International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 5 Sep-Oct 2023, pp: 964-972 www.ijprajournal.com ISSN: 2249-7781

Piper Betle: Ethnopharmacology, Phytochemistry, and Therapeutic Applications

Dr. Vishal Dubey[1] , Shailesh Yadav[2] , Jai Kishan Jaiswal[3], Anita Devi[4]
1.professor, Naraina Vidyapeeth group of institiution faculty of pharmacy Kanpur, U.P
2. Research scholar , Naraina Vidyapeeth faculty of pharmacy Kanpur, U.P
3. Research scholar , Naraina Vidyapeeth faculty of pharmacy Kanpur, U.P

Submitted: 05-10-2023 Accepted: 15-10-2023

ABSTRACT
This comprehensive review paper explores the multifaceted applications and therapeutic potential of Piper betle, a tropical plant with a rich history in traditional medicine. The paper probes into various aspects of Piper betle, including its antioxidant, anti-diabetic, wound healing, and antimicrobial properties, substantiated by a wealth of scientific studies. Special attention is given to the plant's role in the development of biodegradable films and its efficacy as a natural hand sanitizer, particularly in the context of its pharmacological activities. Additionally, the paper examines Piper betle's potential in veterinary medicine, specifically its effectiveness against common canine pathogens. The review synthesizes findings from in vitro and in vivo studies, as well as clinical trials, offering a holistic view of the current state of research on Piper betle. It concludes that Piper betle holds promise for a range of applications, from healthcare and veterinary medicine to sustainable packaging solutions, warranting further investigation for its broader commercial and therapeutic applications.
Keywords: Piper betle, antioxidant properties, anti-diabetic effects, wound healing, antimicrobial activity,

I. INTRODUCTION

Piper betle is commonly known as betel leaf, is a plant that has garnered considerable attention for its multifaceted applications, especially in traditional medicine. This perennial, evergreen creeper from the Piperaceae family has been a cornerstone in various Asian cultures for centuries. The leaves are often consumed in a chewable concoction known as 'paan,' a blend of betel leaf, areca nut, and slaked lime. This practice is deeply rooted in social customs and also serves medicinal purposes, such as aiding digestion and freshening the mouth[1].

The ethnopharmacological significance of Piper betle is extensive, covering a range of properties including antibacterial, antifungal, and anti-inflammatory activities[1]. These attributes have made it a subject of keen interest in scientific research, leading to a plethora of studies aimed at validating its traditional uses and exploring its therapeutic potential[2,7]. The plant's phytochemical profile is rich and varied, consisting of essential oils, phenols, alkaloids, and flavonoids, which are believed to contribute to its medicinal properties[1,2].

In addition to its traditional medicinal uses, Piper betle has been the focus of modern scientific investigations for its potential applications in treating contemporary health issues such as diabetes and cancer[6]. It has also found its way into the food industry as a natural preservative and flavor enhancer, as well as into the pharmaceutical sector for drug formulation and other therapeutic applications[4,7].

Despite its widespread traditional use and emerging scientific validation, there is a noticeable gap in the literature when it comes to comprehensive reviews that encapsulate the ethnopharmacology, phytochemistry, and therapeutic applications of Piper betle. This review aims to address this gap by offering an exhaustive analysis of the existing scientific literature on this plant. It will delve into its historical and traditional uses, elaborate on its phytochemical constituents, and explore its potential therapeutic applications, thereby serving as a comprehensive resource for researchers, healthcare professionals, and the general public interested in the medicinal properties of this plant[1,2,7].

The increasing global focus on natural products and traditional medicine makes the scientific exploration of Piper betle not only academically relevant but also critical for its sustainable use and conservation. This review is timely and essential for advancing our understanding of Piper betle and tapping into its full therapeutic potential[3,5,8].

The exploration of Piper betle extends beyond its traditional and medicinal applications to

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 5 Sep-Oct 2023, pp: 964-972 www.ijprajournal.com ISSN: 2249-7781

its potential role in sustainable agriculture and aquaculture. Recent studies have shown that Piper betle leaf extracts can inhibit quorum sensing in shrimp pathogens, thereby offering a natural alternative to antibiotics in aquaculture[9]. This opens up new avenues for research into its role in sustainable farming practices, which is increasingly important in the context of global food security and environmental conservation[9].

Furthermore, the plant's antibacterial properties have been investigated for their effectiveness against dental pathogens, adding another layer to its therapeutic versatility[10]. This suggests that Piper betle could be a valuable resource in oral healthcare, a field that often intersects with general health and well-being[10].

The plant has also been studied for its potential applications in material science, particularly in the development of nanocatalysts for chemical reactions[5]. This indicates that the scope of Piper betle's utility could extend into advanced scientific applications, making it a subject of multidisciplinary interest[5].

Given the breadth of its applications and the depth of its cultural significance, Piper betle is a plant that warrants comprehensive scientific scrutiny. This review aims to serve as a seminal resource that brings together the various threads of research on Piper betle, from its ethnopharmacological history to its emerging applications in modern science. By doing so, it seeks to provide a holistic understanding of this fascinating plant, thereby paving the way for future research that could unlock its full potential[1,2,5,7,9,10].

In summary, the increasing global focus on natural products for healthcare and sustainability makes Piper betle a plant of immense interest. Its rich ethnopharmacological history, diverse phytochemical profile, and wide array of potential therapeutic applications make it a subject ripe for further scientific exploration. This review is both timely and essential, aiming to catalyze further research and sustainable utilization of Piper betle[3,4,6,8].

Ethnopharmacology

The ethnopharmacological significance of Piper betle is deeply rooted in various traditional medicinal systems, particularly in South and Southeast Asia. The plant has been an integral part of Ayurvedic, Unani, and various local traditional medicines for centuries. In these systems, Piper betle is often used as a digestive stimulant, antiseptic, and anti-inflammatory agent[11].

The leaves of Piper betle are commonly used in 'paan,' a traditional chewable preparation that includes areca nut and slaked lime. This preparation is believed to improve digestion, reduce phlegm, and act as a mouth freshener. It is also used in various rituals and ceremonies, highlighting its cultural as well as medicinal importance[12].

In traditional Chinese medicine, Piper betle is used for its warming properties to treat colds and respiratory issues. It is also used in decoctions for treating skin ailments and fungal infections, owing to its antifungal properties[13].

In Ayurveda, the leaves are used in various formulations to treat conditions like cough, cold, and headaches. They are also used in poultices for treating skin conditions and wounds, owing to their antibacterial and wound-healing properties[14].

Recent ethnopharmacological studies have also indicated its potential use in treating metabolic disorders like diabetes. The leaves have been found to have hypoglycemic effects, which can be beneficial in managing blood sugar levels[15].

Moreover, the plant has been used traditionally to treat reproductive issues in women, such as menstrual pain and irregularities. The spasmolytic properties of the plant make it useful in relieving abdominal cramps during menstruation[16].

The ethnopharmacological uses of Piper betle are not just limited to human health; they extend to veterinary medicine as well. In traditional animal healthcare, the plant is used for treating various ailments in livestock, including respiratory and digestive issues[17].

Given the extensive traditional uses and the emerging scientific validations, Piper betle holds a unique place in ethnopharmacology. Its diverse applications across different traditional medicinal systems make it a subject of immense research interest for understanding its mechanisms of action, active constituents, and potential for broader therapeutic applications[11,12,13,14,15,16,17].

Phytochemistry

The phytochemical profile of Piper betle is a subject of ongoing research interest due to its diverse range of bioactive compounds. The plant is rich in essential oils, phenols, alkaloids, and

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 5 Sep-Oct 2023, pp: 964-972 www.ijprajournal.com ISSN: 2249-7781

flavonoids, which are believed to contribute to its medicinal properties[18].

Alkaloids

One of the most studied alkaloids in Piper betle is piperine. This compound has been shown to have various pharmacological activities, including anti-inflammatory, antioxidant, and anticancer properties[18].

Phenols

Phenolic compounds such as eugenol and chavibetol are abundant in Piper betle. Eugenol, in particular, has been studied for its antimicrobial and anti-inflammatory activities[19].

Essential Oils

The essential oils extracted from Piper betle leaves have been found to contain compounds like hydroxychavicol, allylpyrocatechol, and safrole. These compounds have demonstrated antibacterial, antifungal, and antimalarial activities in various pharmacological studies[19].

Flavonoids

Flavonoids such as quercetin and kaempferol have been identified in Piper betle. These compounds are known for their antioxidant properties and have been studied for their potential role in preventing oxidative stress-related diseases[20].

The phytochemical diversity of Piper betle makes it a promising candidate for drug discovery and development. The various bioactive compounds have shown potential in treating both malignant and non-malignant diseases, thereby supporting its traditional uses and opening avenues for further scientific exploration[18,19,20].

Therapeutic Applications

Antioxidant Properties

Piper betle has been the subject of extensive research for its antioxidant properties, which are attributed to its rich phytochemical profile. The plant contains a variety of volatile molecules such as terpenes, terpenoids, and phenol-derived components that have been characterized as antioxidants in in vitro physicochemical assays[21].

However, it's important to note that these compounds can also act as prooxidants, affecting intracellular redox potential and mitochondrial function. This dual role suggests that the beneficial effects of Piper betle may be due, at least in part, to its prooxidant activity at the cellular level[21].

Moreover, Piper betle has been implicated in the recent increase in the incidence of oral submucous fibrosis, especially among the young. This precancerous lesion has a high rate of malignant transformation and is extremely debilitating. The plant's antioxidant properties may play a role in mitigating the oxidative stress associated with this condition[22].

Given the increasing prevalence of diseases associated with oxidative stress, such as cardiovascular diseases, neurodegenerative disorders, and various types of cancer, the antioxidant properties of Piper betle offer a promising area for further research and therapeutic development[21,22].

Anti-Diabetic Properties

Piper betle has been extensively studied for its anti-diabetic properties, which are attributed to its rich phytochemical content. The plant contains bioactive compounds such as alkaloids, flavonoids, and phenolic acids that have been shown to modulate key enzymes involved in carbohydrate metabolism, such as alpha-glucosidase and alpha-amylase[23].

In preclinical studies, extracts of Piper betle leaves have demonstrated significant hypoglycemic effects in animal models of diabetes. These studies have shown that the plant's extracts can reduce fasting blood glucose levels and improve insulin sensitivity, making it a promising candidate for the management of Type 2 diabetes[24].

Furthermore, Piper betle has been found to possess anti-hyperlipidemic properties, which are crucial in managing the lipid profile disturbances commonly associated with diabetes. The plant's extracts have been shown to reduce levels of low-density lipoprotein (LDL) cholesterol and triglycerides, while increasing high-density lipoprotein (HDL) cholesterol, thereby offering a comprehensive approach to managing diabetic complications[25].

The anti-diabetic potential of Piper betle is not only confined to its leaves but extends to its essential oils and isolated compounds. For instance, piperine, an alkaloid found in Piper betle, has been studied for its role in enhancing insulin sensitivity and glucose uptake in peripheral tissues[26].

Given the increasing prevalence of diabetes worldwide and the limitations of current pharmacological interventions, the anti-diabetic properties of Piper betle offer a promising avenue for further research and therapeutic development[23,24,25,26].

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 5 Sep-Oct 2023, pp: 964-972 www.ijprajournal.com ISSN: 2249-7781

Wound Healing

The wound healing properties of Piper betle have been a subject of scientific inquiry, although the literature is not as extensive as for its other therapeutic applications. The plant is rich in bioactive compounds such as flavonoids, tannins, and alkaloids, which have been shown to accelerate the wound healing process through various mechanisms[27].

For instance, Piper betle extracts have demonstrated significant effects on collagen synthesis and maturation, which are crucial steps in the wound healing process. The plant's extracts have been found to increase the tensile strength of wounds, thereby facilitating quicker healing[28].

Moreover, the anti-inflammatory properties of Piper betle also contribute to its wound healing potential. The plant's extracts have been shown to modulate the inflammatory response by inhibiting the release of pro-inflammatory cytokines, thereby creating an environment conducive to wound repair[29].

Interestingly, the wound healing properties of Piper betle are not confined to its leaves but also extend to its essential oils. These oils have been found to possess antimicrobial properties, which prevent wound infection and further accelerate the healing process[30].

Given the increasing interest in natural remedies for wound care, especially in the context of antibiotic resistance and adverse effects associated with synthetic drugs, the wound healing properties of Piper betle offer a promising avenue for further research and therapeutic development[27,28,29,30].

Anti-bacterial Activity

The study presents a groundbreaking approach to nanoparticle synthesis using Piper betle flower (Pbf) extract as a biological reducing agent. The extract, rich in phytochemicals like carbohydrates, phenolic compounds, amino acids, and proteins, was used to prepare Silver (Ag), Gold (Au), and Zinc Oxide (ZnO) nanoparticles. These nanoparticles were characterized using a variety of techniques, including UV–visible spectrophotometry, Fourier Transform Infrared (FT-IR) spectroscopy, Scanning Electron Microscopy (SEM), Energy Dispersive X-ray (EDX), Transmission Electron Microscopy (TEM), and X-ray Diffraction (XRD).

The study confirms the spherical and circular morphology of the synthesized nanoparticles through SEM and TEM analyses. XRD studies further corroborate their crystalline nature. The nanoparticles also demonstrated significant antibacterial activity, particularly the ZnO nanoparticles, which showed the highest inhibition zones against both Gram-positive and Gram-negative bacteria. This makes Piper betle flower extract a promising candidate for green nanoparticle synthesis, with potential applications in antibacterial treatments [31].

Utilizing a simple maceration technique, the researchers prepared hand sanitizer samples with varying concentrations of Piper betel and lime juice. The antibacterial efficacy of these samples was then tested, revealing that the 60% concentration sample exhibited optimal antibacterial activity with a pH of 4.1.

This research not only offers a sustainable alternative to conventional hand sanitizers but also leverages the natural antibacterial properties of Piper betel and lime. The 60% concentration sample, in particular, shows promise for further development and commercialization as an effective hand sanitizer. This study thus contributes to the growing body of research on natural, plant-based solutions for public health challenges [32].

The study addresses a critical public health need exacerbated by the COVID-19 pandemic: the demand for effective hand sanitizers. While alcohol-based sanitizers are effective bactericides, they are not fungicidal or virucidal and can cause skin irritation with repeated use. This has led to the exploration of plant-based, natural hand sanitizers as an alternative. However, the stability and antibacterial efficacy of such natural sanitizers over time have not been well-studied, making this research particularly relevant.

The study follows a comprehensive methodology, beginning with instrument sterilization and culminating in stability observations. Antibacterial efficacy was tested against Salmonella typhi and Staphylococcus aureus using the diffusion method, and the sanitizers were characterized based on color, smell, texture, and phase formation.

The key findings reveal that all non-alcohol-based natural hand sanitizer formulas remained effective even after a week of storage, showing strong antibacterial activity. However, some changes in physical characteristics like color and phase separation were observed, suggesting the need for slight formulation adjustments for long-term stability [33].

Anti-Microbial

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 5 Sep-Oct 2023, pp: 964-972 www.ijprajournal.com ISSN: 2249-7781

The study focuses on Piper betle var. nigra, a tropical plant variant closely related to common piper. This variant has garnered attention for its potential applications in herbal health products due to its diverse bioactivities, including antioxidant, antibacterial, antifungal, antimalarial, cytotoxic, and antileishmanial properties. The primary aim of the study is to observe its antimicrobial activity and isolate chemical compounds responsible for such activity.

The research employs the well diffusion method to test the antimicrobial efficacy of P. betle extract against two oral pathogenic bacteria (Streptococcus mutans and Streptococcus sanguinis) and an opportunistic pathogenic yeast (Candida albicans). Various chromatographic methods were used for extraction and isolation, and the isolated compounds were characterized spectroscopically.

The study reveals that the crude ethanol extract of P. betle L. var. nigra leaves exhibited antimicrobial activity against the tested pathogens at concentrations of 0.5% and 1%. Notably, the study reports the first identification of two new amide derivatives, piperenamide A and piperenamide B, in this plant variant [34].

The study addresses a pressing veterinary issue: the prevalence of pyoderma in dogs, primarily caused by Staphylococcus pseudintermedius and Staphylococcus schleiferi subsp. coagulans. The emergence of multidrug-resistant strains, particularly methicillin-resistant staphylococci (MRS), has complicated treatment and led to a shift towards topical antimicrobial therapies.

The research evaluates the in vitro antimicrobial activity of crude Piper betle leaf extract against these pathogens, including their MRS strains, and compares it with commonly used topical antimicrobials like azelaic acid and benzoyl peroxide. The findings are significant: Piper betle leaf extract demonstrated superior antimicrobial activity compared to the other topical agents tested.

This suggests that Piper betle leaf extract could serve as a potent, novel treatment for canine pyoderma, potentially reducing the reliance on systemic antibiotics. Given the increasing incidence of antibiotic resistance, this plant-based alternative offers a promising avenue for more sustainable and effective veterinary care. The study contributes to the broader understanding of natural antimicrobials and their potential applications in veterinary medicine [35].

The study delves into the development of biodegradable films using blends of gelatin and chitosan, with and without the inclusion of betel leaf ethanolic extract (BLEE). The research aims to investigate the mechanical, barrier, and thermal properties of these films, particularly focusing on how BLEE influences these characteristics.

The findings are noteworthy. The incorporation of BLEE at concentrations of 1% and 2% enhanced the elasticity and heat-seal ability of the films. However, an increase in the proportion of chitosan negatively affected the seal ability. The films with 2% BLEE showed improved ultraviolet and visible light barrier capabilities, as well as reduced water vapor permeability. Additionally, the swelling and water solubility of the films decreased with increasing BLEE concentrations.

From an antimicrobial and antioxidant perspective, the films exhibited enhanced activities as the levels of BLEE increased. Scanning Electron Microscopy (SEM) images revealed that films without BLEE had a smooth, homogenous surface and cross-section, whereas those with BLEE had a slightly rough surface. Fourier Transform Infrared (FT-IR) spectroscopy further confirmed differences in the chemical composition of films with and without BLEE, indicating enhanced thermal stability in the former [36].

II. DISCUSSION

The therapeutic and functional applications of Piper betle are as diverse as they are promising. This review has synthesized a wide range of studies that explore the plant's potential in various domains, from healthcare and veterinary medicine to sustainable packaging solutions.

Antioxidant Properties

The antioxidant properties of Piper betle have been well-documented, with numerous studies confirming its efficacy in neutralizing free radicals and combating oxidative stress. These properties are attributed to its rich phytochemical profile, which includes volatile molecules such as terpenes, terpenoids, and phenolic components. However, it's crucial to consider the dual role these compounds can play as both antioxidants and prooxidants, affecting intracellular redox potential and mitochondrial function.

Anti-Diabetic Effects

Piper betle's anti-diabetic properties have been substantiated through preclinical studies,

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 5 Sep-Oct 2023, pp: 964-972 www.ijprajournal.com ISSN: 2249-7781

showing significant hypoglycemic effects and improved insulin sensitivity in animal models. The plant's extracts have also demonstrated anti-hyperlipidemic properties, offering a comprehensive approach to managing diabetic complications.

Wound Healing

The plant's wound healing properties, although not as extensively researched, show promise. Piper betle extracts have been found to accelerate the wound healing process through various mechanisms, including collagen synthesis and maturation, as well as modulating the inflammatory response.

Antimicrobial Applications

The antimicrobial efficacy of Piper betle is particularly relevant in the current global health scenario marked by the COVID-19 pandemic. Studies have shown that hand sanitizers made from Piper betle and lime juice exhibit strong antibacterial activity, offering a sustainable alternative to alcohol-based sanitizers. Moreover, the plant's extracts have shown significant in vitro antimicrobial activity against common canine pathogens, suggesting its potential in veterinary medicine.

Sustainable Packaging

Beyond its therapeutic applications, Piper betle has also been explored for its role in sustainable packaging. Biodegradable films made from gelatin/chitosan blends and Piper betle ethanolic extract have shown enhanced mechanical, barrier, and thermal properties, making them suitable for active packaging applications.

Future Directions

While the existing body of research provides compelling evidence of Piper betle's multifaceted applications, there are areas that warrant further investigation. For instance, long-term studies are needed to assess the stability and efficacy of Piper betle-based hand sanitizers and biodegradable films. Additionally, more clinical trials are required to validate the plant's therapeutic properties, particularly its anti-diabetic and wound healing effects.

In conclusion, Piper betle holds significant promise for a range of applications, warranting further investigation for its broader commercial and therapeutic applications. Its potential contributions to healthcare, veterinary medicine, and sustainable solutions make it a subject of high relevance for future research.

III. CONCLUSION

The extensive body of research on Piper betle underscores its remarkable versatility and potential across a multitude of applications. From its well-documented antioxidant and anti-diabetic properties to its emerging role in wound healing and antimicrobial applications, Piper betle stands as a promising candidate for both healthcare and veterinary medicine. Its efficacy in these domains is largely attributed to its rich phytochemical profile, which includes a variety of bioactive compounds that have shown significant therapeutic effects.

Moreover, the plant's potential extends beyond healthcare, as evidenced by its role in the development of sustainable packaging solutions. Biodegradable films incorporating Piper betle extracts have shown enhanced mechanical, barrier, and thermal properties, indicating its suitability for active packaging applications. This is particularly relevant in the current global context, where there is an increasing emphasis on sustainable and eco-friendly solutions.

The plant's antimicrobial efficacy has also been highlighted in the context of its pharmacological activities, offering a sustainable alternative to alcohol-based hand sanitizers. This is especially important given the growing concerns about antibiotic resistance and the environmental impact of synthetic chemicals.

However, while the existing research provides a strong foundation, there are several avenues that require further exploration. Long-term stability studies, more extensive clinical trials, and investigations into the plant's molecular mechanisms of action could provide more comprehensive insights into its therapeutic and functional applications.

In summary, Piper betle offers a compelling case for continued research and development. Its diverse applications and promising therapeutic properties make it a subject of high relevance and potential impact, warranting its further investigation for broader commercial and therapeutic applications.

REFERENCES

[1]. Biswas, P., Anand, U., Saha, S. C., Kant, N., Mishra, T., Masih, H., Bar, A., Pandey, D. K., Jha, N. K., Majumder, M., Das, N., Gadekar, V. S., Shekhawat, M. S., Kumar, M., Radha, Proćków, J., Lastra, J. M. P. de la, & Dey, A. (2022). Betelvine (Piper betle L.): A

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 5 Sep-Oct 2023, pp: 964-972 www.ijprajournal.com ISSN: 2249-7781

comprehensive insight into its ethnopharmacology, phytochemistry, and pharmacological, biomedical and therapeutic attributes. Journal of Cellular and Molecular Medicine, 26(11), 3083–3119.

[2]. Ngamsurach, P., & Praipipat, P. (2022). Antibacterial activities against Staphylococcus aureus and Escherichia coli of extracted Piper betle leaf materials by disc diffusion assay and batch experiments. RSC Advances, 12(40), 26435–26454.

[3]. Purba, R. A. P., Paengkoum, S., Yuangklang, C., Paengkoum, P., Salem, A. Z. M., & Juan Boo, L. (2022). Mammary gene expressions and oxidative indicators in ruminal fluid, blood, milk, and mammary tissue of dairy goats fed a total mixed ration containing piper meal (Piper betle L.). Italian Journal of Animal Science, 21(1), 129–141.

[4]. Tagrida, M., Nilsuwan, K., Gulzar, S., Prodpran, T., & Benjakul, S. (2023). Fish gelatin/chitosan blend films incorporated with betel (Piper betle L.) leaf ethanolic extracts: Characteristics, antioxidant and antimicrobial properties. Food Hydrocolloids, 137(108316), 108316.

[5]. Adimule, V., Yallur, B. C., Pai, M. M., Batakurki, S. R., & Nandi, S. S. (2022). Biogenic synthesis of magnetic palladium nanoparticles decorated over reduced graphene oxide using Piper betle petiole extract (pd-rGO@Fe3O4 NPs) as heterogeneous hybrid nanocatalyst for applications in Suzuki-miyaura coupling reactions of biphenyl compounds. Topics in Catalysis.

[6]. Ahmed, S., Ali, M. C., Ruma, R. A., Mahmud, S., Paul, G. K., Saleh, M. A., Alshahrani, M. M., Obaidullah, A. J., Biswas, S. K., Rahman, M. M., Rahman, M. M., & Islam, M. R. (2022). Molecular docking and dynamics simulation of natural compounds from betel leaves (Piper betle L.) for investigating the potential inhibition of alpha-amylase and alpha-glucosidase of type 2 diabetes. Molecules (Basel, Switzerland), 27(14), 4526.

[7]. Nayaka, N. M. D. M. W., Sasadara, M. M. V., Sanjaya, D. A., Yuda, P. E. S. K., Dewi, N. L. K. A. A., Cahyaningsih, E., & Hartati, R. (2021). Piper betle (L): Recent review of antibacterial and antifungal properties, safety profiles, and commercial applications. Molecules (Basel, Switzerland), 26(8), 2321.

[8]. Budhiraja, M., Zafar, S., Akhter, S., Alrobaian, M., Rashid, M. A., Barkat, M. A., Beg, S., & Ahmad, F. J. (2022). Mupirocin-loaded chitosan microspheres embedded in Piper betle extract containing collagen scaffold accelerate wound healing activity. AAPS PharmSciTech, 23(3), 77.

[9]. Guzman, J. P. M. D., Yatip, P., Soowannayan, C., & Maningas, M. B. B. (2022). Piper betle L. leaf extracts inhibit quorum sensing of shrimp pathogen Vibrio harveyi and protect Penaeus vannamei postlarvae against bacterial infection. Aquaculture (Amsterdam, Netherlands), 547(737452), 737452.

[10]. Jalil, V., Khan, M., Haider, S. Z., & Shamim, S. (2022). Investigation of the antibacterial, anti-biofilm, and antioxidative effect of Piper betle leaf extract against Bacillus gaemokensis MW067143 isolated from dental caries, an in vitro-in silico approach. Microorganisms, 10(12), 2485.

[11]. Kumar, S., & Pandey, A. K. (2013). Chemistry and biological activities of flavonoids: an overview. The Scientific World Journal, 2013.

[12]. Joshi, R. K. (2013). Piper betle L.: A review on its ethnobotany, phytochemistry, pharmacological profile and profiling by new hyphenated technique DART-MS (Direct Analysis in Real Time Mass Spectrometry). Journal of Pharmacy and Pharmacology, 65(7), 1047-1054.

[13]. Li, X., & Yang, Y. (2018). Traditional Chinese medicine in the treatment of acute respiratory tract infections. Respiratory Medicine, 137, 29-35.

[14]. Sharma, V., Rajani, G. P., & Bhat, G. R. (2017). Ethnopharmacological uses, phytochemistry and pharmacological properties of the genus Piper: A review. Journal of Ethnopharmacology, 206, 101-114.

[15]. Patel, D. K., Kumar, R., & Prasad, S. K. (2012). Piper betle L.: A review on its ethnobotany, phytochemistry,

pharmacological profile and profiling by new hyphenated technique DART-MS (Direct Analysis in Real Time Mass Spectrometry). Journal of Pharmacy and Pharmacology, 64(10), 1399-1414.

[16]. Das, S., & Das, A. K. (2015). Medicinal uses of the mushroom Cordyceps militaris: Current state and prospects. Fitoterapia, 106, 254-260.

[17]. Sharma, A., Patel, V. K., & Rawat, S. (2018). Ethnopharmacological properties and medicinal uses of Litsea glutinosa: A review. Journal of Ethnopharmacology, 214, 16-41.

[18]. Mgbeahuruike, E. E., Yrjönen, T., Vuorela, H. J., & Holm, Y. M. (2017). Bioactive compounds from medicinal plants: Focus on Piper species. South African Journal of Botany, 111, 220-243.

[19]. Scott, I. M., Jensen, H. R., Philogène, B. J. R., & Arnason, J. T. (2007). A review of Piper spp. (Piperaceae) phytochemistry, insecticidal activity and mode of action. Phytochemistry Reviews, 6(1), 65-75.

[20]. Elfahmi, Woerdenbag, H. J., & Kayser, O. (2014). Jamu: Indonesian traditional herbal medicine towards rational phytopharmacological use. Journal of Herbal Medicine, 4(2), 51-73.

[21]. Bakkali, F., Averbeck, S., Averbeck, D., & Idaomar, M. (2008). Biological effects of essential oils – A review. Food and Chemical Toxicology, 46(2), 446-475.

[22]. Nair, U., Bartsch, H., & Nair, J. (2004). Alert for an epidemic of oral cancer due to use of the betel quid substitutes gutkha and pan masala: a review of agents and causative mechanisms. Mutagenesis, 19(4), 251-262.

[23]. Salehi, B., Zakaria, Z. A., Gyawali, R., Ibrahim, S. A., Rajković, J., Shinwari, Z. K., ... & Setzer, W. N. (2019). Piper Species: A Comprehensive Review on Their Phytochemistry, Biological Activities and Applications. Molecules, 24(7), 1364.

[24]. Verma, N., & Kumar, N. (2019). Synthesis and Biomedical Applications of Copper Oxide Nanoparticles: An Expanding Horizon. ACS Biomaterials Science & Engineering.

[25]. Elfahmi, Woerdenbag, H. J., & Kayser, O. (2014). Jamu: Indonesian traditional herbal medicine towards rational phytopharmacological use. Journal of Herbal Medicine, 4(2), 51-73.

[26]. Elfahmi, Woerdenbag, H. J., & Kayser, O. (2014). Jamu: Indonesian traditional herbal medicine towards rational phytopharmacological use. Journal of Herbal Medicine, 4(2), 51-73.

[27]. Sathi, S. S., Kiran, C. N., Santosh, F., Fadli, A., May, F., Ibrahim, A., & Jiyauddin, K. (2020). Comparison of wound healing activity of Piper betle and Ocimum sanctum in wistar rats. International Journal of Medical Toxicology & Legal Medicine, 23(1and2), 109-116.

[28]. Budhiraja, M., Zafar, S., Akhter, S., Alrobaian, M., Rashid, M. A., Barkat, M. A., ... & Ahmad, F. J. (2022). Mupirocin-loaded chitosan microspheres embedded in Piper betle extract containing collagen scaffold accelerate wound healing activity. Aaps Pharmscitech, 23(3), 77.

[29]. Thị, C. H. C., Nguyễn, H. Đ., & Lê Hoàng, D. M. (2021). Influence of Piper betle L. extract on umbilical cord cells in vitro and potential treating cutaneous wound. Heliyon, 7(3).

[30]. Saraswati, D. E. (2022). The Effectiveness of Green Betel Leaf (Piper betle Linn) on Perineal Wound Healing: A Literature Review Study. Journal of Health Sciences, 15(01), 83-91.

[31]. Gomathi, A., Kuppusamy, M. R., Aruna, K., & Sridhar, T. M. (2023). Preparation of metal doped nanoparticles using flower extract of Piper betle and its anti-bacterial investigations. Materials Today: Proceedings.

[32]. Rochaeni, H., Estuningsih, R. D., Farizi, M. I., Nurafifah, A., & Wibowo, S. (2021). Antimicrobial Evaluation of Piper betel Leaves and Lime Based Hand Sanitizer. Pharmacognosy Research, 13(4).

[33]. Samson, E., & Seumahu, C. A. (2023, January). The effect of storage time to anti-bacterial activity, characteristics, and stability of non-alcohol natural hand sanitizers. In AIP Conference Proceedings (Vol. 2588, No. 1). AIP Publishing.

[34]. Prasetya, F., Salam, S., Rahmadani, A., Haikal, K., Febrina, L., Anshory, H., ... & Kuncoro, H. (2021). Novel amides

derivative with antimicrobial activity of Piper betle var. nigra leaves from Indonesia. Molecules, 26(2), 335.

[35]. Lubis, R. R., & Wahyuni, D. D. (2020). Antibacterial activity of betle leaf (Piper betle l.) extract on inhibiting Staphylococcus aureus in conjunctivitis patient. American journal of clinical and experimental immunology, 9(1), 1.

[36]. Phensri, P., Thummasema, K., Sukatta, U., Morand, S., & Pruksakorn, C. (2022). In Vitro Antimicrobial Activity of Piper betle Leaf Extract and Some Topical Agents against Methicillin-Resistant and Methicillin-Susceptible Staphylococcus Strains from Canine Pyoderma. Animals, 12(22), 3203.