of biological properties that have been the subject of extensive research. Phenolic compounds such as hydroxychavicol and eugenol exhibit significant antioxidant activity, neutralizing free radicals and protecting cells from oxidative damage [26].

The target metabolome fragment (TMF) of *P. betle* has demonstrated pronounced antimicrobial properties, as confirmed by a number of studies. It has been established that compounds such as hydroxychavicol are responsible for these properties, exhibiting antibacterial (against *Staphylococcus aureus* and *Escherichia coli*) [27] and fungicidal activity [28]. Hydroxychavicol, eugenol, allylpyrocatechol, carvacrol, and methyleugenol, all constituents of *P. betle*, have demonstrated antifungal activity against various fungal species [27, 21, 16]. In two studies published in 2023, the pronounced antimicrobial activity of *P. betle* leaf extracts against pathogenic bacterial strains was confirmed. For instance, a study conducted by Lao R.C.C. et al. showed that an ethanolic extract of *P. betle* leaves is active against the *Staphylococcus aureus* ATCC 29213 strain and is capable of disrupting the biofilms it produces [29]. Jantorn P. et al. demonstrated that *P. betle* leaf extract is effective against clinical isolates of *Staphylococcus pseudintermedius*, including both methicillin-sensitive (MSSP) and methicillin-resistant (MRSP) strains, highlighting the potential of *P. betle* as a natural antimicrobial agent [30].

P. betle leaves possess antiparasitic properties and also inhibit the growth and viability of protozoa (*Giardia intestinalis*) [31]. Some studies have shown that compounds such as hydroxychavicol may have beneficial effects in cancer treatment [32]. It has been shown that *P. betle* leaves have a stimulating effect on the central nervous system, associated with stimulant, euphoric, and cognitive properties, making it a compound of interest for neuropharmacological research [5].

Hydroxychavicol, abundantly present in *P. betle* L., has been studied for its anti-inflammatory potential. It acts by inhibiting the production of inflammatory mediators, suggesting its potential application in the treatment of inflammatory diseases [33].

A number of human studies have investigated the effects of *P. betle* TMF compounds on sperm function. A study [34] showed that regular consumption of this plant may have a negative impact on sperm quality. In a study of spermatogenesis in male Wistar rats, administration of the extract at doses of 200, 400, and 800 mg/kg body weight for 30 days reduced sperm count, concentration, motility, and normal morphology.

When studying the effect of the extract on the estrous cycle in female rats, a change in the duration of the cycle was observed, suggesting an influence of *P. betle* on the regularity of the reproductive cycle [35]. Furthermore, these studies have shown that components of the plant's TMF can interfere with normal sperm production, affect testicular function and sperm quality, and may potentially disrupt ovarian function and oocyte maturation, consequently affecting the estrous/menstrual cycle. It is important to note that the impact of *P. betle* on reproductive health may vary depending on the dose, frequency, and duration of use.

Animal studies have also investigated the potential effect of *P. betle* TMF on blood glucose levels. A study published in 2025 [36] showed that *P. betle* extracts can reduce blood glucose levels in diabetic rats, indicating its potential use in the treatment of type 2 diabetes.

A comparison of scientific data on the key bioactive compounds of the *P. betle* TMF growing in different regions and studies of their biological activity is presented in Table 1.

Prospects for research on *Piper betle* for the development of reproductive health products

Extracts obtained from *P. betle* possess antioxidant properties due to the presence of hydroxychavicol and eugenol, suggesting a potential role in protecting reproductive cells from oxidative damage [50]. Studies indicate that the complex of bioactive compounds in the *P. betle* TMF exhibits anti-inflammatory properties, which may help reduce inflammation in the organs of the reproductive system. Some researchers suggest that these effects may be attributed to compounds such as eugenol [1]. Certain compounds of the *P. betle* TMF have demonstrated a modulating effect on sex hormones, such as estradiol and progesterone. This could potentially have a positive impact on the hormonal regulation associated with reproductive health [51].

Extracts from *P. betle* have shown antimicrobial activity against various bacterial strains (*Staphylococcus aureus*, *Escherichia coli*) and fungi (*Trichophyton rubrum*, *T. mentagrophytes*, *Microsporum gypseum*, *Epidermophyton floccosum*, and *Candida albicans*), which is important for the prevention of sexually transmitted infections that affect reproductive health [52, 53]. Individual studies indicate that extracts from *P. betle* possess antitumor activity *in vitro*, particularly in the context of reproductive organ cancers [54].

Despite the need for further research, an analysis of published scientific data suggests that the bioactive compounds of the *P. betle* TMF may have a beneficial effect on libido and sexual function, which could indirectly contribute to reproductive health [55].

CONCLUSION

P. betle is a plant of cultural, nutritional, and medicinal significance in countries where it grows wild

TABLE 1

COMPARATIVE DATA FROM STUDIES OF THE CHEMICAL COMPOSITION AND BIOLOGICAL ACTIVITY OF *P. BETLE* IN THE INDONESIAN-ASIAN REGION

Geographical range	Key BACs of the TMF isolated from <i>P. betle</i> leaves	The described biological and pharmacological properties of BACs
Indian region	Eugenol [37, 38]	Anticariogenic, antiprotozoal [37] Antioxidant [38, 39, 40] Anti-inflammatory [39, 41]
		Antifungal, antioxidant [37]
	Hydroxychavicol [42] Allylpyrocatechol [37] Chavicol [43]	
Asian region	Allylpyrocatechol diacetate [44]	Antidiabetic [44]
	Chavibetol acetate [44]	Antinociceptive [44] Antimicrobial [44] Insecticidal [44] Antioxidant [44] Gastroprotective [44] Antidiabetic [44]
	3-Fluoro-2-propynenitrile [45] Tris(trifluoromethyl)phosphine [45]	Antimicrobial [45]
	Coniferyl aldehyde [7]	Anti-inflammatory [46]
Bali and the Indonesian region	Eugenol [47]	Antifungal [47]
	Hydroxychavicol [48]	Anti-inflammatory [48] Antioxidant [48]
China	Eugenol [41]	Antibacterial [41] Antioxidant [41]
	Lignans: Licarin A [49]	Antipruritic [49]

or is cultivated for practical use. Its success as an agricultural crop largely depends on specific environmental conditions, and a thorough understanding of the plant's biological characteristics is crucial for its sustainable cultivation and conservation within its natural range.

The complex mixture of BACs within the *P. betle* TMF is responsible for various types of pharmacological activity, which justifies its use in traditional medicine and has generated growing interest from the medical research community. Across its geographical range, *P. betle* exhibits variability in the chemical composition of its TMF in terms of the presence and content

of alkaloids, phenolic compounds (including flavonoids), and volatile components. These compounds confer unique properties upon the plant, making it a vital component of traditional medicine in the countries where it grows.

It is important to note that the chemical composition of the *Piper betle* TMF can vary depending on various factors, such as the diversity of plant species in the surrounding tropical biocenosis, climatic conditions, and the geographical region of growth. This adaptive variability underscores the importance of conducting targeted studies to determine the chemical composition of the plant in each specific region.

At the same time, the impact of traditional remedies derived from this plant on human health improvement remains a poorly understood topic with respect to the safe use of ethnomedicine, an issue that warrants serious attention in future research. Consequently, further studies are clearly needed to investigate the molecular biological activity underlying the pharmacological characteristics of the chemical components of the medicinal plant *P. betle*. Furthermore, clinical trials are required to elucidate the full spectrum of pharmacological effects of drugs developed from *P. betle* plant material.

P. betle exhibits a wide range of biological activities associated with its TMF: from antimicrobial properties to anti-inflammatory, antioxidant, central nervous system-stimulating, and antiparasitic effects, and even prospects in cancer therapy. This diversity of biological properties makes *P. betle* an intriguing subject for research and a valuable resource in both traditional and modern medicine. Current research is underway to explore the potential of *P. betle* as a source of anti-inflammatory, antimicrobial, antidiabetic, and anti-cancer agents. However, it should be noted that most of these experiments are in the early stages, and further research is required to confirm and clarify their potential benefits for humans.

Despite the abundance of scientific publications, most research on the effects of *P. betle* on human reproductive health remains at the preclinical level. Some animal studies have demonstrated a positive effect of *P. betle* bioactive compounds on oogenesis, cycle regularity, and sperm quality; however, the data obtained require more rigorous clinical confirmation. Given the traditional use of this plant by various peoples of the Indonesian–Asian region as an aphrodisiac, and the presence of active compounds that potentially influence hormone regulation and inflammatory processes, *P. betle* represents a promising subject for further research on supporting human reproductive health.

Conflicts of interest

The authors declare no conflicts of interest.

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