



A Scoping Review : Traditional uses and pharmacology study of Piper crocatum

Zia Azzahra¹, Nurbaiti^{1*}, Tiara Syahfitri¹, Asty Yolandari¹, Hesti Larasati¹, Azmi Habibah¹, Gemmy Sarina¹

¹Department of Pharmacy, Faculty of Science and Health, University Muhammadiyah Riau

²Department of Pharmacy, Faculty of Health, University of Esa Unggul

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***Corresponding author:**

Nurbaiti

email: nurbaiti@umri.ac.id

ABSTRACT

Red betel plant (*Piper crocatum*) is rich in bioactive compounds such as flavonoids and alkaloids, which possess potential antioxidant and anti-inflammatory properties. This study aims to identify the pharmacological effects of red betel through a systematic literature review following the PRISMA guidelines. Data were collected from various scientific databases, including PubMed, ScienceDirect, and Google Scholar, using the keywords "red betel," "Piper crocatum," "antioxidant," and "antibacterial." Articles that met the inclusion criteria were selected based on abstracts and full texts, encompassing studies on red betel written in English or Indonesian and employing experimental methods. The analysis revealed that ethanolic extracts of red betel leaves were the most extensively studied. White rats were the commonly used animal model. Several studies indicated that these extracts contain active compounds capable of scavenging free radicals and reducing inflammation. White rats were frequently utilized to evaluate pharmacological activity, particularly in models of acute and chronic inflammation. The findings suggest the potential development of topical herbal products based on ethanolic extracts of red betel leaves as anti-inflammatory agents for the treatment of skin diseases.

Keywords:

Antibacterial; Antioxidant; Antiseptic; Extraction; Experimental; Red betel; *Piper crocatum*

INTRODUCTION

Indonesia is a country with rich biodiversity, offering a wide array of potential medicinal sources. The use of natural ingredients and traditional medicines for health maintenance and disease treatment has shown a consistent increase over the years. However, their widespread and optimal utilization is still hampered by several challenges, including a lack of information regarding the safety and efficacy of the medicinal plants themselves (Zulaikha, 2018).

Several studies have reported the potential of red betel leaf (*Piper crocatum* Ruiz & Pav.) as a natural antibacterial agent in addressing oral and dental health problems. Red betel leaf contains secondary metabolites such as essential oils, flavonoids, alkaloids, and phenolic compounds that actively inhibit the growth of *Streptococcus mutans*. Therefore, this review focuses on the antibacterial activity found in red betel leaf, which has been extensively researched. This review will also discuss the relationship between the antibacterial activity and the chemical structure of several compounds contained within red betel leaf extracts (Heliawati et al., 2022).

Numerous studies have reported the effectiveness of red betel leaf within ethnobotanical and ethnopharmacological contexts. It has been used in various traditional treatments, including but not limited to, remedies for toothaches, fungal-induced vaginal discharge, ulcers, diabetes, eye ailments, and shortness of breath. Ethnopharmacological studies indicate that red betel leaf possesses a range of

activities, such as antifungal, antibacterial, antioxidant, antihyperglycemic, and anti-inflammatory properties. These findings have led to the reclassification of red betel leaf from an ornamental plant to a medicinal one. Phytochemical analysis reveals that *P. crocatum* Ruiz & Pav. contains secondary metabolites, including flavonoids, essential oils, alkaloids, saponins, tannins, terpenoids, and phenolic compounds, which substantiate its previously reported biological activities (Kurnia et al., 2024).

The potential of red betel as a source of efficacious bioactive compounds has attracted significant interest from researchers to further uncover its benefits. A number of studies have been conducted to test the effectiveness of red betel in treating various conditions, such as bacterial infections, inflammation, and skin diseases. Previous research findings indicate that red betel possesses considerable potential for antibacterial, anti-inflammatory, and antioxidant activities.

Through this literature review, it is hoped that accurate and current information regarding the potential of red betel leaf as a natural medicinal substance can be obtained. Furthermore, this study is expected to provide a foundation for more in-depth future research on red betel leaf.

Although previous studies have reported various benefits of red betel leaf in medicine, most of this research remains limited in scope, and further investigation is required to confirm these earlier findings. Moreover, more targeted research is necessary to identify the primary active compounds in red betel leaf responsible for its biological activities.

Thus, this literature review is expected to make a significant contribution to the scientific knowledge concerning red betel and to open new opportunities for its utilization in the pharmaceutical and medical fields.

Nevertheless, further research is still needed to thoroughly investigate the mechanisms of action of the bioactive compounds in red betel and any potential side effects that may arise from its use. Therefore, this literature review aims to:

1. Summarize and analyze the findings of previous research on the chemical profile, pharmacological activities, and potential therapeutic uses of red betel.
2. Identify research gaps that still need to be addressed concerning red betel.
3. Evaluate the potential for developing red betel as a raw material for natural medicines.
4. Provide recommendations for future research to support the optimal development and utilization of red betel.

METHODS

A systematic search was conducted using the Google Scholar database, which yielded a total of 21,500 articles, along with 18 articles from other databases published between 2011 and 2024. To ensure comprehensive coverage, a combination of keywords was used: "Sirih Merah," "Piper crocatum," "Antibacterial," "Antiseptic," and "Extract." The search was further restricted to articles focusing on pharmaceutical sciences, red betel leaf research, and health.

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework was adopted to guide the article selection process. This process involved three main stages: identification, screening, eligibility assessment, and inclusion. Relevant keywords were identified by consulting previous research, thesauruses, and expert recommendations. The initial search yielded a total of 21,516 articles.

Table 1. Inclusion and Exclusion Criteria

Criteria	Eligibility	Exception
Time	Minimum publication time of article is 2011	<2011
Language	Indonesia and English	Discussing other than Bahasa Indonesia, Indonesian and English
Type paper	Journal articles	Proceeding articles, reviews, books, book series, and personal blogs

Based on the inclusion and exclusion criteria that have been established and detailed in Table 2, a total of 2.200 articles were declared eligible for further review. These criteria included the literature type (journal), language (English), and field of study (agricultural and biological sciences, environmental science, and social sciences). Full-text access was obtained for the 2.200 articles deemed relevant. After undergoing a rigorous review process based on the inclusion and exclusion criteria, 30 articles were identified as suitable for more in-depth analysis (Table 1).

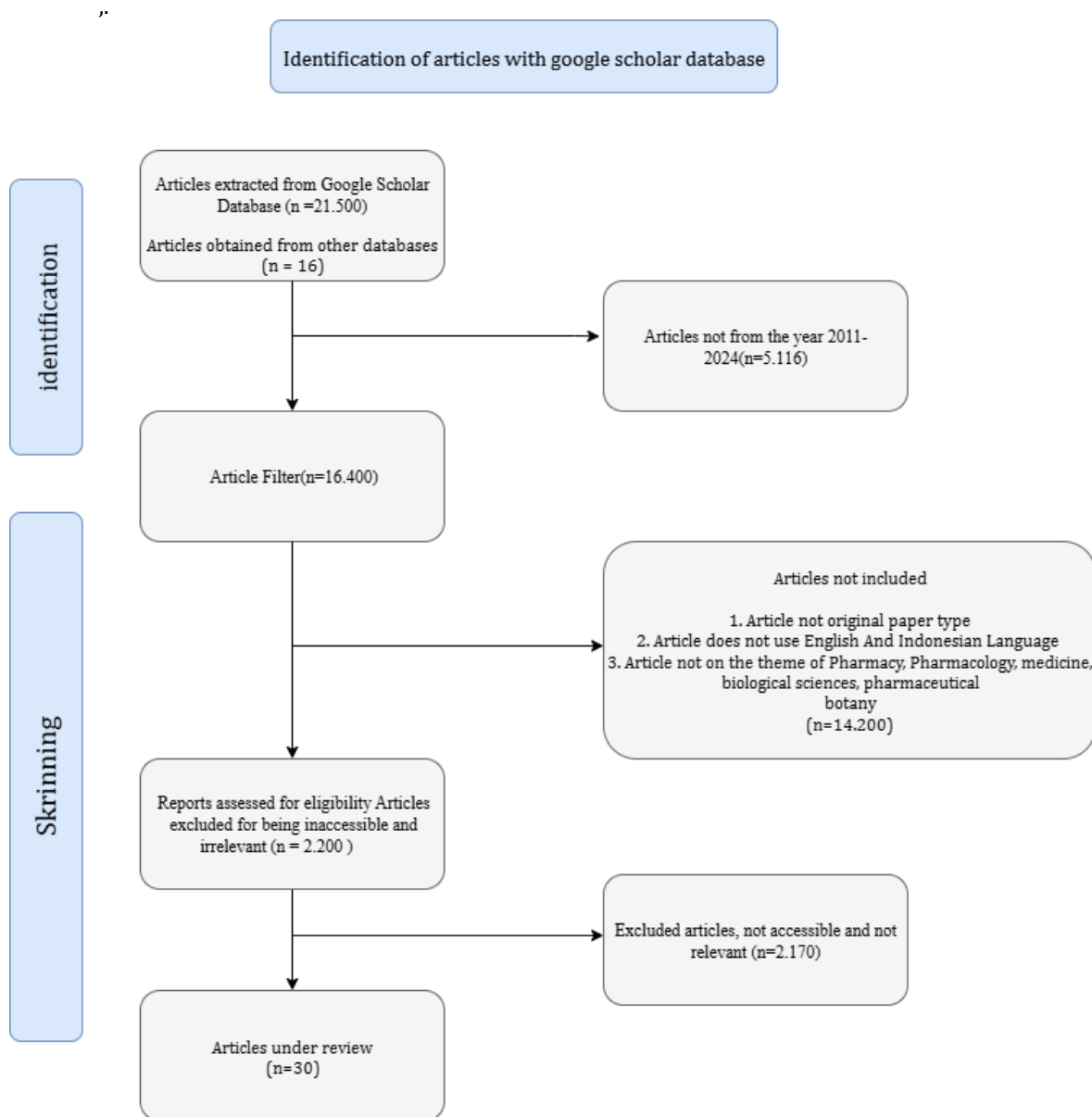


Figure 1. literature selection process

RESULTS AND DISCUSSION

This section presents an analysis of 30 selected articles, focusing on themes, participant characteristics, duration, and project outcomes (summarized in tables and diagrams).

Table 2. Table of Selected Article Analysis

No	Author	Solvent	Sample Part	Test Animal / Microorganism	Extraction Method	Pharmacological Effect
1	Kusuma, 2017	70% Ethanol	Leaf	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>E. coli</i> , and <i>C. albicans</i>	Maceration	Antibacterial
2	Januarti, 2019	Hexane and Ethyl Acetate	Leaf	<i>Staphylococcus epidermidis</i>	None	Antibacterial, Antiseptic, Anticancer
3	Retna, 2018	Sterile Aquades, NaCl Solution	Leaf	<i>Staphylococcus aureus</i>	Diffusion	Antibacterial, Antiseptic, Diuretic
4	Kurnia, 2022	Methanol and Sterile Water	Leaf	<i>S. mutans</i> , <i>S. sanguinis</i> , <i>E. faecalis</i> , <i>C. albicans</i>	Maceration, Diffusion	Antibacterial, Antifungal, Antiviral
5	Heliawati, 2022	Methanolic Solvent, Propylene Glycol	Leaf	<i>S. mutans</i>	None	Antibacterial
6	Anak, 2013	96% Ethanol	Leaf	<i>Rattus norvegicus</i>	Percolation	Antitumor, Anti-inflammatory, Antimicrobial
7	Wisnu, 2018	Aquades	Leaf	<i>Candida albicans</i> , <i>Vibrio cholera</i>	Steam Distillation	Antimicrobial
8	Julianti, 2018	10% DMSO, Tween 80, Aquades	Leaf	<i>Staphylococcus aureus</i>	Maceration	Antibacterial
9	Muhammad, 2018	Not specified	Leaf	None	Percolation	Antidiabetic
10	Ika, 2019	Hexane and Ethyl Acetate	Leaf	<i>Staphylococcus epidermidis</i>	Maceration	Antiseptic
11	Vilia, 2017	96% Ethanol	Leaf	<i>Microorganisms</i> , <i>Malassezia furfur</i>	Extraction	Antibacterial
12	Noor, 2013	70% Alcohol, Sterile Aquadest	Leaf	None	Not specified	Antiseptic
13	Rosanita, 2022	None	Leaf	<i>Microorganisms</i> , <i>Malassezia furfur</i>	Maceration	Antibacterial
14	Wardatul, 2019	None	Leaf	Not specified	Steam Punching Technique	None
15	Devi, 2016	Sterile Aquadest	Leaf	None	None	No pharmacological effect reported

No	Author	Solvent	Sample Part	Test Animal / Microorganism	Extraction Method	Pharmacological Effect
16	Triana, 2014	80% Ethanol	Leaf	Microorganisms	Microwave Assisted Extraction (MAE)	Antimicrobial
17	Khalisa, 2014	Chloroform, Ether, Acetone, Hexane, Alcohol, Ethanol	Leaf	None	Microwave Assisted Extraction (MAE)	Antibacterial
18	Puspa, 2018	30% Ethanol	Leaf	<i>Staphylococcus</i> , <i>Bacillus subtilis</i> , <i>E. coli</i> , <i>P. aeruginosa</i>	Maceration	Antioxidant, Antihyperglycemic, Anticancer
19	Nurul, 2020	500 mL Water	Leaf	None	Extraction method	Antiseptic, Antibacterial
20	Eprina, 2021	70% Ethanol	Leaf	<i>Rattus norvegicus</i>	Maceration	Antidiabetic, Antioxidant
21	Suprianto, 2015	Water	Leaf	None	Extraction method	Antimicrobial
22	Mega, 2020	Aquabidest	Leaf	None	None	None
23	Anika, 2012	70% Ethanol	Leaf	<i>Staphylococcus aureus</i> ATCC 6538	Extraction method	Antibacterial
24	Sri, 2017	96% Ethanol, 0.9% NaCl	Leaf	<i>Candida albicans</i> ATCC 10231	Maceration	Disrupts fungal cell membrane, causes osmotic pressure effect
25	Syahrizal, 2019	70% Ethanol	Leaf	<i>Rattus norvegicus</i>	Maceration	Significantly reduces blood glucose levels
26	Fira, 2011	96% Ethanol	Leaf	None	Extraction	Antibacterial
27	Fira, 2016	Alcohol, Ethanol, Hexane	Leaf	<i>Rattus norvegicus</i>	Extraction	Antibacterial
28	Popy, 2016	None	Leaf	<i>Rattus norvegicus</i>	Extraction	Antibacterial
29	Novia, 2015	30% Ethanol, 70% Ethanol	Leaf	None	Extraction	None
30	Fira, 2011	0.9% NaCl	Leaf	<i>Staphylococcus aureus</i>	Extraction	Antibacterial

Solvent Profile

In this study, 70% ethanol and aquadest dominated the use of solvents, reflecting a trend in selecting polar solvents in chemical research. Ethanol, particularly at a concentration of 70%, is a frequently used solvent due to its ability to dissolve various types of polar and non-polar compounds, as well as being relatively safe and easy to obtain. Theoretically, ethanol has the ability to form hydrogen bonds with the molecules of dissolved compounds, which makes it very effective in dissolving organic compounds, both those with high and low polarity. Furthermore, ethanol is more stable at room temperature and has a relatively low boiling point, making it suitable for use in research that requires good temperature control. The use of 70% ethanol is also quite popular due to its ability to extract bioactive compounds from natural materials, as is often found in phytochemical and pharmaceutical studies.

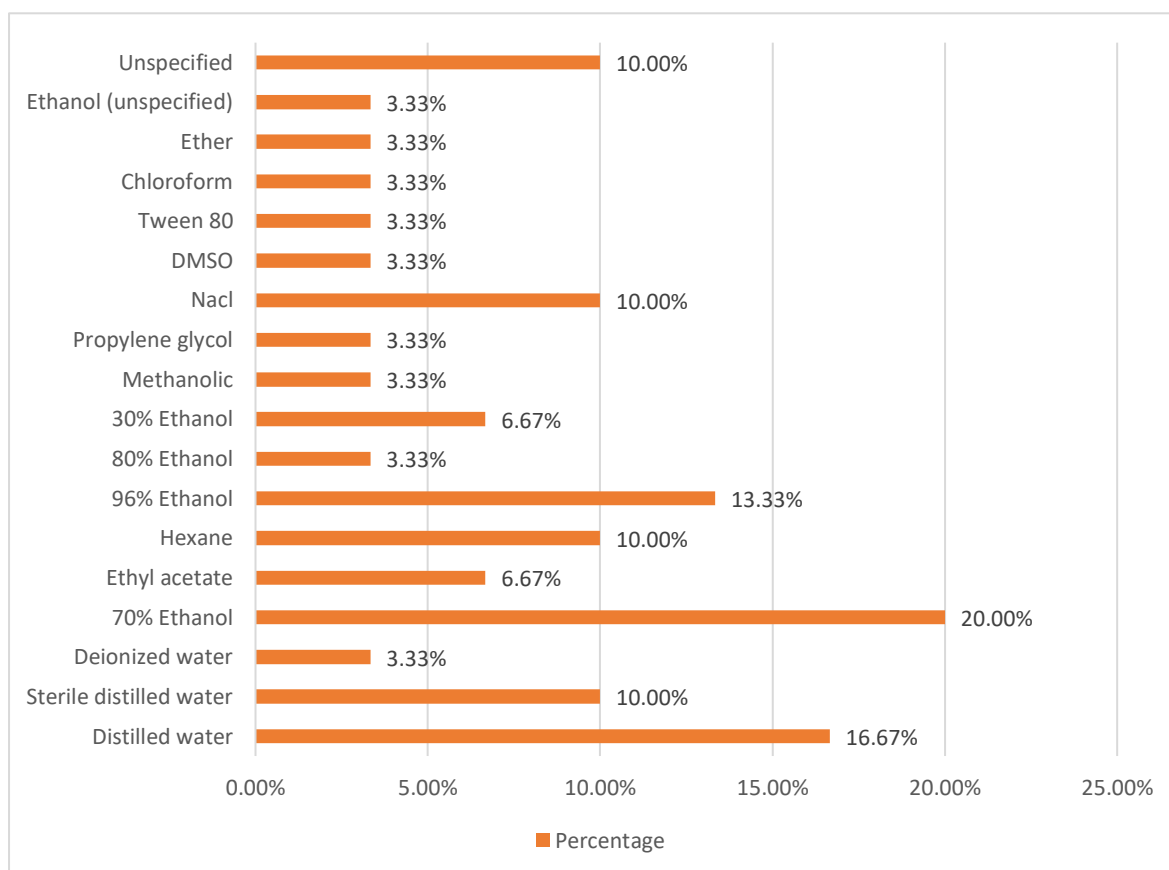


Figure 2. Solvent Profile

Besides ethanol, the use of methanol is also common in chemical research due to its similar polarity properties, which allow for the dissolution of polar compounds. Methanol, although more toxic than ethanol, is often chosen when a stronger solvent is needed or when ethanol is not effective enough in dissolving certain compounds. A study by Tsuchiya et al. (2005) showed that methanol can dissolve a large number of bioactive compounds that are insoluble in water or other solvents like ethanol. Nevertheless, the presence of solvents like methanol and DMSO, which were only used once in certain studies, indicates that these solvents are used for specific applications, such as in the extraction of more complex compounds or those requiring solvents with more extreme polarity.

Furthermore, the use of aqueous solvents like aquadest also indicates that non-organic polar solvents have a very important role in chemical research. Water, as a universal solvent, is often used to dissolve polar compounds that are more soluble in water-based media. Previous research by Bünzli et al. (2014) revealed that aquadest is a primary choice in the extraction and analysis of natural polar compounds due to the strong polar interaction of water with various molecules of these compounds.

Thus, the choice of solvent greatly depends on the chemical properties of the compound to be analyzed and the objective of the experiment itself.

Profile of the Plant Part Utilized

Based on the analysis of 30 articles, all studies used red betel leaf as the utilized part, with a percentage reaching 100%. This indicates that red betel leaf is the most dominant and relevant plant part in various studies, likely due to its rich content of active compounds, such as flavonoids, tannins, saponins, and essential oils. The popularity of this leaf also reflects its role as a versatile natural ingredient in various fields, from traditional medicine to modern research. The absence of the use of other plant parts, such as stems, flowers, or roots, indicates a specific research focus on the biological and chemical potential contained within red betel leaves.

Red betel leaf (*Piper crocatum*) is known to have a rich phytochemical content, such as flavonoids, tannins, saponins, essential oils, and alkaloids. Flavonoids, for example, play an important role as antioxidants capable of fighting free radicals and providing protection against cell damage. The tannin content in red betel leaf functions as an antibacterial and antifungal agent, making it effective in treating infections. The saponins found in this leaf have immunomodulatory activity, helping to strengthen the immune system. Additionally, the essential oils in red betel leaf are known to have strong antimicrobial properties, which support its use in treating wounds and skin infections. These compounds not only support its use in traditional medicine but also form the basis for modern research to develop natural-based medicines.

Several studies have demonstrated the potential of red betel leaf in the health sector. For instance, a study by Handayani et al. (2021) showed that the ethanol extract of red betel leaf has significant antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*. Another study by Prasetyo et al. (2020) found that the flavonoid compounds in this leaf have the ability to inhibit the growth of cancer cells in vitro, showing promising anti-cancer potential. In traditional literature, red betel leaf has also long been used as a natural antiseptic to treat wounds, body odor, and oral problems such as canker sores. These studies strengthen the understanding that red betel leaf not only has a diverse phytochemical content but is also applicable for various medical and non-medical purposes, making it a highly relevant natural ingredient for further research.

Profile of Test Animals Or Microbes

Based on data from the 30 analyzed articles, the test animals and microbes used in red betel leaf research show diverse variations. *Staphylococcus aureus* and *Rattus norvegicus* were the most frequently used test subjects, each appearing 5 times (16.67%), indicating a focus on pathogenic bacteria causing infections and an animal model for testing the biological effects of red betel leaf. Other frequently tested microbes include *Candida albicans* 4 times (13.33%), which shows attention to the antifungal properties of this leaf, as well as *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus epidermidis*, and *Streptococcus mutans*, each tested twice (6.67%).

A small number of articles tested other microbes such as *Vibrio cholera*, *Malassezia furfur*, *Aggregatibacter actinomycetemcomitans*, *Staphylococcus*, and *Bacillus subtilis*, each with a percentage of 3.33%, reflecting testing in more specific contexts. A total of 3 articles (10%) mentioned the use of microorganisms in general without specification, while 10 articles (33.33%) did not involve tests on animals or microbes at all. The total percentage exceeding 100% indicates the possibility of using more than one test subject in some studies. This profile highlights the flexibility of red betel leaf as a potential material for various antimicrobial, antifungal, and biological testing applications in animal models.

Staphylococcus aureus is often used in research as a model pathogen due to its ability to cause various infections in humans, including skin infections, pneumonia, and sepsis. This bacterium has complex pathogenic mechanisms, such as the ability to form biofilms and produce various virulence factors, which makes it a primary choice in infection studies. Theoretically, *S. aureus* is a Gram-positive microorganism frequently used in antibacterial testing due to its widespread presence and its frequent cause of difficult-to-treat nosocomial infections, especially with the emergence of antibiotic-resistant strains like MRSA (Methicillin-Resistant *Staphylococcus aureus*). The use of *S. aureus* in testing the antibacterial activity of red betel leaf, for example, can provide an overview of this plant's potential in combating a pathogen that has become a major challenge in the medical world. Furthermore, *S. aureus* is easy to grow in laboratory cultures and can be tested under various conditions, making it a very flexible and practical model for further testing of antimicrobial agents.

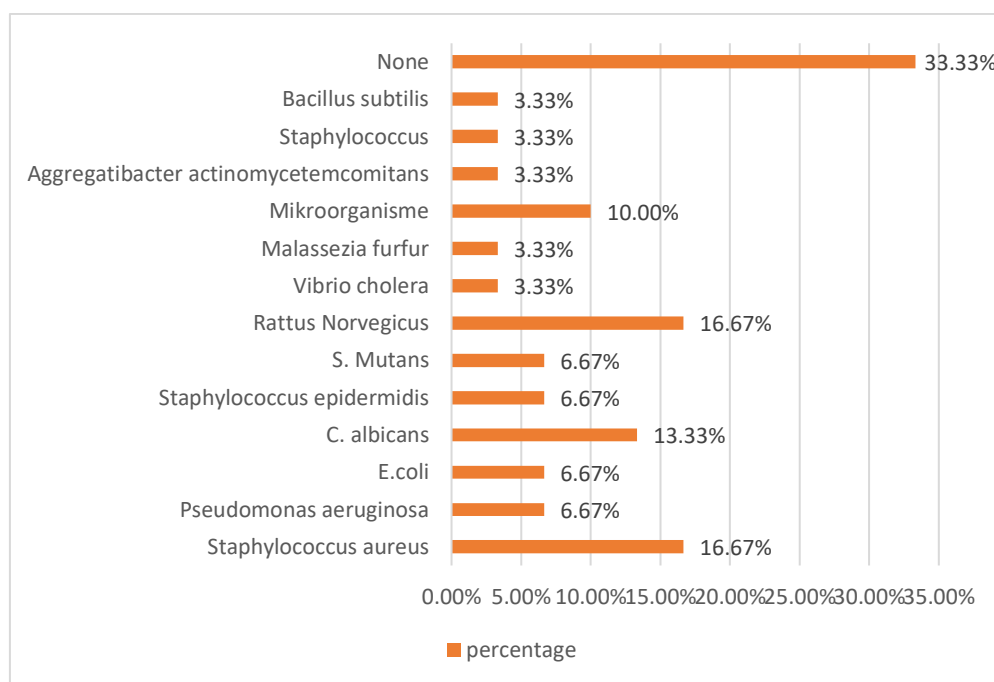


Figure 3. Profile Of Test Animals Or Microbes

Other research delving into the use of *S. aureus* as a test subject also demonstrates the importance of this bacterium in testing various natural extracts. For example, a study by Suryani et al. (2019) showed that red betel leaf extract has antibacterial potential against *S. aureus*, indicating its ability to inhibit the growth of this bacterium. Another study by Nurfaidah et al. (2020) also confirmed that red betel leaf contains active compounds that can affect the bacterial cell membrane and inhibit the metabolic processes of *S. aureus*. Furthermore, in vivo use in animal models, such as *Rattus norvegicus*, is also common in this research to evaluate the systemic effects of red betel leaf extract against infections caused by *S. aureus*. This allows researchers to evaluate the potential of red betel leaf in reducing infection symptoms at the whole organism level, as well as providing deeper insights into its effectiveness and safety as a therapeutic agent.

Besides *S. aureus*, many other studies also use test animals to explore the biological effects of various natural extracts. For instance, *Rattus norvegicus*, or the laboratory rat, is often used in research due to its similarity to humans in terms of physiology and pathophysiology. This test animal is frequently used to test the antimicrobial, anti-inflammatory, or anticancer potential of plant extracts. Research by Prabhu et al. (2016), for example, used *Rattus norvegicus* to test the anti-inflammatory effect of red betel leaf extract, which showed positive results. Moreover, this test animal also allows for the evaluation of the toxicity, biodistribution, and side effects of the extract. The advantage of using test animals like rats is their ability to provide more comprehensive data on the biological impact of a substance, which is crucial in the development of plant-based therapies.

Profile Of Extraction Method

Based on the analysis of 30 research articles on red betel leaf, the most widely used extraction method is maceration, which was applied in 9 articles (30%). This method is likely the primary choice due to its simplicity, relatively low cost, and its ability to effectively extract active compounds. Additionally, general extraction methods were also used 5 times (16.67%), indicating that some studies might not have specified the technique used.

Other methods employed include diffusion, percolation, and microwave-assisted extraction (MAE), each with a frequency of 2 times (6.67%), as well as steam distillation and steam-knock techniques, each used once (3.33%). This variation reflects the exploration of different techniques to maximize the yield of bioactive compounds, such as flavonoids and essential oils, from red betel leaf.

However, 5 articles (16.67%) did not report the extraction method, which may indicate the use of the material in its raw form or a lack of detailed documentation. The total percentage of 90% suggests the possibility that some articles did not mention or used more than one extraction method. This profile emphasizes a preference for simple and efficient techniques, with little exploration of more complex methods.

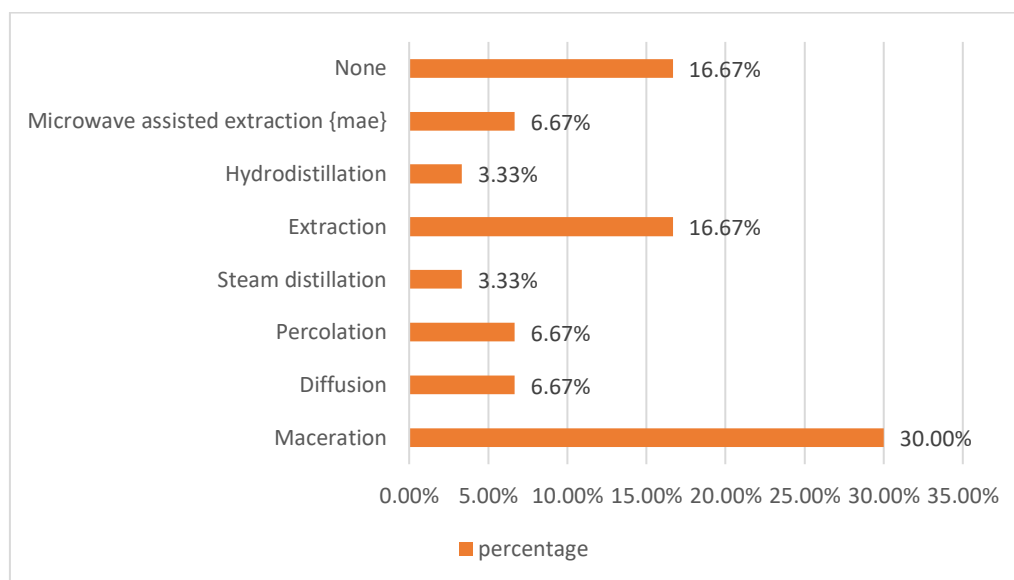


Figure 4. Diagram Of Extraction Method Profile

Maceration is the most widely used extraction method in red betel leaf research due to its simplicity and relatively low cost. Theoretically, maceration is effective for extracting polar and non-polar compounds, such as flavonoids and essential oils, using solvents like ethanol or aquadest. Its easy process, without requiring special equipment, makes this method a primary choice for obtaining extracts with a high content of bioactive compounds. Other research, such as that conducted by Farag et al. (2013), also shows that maceration is effective for extracting polyphenolic compounds from herbal plants.

Although maceration is dominant, some studies also use other methods like microwave-assisted extraction (MAE) and percolation to increase extraction efficiency. MAE, for instance, can speed up the extraction process and produce extracts with higher compound yields in a short time, although it requires more expensive equipment. Research by Zhuang et al. (2015) showed that MAE provides better extraction results, but due to its higher cost, this method is less popular than maceration. This explains why maceration remains the primary choice in red betel leaf research.

Profile of Pharmacological Effects

Based on the analysis of 30 research articles on red betel leaf, the most frequently reported pharmacological effect is antibacterial, with a frequency of 14 times (46.67%). This indicates the primary potential of red betel leaf as an agent to inhibit or kill bacteria, which supports its use in both medical and traditional applications to combat infections. Furthermore, antiseptic effects were reported in 5 articles (16.67%), reinforcing its role as a natural ingredient for maintaining hygiene and preventing microbial growth.

Other reported pharmacological effects include antimicrobial (13.33%), antihyperglycemic (10%), as well as antioxidant, antifungal, and anticancer, each reported twice (6.67%). Some specific effects, such as antiviral, antitumor, anti-inflammatory, and antidiuretic, were reported only once (3.33%), indicating a more limited research focus on these aspects. A total of 4 articles (13.33%) did not report any pharmacological effects, which might indicate non-pharmacological testing or a lack of documentation of the observed effects.

The total percentage of 133.33% indicates the possibility that some articles listed more than one pharmacological effect. This profile underscores the versatility of red betel leaf in various

pharmaceutical applications, with a primary focus on its antibacterial properties and broad antimicrobial protection.

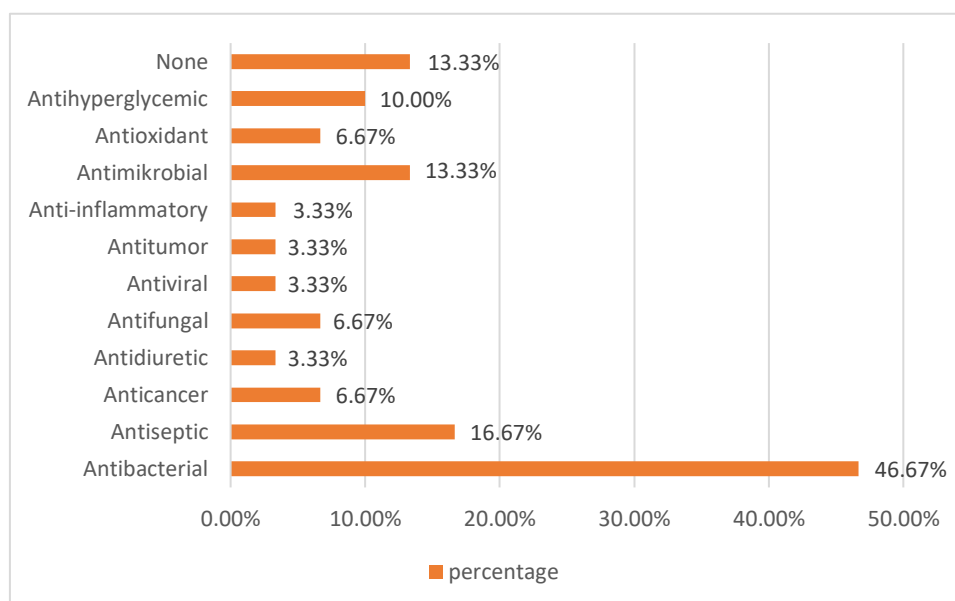


Figure 5. Pharmacological Effects

Red betel leaf has strong antibacterial potential thanks to its content of active compounds such as flavonoids, terpenoids, and essential oils. These compounds work by damaging the bacterial cell membrane and inhibiting metabolic processes, which makes them effective against pathogenic bacteria like *Staphylococcus aureus* and *Escherichia coli*. Research by Suryani et al. (2019) and Harahap et al. (2020) supports these findings, by showing that red betel leaf extract inhibits the growth of various pathogenic bacteria.

Besides being antibacterial, red betel leaf also shows significant antiseptic effects. A study by Salim et al. (2018) confirmed the strong antiseptic activity of red betel leaf extract, making it a potential natural ingredient for hygiene and wound care products. In addition, red betel leaf extract also has antimicrobial, antioxidant, antihyperglycemic, and antifungal activities, which are reinforced by other studies showing its potential in treating diabetes.

Overall, red betel leaf offers a variety of pharmacological benefits, with a primary focus on antibacterial and antimicrobial activities, as well as potential for other medical applications, such as diabetes treatment and as an antioxidant. The diversity of its pharmacological effects makes it a natural ingredient with great potential in the development of drugs and healthcare.

CONCLUSION

Red betel leaf (*Piper ornatum*) has been extensively researched, using in vitro, in vivo, and several clinical trials, to test its medicinal properties. These studies have examined the content of active compounds such as flavonoids, alkaloids, tannins, saponins, and essential oils. The results show a variety of properties, including antibacterial, antifungal, antioxidant, anti-inflammatory, antidiabetic, and anticancer. These properties are attributed to its active compound content; for example, flavonoids and tannins as antioxidants, while alkaloids and saponins as antibacterial and anti-inflammatory agents. Nevertheless, further research, especially larger-scale clinical trials in humans, is still needed to fully confirm its effectiveness and safety, as well as to determine the appropriate dosage and potential interactions with other drugs.

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