

Medical and Health Science Journal



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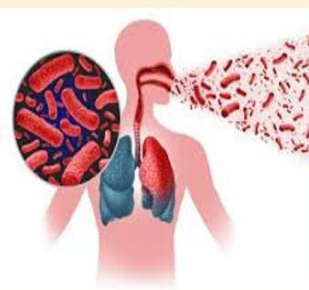


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ORIGINAL ARTICLE

The Effectiveness of Red Piper Crocatum as a Natural Antiseptic in Reducing Fluor Albus Symptoms in Women of Reproductive Age

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ABSTRACT

Background & Aim: One of the most common reproductive health issues experienced by women is Fluor Albus (vaginal discharge). In general, women with fluor albus produce excessive mucus accompanied by an unpleasant odor. This study aims to analyze the effect of boiled Red Piper crocatum as a natural antiseptic on the reduction of Fluor Albus symptoms in women of reproductive age in Sidodadi Village, Sukosewu Subdistrict, Bojonegoro Regency.

Methods: This research employed a pre-experimental design method, utilizing a one-group pre-test and post-test approach. The population consisted of 32 respondents, all of whom were included in the sample using a total sampling technique. Data were analyzed using a paired t-test. The results showed a p-value of 0.000, indicating that $p < 0.05$, and therefore, the alternative hypothesis (H_1) was accepted.

Result: This means that boiled Piper Crocatum significantly reduces Fluor Albus symptoms in women of reproductive age in Sidodadi Village, Sukosewu Subdistrict, Bojonegoro Regency.

Conclusion: Conclusion of this study Maintaining the normal flora of the vagina can be supported by using boiled Red Piper Crocatum water to reduce pathological vaginal discharge symptoms, due to its clinically proven active compounds.

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Introduction

Reproductive health is a state of complete physical, mental, and social well-being, encompassing not only the absence of disease or physical disability, but also all matters related to the reproductive system and its functions and processes (1). Women often face various issues in the vaginal area. Most cases involve problems related to fluor albus. Fluor albus itself varies in consistency, color, and odor. Generally, women experiencing fluor albus produce excessive mucus and may have an unpleasant odor (2).

The signs and symptoms of fluor albus are caused by inflammation and infection in the vaginal area. Persistent fluor albus that does not improve with medication should raise concerns about the possibility of cervical cancer (3). People worldwide, including Indonesia, are increasingly prioritizing the use of natural remedies (back to nature). The utilization of herbal medicine is widely discussed, including its benefits and efficacy. One of the plants that can be utilized is red piper crocatum (4).

The Maternal Disease Obstetric Caribbean (MDOC) in America states that fluor albus is experienced by 72.3% of women of childbearing age and 27.7% of couples of reproductive age (PUS). The WHO reports that 75% of women worldwide have experienced fluor albus, while in Europe, the figure is 25%. In Indonesia, about 90% of women are at risk of experiencing fluor albus. This is because Indonesia is a tropical climate region, which allows fungi to thrive and leads to many fluor albus cases. Symptoms of fluor albus are also experienced by adolescent girls aged 15-24 years, accounting for about 31.8% (5). At the Sukosewu Health Center in 2021, there were 54 patients with fluor albus, while in 2022, there were 61 patients. This indicates increased fluor albus patients (6).

Red piper crocatum is one of the potential medicinal plants that is empirically known to have properties for healing various types of diseases, including fluor albus. Red betel leaves contain phytochemical compounds, including essential oils. This plant is commonly found in Indonesia as a herbal remedy. Red piper crocatum has antifungal properties, necessary for inhibiting pathogenic bacteria (7). Additionally, red Piper crocatum has higher antimicrobial and antiseptic content than green betel leaves, and it also contains carvacrol, which functions as an antiseptic to maintain oral health, treat fluor albus, and eliminate unpleasant odors (8). In 2020, it was estimated that 75% of

women in Indonesia would experience fluor albus, and this number is expected to continue to rise in the following years. Research in East Java shows that 75% suffer from fluor albus, with 45% experiencing it more than once in their lifetime (9).

The leading causes of fluor albus are infections from bacteria such as *Trichomonas Vaginalis* and *Candida Albicans*. Fluor albus itself is characterized by excessive vaginal discharge that is not menstrual blood (10). Generally, fluor albus can be caused by several factors, including a lack of attention to personal hygiene, washing the genital area incorrectly, engaging in very strenuous physical activity, not changing sanitary pads promptly during menstruation, unhealthy lifestyle patterns, severe psychological stress, excessive use of feminine hygiene soaps, humid weather conditions, hormonal imbalances, and frequently scratching the genital area. These conditions can damage the internal reproductive organs and may also lead to infertility. Therefore, maintaining personal hygiene is crucial to prevent fluor albus (3).

Fluor albus can be addressed in various ways, starting with personal hygiene practices, using cotton or moisture-absorbing underwear, maintaining a healthy diet, getting adequate rest, exercising regularly, and avoiding stress. Fluor albus can be treated with pharmacological medications such as fluconazole and metronidazole (1). However, treatment is not limited to pharmacological methods; non-pharmacological treatments can also be performed using red piper crocatum. The boiled water from red piper crocatum can be used in the intimate area by being applied once a day (11).

From the various research findings and preliminary surveys mentioned above, it can be concluded that fluor albus should be treated if it becomes abnormal, and the use of red piper crocatum can be considered for addressing leukorrhea in women of childbearing age as a natural antiseptic.

Methods

This study uses a pre-experimental research design with a one-group pre-test post-test design method. The population in this study consists of women of childbearing age experiencing fluor albus in Sidodadi Village, totaling 32 women of childbearing age. The sample size determination in this study aims to test the hypothesis regarding the odds ratio. Thus, the sample size is set at 32 respondents. The sampling technique used in this study is Non-Probability Sampling with a Total

Sampling method. The sample selection is based on inclusion criteria, namely, women of childbearing age who experience fluor albus, are willing to be respondents, and patients with pathological fluor albus. The independent variable in this study is red piper crocatum, while the dependent variable is fluor albus in women of childbearing age. Data analysis is conducted through univariate analysis to determine the percentage of each variable and bivariate analysis using the dependent T-test (paired), with the test results indicating $p < 0.05$, thus H1 is accepted with a confidence level or confidence interval of 95%.

Results

Fluor Albus before giving the red piper crocatum

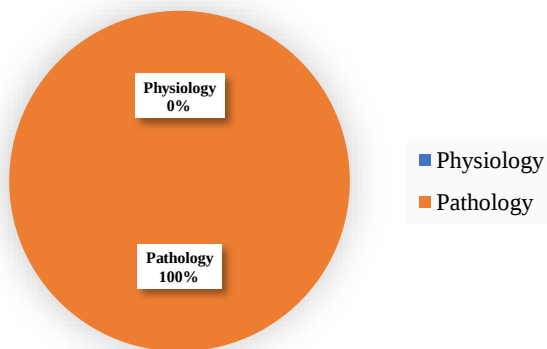


Diagram 1. Frequency distribution of fluor albus before giving of red piper crocatum in women of childbearing age

The data from Diagram 1 show that the respondents experiencing fluor albus before being given red piper crocatum predominantly suffered from pathological fluor albus. A total of 32 respondents accounted for 100% of the sample.

Fluor Albus after being given the red piper crocatum

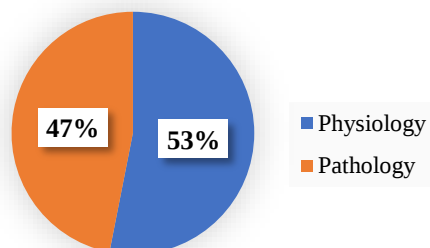


Diagram 2. Frequency distribution of fluor albus after given of red piper crocatum in women of childbearing age

The data from Diagram 2 shows that after being given red piper crocatum, more than half of the respondents experienced reduced symptoms of pathological fluor albus. Seventeen respondents, accounting for 53.1% of the sample, were classified as having physiological fluor albus.

Table 1. The effectiveness of boiled red piper crocatum as a natural antiseptic in reducing symptoms of fluor albus in women of childbearing age

Fluor Albus	age			
	Before giving red piper crocatum		After being given red piper crocatum	
	N	Percentage (%)	N	Percentage (%)
Physiology	0	0	17	53,1
Pathology	32	100	15	46,9
Total	32	100	32	100

Value of $\alpha = <0,05$, Value of $\rho = 0,000$

Discussion

Identification of Fluor Albus Before Administration of Red Piper Crocatum

Based on Diagram 1, it can be interpreted that the majority (100%) of women of childbearing age experienced pathological fluor albus before being given boiled red piper crocatum water, with a total of 32 respondents. There were no respondents (0%) who experienced physiological fluor albus. The study's results on women of childbearing age in Sidodadi Village, Sukosewu District, Bojonegoro, before giving boiled red piper crocatum water showed a mean value of 1.00.

Several studies have identified factors contributing to this condition, including occupation, contraceptive use, and vulvar hygiene. In this study, the most prominent factor was the use of contraceptives, with a significant value of $\rho = 0.001$, indicating that women of childbearing age using hormonal contraceptives have a 60 times higher chance of experiencing fluor albus compared to those using non-hormonal contraceptives. Thus, it can be concluded that contraceptive use is a risk factor for fluor albus (12). Meanwhile, in the study by Wardani & Sundayani (2021) Factors influencing fluor albus included age, education, menstrual cycle, marital status, knowledge, and behavior. However, the menstrual cycle was the most significant factor,

with a value of $\rho = 0.000$. Each menstrual cycle causes changes in the vaginal, cervical, and uterine tissues due to estrogen, leading to the secretion of somewhat sticky and smooth mucus, which marks the interval between menstruations. In the vagina, this mucus is processed with the help of bacteria that usually reside there to produce weak acid. This acid prevents harmful bacteria from growing in the vagina. Vaginal cells and mucus from the cervix contribute to the amount of fluor albus produced. Pathological fluor albus arises due to certain medical conditions, most commonly caused by infections from parasites/fungi/bacteria (14).

Fluor albus should not be considered a trivial matter, as inadequate management of fluor albus can lead not only to infertility or ectopic pregnancy but can also be an early sign of cervical cancer, which can result in death if not consulted with health professionals early through health promotion efforts. This can increase the knowledge of women of childbearing age regarding fluor albus, thereby preventing the occurrence of pathological fluor albus (15).

Identification of Fluor Albus After Being Given Red Piper Crocatum

Diagram 2 shows that more than half (53.1%) of women of childbearing age experienced reduced symptoms of pathological fluor albus after being given boiled red piper crocatum water, resulting in 17 respondents classified as having physiological fluor albus. Meanwhile, nearly half (46.9%) of women of childbearing age still experienced pathological fluor albus, totaling 15 respondents. The study's results on women of childbearing age in Sidodadi Village, Sukosewu District, Bojonegoro, after being given boiled red piper crocatum water, showed a mean value of 1.53.

This study aligns with Dewi (2020) Regarding using boiled red piper crocatum and green piper betle water on women of childbearing age who are experiencing fluor albus. Red piper crocatum used as a traditional medicine showed that pathological fluor albus in this study could either heal or show a reduction in physiological and pathological fluor albus symptoms from this traditional medicine group, with significant results ($\rho=0.001$). Therefore, after using boiled red piper crocatum water and boiled green piper betle water, it can be concluded that both reduce fluor albus symptoms. The properties and benefits of red piper crocatum and green piper betle are used to minimize fluor albus and maintain women's health, as both contain alkaloids, tannins, saponins, and flavonoids that have antimicrobial properties capable of killing

Candida albicans, the main cause of fluor albus. Similarly, Firmanila et al. (2016) Showed that boiled red piper crocatum water significantly affected the reduction of leukorrhea in women, with a p-value of 0.001. This indicates a decrease in symptoms of pathological fluor albus in women, due to the clinically proven content of red piper crocatum in addressing fluor albus.

Pathological fluor albus is one indication of various diseases such as vaginitis, candidiasis, and trichomoniasis, which are symptoms of sexually transmitted diseases (STDs), especially in women who have changed sexual partners. Fluor albus can also indicate an infection in the pelvic cavity, such as an infection in the fallopian tubes, accompanied by severe abdominal pain. Abnormal fluor albus that is not adequately managed and persists for a long time can lead to reproductive tract infections and may cause infertility (18).

Effectiveness of Red Piper Crocatum as a Natural Antiseptic in Reducing Symptoms of Fluor Albus in Women of Childbearing Age

Based on Table 1, the effect of boiled red piper crocatum water on the reduction of fluor albus symptoms in WUS can be interpreted as follows: the majority of respondents in Sidodadi Village, Sukosewu District, experienced symptoms of pathological fluor albus, with a total of 32 (100%) respondents before being given red piper crocatum. There were no respondents (0%) who experienced physiological fluor albus. After the administration of red piper crocatum in Sidodadi Village, nearly half of the respondents who experienced symptoms of pathological fluor albus showed improvement, with 15 (46.9%) respondents, while those who experienced physiological fluor albus increased to 17 (53.1%) respondents. The study's results on women of childbearing age in Sidodadi Village, Sukosewu District, Bojonegoro Regency, after the boiled red piper crocatum water showed a mean value of 1.53.

Data analysis in this study used the T-test with SPSS software on a computer, with a significance level of 5%. A p-value of 0.000 was obtained, where $p\text{-value} < 0.05$, indicating that H_0 is rejected and H_1 is accepted. This means red piper crocatum is effective as a natural antiseptic in reducing symptoms of fluor albus in women of childbearing age in Sidodadi Village, Sukosewu District, Bojonegoro Regency.

This is in line with the study by Passe et al. (2021), which used the McNemar statistical test and obtained a result of $\rho=0.008$, indicating that $\alpha < 0.05$. Among 30 respondents who reported fluor

albus, after the administration of boiled red piper crocatum water, 27 respondents no longer experienced fluor albus. Therefore, boiled red piper crocatum has an effect on fluor albus in women of childbearing age.

The study by Kurniawati et al. (2014) Used a completely randomized design (CRD) with a factorial pattern, involving two factors: a combination of boiled green piper betle and red piper crocatum, with sterile aquades as a negative control. The observed variable was the growth of colonies in each treatment combination, showing that red piper crocatum has high antimicrobial activity, as evidenced by the absence of colony growth after treatment. Red Piper Crocatum contains essential oils with antifungal properties against *Candida albicans*, similar to green piper betle, which can function as antifungal and bactericidal agents.

The use of red piper crocatum can reduce issues related to fluor albus, making it a viable herbal treatment derived from plants and pure natural ingredients that have no side effects, with a much lower risk compared to synthetic chemical drugs (20). Additionally, maintaining personal hygiene of the female genital area in a clean and dry state is essential. Overuse of antiseptics for rinsing or washing the vagina can prevent beneficial *Lactobacillus* bacteria from effectively preventing harmful bacteria from entering the vagina (21). Therefore, to maintain normal vaginal flora, the researcher used boiled red piper crocatum water for cleansing to reduce symptoms of pathological fluor albus, due to the clinically proven content of red betel leaves in addressing fluor albus.

Conclusion

The study's results indicate that red piper crocatum is effective as a natural antiseptic in reducing symptoms of fluor albus in women of childbearing age, with a p-value of $p = 0.008$, which indicates that $\alpha < 0.05$. Among 30 respondents who reported fluor albus, after the administration of boiled red piper crocatum, 27 respondents experienced a significant reduction in symptoms of pathological fluor albus in Sidodadi Village, Sukosewu District, Bojonegoro Regency.

Conflict of Interest

No conflict of interest in this study

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REVIEW ARTICLE

Effectiveness of Water-Based Exercise/Aquatic Exercise for Individuals with Low Back Pain: a Literature Review

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ABSTRACT

Background: Low back pain (LBP) is a common complaint that affects many individuals and can significantly reduce quality of life. Water-based exercise has been proposed as an effective therapeutic method to reduce pain and improve physical function in patients with LBP.

Methods: A literature review was conducted by searching for relevant studies in reputable medical databases. Inclusion criteria included studies that compared water-based exercise with land exercise in individuals with LBP.

Results: Studies show that both water-based exercise and land exercise are effective in reducing low back pain. However, water-based exercise tends to overestimate its effect due to publication bias. Nonetheless, water-based exercise provided a significant reduction in VAS scores. Land exercise showed additional benefits with significant improvements in emotional role and physical function on the SF-36, as well as a decrease in the ODI.

Conclusion: Based on a literature review of seven selected articles, water-based exercises have been shown to be effective in reducing pain in cases of low back pain (LBP). However, its application must consider the technical conditions and medical history of the patient.

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Introduction

Indonesia is the fourth country with the highest prevalence of LBP [1]. According to World Health Organization (WHO) data in 2018, the prevalence of musculoskeletal diseases in Indonesia diagnosed by health workers was 11.9%, including LBP estimated between 7.6% and 37% [2]. Low Back Pain (LBP) affects 619 million people worldwide and is expected to increase to 843 million cases by 2050, largely due to population expansion and aging.

Low back pain (LBP), also known as low back pain, is pain felt in the lower back region. This pain can be localized pain, radicular pain, or both. Low back pain (LBP) is one of the most common musculoskeletal disorders and can occur in anyone [3]. Risk factors that can cause LBP include individual factors such as age, gender, Body Mass Index (BMI), smoking habits, physical fitness, history of skeletal disease, trauma, and psychological and psychosocial problems. Work-related risk factors such as workload, excessive physical activity, and stress [4]. LBP is categorized into specific or non-specific. Specific LBP is pain caused by a specific disease or structural problem in the spine, or pain radiating from other parts of the body. Whereas, non-specific LBP occurs when a specific disease or structural reason to explain the pain cannot be identified. Non-specific low back pain falls into 3 subtypes: acute, subacute, and chronic low back pain. This division is based on the duration of the back pain. Acute low back pain is an episode of low back pain lasting less than 6 weeks, subacute low back pain between 6 and 12 weeks, and chronic low back pain lasting 12 weeks or more [5].

Physiotherapy plays an important role in the treatment of LBP, especially in healing to overcome the obstacles and limitations of patients to perform daily functional physical activities. Aims to reduce pain in the patient's lower waist and increase muscle strength while restoring the ability of physical activity in patients with LBP. The modalities used are Transcutaneous Electrical Nerve Stimulation (TENS), Extracorporeal Shock Wave Therapy (ESWT), pilates exercise, massage, stretching, line exercise, land exercise, and water-based exercise [6].

Water-based exercise is a water-based therapy that generally helps improve muscle strength, cardiovascular fitness, and balance. Water-based exercise is used as a physical therapy program for NPB cases. The buoyancy effect makes it easier to perform underwater movements that are difficult to do on land, strengthening the

muscles of the abdomen, lower back, and pelvis, these muscles are used to contract and regulate the posture of the lumbar spine [7]. Among the many therapeutic exercises available, therapeutic aquatic exercise is often prescribed by doctors for chronic low back pain, and it is becoming increasingly popular for the treatment of chronic low back pain [8]. The drawback of water exercise is that it can only be done underwater. Lack of coordination with the patient causes the intervention to be unsuccessful because the patient is not familiar with the treatment [9]. Therefore, water exercise results in optimal body composition improvement and reduction of low back pain [10].

In this article, we chose to conduct secondary research because we wanted to review the scientific literature on water-based exercise for low back pain. By doing so, readers can more easily find new insights that are broad, evolving and systematic enough to provide a comprehensive overview of the topic. This secondary research also contains strong scientific evidence to support the claims and recommendations about water-based exercise for low back pain. This is important to provide accurate and useful information for readers. The purpose of this study was to determine how effective water-based exercise intervention is in physiotherapy for LBP patients. Researchers concluded that water-based exercise is very effective for reducing pain in patients. In addition, researchers also showed that the water-based exercise program can prevent and reduce the risk of low back pain and can provide knowledge related to the water-based exercise program so that it can be applied to prevent and reduce the risk of low back pain.

Methods

The study design of this research is a meta-analysis. Compared to individual studies that contribute to a combined analysis, a meta-analysis is a quantitative and formal epidemiologic methodology used to systematically assess previous research studies to reach conclusions about the research subject. The results of a meta-analysis may include more precise estimates of the effect of treatment, disease risk factors, or other factors. Literature sources using Google Scholar were used to search for data with keywords such as "low back pain", "water-based exercise", "land exercise", and "hydrotherapy". The journals used were published between 2012 and 2022, and had an RCT (Randomized Controlled Trials) study type.

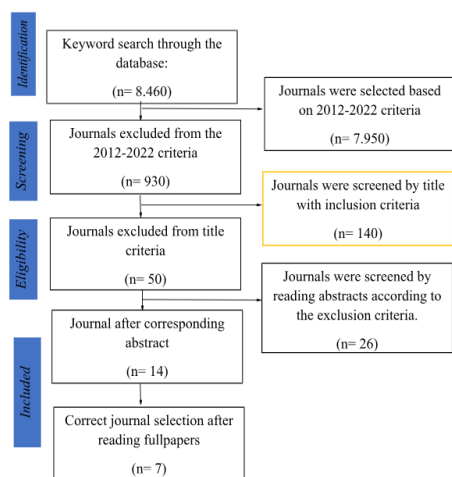


Figure 1 Prisma Flow Chart

After finding relevant journals, a valid measurement of the quality of the clinical trial methodology was conducted in the form of a PEDro scale to obtain a total score, which can be used as an interval level measurement and subjected to parametric statistical analysis. The PICO standards used were (P) low back pain patient, (I) aquatic/water-based exercise, (C) land exercise, (O) pain reduction.

Table 1 Pedro Analysis

PEDro Scale	Maurício Antônio da Luz Jr, et al., (2014)	Tomislav Nemčić <i>et al.</i> , (2013)	Hend M.T, Nasar, M.Sc <i>et al.</i> , (2021)	Nilay Çömük <i>et al.</i> , (2020)	Meng-Si Peng, MSc <i>et al.</i> , (2022)	Suttinee Phattharasu pharerk <i>et al.</i> , (2018)	A. I. Cuesta-Vargas <i>et al.</i> , (2012)
Eligibility	yes	yes	yes	yes	yes	yes	yes
Random allocated	1	1	1	1	1	1	1
Concealed allocation	1	1	1	1	1	1	1
Baseline Comparability	1	1	1	1	1	1	1
Blinding all subjects	1	1	0	0	1	1	1
Blinding all therapist	1	0	0	0	1	1	0
Blinding all assessors	1	0	0	0	1	0	0
Adequate follow-up	1	1	1	1	1	1	1
Intention-to-treat analysis	1	1	1	1	1	1	1
Between-group comparisons	1	1	1	1	1	1	1
Point estimated variability	1	1	1	1	1	1	1
Score	10/10	8/10	7/10	7/10	10/10	9/10	8/10
Quality	Excellent	Good	Good	Good	Excellent	Good	Good

Results

The search results obtained six articles where four articles had a low risk of bias and two articles with a moderate risk of bias. The results and discussions in the articles used as the basis for this research study can be accounted for. The PICO

appraisal of the articles can be seen in Figure 2 Forest plot.

The results of the analysis in this study, showed a decrease in pain in patients with LBP who were given Aquatic Based Exercise by -1.22 units compared to patients given Land Based Exercise (SMD = -1.22; 95% CI = -3.35 to 0.90) and the results were statistically significant

($p < 0.00001$). Heterogeneity of the study data showed $I^2 = 97\%$ (random effects model).

The funnel plot shows that the distribution of effect estimates from primary studies with this RCT meta-analysis design lies more to the right of the mean vertical line of the estimate than to the left, indicating publication bias. Because the publication bias tends to be to the right of the mean vertical line which is different in direction from the location of the diamond shape in the forest plot, the publication bias tends to overestimate the effect of

Aquatic Based Exercise on pain reduction in Low Back Pain patients (overestimate).

To see the level of effectiveness of the aquatic/water-based exercise program as a Physiotherapy service in LBP cases can be reviewed through many things such as patient conditions, adequate place facilities, patient age criteria and congenital disease factors suffered. The characteristics of respondents in the research articles reviewed can be seen in Table 2 Literature review.

Table 2 Literature Review

Title & Author	Background	Method	Result
Effectiveness of Mat Pilates or Equipment-Based Pilates Exercises in Patients With Chronic Nonspecific Low Back Pain: A Randomized Controlled Trial (da Luz Jr M. A et al, 2014)	The Pilates method is widely used for patients with chronic low back pain. Pilates can be done in 2 ways: with specific equipment or without equipment (also known as mat Pilates).	The patients were randomly allocated to 1 of 2 groups: mat Pilates group ($n=43$) and equipment Pilates group ($n=43$). Both groups attended 12 Pilates sessions over 6 weeks.	Equipment-based Pilates was superior to mat-based Pilates in the 6-month follow-up for disability and kinesiophobia outcomes. These benefits were not observed for pain intensity and globally perceived effects in patients with chronic non-specific low back pain.
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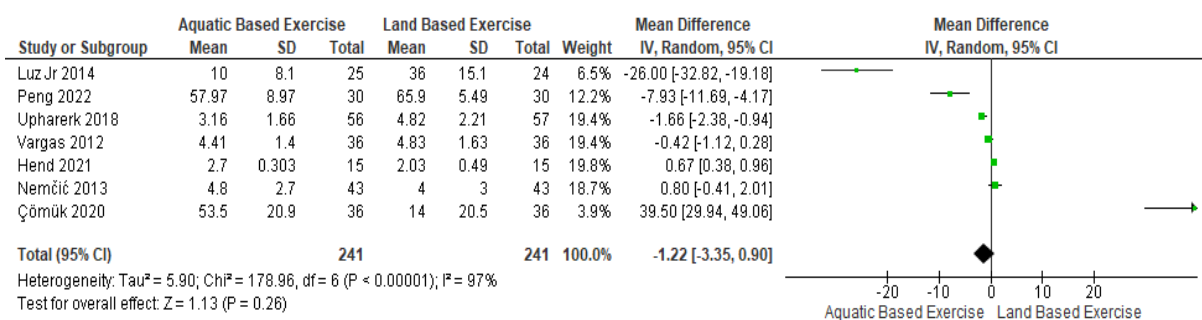


Figure 2 Forest Plot

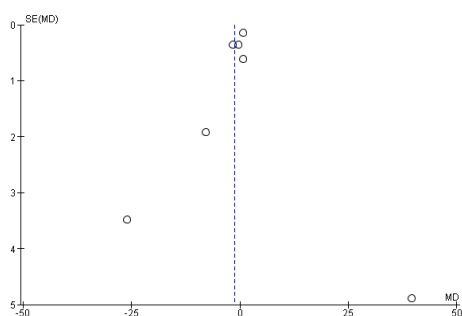


Figure 3 Funnel Plot

Discussion

In the seven selected articles that became the basis of the research, there were four articles that used a comparison intervention between water-based exercise and land exercise in Low Back Pain (LBP) cases. Four journals used water-based exercise and land exercise as a comparison of interventions in low back pain (LBP) cases. One article only used water-based exercise, while the

other two articles only used land exercise as an intervention. The analysis showed that water-based exercise was significantly more effective in reducing pain in LBP patients than land exercise.

The age of the participants in these seven articles ranged from 20 to 50 years old, taking into account inclusion and exclusion criteria and specific characteristics associated with Low Back Pain (LBP). Each article drew participants from their own local population, reflecting geographical diversity from America, Croatia, Egypt, Turkey, China, Thailand and Spain. Although the results did not show significant differences between these studies, the overall research confirmed that water-based exercise is effective as part of physical therapy to reduce pain in LBP.

Compared to land exercise, water-based exercise has been shown to reduce pain intensity, increase lumbar range of motion, and reduce the level of functional disability in patients with chronic mechanical low back pain. Water-based exercise lowers the load on the spine and joints, allowing for more free and comfortable movement. In addition, the therapeutic properties of water can reduce inflammation and promote muscle relaxation. Therefore, aquatic therapy can be a better and safer option for patients with this condition, especially for those who may experience problems or discomfort when performing exercises on land [11].

Patients with chronic low back pain who underwent water-based exercise showed greater improvements in function, pain reduction, quality of life, sleep quality, and mental state compared to those who used conventional physical therapy [12]. Water-based exercise was shown to be a safe treatment for chronic low back pain, and most participants undergoing this therapy were willing to recommend it to other patients with similar conditions [8].

In the research of Balci et al. (2020) in 15 patients given aquatic exercise in an indoor swimming pool with a water temperature of 36°C [11]. There are results that show differences between aquatic therapy exercise and land exercise in reducing pain during activity after treatment. This may be due to the type of exercise and environmental factors in the water that make a difference in aquatic exercise [12]. In the aquatic exercise group, the whole body participates in the therapy session and perhaps the mobility and strength of the whole body has increased which is concluded as a decrease in pain during activity [13].

In line with the research of Balci et al., (2020), aquatic exercise is also proven to be more

effective than land exercise in reducing pain severity, reducing the level of functional disability, and increasing lumbar range of motion in patients with chronic low back pain. In this study, the exercises used consisted of stretching and strengthening exercises [14].

The effectiveness of aquatic exercise has been tested on participants using the Visual Analog Scale (VAS), Physical Disability Index (PDI), and Oswestry Disability Index (ODI), as well as follow-up for 1-12 months after the program is completed. The results showed that this exercise is effective in reducing pain in individuals with low back pain (LBP). Aquatic exercise offers a low-impact, supportive environment that reduces stress on the spine and joints, making it especially suitable for individuals with musculoskeletal pain. The buoyancy of water helps to offload body weight, allowing patients to perform movements that might be difficult or painful on land. In addition to pain reduction, aquatic therapy has been associated with improvements in physical function, range of motion, and overall quality of life. These benefits make it a valuable component in the multidisciplinary management of chronic low back pain [15-16].

Conclusion

Based on a literature review of seven selected articles, water-based exercise has been shown to be an effective and safe exercise in reducing pain in low back pain (LBP) patients. Water-based exercise offers several advantages over land-based exercise, including greater pain reduction, improved physical function, and fewer side effects. The researchers found that water-based exercise was able to reduce pain levels faster in their study sample than land-based exercise.

Conflict of Interest

No conflict of interest in this study

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ORIGINAL ARTICLE

Osteoarthritis Therapy: Which is More Effective, Laser Therapy or a Combination of TENS IR

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ABSTRACT

Background: Osteoarthritis (OA) is a progressive joint disorder characterized by cartilage degeneration, commonly affecting older individuals. Knee OA is one of the most frequently encountered forms and often leads to chronic pain and impaired mobility. Non-pharmacological interventions have been increasingly utilized to manage OA symptoms, particularly pain. Among these are Low-Level Laser Therapy (LLLT), Transcutaneous Electrical Nerve Stimulation (TENS), and Infrared (IR) therapy. These modalities aim to decrease pain severity and improve the quality of life. This study was designed to compare the effectiveness of LLLT and the combined application of TENS and IR in alleviating knee pain in OA patients at RSI A. Yani Hospital, Surabaya

Method and Result: A quantitative approach was applied using a two-group post-test-only experimental design to analyze the influence of independent treatments on pain reduction. The study was conducted from February to August 2024. Participants were selected through purposive sampling based on predefined criteria. Data normality was assessed using the Kolmogorov-Smirnov test. Since the data were not normally distributed, the Mann-Whitney U test was used to determine statistical differences between the two treatment groups. The statistical analysis using the Mann-Whitney test yielded a p-value of 0.417 ($p > 0.05$), indicating no significant difference in pain reduction between the LLLT group and the TENS+IR group.

Conclusion: The findings suggest that both LLLT and the combined use of TENS and IR are equally effective in managing knee pain in osteoarthritis patients. As neither treatment showed superior outcomes, both can be considered valid non-pharmacological options in OA pain management protocols. Further studies with larger sample sizes and longitudinal assessment are recommended to confirm and expand upon these findings.

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Introduction

Osteoarthritis (OA) is a degenerative disease of the joints that attacks the joint cartilage and is one of the types of arthritis common in older people [1]. Osteoarthritis genu is a degenerative disease of the joints caused by several factors. This disease is characterized by the occurrence of cartilage damage. The symptoms of genuine osteoarthritis are progressive, with complaints occurring slowly and gradually worsening [2]. Osteoarthritis occurs because the joint repair process is unable to compensate for the damage that occurs. Osteoarthritis can affect both men and women. Under the age of 45 OA attacks more men, and above 55 more women [3].

From a rehabilitation point of view, Osteoarthritis genu can cause various degrees of disorders such as impaired muscle strength, restricted range of joint movement, pain, muscle spasms, and disabilities such as inability to perform certain activities such as standing up from sitting, bowing, kneeling, long-standing. As a result of decreased mobility. Even levels of functional limitation such as disruption of walking, running, and climbing stairs [4].

Low-Level Laser Therapy (LLLT) is a non-invasive light source treatment that produces a single wavelength of light. It doesn't emit heat, noise, or vibration. It's also called photobiology or biostimulation. LLLT is believed to affect the function of connective tissue cells (fibroblasts), accelerate connectivity repair, and act as an anti-inflammatory agent. This light has a good effect on pain, inflammation, and tissue repair [5].

Transcutaneous Electrical Nerve Stimulation (TENS) can reduce pain because the effect of electrical stimulation applied to the nerve fiber will result in antidromic activation, with the presence of this antidromic activation can lead to vasodilatation and suppression of sympathetic activity thus improving blood flow and transportation of material that affects pain is also increased. The administration of Infra Red (IR) intervention with a penetration depth of about 3 mm into skin tissue will cause vasodilation and circulation to become smooth in skin tissues which will lead to reabsorption and relaxation so that the muscles become elastic and flexible which leads to increased muscle flexibility to increase the range of

joint movement and stretch pain disappears so that pain is reduced [6].

Both modalities can reduce pain, in the case of pain Osteoarthritis of the knee, but there is still a minimum of research that proves which modality is better in reducing pain in the case of Osteoarthritis of the knee so the author is interested to know the difference between the influence of LLLT and TENS IR on the reduction of pain in knee Osteoarthritis.

Methods

This type of research uses pre-experimental with one-group pretest-posttest methods, that is, experimental research that is carried out on only one group without a control group. The research was conducted at RSI Ayani Surabaya in February-July 2024. Sampling is done purposive sampling. The inclusion criteria are Osteoarthritis patients who come to Poli Medical Rehabilitation criteria, while the exclusion is post foot surgery, post knee injection. The total sample in this study was 45 patients with osteoarthritis. The measured variable is the VAS score, before and after therapy of LLLT and TENS IR. The therapy doses of LLLT is 9 joules / cm² applied to the patient's 5 pain points (1.8 J/cm² per point), therapeutic treatment 2 times a week, Transcutaneous Electrical Nerve Stimulation (TENS) is duration of use 10 minutes with a power of 80-120 Hz, and Infra Red (IR) is 10-15 minutes with the distance 30-45 cm [7,8]. The type of data collected is primary data and secondary data obtained from medical records. Data processing and analysis using test analysis paired with T-test and Mann-Whitney's SPSS program. This study was approved by KEP Rumah Sakit Islam Surabaya, No. 106.EC.KEP.RSIAY.06.23.

Results

There were 45 samples that met the inclusion criteria. The characteristics of the samples are provided in Table 1. It can be seen that the distribution of samples in terms of age is evenly distributed between the ages of 30-89 years with the age group 60-69 years dominating (37.8%). The average age is 64.68 years (Table 1). Furthermore, the number of female samples (80%) is higher than the male (20%).

Table 1. Sample Characteristic

Sample Characteristic		Frequency (n=45)	Percentage (%)
Age	30-39	1	2,1
	50-59	14	31,1
	60-69	17	37,8
	70-79	10	22,3
	80-89	3	6,7
Gender	Men	9	20
	Women	36	80

From the SPSS statistical test results (Table 2. The VAS Average in Laser Therapy is 4,62, while the VAS Average in TENS IR Therapy is 4,8. Based on Mann Whitney's analysis results showed that the p-value is 0.417 ($p > 0.05$), which means that

there is no significant difference between the effectiveness of laser therapy and the combination of Transcutaneous Electrical Nerve Stimulation Infra-Red for pain reduction in osteoarthritis.

Table 2. Analysis of Therapy

Therapy	N	VAS Average	Asym. Sig. (2-tailed)
Laser	45	4,62	0.147
TENS IR	45	4,8	

Discussion

The Effects of Laser Therapy

Effects of low-intensity laser therapy in pain reduction in knee joint osteoarthritis. Lasers are rays that are amplified by the emission of radiation from the stimulation of special substances. The laser used is a low-level laser therapy that has a power output of 1 mW to 75 mW, this type of laser interaction with tissues has biological effects that can be used to treat cases of osteoarthritis. The laser also reduces pain and affects peripheral nerve activity. The effect of HeNe injection on peripheral sensory nerve latency in humans suggests that low-dose laser administration to the periphery nerve results in a significant decrease in the velocity of sensory nerve conduction. It shows the pain reduction mechanism of the laser. The mechanism of low-intensity laser pain reduction is by reducing the speed of sensory nerve transmission [6]. The results of this study demonstrate a significant reduction in pain levels among knee osteoarthritis (OA) patients following low-intensity laser therapy, as evidenced by the statistically significant decrease in VAS scores ($p = 0.000$). This finding aligns with previous research indicating that Low-Level Laser Therapy (LLLT) exerts analgesic effects through several mechanisms, including modulation of inflammatory mediators, increased microcirculation, and stimulation of endorphin release. A meta-analysis by Stausholm et al. confirmed that LLLT significantly improves pain

and functional outcomes in knee OA when appropriate parameters are applied [7-9]. Moreover, LLLT has been shown to promote tissue repair and reduce oxidative stress, contributing to long-term pain relief [10]. The use of LLLT as a non-invasive modality offers a valuable alternative or adjunct to pharmacologic interventions, particularly for patients who are contraindicated for NSAIDs or other systemic therapies. These results suggest that integrating LLLT into standard rehabilitation protocols may enhance patient outcomes and reduce reliance on long-term medication use in OA management [7-8].

Effects of Combination Therapy TENS IR

Transcutaneous Electrical Nerve Stimulation (TENS) is an alternative therapy to reduce chronic pain in osteoarthritis. The electric current is generated through this device for nerve stimulation through the skin. TENS antidromic stimulation can block the transmission of stimuli from the nociceptor to the spinal cord. TENS also activates the autonomous nervous system which will trigger a vasomotor stimulus response that will subsequently modify tissue chemistry to reduce pain. Infra-Red has also been widely used to deal with various musculoskeletal problems, including osteoarthritis. Infrared raises the temperature of the underlying tissue. Increased tissue temperature can lead to vasodilatation, increased cellular activity, an increased pain

threshold, as well as reduced muscle spasms.⁷ In this study, there was an effect of pain reduction before and after TENS IR therapy on knee osteoarthritis. Based on analysis of VAS data score on OA patients before and after TENS IR therapy for 6 months with statistical test paired sample T-test obtained results with a value of $p = 0,000$ ($p < 0.05$), which means there is a significant effect of TENSIR therapy on the reduction of pain in OA patient. TENS functions by stimulating large-diameter afferent fibers, which inhibit nociceptive transmission at the spinal cord level, thereby reducing pain perception.⁹ The addition of infrared therapy enhances therapeutic outcomes by improving local blood flow, reducing inflammation, and promoting tissue repair [10]. A randomized controlled trial by Taspinar et al. also demonstrated that TENS combined with physical modalities significantly improved pain and physical function in OA patients [11]. Furthermore, a recent study by Hsieh et al. (2023) highlighted that multimodal physical therapy, including TENS and IR, resulted in sustained pain relief and better adherence among elderly OA patients [12]. These findings suggest that the TENS-IR combination offers a synergistic effect and may serve as an effective, safe, and accessible adjunct in long-term OA management, particularly for patients seeking to minimize reliance on pharmacologic agents.

Comparison of The Effects of Laser Therapy and TENS IR Therapy on Osteoarthritis of the Knee Joint.

In this study, based on Mann Whitney's analysis results showed that the p value is 0.417 ($p > 0.05$), which means that there is no significant difference between the effectiveness of laser therapy and the combination of Transcutaneous Electrical Nerve Stimulation Infra Red for pain reduction in osteoarthritis patients at RSI Surabaya A Yani Medical Rehabilitation Clinic. Results show that both low-intensity laser therapy and TENS IR, are equally effective in relieving pain in knee osteoarthritis.

These findings are consistent with previous studies indicating that both Low-Level Laser Therapy (LLLT) and the combination of Transcutaneous Electrical Nerve Stimulation and Infrared therapy (TENS+IR) can provide effective analgesia in patients with knee osteoarthritis, although neither appears to be superior [13]. A systematic review by Stausholm et al. (2019) concluded that LLLT significantly

reduces pain and improves function in knee OA when appropriate doses are used [14]. Similarly, TENS has been shown to reduce pain intensity and improve quality of life in OA patients, especially when combined with other modalities such as infrared therapy [15]. The lack of statistically significant difference in this study may be due to comparable mechanisms of action shared by both interventions, such as enhanced local circulation, anti-inflammatory effects, and neuromodulation of pain pathways. Furthermore, variations in individual pain perception, disease severity, and treatment duration might also influence outcomes. These results suggest that clinicians can flexibly choose either modality based on patient preferences, availability, or contraindications, as both offer similar benefits in pain management for knee osteoarthritis.

In addition to pharmacological and non-pharmacological therapy, osteoarthritis patients receive education to practice fasting and physical exercise to reduce obesity. Obesity is one of the controllable risk factors for osteoarthritis. Therefore, physical exercise is necessary not only to maintain general fitness but also to reduce body weight, which is one of the risk factors for the occurrence and worsening of osteoarthritis, and of course, it should be chosen in a way that does not directly burden the knee joints. In addition, physical exercise also helps reduce complaints, particularly joint pain [16].

Conclusion

Low Level Laser Therapy and Transcutaneous Electrical Nerve Stimulation (TENS) Infra Red (IR) are both effective in reducing pain in osteoarthritis.

Conflict of Interest

No conflict of interest in this study

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ORIGINAL ARTICLE

Genotypic and Phenotypic Identification of Dermatophytes among Clinical Isolates

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ABSTRACT

Background: The prevalence of superficial fungal infections varies based on environmental and hygienic conditions. Dermatophytes, particularly *Trichophyton rubrum* and *T. mentagrophytes*, are keratinophilic fungi responsible for the majority of these infections. Their ability to produce proteases and keratinases active at acidic pH facilitates colonization of human skin. This is a fundamental mechanism observed in *Trichophyton rubrum* and *Trichophyton mentagrophytes* in establishing superficial infection.

Methods: A total of 200 clinical samples from patients with suspected dermatophytosis were examined using potassium hydroxide (KOH) mount and culture techniques. Culture-positive isolates were further identified through conventional mycology and molecular methods, including PCR and sequencing using species-specific ITS2 primers for *T. rubrum* and *T. mentagrophytes*. Clinical profiles, treatment history, and recurrence patterns were also analyzed.

Results: Among 200 KOH-positive samples, 140 yielded culture-positive results, of which 60 isolates were identified as dermatophytes. Molecular identification confirmed 20 isolates as *T. rubrum* and 40 as *T. mentagrophytes*. Clinically, 43.34% of cases were naïve infections, 50% had ongoing antifungal treatment for 1–2 years (recalcitrant cases), and 6.66% were categorized as reinfections due to recurrence of lesions post-therapy. The mean patient age was 30.02 ± 10.95 years, with a male-to-female ratio of 2:1.

Conclusion: *Trichophyton mentagrophytes* was more prevalent than *T. rubrum* among dermatophyte-positive cases. The high rate of recalcitrant and recurrent infections highlights the need for accurate species-level diagnosis using molecular tools to guide effective antifungal management strategies.

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Introduction

Dermatophytes are keratinophilic fungi that cause superficial fungal infection; grow on skin, mucous membranes, hair and nails. Dermatophytes are not a part of the normal human microbial flora but are well adapted to host keratin utilizing it as a source of nutrition for establishing infection [1].

The prevalence rate of superficial fungal infection differs from place to place according to environmental condition and also due to poor hygienic condition of population. In India most of the places are very hot and humid climate because of that our country has more prevalence rate of superficial fungal infections[2-4]. In spite of therapeutic advances in the last decades, the prevalence of cutaneous mycoses is still increasing [5]. Most of the people are living in very low socioeconomic status, crowded living environment, and poor medical care and wearing of dirty clothing which adds to the increased prevalence of cutaneous fungal infections [3]. This infection does not cause any death but it may lead to morbidity and plays a more important role in health related problems. Dermatophytes are mycelial group of closely related keratinophilic fungi, originally saprobial. Dermatophytosis is also termed as Tinea and the clinical conditions are named as “Tinea” followed by the anatomical site of infection in latin eg., tinea capitis, tinea corporis, and tinea pedis etc.

Dermatophytes comprise of 52 species of keratin degrading ascomycetes belonging to genera Trichophyton, Microsporum, Epidermophyton, Arthroderma, Lapophyton, Nanninzia, Ctenomyces, Guarromyces, Paraphyton. But human dermatophytosis is caused primarily by Trichophyton rubrum (*T. rubrum*), *Trichophyton mentagrophytes* (*T. mentagrophytes*), Trichophyton interdigitale, Epidermophyton floccosum and Microsporum canis and others. Globally Trichophyton rubrum commonly causes 50–80% of onychomycosis and tinea pedis but in India Trichophyton mentagrophyte is more prevalent in Tinea corporis and Tinea cruris [2].

During the initial stages of the infection, dermatophytes facilitate adhesions on host cell. It is initiated by a specific interaction of carbohydrate-binding proteins (lectin) with sugar (Sialic acid) as a terminal carbohydrate on the surface of the human cell. Proteases and keratinases are expressed by common dermatophytes: Trichophyton rubrum and *Trichophyton mentagrophytes* which have optimum activity at acidic pH values, and are able to establish

contact with human acidic skin due to the environment. The secretion of these proteases and peptidase, have been identified as an important step in fungal pathogenicity and virulence. The metabolism of some amino acids shifts the extracellular pH from acidic to alkaline values at which most known keratinolytic proteases have optimal enzymatic activity. This is a fundamental mechanism observed in Trichophyton rubrum and *Trichophyton mentagrophytes* in establishing superficial infection [3].

Their ability to utilize keratin as major nutrient source and high affinity for keratin facilitates them to invade keratinized structures like nails, skin and hair causing superficial infections known as dermatophytoses in humans and animals. This is commonly known as ring worm infection. The infection is generally cutaneous and restricted to the nonliving cornified layers as the fungi is unable to penetrate the deeper tissues or organs of immunocompetent hosts.

Material and Method

The clinical isolates were collected for a period of four years, from August 2015 to July 2019. All the samples (n=280) received in the mycology laboratory from out patients department (OPD) of tertiary care Guru Teg Bahadur hospital, Delhi. Institutional ethical committee approval was obtained prior to commencement of the study. Written informed consent was taken from each participant. The patient information sheet for participation in the research project was provided to each participant.

Clinical sample collection

Scrappings were collected from the affected nail and skin surface of patients referred from OPD with suspected dermatophytosis. The affected sites were decontaminated with 70% alcohol and the nail clippings from the discoloured, thickened nail bed, or nail plate was collected. The skin sample was taken from the advancing edge of lesions by scraping from the centre to edge using a sterile scalpel. Samples were divided into two portions for direct microscopy and fungal culture.

Microscopic identification

Microscopic identification of the samples were done using 40% Potassium Hydroxide (KOH). The specimen was briefly heated and then observed microscopically under 40 X magnification. The

presence of fungal hyphae, arthroconidia, was considered as a positive result for suspected dermatophyte infection.

Phenotypic confirmation of the species

A portion of the samples were cultured on Sabouraud's Dextrose agar (Hi-media, Mumbai) with antibiotics such as chloramphenicol (0.05 gm/l), Gentamicin (20mg/l) and Cyclohexamide (0.5 gm/l) (Hi-media, Mumbai). All inoculated tubes were incubated at 25°C for 3-4 weeks till optimal growth. After the growth, the etiological agent was confirmed by characteristic morphology of colony (pigmentation of the surface and reverse side, topography, texture and the rate of growth) and by studying the microscopic appearance of fungus on LPCB mounts. The species were confirmed by size and shape of macro conidia, microconidia, spirals, nodular organs and pectinate branches [1].

Genotypic confirmation of the species

These isolates were further confirmed by PCR and sequencing using species specific primers of *Trichophyton rubrum* and *Trichophyton mentagrophytes* [2].

DNA extraction

DNA was extracted from the cultures grown on SDA by using commercially available DNA extraction kit (Hi Yield genomic DNA kit, RBC, Taiwan).

Polymerase Chain Reaction (PCR)

On the basis of sequences of internal transcribed spacer to in NCBI nucleotide data base primer of *Trichophyton rubrum* and *Trichophyton mentagrophytes* were used shown in table-1 and the PCR product length of two primer sets were 203 base pair and 130 base pair respectively. For PCR each tube contained a total volume of 25 µl mix including 2.5 µl buffer (10X), 5 µl of Q-buffer, 0.5 µl dNTPs (200 µM), MgCl₂ 0.5 µl (1.5 mM), 0.15 µl Taq polymerase, 1 µl of each primer, forward and reverse (10 µM), 5 µl of the extracted DNA and nuclease free water to make up the volume. All PCR reagents were purchased from Qiagen, and amplification was performed on a thermo-cycler (Eppendorf) at the thermal profile shown in table 2 and 3 [3-4]. Standard ATCC control strains were used as positive controls (*T. mentagrophytes* ATCC. 28185) [5].

Table 1 Primer sequences

S. No.	Region	Primer name	Primer sequence
1	ITS 2	*TR F	F 5' TCTTTGAACGCACATTGCGCC 3'
		TR R	R 5' CGGTCCTGAGGGCGCTGAA 3'
2	ITS 2	*TM F	F 5'-CAAACGTCCGTCAGGGTGAGC 3'
		TM R	R 5'-TAGCCACTAAAGAGAGGCTCGC 3'

*TR: *T. rubrum*

*TM: *T. mentagrophyte*

Table 2 Thermal profile of *T. rubrum* -

Temperature	Time	Cycles	Phase
95°C	10 min	1	Initial Denaturation
95°C	60 sec	35	Denaturation
60°C	45 sec		Annealing
72°C	60 sec		Extension
72°C	7 min	1	Final extension
4°C	∞	1	Hold

Table 3 Thermal profile of *T. mentagrophytes* –

Temperature	Time	Cycles	Phase
95°C	10 min	1	Initial Denaturation
95°C	60 sec	35	Denaturation
65°C	30 sec		Annealing
72°C	60 sec		Extension
72°C	7 min	1	Final extension
4°C	∞	1	Hold

The amplified PCR products were analyzed by electrophoresis on 1.2% agarose gel, at 125 V and 15 mA current in 10 slot apparatus for 40 minutes, stained with Ethidium Bromide.

Sequencing

Purification of the PCR product was done using Gel purification kit protocol (Qiagen, Germany). Sequencing was done as per protocol used by big dye terminator method followed by Sanger sequencing method. The sequence analysis was performed by comparison of the nucleotide with dermatophyte reference nucleotide sequences obtained from the gene bank data base (<http://www.ncbi.nih.gov/gene>), match sequence with data base and submit the sequence in gene bank data base for the accession number.

Statistical analysis

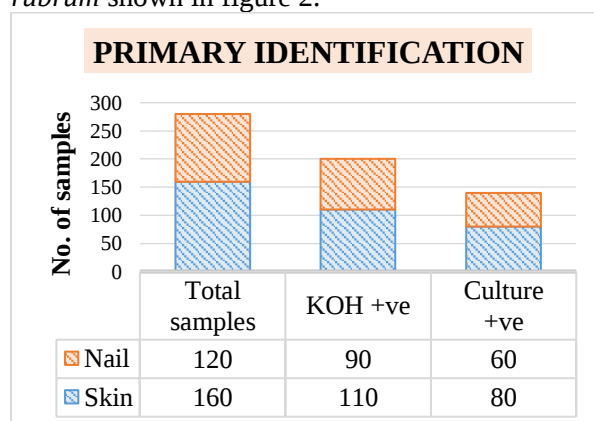
Bionumerics software (Applied Maths and Ghent) was used for consensus and concatenation of the sequences. The sequences and amino acid sequences depicted by using the ExPASy online tool (<https://web.expasy.org/translate/>) were aligned.

Results

Identification of Culture

A total of 280 samples were collected, which included 120 onychomycosis and 160 tinea infection. Out of 120 nail samples, 90 were found to be KOH positive, and 60 samples were culture positive for dermatophytes and non-dermatophytes. Among 60 isolates from nail sample (Figure-1), 19 isolates were identified as *T. rubrum* and 5 isolates as *T. mentagrophytes* complex. Similarly, of 160 skin samples, 110 cases were observed as KOH positive, of which 80 samples were culture positive. Of 80 culture isolates 35 isolates were characterized as *T. mentagrophytes* complex and 1 isolate as *T. rubrum*. A total of 60 culture isolates (nail and

skin) as confirmed by LPCB, PCR and reconfirmed by sequencing, 40 isolates are of *T. mentagrophytes* complex and 20 isolates are of *T. rubrum* shown in figure 2.

**Figure 1** Screening of Dermatophytic samples**Table 4** Distribution by KOH and culture among the patients-table and text *not matching*

Cases	Total Cases	Skin (%)	Nail (%)
Total Cases	280	160(57.14%)	120(42.86%)
KOH positive	200	110(55%)	90(45%)
Culture positive	140	80(57.14%)	60(42.86%)
<i>T. mentagrophytes</i>	40	35(87.5%)	5(12.5%)
<i>T. rubrum</i>	20	1(5%)	19(95%)

Phenotypic Distribution of Isolates:

In this study, a total of 280 samples suspected of dermatophytosis were collected, with 200 samples confirmed by KOH for fungal elements (110 cases of Tinea and 90 of onychomycosis).

From 110 Tinea cases 80 were found to be culture positive similarly out 90 onychomycosis cases 60 cases were culture positive.

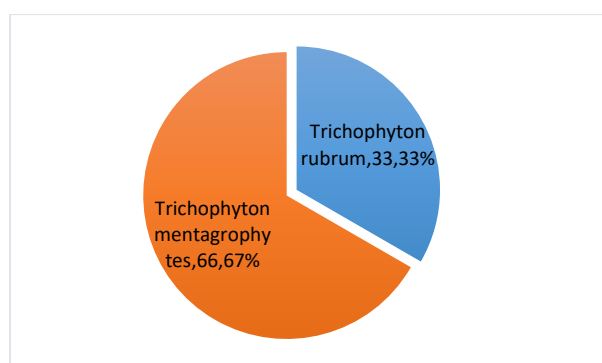


Figure 2 Phenotypic distribution of the Culture isolates

Phenotypic Distribution of *T. mentagrophytes* 40/60 (66.67%) and *T. rubrum* 20/60 (33.33%) among the nail and skin samples.

- The patients mean age with standard deviation was 32.51 ± 11.32 years. The duration of dermatophytic infection in the cases ranged from 3 months to 10 years ($9.8 \text{ months} \pm 5.45 \text{ months}$).
- Out of 60 culture positive patients included skin and nail also, 43.34% cases were naïve, reported infection for the first time; 50% cases were on antifungal treatment for 1-2 years and 6.66% cases were with recurrence's which were presenting with lesions at the same or different site after completion of previous therapy. These were categorized as naïve, recalcitrant and reinfection respectively.

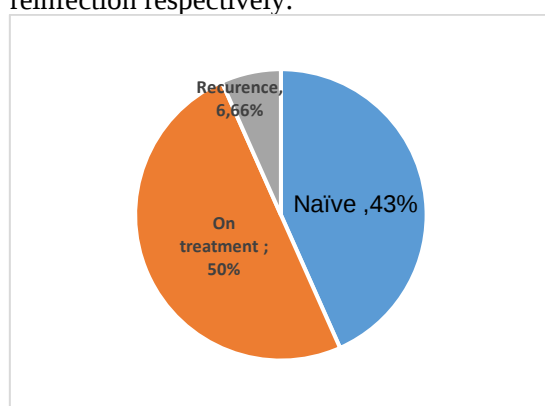


Figure 3 Pie chart showing categorization of patients on the basis of their treatment

➤ **Phenotypic characteristics of *Trichophyton mentagrophytes***

Microconidia of *Trichophyton mentagrophytes* complex were spherical, sessile, arranged in dense, grape-like clusters or along the hyphae.

Macroconidia were 3-8 celled, smooth and thin walled, clavate to cigar-shaped (Figure 4a & 4b).

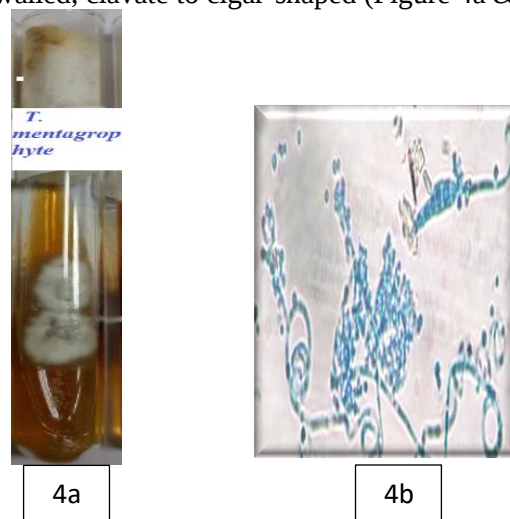


Figure 4 (4a) culture of *T. mentagrophytes* and (4b) LPCB of *T. mentagrophytes*

➤ **Phenotypic Characteristics of *Trichophyton rubrum***

Colonies were fluffy to cottony, white and most of the isolates turned rose when aging, reverse showed wine red pigmentation (Figure 5). Macroconidia seen occasionally, but when present are thin walled, poorly differentiated with variable size cylindrical to cigar-shaped. Microconidia were peg-shaped to pyriform. Sessile alongside undifferentiated hyphae (Figure 5a & 5b).

LPCB of *T. rubrum*.



Figure 5 (5a) culture of *T. rubrum* and (5b)

All isolates were subjected to PCR using species specific primer of the ITS region for further confirmation. The site of infection are shown in figure 6a- 6d before isolation of *T. rubrum* and *T. mentagrophytes* complex.



6a. Onychomycosis



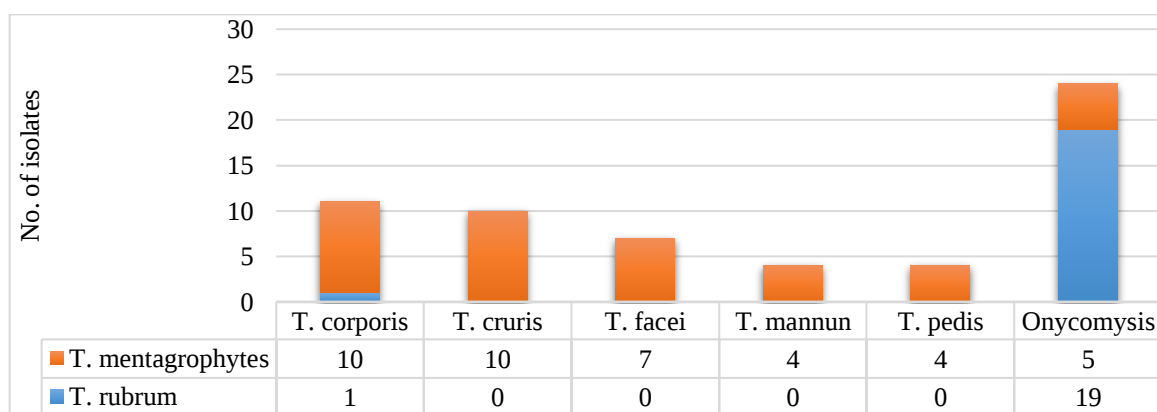
6b. Tinea corporis



6c. Tinea manuum



6d. Tinea corporis

Figure 6 Lesion of Infection**Figure 7** Distribution of *T. mentagrophyte* and *T. rubrum* with their site of infection.**Clinical Manifestation:**

Amongst the 60 isolates, tinea corporis was predominant clinical presentation in 11 cases (18.33%) followed by *T. cruris* 10 (16.67%), *T. faciei* 7 (11.67%) and *T. pedis* in 4 (6.67%)

(Figure-7). *T. mentagrophytes* complex was the major causative agent except in one case of *T. corporis*, *T. rubrum* was isolated on culture. While in 24 (40%) cases of onychomycosis, *T. rubrum* 19/24 (79.17%) was isolated followed by *T. mentagrophytes* complex in 5 cases (20.83%).

Table 5 Age and Sex distribution with species

Age Group (years)	<i>Trichophyton mentagrophytes</i> Complex				<i>Trichophyton rubrum</i>			
	Male		Female		Male		Female	
	Skin	Nail	Skin	Nail	Skin	Nail	Skin	Nail
10-20	8	0	0	0	0	0	0	0
21-30	8	1	2	0	0	7	0	4
31-40	6	1	5	1	0	2	1	0
41-50	2	0	2	2	0	1	0	2
51-60	1	0	1	0	0	3	0	0
Total	25	2	10	3	0	13	1	6

Age Distribution:

- The prevalence of Dermatophytic infection was more common in male patients 40/60 (66.67%) as compared to female patients 20/60 (33.33%) in both onychomycosis and Tinea infection.

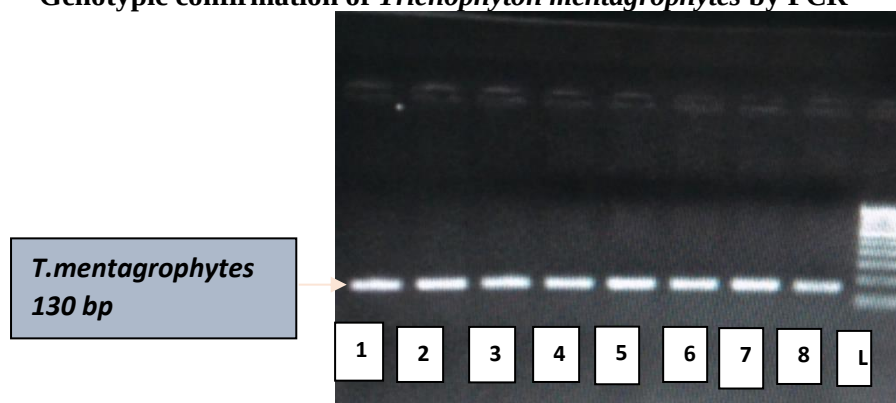
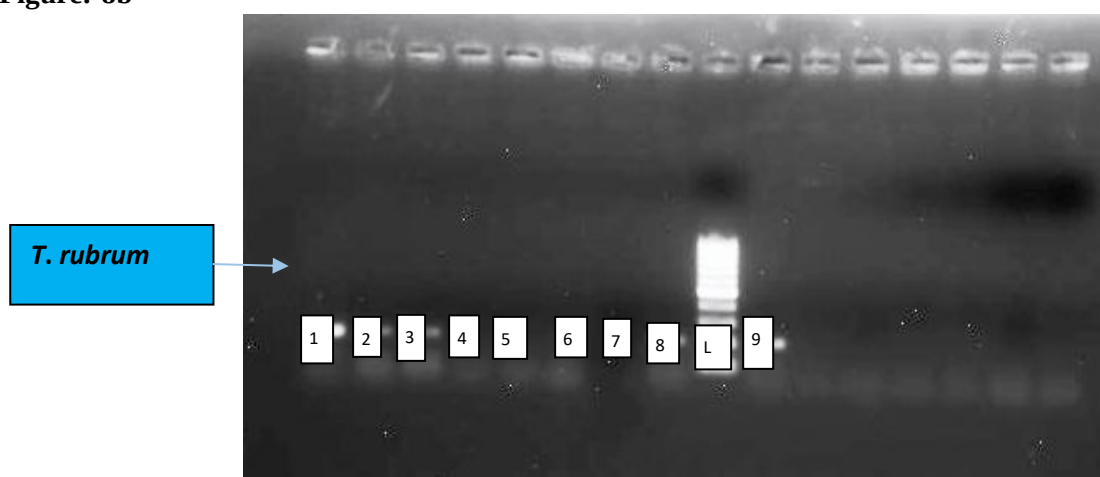
Genotypic confirmation of *Trichophyton mentagrophytes* by PCR**Figure 8a:** Gel picture below showing bands at 130 bp for 8 isolates of *T. mentagrophytes* (figure:- 8a and figure:-8b).

Figure showing Lane 1-8 and L (ladder). Where lane 1-8 showing bands of samples of *T. mentagrophytes*, and L is 100 base pair molecular weight marker (Fermentas).

➤ Genotypic Confirmation of *Trichophyton rubrum* by PCR**Figure:-8b****Figure 8b:** Gel picture showing bands at 203 bp for 5 PCR products of *T. rubrum* strains. Figure showing Lane 1-7, L (ladder) and 8. Where lane 1-3, 7 & 8 are samples of *T. rubrum*, Lane 4-6 are negative control (no template) and L is 100 base pair molecular weight marker (Fermentas).

Sequencing

Purification of PCR products was done by Sodium Acetate Manual method and DNA sequence analysis was performed and by comparison of the nucleotides with dermatophytes reference nucleotide sequences obtained from the gene bank database (<http://www.ncbi.nih.gov/gene>), *T. mentagrophytes* and *Trichophyton rubrum* were showing 99% similarity with the reference strain. The

representative sequence obtained were submitted to the gene bank database; and Accession numbers were obtained, total sequence submitted 12 numbers that are *T. mentagrophytes* accession no. are (9 sequences) **MW497552 to MW497560**, (3 sequences) **MH644185, MH745112 & MH778308** and total sequence submitted 19 numbers that are *Trichophyton rubrum* accession no.- (16 sequences) **MW506332 to MW506347** and (3 sequences) **MH497367 to MH497369**.

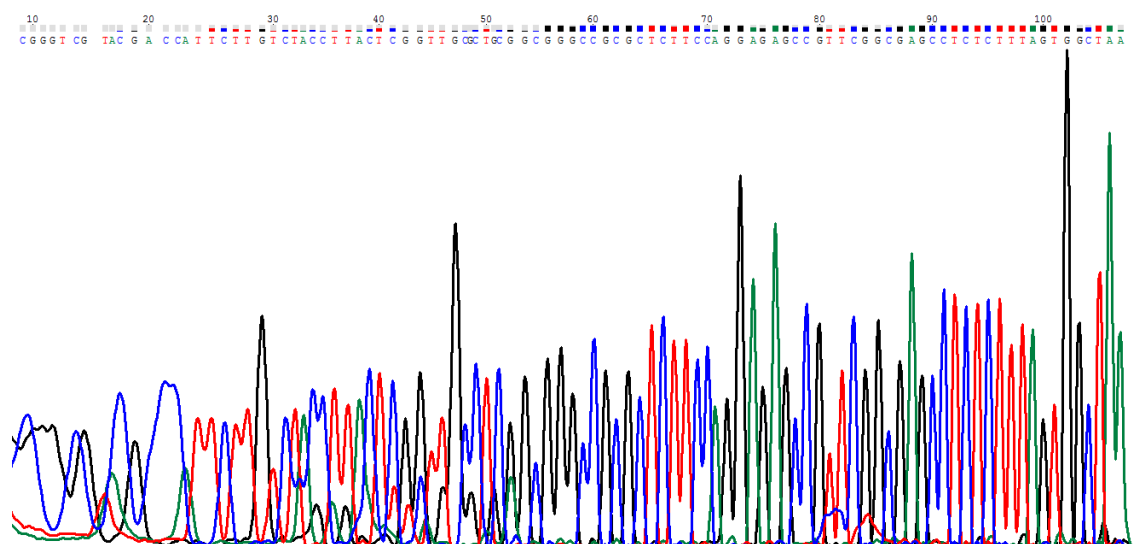


Figure 9 Showing Electropherogram of *T. mentagrophytes*

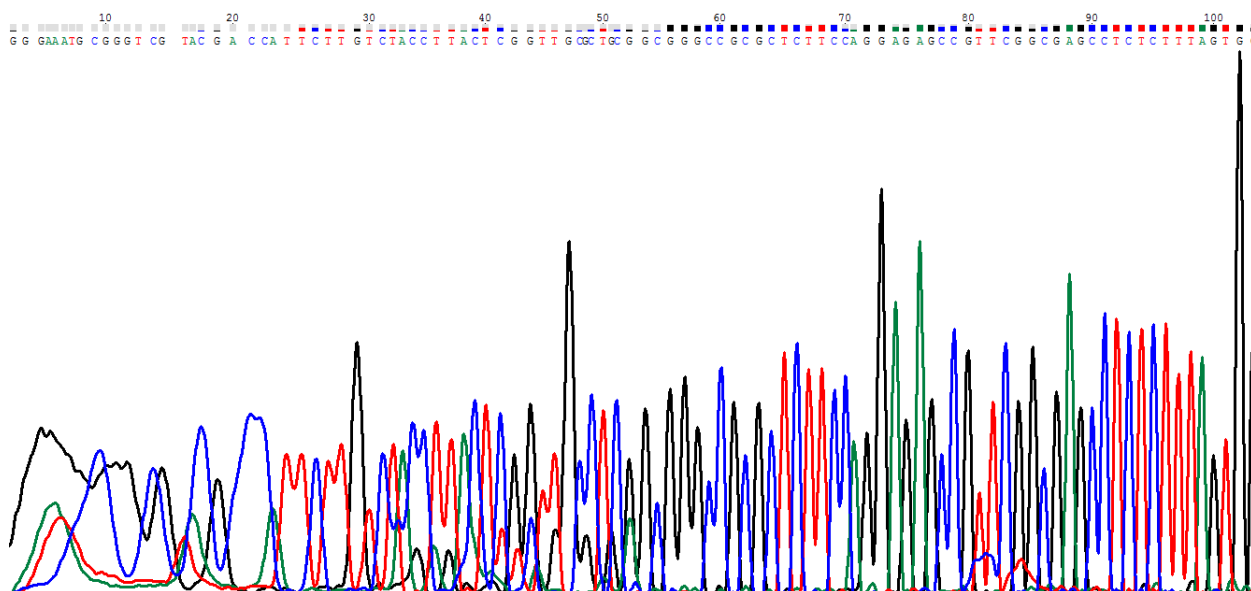


Figure 10 Showing Electropherogram of *T. rubrum*

Discussion

The demographic and microbiological profile observed in this study reflects current epidemiological patterns of dermatophytosis. The mean age of 30.02 ± 10.95 years indicates a higher prevalence among young adults, potentially due to greater exposure to shared public spaces and increased perspiration, which creates an ideal environment for fungal proliferation. The male predominance (2:1 ratio) is consistent with recent findings, suggesting that occupational exposure, outdoor activities, and behavioral factors may contribute to higher infection rates in males [6]. Although 200 samples were positive by KOH examination, only 140 yielded positive cultures, highlighting the limitations of microscopy alone and the need for complementary culture and molecular diagnostics. Interestingly, *T. mentagrophytes* was more frequently isolated than *T. rubrum*, indicating a potential shift in dominant species distribution, which has also been reported in recent studies across Asia and Europe [7-8]. Molecular identification using ITS2-based PCR and sequencing enhances diagnostic accuracy, particularly in distinguishing closely related species within the *T. mentagrophytes/T. interdigitale* complex, and is critical in the context of increasing antifungal resistance and clinical recalcitrance [9]. The discrepancy between KOH and culture positivity is consistent with previous findings and may be attributed to nonviable fungal elements, sample quality, or contamination during transport or processing [10].

The predominance of *Trichophyton mentagrophytes* (66.7%) over *T. rubrum* (33.3%) is notable and suggests a shift in the species distribution of dermatophytes, a trend increasingly reported in India and other parts of Asia. Traditionally, *T. rubrum* was the most prevalent dermatophyte worldwide. However, emerging data now show a rising incidence of *T. mentagrophytes* complex, particularly strains associated with chronic and treatment-resistant cases [11-12]. Molecular methods such as ITS2 sequencing provide superior resolution in distinguishing species within the *T. mentagrophytes/T. interdigitale* complex, which is vital for epidemiological monitoring and therapeutic decision-making. Clinically, the high proportion of recalcitrant cases (50%) highlights growing concerns regarding antifungal resistance and inappropriate or

prolonged treatment regimens. This is in line with several studies that have identified reduced susceptibility to commonly used antifungal agents—especially terbinafine—among *T. mentagrophytes* isolates [13]. Inadequate dosing, poor adherence, and empirical treatments without species confirmation may contribute to chronicity and relapse. These findings reinforce the need for targeted antifungal therapy based on species identification and antifungal susceptibility testing in persistent cases.

The recurrence rate of 6.66% and the presence of reinfections also underscore the challenges in managing dermatophytosis, especially in tropical climates where reinfection risk is high due to humidity, crowded living conditions, and poor hygiene. Reinfection may also reflect environmental reservoirs, fomite transmission, or untreated household contacts. Public health measures focusing on hygiene education, avoidance of self-medication, and treatment of close contacts are essential to control reinfection cycles [14-15].

The demographic profile of patients in this study, with a mean age of 30.02 ± 10.95 years and a male-to-female ratio of 2:1, is consistent with existing literature. Young adult males tend to have higher occupational exposure, greater physical activity, and more frequent use of occlusive footwear or clothing, increasing their vulnerability to dermatophyte infections [16]. This trend is frequently attributed to increased occupational exposure, physical activity, and the use of occlusive footwear or tight clothing, which create warm and moist environments conducive to fungal growth [14-15]. Men are also more likely to work in outdoor or industrial settings, where hygiene conditions may be suboptimal, increasing the risk of acquiring superficial fungal infections. Moreover, gender-based differences in health-seeking behavior can influence diagnosis rates; women may be more likely to seek early medical attention, while men often delay treatment until the infection becomes severe or widespread [16]. Hygiene practices and cultural norms may also play a role in differential exposure and susceptibility between genders. Additionally, dermatophytosis is frequently reported among individuals in their second and third decades of life due to increased social interaction, use of shared facilities (e.g., gyms, dormitories), and lifestyle habits that promote transmission [10]. Understanding these demographic patterns is critical for designing effective prevention and education

strategies that are tailored to the most affected populations, particularly in resource-limited settings where recurrence and chronicity are common [17-18]. Gender-based differences in healthcare-seeking behavior and hygiene practices may also contribute. Understanding the demographic and clinical characteristics of affected populations is essential for designing preventive strategies and tailoring health education efforts.

Conflict of Interest

No conflict of interest in this study

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ORIGINAL ARTICLE

Evaluation of the Tuberculosis Surveillance System in Depok, West Java

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ABSTRACT

Depok is one of the cities with a high number of TB cases in West Java. The implementation of TB surveillance in Depok revealed challenges in meeting TB control indicators. Evaluating the surveillance system is essential to assess the quality of the existing system and identify barriers in TB surveillance implementation. Therefore, this study aims to evaluate TB surveillance system in Depok based on its components and attributes. This study was an assessment that describes the implementation of the TB surveillance system using both quantitative and qualitative approaches. It highlighted the systemic challenges that hindered effective TB control, such as inadequate knowledge of legal aspects, insufficient private-sector engagement, lack ability of data analysis and interpretation, the high percentage of TB officers who had not received the training was partly due to staff turnover, complex data collection, and low utilization of surveillance data for decision-making. To enhance the effectiveness of TB control efforts, this study recommends targeted training for healthcare workers, sufficient budget allocations, and simplified data management systems.

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Introduction

Tuberculosis (TB) is an infectious disease caused by the *Mycobacterium tuberculosis*, which remains a leading global health problem. Additionally, TB is among the top 10 causes of death worldwide and the leading cause of death from a single infectious agent [1]. Indonesia has the second-highest number of TB cases globally after India, accounting for 8.5% of cases [2]. West Java, along with East Java and Central Java, is among the three provinces with the highest number of TB cases in Indonesia. According to the 2020 Indonesian Health Profile, these three provinces accounted for 46% of all TB cases in the country. In addition to being among the provinces with the highest TB cases in Indonesia, West Java has a high Case Notification Rate (CNR) for all TB cases, exceeding the national average. Data from 2020 indicated a CNR in West Java of 159 cases per 100,000 population, compared to the national average of 130 cases per 100,000 population [3]. Depok is one of the cities with a high number of TB cases in West Java. Based on the 2020 Depok Health Profile, the number of TB cases in Depok was 3,311, with a CNR of 133 cases per 100,000 population [4]. This figure represents an increase compared to the CNR in 2015, which were 121 cases per 100,000 population [5].

Surveillance is one of the TB control outlined in the Minister of Health Regulation Republic Indonesia No. 67 of 2016. According to this regulation, TB surveillance involves the systematic, and continuous monitoring and analysis of data and information regarding TB occurrences or health issues and the factors influencing them, aimed at guiding effective and efficient control actions [7]. Several indicators are used to assess the progress or success of TB control, including impact indicators, main indicators, and operational indicators. Impact indicators, for example, can be measured through the prevalence rate of TB. Meanwhile, main indicators are evaluated based on the treatment coverage of all treated TB cases, the Case Notification Rate (CNR), the treatment success rate of all TB patients, the detection rate of drug-resistant TB cases, the treatment success rate for drug-resistant TB patients, and the percentage of TB patients who are aware of their HIV status [6].

The implementation of TB surveillance in Depok revealed challenges in meeting TB control indicators. The TB prevalence in Depok was 133 cases per 100,000 population, exceeding the target of 117 cases per 100,000 population set for 2020.

Furthermore, the treatment coverage rate in 2020 was only 47.40%, representing a significant decline from 2016, when it reached 119.91%. TB mortality rates also increased from 0.78 deaths per 100,000 population in 2016 to 3.54 deaths per 100,000 population in 2020 [7].

Evaluating the surveillance system is essential to assess the quality of the existing system and identify barriers in TB surveillance implementation. Therefore, this study aims to evaluate the TB surveillance system in Depok based on its components and attributes to provide appropriate suggestions and recommendations.

Methods

The evaluation of the TB surveillance system in Depok is an assessment that describes the implementation of the TB surveillance system using both quantitative and qualitative approaches. The quantitative approach was employed to describe the TB surveillance system through observations of TB surveillance reports from Public Health Centers (PHCs), hospitals, clinics/private practitioners, and Depok Health Office in 2021. The qualitative approach was used to describe the surveillance system and the challenges encountered during its implementation, conducted through in-depth interviews with nine TB officers at PHCs and eight TB officers at hospitals. The questionnaire utilized was based on the Guidelines for Monitoring and Evaluating Communicable Disease Surveillance Systems and Response Systems issued by the World Health Organization [8]. Ethics approval is not required for this study.

Result

1. Structure of The System

1.1. Legal Aspects

The legal framework for implementing the TB surveillance system in Indonesia was regulated under the Ministry of Health Regulation No. 67 of 2016. Based on interviews with TB officers at PHCs and hospitals, it was found that 59% of the officers were unaware of this regulation. When viewed by the type of healthcare facility, the percentage of TB officers at hospitals who were unaware of the legal aspects was higher compared to TB officers in PHCs. Figure 1 showed that only 25% of TB officers in hospitals were aware of the legal aspects of the implementation of the TB surveillance system in Indonesia.

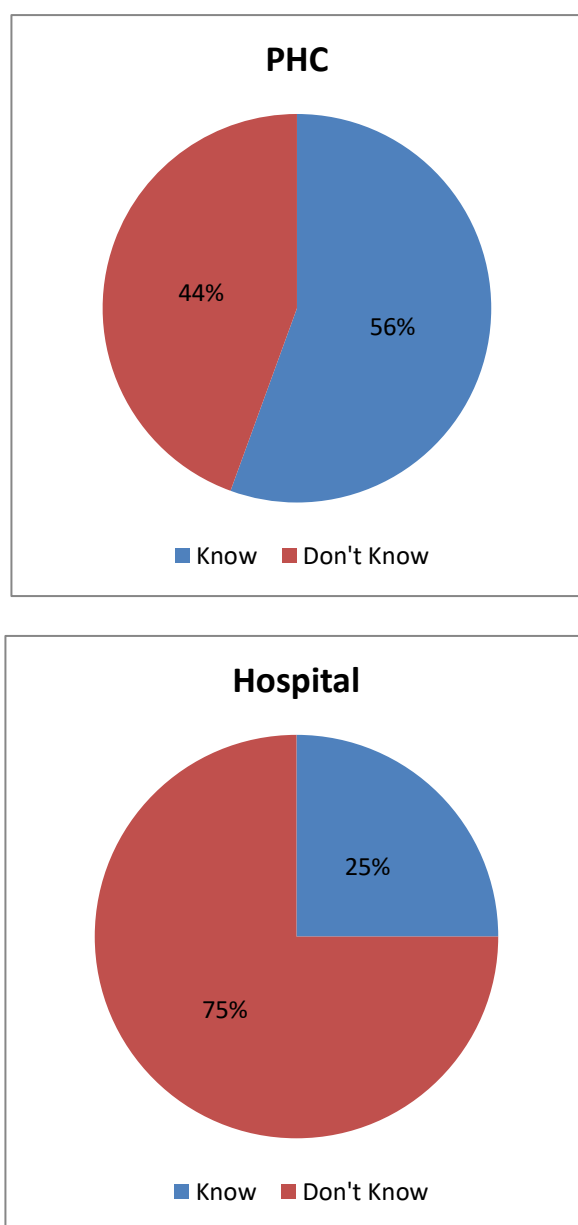


Figure 1. Knowledge of TB Officers in Health Facilities regarding the Legal Aspects of the TB Surveillance System in Depok

TB officers who are also healthcare workers (HCWs) are at an increased risk of contracting TB due to their exposure in clinical settings. A study conducted in Yogyakarta, Indonesia, assessed the knowledge and attitudes of HCWs towards TB and identified factors influencing their understanding. The findings highlighted that inadequate knowledge among HCWs can lead to suboptimal TB control practices, potentially increasing the risk of transmission within healthcare facilities.(9) Furthermore, a review on the medico-legal aspects of TB emphasized the importance of HCWs' understanding of legal frameworks governing TB control. Such knowledge ensures that patient rights are respected, confidentiality is maintained, and legal

obligations are fulfilled, thereby enhancing the effectiveness of TB control programs [10].

1.2. Coordination

Depok Health Office (Dinkes) faced coordination challenges with the private sector. In 2021, only 1% of private practitioners collaborated with the Health Office in recording and reporting TB cases, as illustrated in Figure 2.

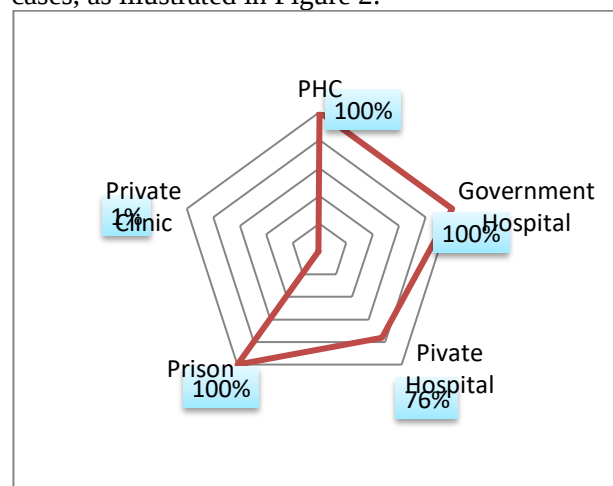


Figure 2. Proportion of Healthcare Facilities Reporting TB Cases in Depok

Besides that, The Health Office had also partnered with a professional organization called the Coalition of Professional Organizations for Tuberculosis Control (KOPI TB). This organization aimed to enhance the involvement of practitioners in national TB control, ensure TB management according to the International Standards for Tuberculosis Care (ISTC) and the National Guidelines for TB Medical Management, notify patients within the National TB Program's information system, and support the success of TB control. In addition, Dinkes had also partnered with communities such as Penabulu-STPI Consortium, which received grants from the Global Fund, and the Indonesian TB Eradication Association (PPTI), which received funding from the local government's budget (APBD) in Depok.

Although advocacy had been conducted, the low interest of the private sectors in collaborating remained challenges for the Health Office in increasing the involvement of the private sectors in national TB control program. Effective TB control relies heavily on coordinated efforts among healthcare providers, public health agencies, and community organizations. A comprehensive model for TB control emphasizes the importance of collaboration between public health staff and private-sector practitioners. This coordination ensures that all parties are aware of their roles and responsibilities, leading to more efficient and

effective TB prevention and treatment strategies [11].

2. Core Functions of Surveillance System

2.1. Case Detection

According to Ministry of Health Regulation No. 67 of 2016, TB case detection was conducted both actively and passively [6]. Based on interview results, it was found that TB case detection in Depok had been carried out passively and actively. Passive case detection was performed through examinations of patients visiting healthcare facilities, while active case detection was conducted through household contact investigations, screenings of prison inmates as part of health day activities in collaboration with HIV and Non-Communicable Diseases (NCD) programs, and TB screenings in 10 PHCs areas targeting the community and high-risk populations.

Despite various efforts, the percentage of TB case detection in Depok in 2021 remained relatively low. Out of an estimated 6,973 TB cases, only 3,974 cases (57%) were detected and treated (Figure 3). One of the reasons for the low percentage of TB case detection was the suboptimal implementation of contact investigations. Based on data observations, 7,553 individuals were investigated from 1,586 index cases. This indicated that the ratio of close contacts investigated was only 5. This figure fallen significantly short of expectations, as Ministry of Health Regulation No. 67 of 2016 stipulated that contact investigations should involve at least 10–15 close contacts per index case.

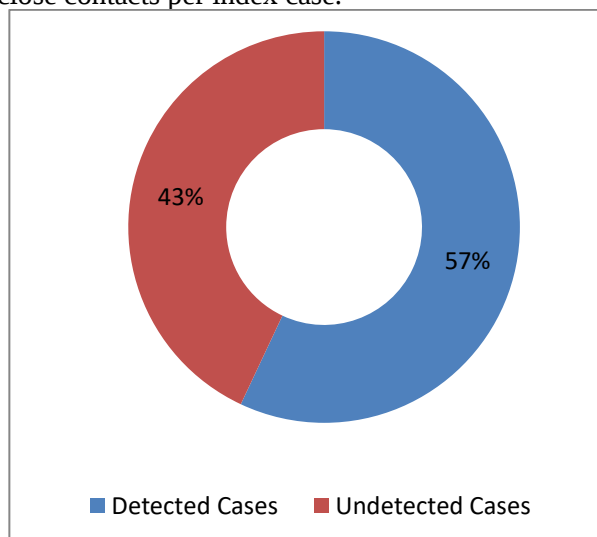


Figure 3. Coverage of TB Case Detection in Depok

Effective tuberculosis (TB) control hinges on the timely detection and treatment of cases. Active case-finding interventions, particularly those implemented within communities, have been shown to identify and treat more individuals with TB compared to standard case detection methods. These interventions involve proactive screening and

outreach efforts that reach populations who may not seek care due to various barriers, thereby reducing transmission rates and improving public health outcomes [12].

2.2. Case Confirmation

TB case confirmation could be done either bacteriologically or clinically. Based on Figure 4, the overall TB case diagnosis in Depok was considered good, as it meted the ideal proportion between bacteriologically confirmed and clinically diagnosed cases, in accordance with the criteria issued by the Ministry of Health of Indonesia, which was 60:40. [6].

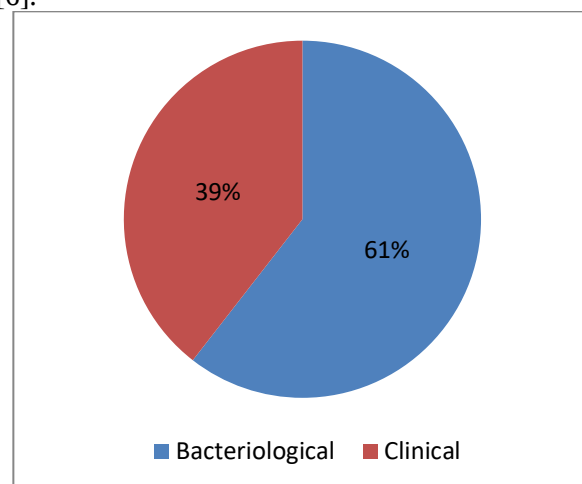


Figure 4. Comparison of Bacteriological and Clinical TB Case Diagnoses in Depok

Accurate and timely diagnosis is fundamental to effective TB control. Early detection enables prompt initiation of treatment, reducing transmission rates and improving patient outcomes. Advancements in diagnostic technologies, such as molecular tests and rapid point-of-care devices, have significantly enhanced the ability to identify TB cases more efficiently. These innovations are particularly crucial in resource-limited settings, where traditional diagnostic methods may be inadequate [13].

2.3. Analysis and Interpretation

Analysis and interpretation of data were crucial to determine appropriate actions that should be taken in response to the situation. At the Health Office level, analysis and interpretation of TB data collected through the TB Information System (SITB) had been conducted. This data was analyzed descriptively in the form of graphs and used for evaluation and decision-making. However, at the hospitals and PHCs level, not all healthcare facilities perform analysis and interpretation of the collected TB data. According to interview results, it was found that 65% of healthcare facilities had not conducted

analysis and interpretation of the collected data. The percentage of PHCs that had not performed data analysis and interpretation was higher compared to that of hospitals (Figure 5). Furthermore, among all healthcare facilities that had conducted analysis, none had performed analytical analysis. The analysis conducted was purely descriptive.

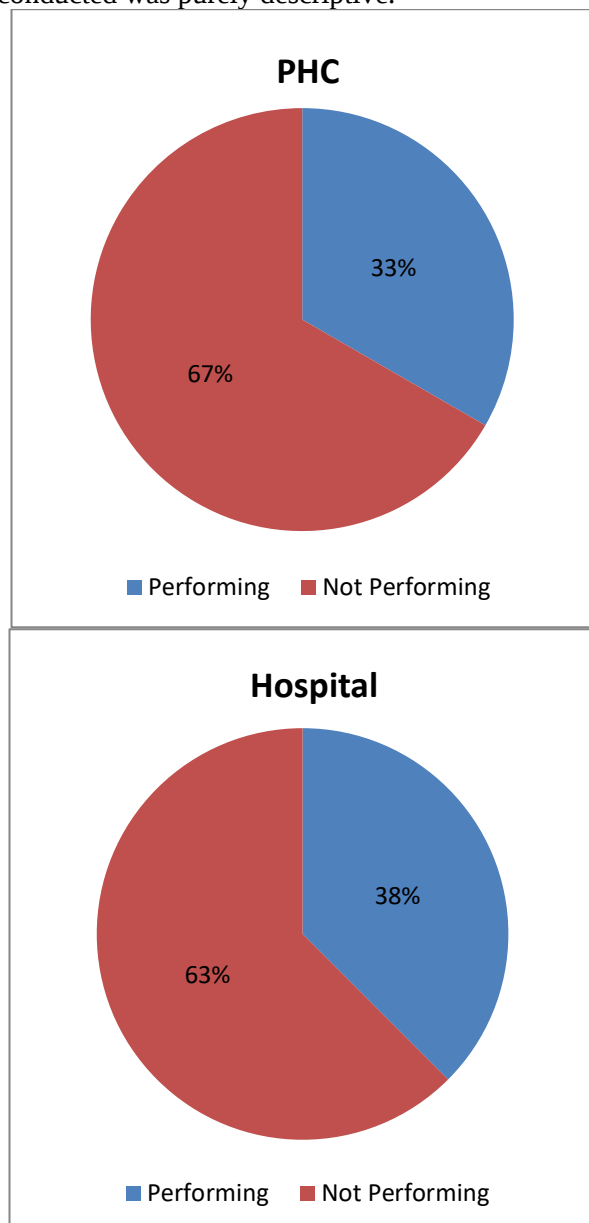


Figure 5. Percentage of Healthcare Facilities Performing Data Analysis and Interpretation in Depok

There are several reasons that TB officers at PHCs and hospitals did not perform analysis and interpretation of the available data. The first reason was the shortage of human resources (HR), which forced officers to take on multiple roles. At hospitals, TB officers were generally nurses who also served as medical assistants and provided patient care. Additionally, at PHCs, TB officers were also responsible for other programs. This resulted in difficulties in performing data analysis and

interpretation. The second reason was a lack of time, as officers must divide their time to manage other responsibilities. Moreover, in 2021, their time was further occupied with handling the COVID-19 pandemic, which affected the entire world. During that year, officers were not only busy with COVID-19 case tracing and testing but also involved in vaccinating the community. The third was the lack of ability and commitment among officers to perform data analysis and interpretation. Instead of conducting their own analysis, TB officers relied solely on the graphs produced by the TB Information System (SITB).

Accurate data enables health authorities to monitor disease trends, identify high-risk populations, and allocate resources efficiently. Implementing robust data management systems enhances the capacity to track TB cases, treatment outcomes, and program performance, thereby facilitating informed decision-making and timely interventions [14]. The proficiency of TB officers in data analysis and interpretation is crucial for the success of TB control programs. Training TB officers in these skills has been shown to significantly increase TB case detection rates. A systematic review and meta-analysis revealed that providing training to health professionals and volunteers led to a 60% increase in TB case detection [15].

Furthermore, enhancing TB officers' abilities in data analysis and interpretation contributes to improved infection control practices. Studies have demonstrated that training TB officers in TB infection control measures positively influences their knowledge, attitudes, and practices, thereby reducing the risk of TB transmission within healthcare settings [16].

2.4. Feedback

Feedback was a response from the higher-level surveillance unit (Depok Health Office) regarding the implementation of TB surveillance at healthcare facilities. Based on interview results, all TB officers at PHCs and hospitals reported that TB supervisor at the Depok Health Office provided feedback to all healthcare facilities regarding the implementation of TB surveillance. That feedback was provided through periodic meetings, which occurred every three months, as well as direct discussions, phone calls, or WhatsApp messages.

Regular mentorship and feedback from higher-level units have been shown to significantly improve TB program performance in health facilities. A study highlighted that evidence-based mentorship, feedback, and decision-making were key components of the Standard of Care (SOC)

approach, leading to enhanced TB control efforts. This approach not only improved the quality of care but also strengthened the sense of ownership among health facility managers and workers, ensuring the sustainability of TB program support [17].

3. Support Functions of Surveillance System

3.1. Guideline

Guideline was the foundation for carrying out activities, including TB control. Guideline for TB control was necessary to ensure that those involved and the public were aware of the indicators and steps required to eliminate TB cases. In Indonesia, the guideline for TB control was the Ministry of Health Regulation No. 67 of 2016. This regulation included explanations on TB control targets, strategies, activities, and also contained details on TB surveillance [6].

Based on interviews, it was found that 41% of healthcare facilities could not provide the relevant guideline during the interview, either in hard or digital format. Their inability to present the guidelines was partly due to a turnover of TB officers, leaving new staff unaware of the guidelines' existence. Additionally, some respondents stated that the strategies and activities to be carried out were the responsibility of TB officers at the Health Office, so program officers at PHCs and hospitals only needed to implement them.

Evidence-based guidelines provide standardized protocols for diagnosing, treating, and preventing TB, ensuring consistency and quality across healthcare settings. These guidelines are essential for guiding HCWs in implementing best practices and adhering to recommended procedures [18].

3.2. Training

Training was one of the efforts to enhance the capacity of officers in TB surveillance activities. Some of the basic training required for officers included training on case reporting and recording, as well as contact investigation training specifically for TB officers at PHCs. According to interview results, 53% of TB officers reported that they had never received training on TB case reporting and recording through SITB (Figure 6), and 44% reported they had never received training on TB contact investigations (Figure 7).

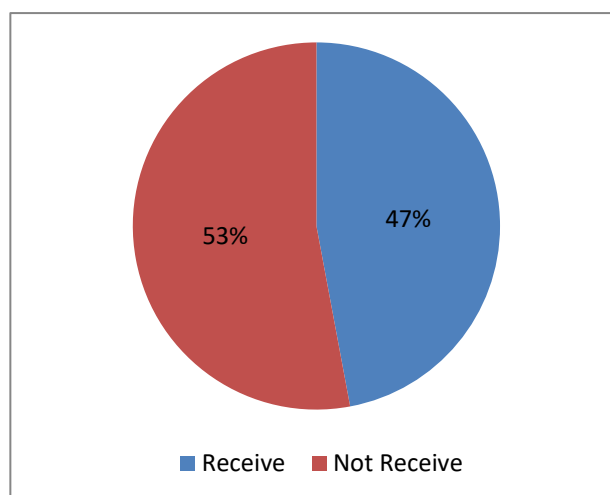


Figure 6. Percentage of TB Officers at Healthcare Facilities Receiving Training on TB Case Recording and Reporting in Depok

Although training on case reporting and recording, as well as contact investigations, had been held before, the high percentage of TB officers who had not received the training was partly due to staff turnover. That caused new officers to rely on previous staff for learning and ask the TB officers at the Health Office about the challenges they faced, or learn independently.

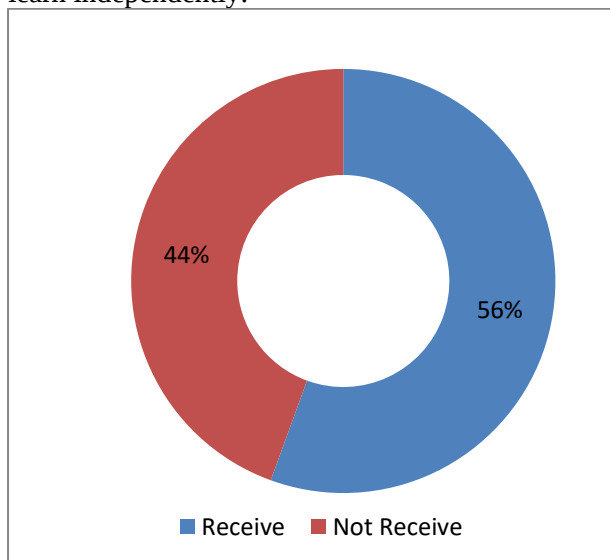


Figure 7. Percentage of TB Officers at Healthcare Facilities Receiving Training on TB Contact Investigation in Depok

Training is a cornerstone of effective TB control, as it equips healthcare workers (HCWs) with the necessary skills and knowledge to manage and prevent the disease. A systematic review and meta-analysis revealed that providing training to health professionals and community volunteers significantly increased TB case detection rates. This enhancement is crucial for identifying and treating

individuals with TB, thereby reducing transmission and improving public health outcomes [15].

Meta-analysis study that studied about effect of tuberculosis infection control training on work performance among health staff in health facilities showed that health personil who received TB training had a 2.35 times better chance of performance compared to health personil without training, and this result was statistically significant (aOR= 2.35; 95% CI= 1.96 to 2.81; $p < 0.001$). (19) It indicates that training can improve the performance of TB officers in health facilities.

3.3. Budget

Regarding the availability of budgets at PHCs and hospitals, 65% of the TB officers interviewed confirmed that they had a budget for the TB program at their institutions. However, 73% of TB officers complained that the available budget was insufficient to implement the TB program (Figure 8). The most frequently complained about budget shortfall was for fieldwork activities in contact investigations.

Adequate funding is essential for the implementation TB control programs. Proper budgeting ensures that all necessary resources—such as diagnostic tools, medications, healthcare infrastructure, and trained personnel—are available to combat TB effectively. Without sufficient financial support, critical components of TB control, including case detection, treatment, and prevention strategies, may be compromised, leading to increased transmission and higher mortality rates. The intersection of TB and health financing requires a collection of health financing approaches, including traditional program management budgets, NGO contracting, social health insurance payments, and social protection payments to patients. Establishing a reliable financing source for public health actions (PHAs) is critical, as dedicated support for PHAs would benefit multiple health areas, particularly TB programs. A lack of such funding can hinder the implementation of effective TB control measures, leading to increased disease burden and associated economic impacts [20].

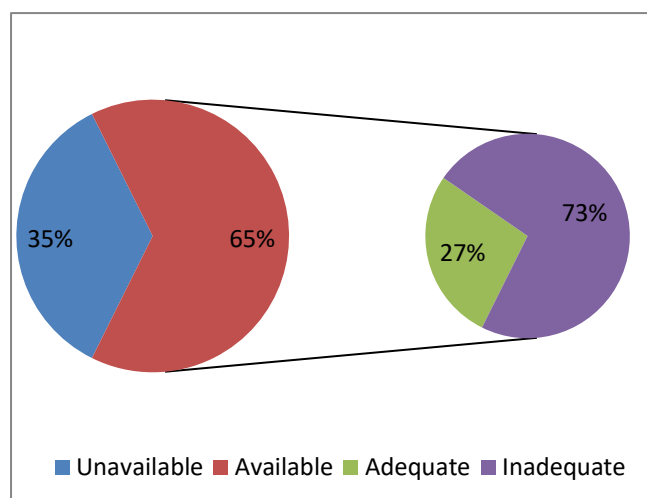


Figure 8. Availability and Adequacy of TB Program Budget at Healthcare Facilities in Depok

4. Surveillance Attributes

4.1. Simplicity

Simplicity was one of the indicators that described the ease with which officers at PHCs and hospitals could carry out TB surveillance activities. According to interview results, 76% of officers at both PHCs and hospitals stated that the TB surveillance system was not simple.

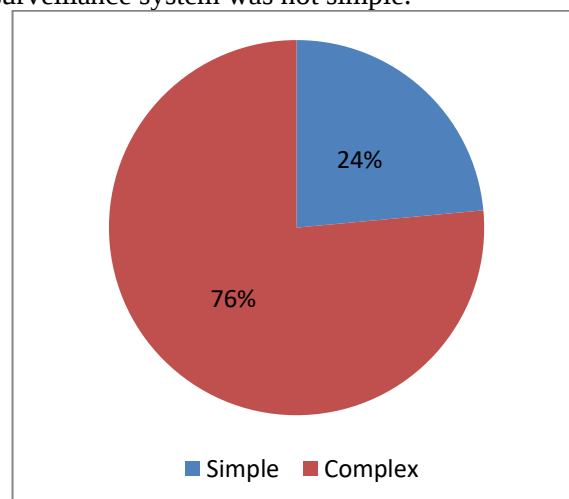


Figure 9. Simplicity of the TB Surveillance System at Healthcare Facilities in Depok

According to the interview results, there were several aspects of the TB surveillance system considered complex. (Figure 10) The aspect most commonly identified as complicated was related to data analysis. Additionally, the large volume of supplementary data and the complex recording and reporting system made officers feel that the TB surveillance system was not simple.

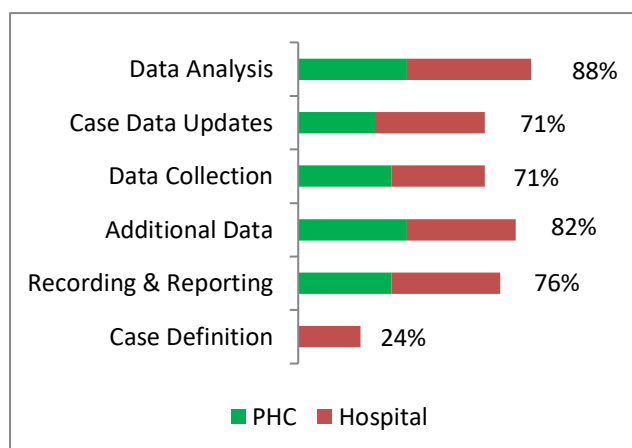


Figure 10. Aspects of TB Surveillance System Perceived as Not Simple in Depok

Simplicity in TB surveillance systems is crucial for effective disease monitoring and control. A study evaluating Ireland's transition from the National Tuberculosis Surveillance System (NTBSS) to the Computerized Infectious Disease Reporting System (CIDR) found that while CIDR improved the flexibility and usefulness of data collection, it did not enhance data completeness and actually increased the median time from diagnosis to notification. This suggests that while advanced systems may offer more features, they can also introduce complexities that hinder timely reporting [21].

The importance of simplicity is further emphasized in the evaluation of TB surveillance systems in Bulilima District, Zimbabwe. The study assessed the perceptions of TB officers regarding the simplicity of the TB case notification surveillance system. Simpler systems were easier to operate and maintain, leading to better data quality and more efficient disease monitoring [22].

4.2. Completeness

The completeness of the reported data referred to the number of TB patients diagnosed clinically and confirmed bacteriologically, as recorded in the SITB, compared to the number of TB cases recorded in the TB 03 book. According to the interview results, it was found that 5% of TB cases in PHCs and hospitals in Depok were not reported in 2021.

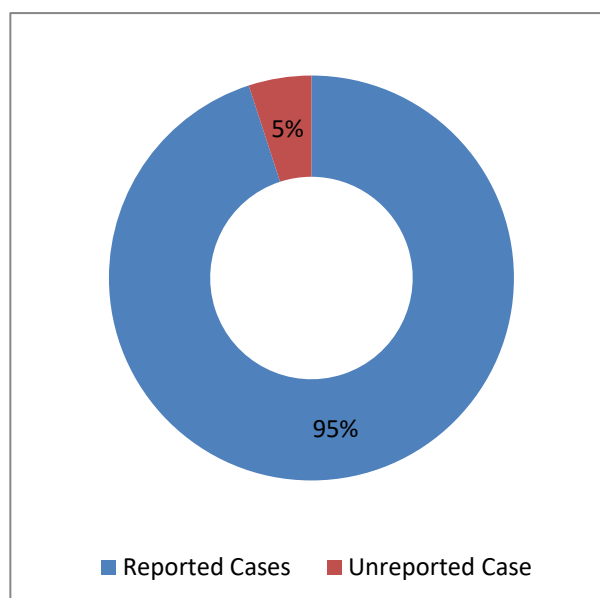


Figure 11. Completeness of Reported TB Case Data at Healthcare Facilities in Depok

Although the percentage of reported TB cases at healthcare facilities had reached 95% (Figure 11), the results do not fully reflect the actual situation because the collected data in hospitals had not been synchronized with the data in the Hospital Management Information System (SIMRS). The data only consisted of patient information recorded in the DOTS clinic at the time of the interview. The lack of synchronization between the SIMRS data and the SITB data, coupled with time constraints, had led to difficulties for staff in tracking and following up on TB cases within the hospital.

Maintaining high standards of data completeness are achievable and beneficial for effective TB control [23]. Evaluating TB notification completeness is important for monitoring TB surveillance systems, while estimating the TB disease burden is crucial for control strategies. A study evaluating TB notification completeness in Poland in 2018 found that while the completeness of reporting was high, certain data elements were missing in some cases. This underscores the need for comprehensive data collection to ensure effective monitoring and response to TB [24].

Similarly, an assessment of the U.S. National Tuberculosis Surveillance System revealed that while most reported cases had complete information, certain data fields, such as the country of birth of the primary guardian for pediatric patients, had lower completeness. This highlights the importance of ensuring that all relevant data fields are consistently reported to enhance the quality of surveillance data [25].

4.3. Usefulness

Data utilization in TB surveillance systems is essential for informed decision-making and effective program implementation. According to the interview results, 65% of TB officers in PHCs and hospitals stated that they had not utilized the data. The collected data was only used for routine reports to the Health Office and had not been used as a reference for policy-making related to TB control.

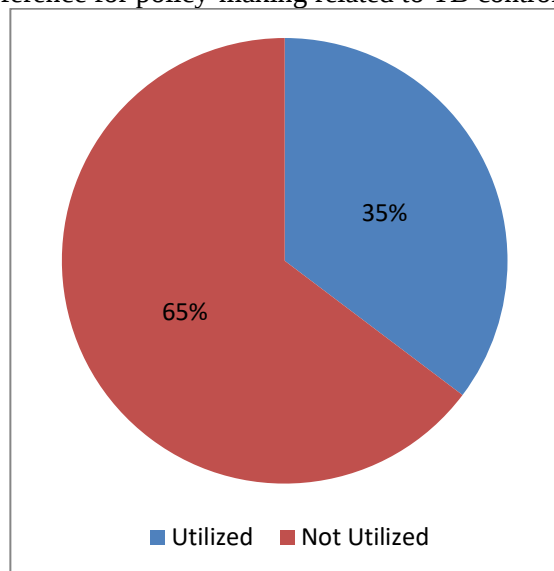


Figure 12. Percentage of TB Data Utilization at Healthcare Facilities in Depok

A study on the use of TB surveillance data for program evaluation highlighted that reliable surveillance systems enable the assessment of TB programs through routinely collected data, facilitating evidence-based evaluations and operational research. By collecting information on each newly reported TB case, it provided comprehensive data that supports public health initiatives, policy development, and resource allocation [26].

Thus, this study was a descriptive assessment and conducted in Pandemic Covid-19. During that year, officers were not only busy with COVID-19 case tracing and testing but also involved in vaccinating the community and it affected to the performance of TB surveillance system. It is a need to future assessment to a better understanding of implementing TB surveillance system in Depok.

Conclusion

This study provided an evaluation of TB surveillance system in Depok, uncovered critical gaps in structure of the system, core functions, support functions, and quality of surveillance system. It highlighted the systemic challenges that hindered effective TB control, such as inadequate

knowledge of legal aspects, insufficient private-sector engagement, lack ability of data analysis and interpretation, the high percentage of TB officers who had not received the training was partly due to staff turnover, complex data collection, and low utilization of surveillance data for decision-making. The research integrated operational, legal, and community engagement aspects, offered fresh insights into the interplay between healthcare systems and TB management, particularly in urban settings like Depok. By bridging these gaps, the findings contributed to advancing the theoretical understanding of the implementation of TB surveillance system.

To enhance the effectiveness of TB control efforts, this study recommends targeted training for healthcare workers, sufficient budget allocations, and simplified data management systems. Strengthening public-private partnerships and leveraging community-based interventions, such as collaborations with professional organizations and grassroots initiatives, are critical for sustainable improvements. Advocacy and education should also be prioritized to increase legal and operational awareness among stakeholders.

Conflict of Interest

No conflict of interest in this study

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ORIGINAL ARTICLE

Antibacterial Activity Test of Green Betel Leaf Extract (*Piper betle* L.) Against *Methicillin-Sensitive Staphylococcus aureus*

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ABSTRACT

Background: Asia is one of the regions with the highest prevalence rates of *Staphylococcus aureus* infection. Green betel leaves (*Piper betle* L.) have been proven to have antibacterial potential with their active compound content, namely essential oils, phenols, chavicol, flavonoids, alkaloids, saponins, tannins, and steroids so it is necessary to investigate whether betel leaf extract has an effect on *Methicillin-Sensitive Staphylococcus aureus* (MSSA). The aim of this study is to analyze the effect of green betel leaf extract on the growth of MSSA.

Methods: This research is a descriptive experimental study regarding the antibacterial activity test of green betel leaf extract against MSSA. The MSSA bacteria used were bacterial preparations in the Microbiology Laboratory of Faculty of Medicine Airlangga University. Green betel leaf extract was obtained from Batu City in 2023. The antibacterial activity test technique used was the dilution test.

Results: In the dilution test, for the growth of MSSA, in tubes with concentrations of 800 mg/mL, 600 mg/mL, 400 mg/mL, 200 mg/mL, and 100 mg/mL appear clear indicates that there is no growth of germs. At a concentration of 50 mg/mL it appears cloudy which indicates the growth of germs. The results obtained for the growth of MSSA on agar plates were at concentrations of 800 mg/mL, 600 mg/mL, 400 mg/mL, and 200 mg/mL, there was no growth of germs. Meanwhile, at concentrations of 100 mg/mL and 50 mg/mL, the growth of MSSA germs was found.

Conclusions: The conclusion of this research is that the minimum inhibitory concentration (MIC) of green betel leaf extract against MSSA is 100 mg/mL and the minimum bactericidal concentration (MBC) of green betel leaf extract against MSSA is 200 mg/mL. Further research is needed on the antibacterial activity of green betel leaf extract against other bacterial species that are resistant to many drugs.

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Introduction

Asia is one of the regions with the highest prevalence rates of *Staphylococcus aureus* infection, with estimated proportions ranging from 28% in Indonesia to less than 70% in Korea for all *Staphylococcus aureus* isolates in early 2010.[1] In Java and Bali, *S. aureus* isolated from skin and soft tissue infections wounds in 257 (45.3%) patients, eight (3.1%) of whom were MRSA.[2] *Staphylococcus aureus* is a human pathogenic bacteria that can cause dangerous diseases. This bacterium is an agent that causes infections in humans including skin and wound infections, pneumonia, meningitis, toxic shock syndrome, scalded skin syndrome, bacteremia, and bone infections.[3,4] *Staphylococcus aureus* can become resistant to oxacillin and related β -lactams by acquiring new penicillin-binding proteins that are enzymatically active but not bound and inactivated by the antibiotics.[5]

Treatment of *Staphylococcus aureus* infection really depends on the type of infection and whether or not there are drug-resistant strains. In general, first-line parenteral antibiotics for MSSA are nafcillin, oxacillin, and first-generation cephalosporins. This therapy has side effects in the form of neutropenia, interstitial nephritis, hepatitis, allergic reactions include anaphylactic shock, urticaria, fever, joint swelling, and skin rashes.[6] This therapy also requires expensive costs, so an alternative treatment using natural ingredients is needed, one of which is using green betel leaves (*Piper betle* L.) which is known for its properties, is easy to obtain, and has an affordable price. Green betel leaves (*Piper betle* L.) have been used as an ingredient for traditional medicine by Indonesians and Asian peoples since a long time ago. Green betel leaves (*Piper betle* L.) are commonly used by people to treat and prevent various diseases such as itching, coughs, colds and toothache.[7] Green betel leaves (*Piper betle* L.) have potential as an antibacterial with their active compounds, namely essential oils, phenols, chavicol, flavonoids, alkaloids, saponins, tannins and steroids.[8]

Previous research stated that green betel leaf extract (*Piper betle* L.) from Makassar and Denpasar could inhibit the growth of *Staphylococcus aureus* using the good method and the active substances flavonoids, tannins and phenols were found in the green betel leaf extract (*Piper betle* L.).[9,10] However, no one has studied the antibacterial activity of green betel leaves grown in the Batu area against MSSA. Based on the problems above, it is necessary to investigate whether green betel leaf extract specifically

planted in the Batu area has an effect on MSSA. The objective of this research is to analyze the effect of green betel leaf extract, specifically planted in the Batu area, on the growth of *Methicillin-Sensitive Staphylococcus aureus*.

Methods

This is a true experimental research, with a posttest-only control group design. This research used a dilution test on *Methicillin-Sensitive Staphylococcus aureus* by administering betel leaf extract (*Piper betle* L.) in various concentrations in vitro. According to Federer's formula, four repetitions were carried out on the sample for each treatment. Samples were taken by random sampling. This research has received ethical clearance from the Health Research Ethics Committee, Faculty of Medicine, Airlangga University, Surabaya.

The materials used in this research were green betel leaves (*Piper betle* L.) obtained from Batu City in 2023 which has been determined, MSSA bacteria obtained from the Department of Microbiology, Faculty of Medicine, Airlangga University, Surabaya. The research was carried out at the Microbiology Laboratory, Faculty of Medicine, Airlangga University, Surabaya. The research was carried out within 11 months (July 2023-May 2024). The green betel leaves were then determined at the Batu Herbal Materia Medica Laboratory UPT. This aims to ensure the correctness of the plants to be used.

Making betel leaf extract using the maceration method. The solvent used is 96% ethanol. Green betel leaves are washed clean and then dried in an oven at 40°C. Then knead and grind until it becomes powder. 500 grams of betel leaf powder was weighed, then soaked in 3.5 liters of 96% ethanol solvent for 5x24 hours and the filtrate was taken for filtration. Stirring was done 12 times for 15 minutes. After 5 days, the betel leaf extract is filtered and squeezed using filter paper and a funnel to separate the filtrate from the dregs. The filtering results are then stored in a new container that is tightly closed. The remaining dregs are macerated with ethanol for two days and stirred occasionally. The extract was filtered after two days, then the filtered results were mixed with the previous filtrate and the solvent was evaporated using a rotary evaporator at a temperature of 55°C. Then concentrate in a water bath at a temperature of 55°C. Obtained 12 grams of thick extract free from solvents and extracts used in subsequent tests. MSSA cultures that were 24 hours old were taken as 0.1 mL of 0.5 Mc Farland (1.5×10^8 CFU/mL). Then placed in a test tube containing a

liquid medium and incubated for 24 hours at 37°C in an O₂ incubator.

The antibacterial activity test against MSSA used the dilution method to determine the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of betel leaf extract (*Piper betle* L.). MIC is the smallest concentration of an antibiotic substance that is still able to inhibit the growth of germs, while MBC is the smallest concentration of an antibiotic substance that is capable of killing germs. In this research dilution test, 9 test tubes were needed, namely 3 control tubes and 6 test tubes. The first and second control tubes are negative controls and the third control tube is positive controls. The first control tube was filled with 2 mL of sterile liquid medium, the second control tube was filled with 1 mL of sterile liquid medium and 1 mL of green betel leaf extract (*Piper betle* L.), and the third tube was filled with 1 mL of sterile liquid medium plus 1 mL of MSSA bacterial colonies.

The first test tubes were filled with 1.6 mL of green betel leaf extract and 0.4 distilled water (800 mg/mL). The second tubes were filled with 0.6 mL of green betel leaf extract and 0.4 distilled water (600 mg/mL). The third to sixth tubes were filled with 1 mL sterile liquid medium. Then 1 mL of the solution from the first test tube is taken and added to the third tube, and so on until the sixth tube. 1 mL of the sixth tube solution was discarded so that the volume of solution for each test tube was 1 mL with different concentrations, namely 800 mg/mL, 600 mg/mL, 400 mg/mL, 200 mg/mL, 100 mg/mL and 50 mg/mL. Then, in the first to sixth test tubes, 1 mL of a colony of *Staphylococcus aureus* bacteria was added so that the final volume of all tubes was 2 mL. MIC is determined by looking at the smallest concentration of green betel leaf extract (*Piper betle* L.) in the tube that is still able to inhibit bacterial growth. The clear tubes after the MIC tube has their specimens taken are then cultured on an Agar plate so that the MBC can be determined.

Results

Extraction of green betel leaves using ethanol produces 50 mL of liquid extract. The results obtained from the MIC test of green betel leaf extract against MSSA were that tubes with concentrations of 800 mg/mL, 600 mg/mL, 400 mg/mL, 200 mg/mL, and 100 mg/mL appeared

clear, indicating that there was no germ growth. At a concentration of 50 mg/mL it appears cloudy which indicates the growth of germs (Figure 1). It can be concluded that the MIC value of green betel leaf extract against MSSA is 100 mg/mL (Table 1).

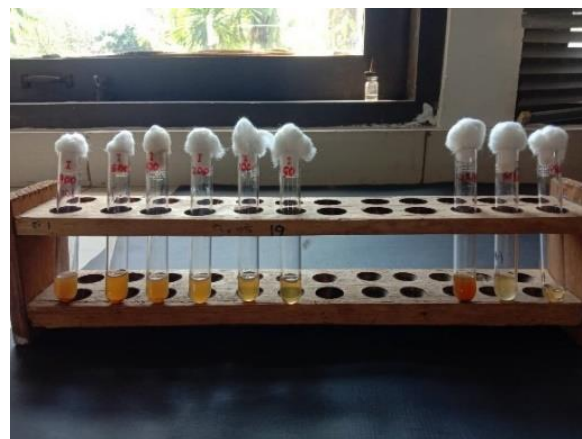


Figure 1. Test tube results in the MSSA bacterial dilution test after 24 hours incubation

After measuring the MIC, tube fluid with a concentration of 800 mg/mL to 50 mg/mL was planted on an agar plate and observations were made to measure the MIC after incubation for 24 hours. The results obtained for the growth of MSSA were at concentrations of 800 mg/mL, 600 mg/mL, 400 mg/mL, and 200 mg/mL, there was no growth of MSSA germs on the agar plates. Meanwhile, at concentrations of 100 mg/mL and 50 mg/mL, MSSA germ growth was found (Figure 2). The first, third and fourth repetitions gave MSSA MBC results of 200 mg/mL and the second repetition gave MSSA MBC results of 100 mg/mL. It can be concluded that the MBC value of green betel leaf extract against MSSA in this study was 200 mg/mL. (Table 2).

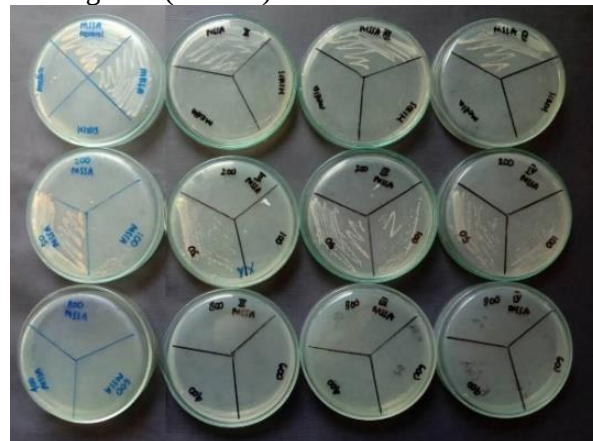


Figure 2. Agar culture results of the entire MSSA bacterial dilution test tube

Table 1. Results of Minimum Inhibitory Concentration (MIC) Test (mg/mL)

	800	600	400	200	100	50
I	-	-	-	-	-	+
II	-	-	-	-	-	+
III	-	-	-	-	-	+
IV	-	-	-	-	-	+

+= Cloudy tube (bacteria grew)

-= Clear tube (bacteria didn't grow)

Table 2. Results of minimum bactericidal concentration (MBC) test (mg/mL)

	800	600	400	200	100	50
I	-	-	-	-	+	+
II	-	-	-	-	-	+
III	-	-	-	-	+	+
IV	-	-	-	-	+	+

+= Agar plate was overgrown with bacteria (bacteria was not dead)

-= Agar plate was not overgrown with bacteria (bacteria was dead)

Discussion

In the green betel leaf extraction process, researchers used ethanol as a solvent because ethanol is an extraction solvent that is widely used for active ingredients that are antibacterial from inside cells. Ethanol is a universal solvent that can extract polar or semipolar compounds, is non-toxic, can mix with water, and the heat required for concentration is less so that the active ingredients used in this research can be extracted properly.[11]

Green betel leaves have antibacterial activity against MSSA bacteria because they contain various antibacterial active ingredients including alkaloids, phenols, flavonoids, essential oils, chavicol, saponins, tannins and steroids. These various compounds play a role in inhibiting cell wall synthesis, disrupting cell membrane permeability, disrupting cell metabolism, damaging nucleic acids, and inhibiting cell protein synthesis so that bacterial cells can die. These compounds have antimicrobial, antioxidant and anti-inflammatory effects.

Other research shows that green betel leaf extract is able to inhibit MSSA bacteria in various concentrations. Research by Tagrida using ethanol extract showed that the MIC of green betel leaves on MSSA was 3.12 mg/mL.[12] Research by Lao shows that the MIC of green betel leaves on MSSA is 2.5 mg/mL.[13] Research by Ali shows that the MIC of green betel leaves on MSSA is 2 mg/mL.[14] Research by Visutthi showed that the MIC of green betel leaves on MSSA was 1.25 mg/mL.[15] Research by Leesombun shows that the MIC of green betel leaves on MSSA is 1.024 mg/mL.[16] Research by Saeloh shows that the MIC of green betel leaves on MSSA is 0.62 mg/mL.[17] Research by Rivera showed that the

MIC of green betel leaves on MSSA was 0.312 mg/mL.[18] Research by Sungkatavat shows that the MIC of green betel leaves on MSSA is 0.25 mg/mL.[19]

Green betel leaf extract can kill MSSA bacteria in various concentrations. Research conducted by Research by Lao shows that the MBC results of green betel leaves on MSSA are 5 mg/mL.[13] Research by Tagrida shows that the MBC results of green betel leaves on MSSA are 3.12 mg/mL.[12] Research by Visutthi showed that the MBC of green betel leaves on MSSA was 1.25 mg/mL.[15] Research by Saeloh shows that the MBC results of green betel leaves on MSSA are 0.62 mg/mL.[17] Research by Rivera showed that the MBC of green betel leaves on MSSA was 0.312 mg/mL.[18] Research by Sungkatavat shows that the MBC of green betel leaves on MSSA is 0.25 mg/mL.[19]

Based on the results of this study, it shows that the MIC of MSSA is 100 mg/mL, and the MBC of MSSA is 200 mg/mL with a typical local plant of green betel leaf which is specifically planted in the Batu area. There are differences in results from several other research results mentioned previously which could be caused by green betel leaf plant factors. This could be caused by the composition of the active ingredients in green betel leaves being influenced by several things. The quality of the active ingredients contained in the green betel leaf medicinal plant can be influenced by external and internal factors. External factors include the growing conditions of green betel plants such as land conditions, temperature, climate, altitude where they grow, environmental pollution, pests, high ultraviolet intensity, heavy metal contamination, and humidity where the plants grow. Internal factors include genetic quality and

plant age. The higher the height at which some plants grow which contain essential oils or the lower the temperature of the environment where they grow, the more the levels of essential oils in these plants will increase.[20]

The difference in antibacterial sensitivity from previous research could be caused by several factors, such as the choice of solution, storage time of green betel leaf extract, method of making the extract, and the bacterial isolates used in the research. The choice of solution in the extraction process requires an appropriate solution because the active compound taken is following the solution used during extraction. Betel leaf extract which has a longer storage time may experience a decrease in quality due to reduced antibacterial compounds. The method of the extraction process can influence the yield value which is related to the success in extracting the amount of active compound. The bacterial isolates and strains used may differ due to differences in research locations, which can influence the results of existing research. The limitation of this research is that betel leaves have various varieties, but this research only examined green betel leaves. Based on the results obtained in this study, a concentration of 100 mg/mL of green betel leaf extract from Batu City inhibits the growth of both MSSA and MRSA bacteria. Additionally, a concentration of 200 mg/mL of green betel leaf extract kills both MSSA and MRSA bacteria. Therefore, this concentration can be developed as a new alternative treatment as an effective antibiotic for killing the growth of MSSA and MRSA bacteria.

Conclusion

Based on this research, it is concluded that green betel leaf extract (*Piper betle* L.) specifically planted in the Batu area has antibacterial activity against MSSA with a minimum inhibitory concentration of 100 mg/mL and a minimum killing concentration of 200 mg/mL. Green betel leaf extract (*Piper betle* L.) specifically planted in the Batu area with a concentration of 200 mg/mL can be developed as a new alternative treatment as an antibiotic that is effective in killing the growth of MSSA bacteria.

Conflict of Interest

No conflict of interest in this study

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ORIGINAL ARTICLE

Trends in Hemodialysis-Related Search Interest in Indonesia: A Decade Google Trends Analysis

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ABSTRACT

Background: End-stage renal disease (ESRD) is increasing in Indonesia, but little is known about how people seek information about hemodialysis online. Understanding this digital behavior is essential for effective health education and access to care.

Methods: Google Trends data (2014–2024) were analyzed for lay and clinical hemodialysis-related terms. Four keywords were selected to capture public search behavior: “cuci darah”, “hemodialisa”, “hemodialisis”, and “hemodialysis”. Trends were compared across time, provinces, as well as related queries.

Results: Searches for hemodialysis steadily increased, with the lay term “cuci darah” dominating over clinical terms. Seasonal peaks were observed in 2019 and 2023, with notable increases during March–April each year. Provinces such as North Sumatra, East Java, and West Java showed the highest interest. Related queries commonly involved definitions (“hemodialisa adalah”) and kidney disease concerns (“gagal ginjal”).

Conclusion: Public online interest in hemodialysis across Indonesia is growing but remains uneven across regions, with persistent reliance on lay terminology. Integrating colloquial language such as “cuci darah” into kidney health promotion and aligning campaigns with seasonal peaks may improve reach and impact. Google Trends can be a practical tool for guiding education and service planning.

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Introduction

Chronic kidney disease (CKD) is a growing global health concern, affecting approximately 10% of the world's population, with a disproportionately rising burden in low- and middle-income countries (LMICs) [1–3]. At its most advanced stage—CKD stage 5 or end-stage renal disease (ESRD)—renal replacement therapy (RRT) becomes essential for survival [4, 5]. The main RRT modalities include hemodialysis, peritoneal dialysis, and kidney transplantation [6], with hemodialysis remaining the most widely used, especially in LMICs due to limited access to transplantation and peritoneal dialysis (PD) infrastructure [7–10].

In Indonesia, CKD is a mounting public health issue, with a prevalence of 0.38% (3.8 per 1,000 population) based on the 2018 Basic Health Research (Riset Kesehatan Dasar, RISKESDAS). Approximately 60% of patients with CKD stage 5 require dialysis [11]. The introduction of the national health insurance scheme (Jaminan Kesehatan Nasional, JKN) in 2014 significantly expanded access to dialysis services, particularly hemodialysis [12]. By 2020, the number of new dialysis patients had tripled compared to 2017. In 2019 alone, Indonesia's Social Security Administrator for Health (BPJS Kesehatan) financed 1.93 million dialysis sessions at a cost of IDR 2.79 trillion [13].

Parallel to this expansion, the internet has become a key source of health information, particularly in countries like Indonesia where digital penetration is rapidly increasing [14, 15]. Google Trends, a publicly available tool, enables researchers to track public interest in specific topics over time using search query data [16–19]. This method, referred to as infodemiology, can provide valuable insights into public engagement, health-seeking behavior, and informational gaps at the population level [20, 21].

Despite the increasing prevalence of ESRD and the scale-up of hemodialysis services in Indonesia, little is known about how the public engages with this topic online. This study aims to explore temporal trends in hemodialysis-related search interest in Indonesia over a ten-year period (2014–2024) using Google Trends. The findings may support the development of more targeted health promotion, service planning, and policy responses.

Materials And Methods

Study Design and Data Source

This study employed an infodemiological approach using publicly available data from Google Trends to analyze public interest in hemodialysis-related search terms in Indonesia. Google Trends normalizes search data, enabling comparisons between terms and regions. The results reflect the proportion of searches for a particular keyword relative to the total number of Google searches conducted in a specified location and period, scaled from 0 to 100. While the data do not provide absolute search volumes, they are valuable for identifying temporal patterns and trends in public interest. Data collection was carried out on July 26, 2025, via the Google Trends platform (<https://trends.google.com>).

Search Terms and Parameters

Four keywords were selected to represent public search behavior related to hemodialysis: “cuci darah,” “hemodialisa,” “hemodialisis” (in Indonesian), and “hemodialysis” (in English). These terms were chosen based on their prevalence in both clinical contexts and everyday language. Searches were conducted separately for each keyword using the following parameters: time frame from January 1, 2014, to December 31, 2024; geographic location restricted to Indonesia; category set to “All categories”; and search type set to “Web Search.”

Data Extraction and Processing

Relative Search Volume (RSV) values were retrieved for each keyword. RSV represents normalized search interest on a scale from 0 to 100, where 100 indicates peak popularity within the selected timeframe and location, and 0 indicates minimal or no search activity. The data were downloaded in .csv format, compiled, and organized using Microsoft Excel 2021 (Version 2507 Build 16.0.19029.20136).

Data Analysis and Visualization

Temporal trends were analyzed by plotting RSV values over time to identify shifts in public interest throughout the 10-year period. Comparative analysis of the four search terms was conducted to assess variations in terminology preference. All data visualizations, including line graphs, were created using Canva (<https://www.canva.com/>), an online graphic design platform.

Results

Temporal Trends in Hemodialysis-Related Search Interest

Between January 2014 and December 2024, the RSV for hemodialysis-related terms in Indonesia demonstrated a general upward trajectory, particularly for the term “cuci darah” (Figure 1; Supplementary Table 1). This term consistently ranked highest in monthly RSV and showed the most substantial growth over the 10-year period. The term “hemodialisa” followed with stable, albeit less dynamic, search interest. In contrast, “hemodialisis” and “hemodialysis” maintained low and relatively flat trends over time. Despite being clinically accurate, these latter terms appear less frequently used by the general public. These findings reflect a persistent public preference for colloquial terminology over medical or English-language alternatives.

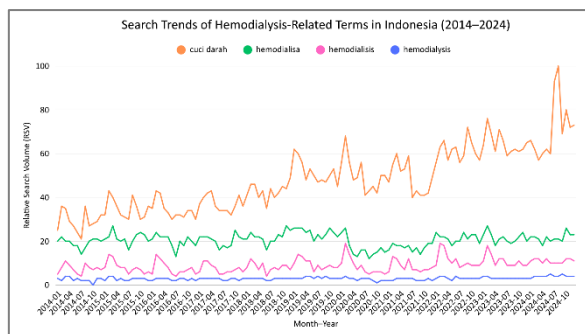


Figure 1. Temporal Trends in Google Search Interest for Hemodialysis-Related Terms in Indonesia (2014–2024). Monthly search interest for four hemodialysis-related terms—“cuci darah” (orange), “hemodialisa” (green), “hemodialisis” (pink), and “hemodialysis” (blue)—in Indonesia from January 2014 to December 2024. Data were obtained from Google Trends and reflect normalized RSV on a scale from 0 to 100. The X-axis is displayed in three-month intervals for readability.

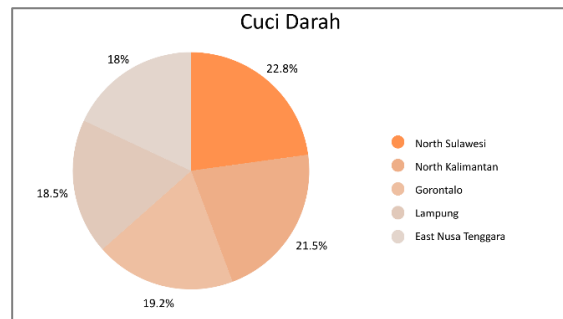
Seasonal Variations and Notable Search Spikes

Visual inspection of monthly trends revealed recurring seasonal fluctuations and several notable spikes, especially in “cuci darah” searches (Figure 1). Peaks were consistently observed in the early months—particularly February—in years such as 2015, 2016, 2018, 2020, 2022, and 2023. Additional spikes occurred from late 2022 into early 2023. A pronounced surge was also observed in the second half of 2024, with RSV peaking at 100 in August and remaining elevated through December. While “hemodialisa” showed mild seasonal variation, these were less pronounced.

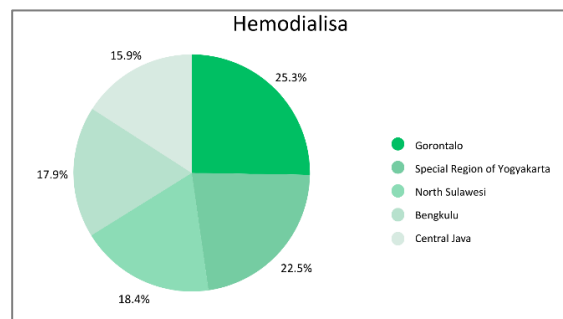
Meanwhile, “hemodialisis” and “hemodialysis” did not exhibit any consistent seasonal patterns.

Geographical Patterns of Search Interest

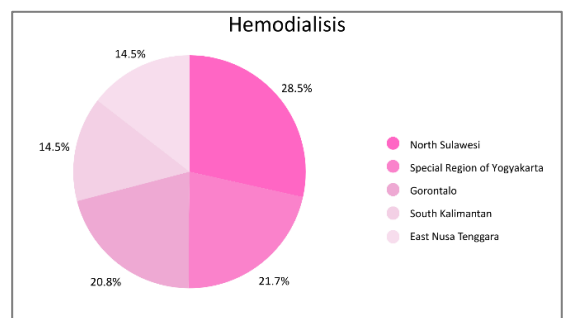
Regional analysis revealed distinct patterns across provinces (Figure 2; Supplementary Table 2). The highest RSV for “cuci darah” and “hemodialisis” was observed in North Sulawesi (100), for “hemodialisa” in Gorontalo (100), and for “hemodialysis” in Yogyakarta (100). Figure 2 presents a visual comparison of the top five contributing provinces for each term.



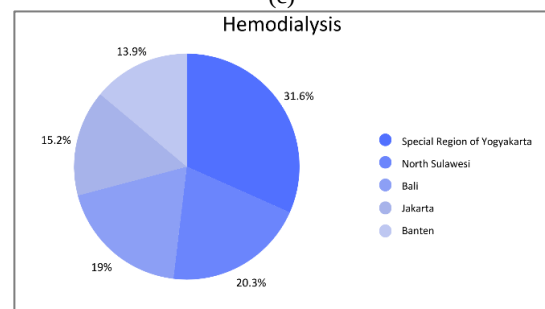
(a)



(b)



(c)



(d)

Figure 2. Top 5 Regions for Each Hemodialysis-Related Search Term in Indonesia (2014–2024). Pie charts displaying the top five provinces with the highest RSV for each term: a. cuci darah, b. hemodialisa, c. hemodialisis, and d. hemodialysis. **Top Associated Search Queries**

Analysis of associated search queries revealed recurring themes across the four hemodialysis-related terms (Table 1). Public interest was not limited to dialysis procedures but extended to kidney disease in general. For instance, “gagal ginjal” and “ginjal” consistently appeared as high-ranking related queries, indicating strong lay concern about underlying kidney conditions. Foundational knowledge gaps were evident from definitional searches such as “cuci darah adalah,” “hemodialisa adalah,” “hemodialisis adalah,” and “hemodialysis adalah,” each reaching peak RSVs of 100. Procedure-related queries were also common, including “cuci darah gagal ginjal,” “proses hemodialisis,” and “hemodialysis patients.” Interestingly, cross-term searches such as “hemodialisa” vs. “hemodialisis” highlighted ongoing public confusion between lay and clinical terminology.

Table 1. Grouped Top Associated Search Queries for Hemodialysis-Related Terms in Indonesia (2014–2024)

Category	Cuci Darah (RSV)	Hemodialisa (RSV)	Hemodialisis (RSV)	Hemodialysis (RSV)
Kidney disease terms	gagal ginjal (49)	ginjal (47), gagal ginjal (32)	ginjal (71), gagal ginjal (34)	dialysis (66)
Definitions / lay queries	ginjal (100), cuci darah adalah (45)	hemodialisa adalah (100)	hemodialisis adalah (100)	hemodialysis adalah (100)
Procedure-related	cuci darah gagal ginjal (48), penyakit cuci darah (38)	hd (33)	proses hemodialisis (35)	hemodialysis patients (91)
Cross-term searches	–	hemodialisa (26)	hemodialisis (39)	hemodialisa (72), hemodialisis (81)

HD: hemodialysis; RSV: Relative Search Volume.

Emerging and Rising Related Queries

The fastest-growing queries over the past decade reflected not only clinical curiosity but also structural aspects of care (Table 2). Breakout search queries—defined as those with exceptionally high growth (over 5,000%)—highlighted evolving public concerns over the decade. Under health financing and access, “cuci darah ditanggung BPJS” emerged as a breakout term, underscoring strong public concern about treatment affordability. Clinical and procedural knowledge queries expanded rapidly, including “kreatinin tinggi,” “penyakit apa yang harus cuci darah,” “jelaskan proses hemodialisis,” and “hemodialysis indications/complications.” Training and education-related searches (e.g., “pelatihan hemodialisa 2023”) pointed to growing professional and academic interest. Meanwhile, technical/clinical terms such as CDL, CRRT, and proses pembentukan urine indicated a subset of users seeking advanced or specialized information. Collectively, these rising queries demonstrate how online search behavior spans from basic lay definitions to specialized clinical knowledge, reflecting the needs of both patients and professionals.

Table 2. Hemodialysis-Related Search Terms with Highest Growth in Indonesia (2014–2024), Grouped by Theme

Category	Cuci Darah (Rising)	Hemodialisa (Rising)	Hemodialisis (Rising)	Hemodialysis (Rising)
Health financing & access	cuci darah ditanggung bpjs (Breakout)	klinik hemodialisa depok (Breakout)	–	–
Clinical/procedure knowledge	kreatinin tinggi (Breakout); cuci darah karena apa (Breakout); penyakit apa yang harus cuci darah	ICD 10 CKD (Breakout)	fungsi ginjal (Breakout); jelaskan proses hemodialisis (Breakout); bagaimana proses pencucian darah	hemodialysis indication s (Breakout); hemodialysis complications (Breakout)

	(Breakout)	(Breakout)		
Training/education	pelatihan hemodialisa 2023 (Breakout); pelatihan hemodialisa 2017 (Breakout)	prinsip utama dari teknologi hemodialisis adalah (Breakout)		
Technical/clinical terms	CDL; CDL cuci darah (Breakout)	proses pembentukkan urine (Breakout); CRRT (Breakout)	double lumen (Breakout)	

Breakout: high growth, over 5,000%; CDL: catheter double lumen; CKD: chronic kidney disease; ICD: international statistical classification of diseases and related health problems; CRRT: continuous renal replacement therapy; Rising: related topics with the biggest increase in search frequency since the last time period.

Discussion

Principal Findings

This study demonstrates a steady increase in online interest related to hemodialysis over the last decade in Indonesia, with a notable dominance of the colloquial term “cuci darah” over its clinical counterparts such as “hemodialisis” and “hemodialysis.” This linguistic preference may be attributed to several sociocultural and systemic factors. The phrase “cuci darah” (literally “blood cleansing”) is easier to understand and more relatable for the general public. It is commonly used in everyday conversations, health services, and public campaigns. For example, during the 2016 World Kidney Day organized by the Indonesian Ministry of Health, the term “cuci darah” was prominently used to refer to hemodialysis procedures, helping increase public awareness through familiar language [22]. The popularity of this term likely contributes to its higher online search frequency compared to more technical alternatives.

Geographic trends revealed consistently high RSVs in provinces such as North Sulawesi and Yogyakarta, suggesting heightened regional awareness or a higher burden of ESRD in those areas. However, national survey data show that

while provinces like Yogyakarta do report a relatively high prevalence of CKD, regions such as East Kalimantan, Central Sulawesi, and West Java have also been identified as areas with elevated CKD incidence based on RISKESDAS 2018 [11]. This discrepancy between online interest and epidemiological burden highlights the importance of further investigating regional awareness, healthcare access, and information-seeking behavior in the context of CKD and hemodialysis services.

Contextual Triggers Behind Search Surges

Elevated search volumes related to hemodialysis were frequently observed in the months surrounding World Kidney Day, a global health campaign held annually in March. In Indonesia, this event is regularly supported by public awareness initiatives from national health organizations, such as Perhimpunan Nefrologi Indonesia (PERNEFRI) and the Indonesian Kidney Foundation, often launched in the weeks leading up to the commemoration [23–26]. These initiatives—including educational outreach, media campaigns, and community activities—may contribute to heightened public interest and increased online searches for kidney-related terms during this period.

A sharp rise in public interest during late 2022 and early 2023 was linked to the pediatric acute kidney injury (AKI) crisis in Indonesia. The outbreak, associated with contaminated syrup medications containing ethylene glycol and diethylene glycol, drew intense media and public attention [27]. By October 2022, the Ministry of Health had reported 206 cases and 99 deaths across 20 provinces [28], prompting urgent recalls, advisories, and regulatory scrutiny [29], with additional cases identified in January 2023 [30]. This visibility likely triggered increased searches for terms such as “cuci darah”, commonly associated with kidney failure treatment.

The substantial public attention to kidney health issues during the latter half of 2024 appears to have significantly influenced online search behavior. Heightened awareness was likely driven by widespread media reports on rising dialysis cases among children, coupled with public health seminars, and advocacy activities by patient groups pushing for improved access and quality of care [31–33]. These developments may have contributed to a surge in online interest, as reflected in the marked increase in search activity for terms related to dialysis observed during this period.

Knowledge-Seeking Behavior in Kidney Health

The consistent presence of ginjal and gagal ginjal among the top related search terms suggests a broad public concern not only with treatment options but also with kidney health in general. This pattern implies that online health-seeking behavior extends beyond the procedure itself [34, 35], reflecting a wider interest in understanding kidney disease and its implications. Such behavior may also be driven by increased media coverage and personal experiences within families, prompting individuals to seek more comprehensive information online [36]. Additionally, the most frequent related queries for hemodialisa, hemodialisis, and hemodialysis were definitional phrases, such as “hemodialisa adalah.” This indicates a foundational gap in public knowledge, with users often searching for basic explanations of the term [37]. These findings highlight the need for targeted public education to accompany awareness campaigns, ensuring that exposure to medical terms leads to informed understanding rather than confusion.

Limitations

This study is subject to several limitations. Google Trends provides relative, not absolute, search volume data and may be influenced by changes in internet access, population size, or search engine usage over time. The analysis does not capture demographic data of search users, limiting inferences about specific subpopulations. Causality also cannot be established between media events and search behavior, as associations are temporal and observational. Furthermore, reliance solely on Google Trends introduces potential bias, as it excludes populations that use other search engines or rely on offline sources of health information.

Conclusion

This study demonstrates the value of Google Trends in capturing public engagement with hemodialysis in Indonesia. Beyond documenting rising interest, the findings highlight the importance of incorporating colloquial terms such as *cuci darah* into health communication to enhance resonance and reach. By identifying regional variations and persistent knowledge gaps, this study provides actionable insights for tailoring kidney health promotion. Public health authorities may also leverage Google Trends for real-time monitoring and evaluation of educational campaigns, ensuring that strategies remain responsive to public needs.

Conflict of Interest

No conflict of interest in this study

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ORIGINAL ARTICLE

The Role Of *Mitragyna speciosa* (Korth) As An Anti-Inflammatory Agent In Wound Healing In Living Cells

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ABSTRACT

Background: Wound is a condition in which the integrity of body tissue is disrupted, leading to the activation of a complex biological process known as wound healing. This process aims to restore the protective skin barrier, prevent infection, and minimize fluid loss. It involves sequential phases of hemostasis, inflammation, proliferation, and remodeling. While inflammation is essential for initiating repair, prolonged or excessive inflammation may delay the healing process. *Mitragyna speciosa* (Korth) is a medicinal plant traditionally used in various cultures and has been reported to exhibit multiple pharmacological properties, including anti-inflammatory, antioxidant, antibacterial, analgesic, and wound-healing activities.

Methods: The present systematic review was conducted to identify and synthesize scientific evidence regarding the potential of *Mitragyna speciosa* extract as a therapeutic agent in wound healing through anti-inflammatory and other biological pathways. Literature searches were performed in ScienceDirect, PubMed, MDPI, DOAJ, and Google Scholar following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results : A total of 1,176 studies were screened, and five experimental studies fulfilled the inclusion criteria. The findings consistently demonstrated that *Mitragyna speciosa* extract suppressed pro-inflammatory mediators such as nitric oxide, reactive oxygen species, tumor necrosis factor-alpha, interleukin-6, and enzymatic pathways including cyclooxygenase-2 and 5-lipoxygenase. In addition, the extract stimulated cell migration, endothelial migration, and angiogenesis, thereby supporting tissue regeneration. Toxicity profiles suggest that the extract is safe at effective concentrations, although responses remain dose-dependent.

Conclusions: Overall, *Mitragyna speciosa* shows promise as a plant-based therapeutic option for wound healing. Nevertheless, current evidence is limited and largely derived from in vitro studies, indicating the need for more extensive in vivo and clinical investigations.

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Introduction

Wounds represent a pathological condition characterized by the loss or damage of body tissues, which may result from trauma, burns, temperature changes, chemicals, electrical injury, or animal bites (Sjamsuhidajat et al., 2017). The wound healing process is a highly coordinated physiological response that aims to restore skin barrier function and prevent infection and fluid loss. Delayed healing can result in severe complications such as chronic wounds, which are difficult to manage and may ultimately lead to amputation (Mills et al., 2020). Similarly, open wounds particularly burns are prone to bacterial invasion, with increased risks of infection and sepsis (Lestari et al., 2023). Wound healing progresses through four overlapping but distinct phases: hemostasis, inflammation, proliferation, and remodeling (Sjamsuhidajat et al., 2017; Zakaria et al., 2023). Factors such as diabetes, obesity, vascular disease, ischemia, aging, and genetic predispositions exacerbate impaired healing and are strongly associated with chronic wound pathology (Huelsboemer et al., 2024; Zhao et al., 2016).

Current wound care strategies range from conventional approaches to advanced therapies. The global market for advanced wound care is projected to reach USD 18.7 billion by 2027, with an estimated compound annual growth rate (CAGR) of 6.6% between 2020 and 2027 (Zakaria et al., 2023). Conventional treatments include the use of anti-inflammatory drugs such as corticosteroids and NSAIDs, which may alleviate inflammation but are associated with adverse gastrointestinal and cardiovascular effects (Agrawal et al., 2024). Systemic and prolonged use of these agents is therefore discouraged. Topical antibiotics have been used to deliver higher drug concentrations directly to the wound site, reducing microbial infections. However, excessive use contributes to antibiotic resistance, delays hypersensitivity responses, and may trigger secondary infections (Goyal et al., 2024). Chronic wound management often requires local debridement, irrigation, and sometimes reconstructive surgery, yet persistent inflammation continues to serve as a major barrier to complete healing (Huelsboemer et al., 2024).

Medicinal plants have historically served as the foundation of modern pharmacology, offering affordable, effective, and holistic therapeutic options with immunomodulatory potential (Goyal et al., 2024). Plant-derived therapies are advantageous due to their abundant availability, low production costs, and reduced risk of microbial

resistance compared to single-compound drugs (Zakaria et al., 2023). One such promising plant is *Mitragyna speciosa* (Korth). (*M. speciosa*), commonly referred to as kratom. Native to Southeast Asia, particularly Indonesia, Malaysia, and Thailand, kratom has been traditionally employed to manage fever, diabetes, diarrhea, pain, wound healing, and withdrawal symptoms (Rahmawati et al., 2024). It has also been reported to enhance energy, act as a mild stimulant, induce euphoria, and contribute to chronic pain management (Tuntiyasawasdikul et al., 2024). Despite its growing popularity, *M. speciosa* has not received approval from the U.S. Food and Drug Administration (FDA) due to concerns regarding potential misuse. Nonetheless, recent reports indicate relatively low abuse potential, with increasing medical and recreational interest observed in the United States and Europe (Rahmawati et al., 2024).

Phytochemical analyses of *M. speciosa* have identified over 40 alkaloids, with mitragynine (66%) as the dominant constituent, followed by paynantheine (8.6%), speciogynine (6.6%), 7-hydroxymitragynine (2%), and speciociliatine (0.8%) (Ahmad et al., 2022). These compounds exhibit diverse pharmacological activities, including analgesic, antinociceptive, antidiarrheal, antioxidant, antibacterial, and anti-inflammatory effects (Salim et al., 2022; Tohar et al., 2019; Tuntiyasawasdikul et al., 2024). Since inflammation is a critical yet potentially detrimental phase of wound healing, prolonged or excessive inflammatory responses can impair tissue repair (Huelsboemer et al., 2024). Compounds derived from kratom may therefore serve as modulators of inflammatory pathways, promoting effective healing (Tohar et al., 2019). This study aims to provide a comprehensive analysis of the anti-inflammatory role of *M. speciosa* in wound healing, supported by experimental evidence. The findings are expected to enhance mechanistic understanding and support the development of safe, effective, and sustainable plant-based wound care therapies.

Methods

Data Sources

A systematic literature review was conducted to identify, collect, and analyze relevant information for this study. The research was designed to address the question of whether *Mitragyna speciosa* (Korth) extract exerts anti-inflammatory effects and accelerates wound healing. The PICO framework (Population, Intervention, Comparison,

and Outcome) was applied, focusing on the anti-inflammatory activity and wound healing effects of *M. speciosa* leaf extract in living cells. The search strategy was implemented using PubMed, ScienceDirect, MDPI, DOAJ, and Google Scholar databases, covering publications between June 2016 and June 2025. Search keywords included: On ScienceDirect: ("Mitragyna speciosa" OR kratom OR mitragynine) AND ("anti-inflammatory" OR "anti-inflammation") AND ("wound healing" OR "wound closure") AND ("in vivo" OR "in vitro"); ("Mitragyna speciosa" OR kratom OR mitragynine) AND ("anti-inflammatory" OR "anti-inflammation") AND ("wound healing" OR "wound closure"); *Mitragyna speciosa*. kratom. inflammatory. wound healing. wound closure; *Mitragyna speciosa*. Anti-Inflammatory Agents. Wound Healing. Macrophage; (kratom OR "Mitragyna speciosa") AND ("anti-inflammatory" OR "wound healing") AND ("animal" OR "cell" OR "model"); ("Mitragyna speciosa extract" OR kratom) AND ("wound closure rate" OR "granulation tissue" OR "re-epithelialization" OR "collagen fiber") AND ("mice" OR "keratinocyte"); and several variations including terms related to extracellular matrix, fibroblasts, COX-2 inhibition, TNF-alpha suppression, and IL-6 regulation. On PubMed: (kratom OR "Mitragyna speciosa") AND ("wound healing" AND "anti-inflammatory"); ("Mitragyna"[Mesh] OR "Mitragyna speciosa"[Supplementary Concept] OR kratom OR mitragynine) AND ("Anti-Inflammatory Agents"[Mesh] OR "TNF-alpha"[Mesh] OR "IL-6"[Mesh]) AND ("Wound Healing"[Mesh] OR "Collagen"[Mesh] OR "Extracellular Matrix"[Mesh]) AND ("Models, Animal"[Mesh] OR "Cells, Cultured"[Mesh]); along with terms such as proliferation, macrophage, and fibroblast. On MDPI: "Mitragyna speciosa. Inflammatory"; "Mitragyna speciosa. M2". On DOAJ: "Mitragyna speciosa. Inflammatory". On Google Scholar: "Mitragyna speciosa (Korth) wound healing inflammation -review".

Study Selection Process

The screening and analysis process involved four independent reviewers (ESAFH, MASJ, KNJR, RAP) following PRISMA guidelines. The initial step included filtering based on publication date (2016–2025) and article type (original research). Duplicate studies were then removed, followed by screening according to inclusion and exclusion criteria. The inclusion criteria were: (1) national or international articles evaluating the anti-inflammatory properties of *M. speciosa* and its relevance to wound healing, either directly through

in vivo wound healing studies or indirectly through in vitro anti-inflammatory mechanisms; (2) publications in English or Indonesian; and (3) experimental studies. Exclusion criteria included: (1) articles not addressing *M. speciosa* as an anti-inflammatory agent in wound healing; (2) reviews, editorials, expert opinions, letters to the editor, and single case reports; (3) literature reviews; and (4) studies without available full-text. The screening process was facilitated using Rayyan software.

Data Extraction and Risk of Bias Assessment

To ensure the validity and reliability of the evidence included in this review, methodological quality was assessed for all studies selected. This evaluation aimed to identify potential sources of bias that could affect study outcomes. Risk of bias assessment was conducted systematically using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Quasi-Experimental Studies. The evaluation process was supported by a large language model (LLM, Gemini) and subsequently reviewed comprehensively by the lead investigator (ESAFH).

Data Synthesis

Due to significant heterogeneity across the extracted studies—including differences in study design (in vitro across various cell lines and in vivo animal models), extraction methods of *M. speciosa*, concentrations used, and outcome measures—a narrative synthesis approach was adopted. The synthesis was conducted thematically, grouping studies according to predefined themes aligned with the review objectives: (1) anti-inflammatory effects through the suppression of inflammatory mediators; (2) potential in wound healing; and (3) safety profile and cytotoxicity. Relevant findings for each theme were summarized and discussed descriptively to highlight patterns, similarities, and differences across studies. The results were presented narratively and supported with a table of study characteristics, including title, year, authors, objectives, samples, instruments, methods, and findings.

Result

Study Selection The initial search identified 1,176 records across the databases ScienceDirect, PubMed, DOAJ, MDPI, and Google Scholar. Four databases (excluding Google Scholar) underwent preliminary filtering to exclude articles published outside the period June 2016–June 2025 and non-research articles, resulting in 95 eligible records. After removing duplicates, 44 articles remained. Subsequent title and abstract screening excluded studies not relevant to the research focus, leaving 8

articles. The eligibility assessment was then applied, whereby articles that met the inclusion criteria were retained and those fulfilling exclusion criteria were removed. Ultimately, 4 studies from these databases were included. The search in Google Scholar followed a slightly different approach due to the platform's limited filtering functions. A total of 599 records were retrieved. After excluding articles published outside 2016–2025, 417 remained.

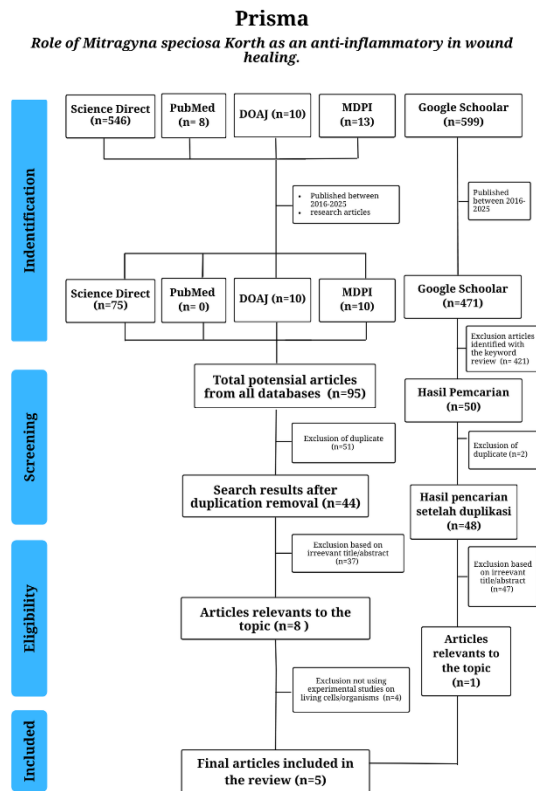


Figure 1. PRISMA Flow Chart

To refine the process and avoid review articles (which were part of the exclusion criteria), the keyword “review” was excluded, yielding 50 records. Duplicate removal reduced this number to 48. Title and abstract screening further excluded irrelevant studies, leaving 1 article. The eligibility assessment confirmed that this study met the inclusion criteria. In total, 5 articles from all databases were included in the final analysis. All five studies included were published between 2016 and 2025 and specifically evaluated the anti-inflammatory effects of *Mitragnya speciosa* in the context of wound healing. Data extraction from these articles covered title, authors, objectives, methodology/instruments, and results, which are summarized in a supplementary table.

Sudy Characteristic

All five included studies were published between 2016 and 2025 and evaluated the anti-inflammatory effects of *M. speciosa* in the context of wound

healing. Data extraction involved collection of study title, authors, objectives, methodology/instruments, and main findings. These details were summarized in a table (see Appendix).

Risk of Bias Assesment

The methodological quality and risk of bias of the five included studies were assessed using the Joanna Briggs Institute (JBI) Checklist for Quasi-Experimental Studies, with the assistance of a Large Language Model (LLM, Gemini). Results indicated variable levels of bias across the studies, but none demonstrated a high risk of bias. Most studies exhibited strong methodological quality in fundamental domains. All clearly defined cause-and-effect relationships and employed appropriate negative controls. Consistency of treatment across groups was also well reported, minimizing performance bias. However, weaknesses were noted in domains with unclear identification, particularly affecting outcome measurement reliability. Studies by Tohar et al. (2019), Tuntiyawasdikul et al. (2024), and Rahmawati et al. (2024) consistently fulfilled most JBI criteria, with transparent reporting, appropriate controls, and robust data analysis. The study by Salim et al. (2022) demonstrated a moderate risk of bias. While most JBI criteria were satisfied, unclear blinding in outcome assessment introduced potential bias. Similarly, Zakaria et al. (2023) showed a moderate risk of bias, primarily due to methodological subjectivity in the scratch assay. This included manual scratch creation, visual boundary determination, semi-manual use of ImageJ, and the absence of blinding procedures. Despite these limitations, no study exhibited high risk of bias. The overall low-to-moderate risk supports the inclusion of all five studies in this systematic review.

Result Synthesis

1. Anti-inflammatory Effects Through Suppression of Inflammatory Mediators

Inflammation is a physiological process of the body in response to harmful stimuli such as infection, injury, and irritants. It functions to clear damaged tissue, combat infection, and initiate healing. However, when prolonged, inflammation may impede the wound healing process (Xu et al., 2021). Extracts of *M. speciosa* have been shown to exert anti-inflammatory effects by suppressing inflammatory mediators through various pathways (Rahmawati et al., 2024; Salim et al., 2022; Tohar et al., 2019; Tuntiyawasdikul et al., 2024; Zakaria et al., 2023). Four of the reviewed studies reported evidence of anti-inflammatory activity through suppression of inflammatory mediators.

The study by Rahmawati et al. (2024) employed RAW 264.7 macrophage cells treated for 1 hour with two types of extracts: crude extract (25, 50, and 100 ppm) and alkaloid extract (6.25, 12.5, and 25 ppm). Cells were subsequently induced with 1 µg/mL lipopolysaccharide (LPS) to trigger inflammation and incubated for 24 hours. Regarding oxidative stress, a significant reduction in reactive oxygen species (ROS) was observed. The strongest reduction occurred at 25 ppm of the alkaloid extract, showing a 64% decrease, followed by the crude extract at 100 ppm with a 50% decrease. Both extracts also reduced nitric oxide (NO) production, with maximum inhibition at 7–8 nM for 100 ppm crude extract and 25 ppm alkaloid extract. The extracts demonstrated a reduction in pro-inflammatory cytokines (TNF-α and IL-6). TNF-α inhibition was observed at concentrations ≥ 12.5 ppm for the alkaloid extract and ≥ 50 ppm for the crude extract, whereas IL-6 inhibition was most effective at 100 ppm crude extract and 25 ppm alkaloid extract. Interestingly, not all concentrations exhibited inhibitory effects; TNF-α increased at 25 ppm crude extract, while IL-6 increased at 25 ppm alkaloid extract. COX-2 and 5-LOX pathways were also affected. COX-2 was inhibited by an average of 33.46% across all alkaloid concentrations, while crude extract showed inhibition only at 25 ppm. 5-LOX inhibition was observed at ≤ 12.5 ppm alkaloid extract (35.06%), with no inhibition observed for crude extract (Rahmawati et al., 2024).

Inhibition of NO production was also demonstrated in the study by Tohar et al. (2019), which utilized *M. speciosa* extracts obtained through Supercritical Fluid Extraction (SFE). Extraction occurred in two steps: the first using pure CO₂, and the second with CO₂ plus ethanol. Fifteen different extracts were tested on RAW 264.7 macrophages inflamed by interferon-γ (IFN-γ) and LPS. Six extracts showed moderate inhibition (51–64%), while nine demonstrated weak inhibition (16–48%). The most potent extract, labeled M5S1, was obtained using step 1 (100% CO₂) at 3000 psi and 60°C, with an inhibition rate of $60.08 \pm 10.02\%$ and cell viability of $91.98 \pm 5.58\%$. M5S1 contained the highest concentration of palmitic acid (34.90%), a known phospholipase A2 inhibitor with anti-inflammatory properties, although other compounds in the extract may also contribute (Tohar et al., 2019). Anti-inflammatory activity was further investigated by Tuntiyawasdikul et al. (2024), who evaluated NO inhibition and inflammatory gene expression. RAW 264.7 macrophages were cultured in 96-well plates for NO assays and 12-well plates for gene expression assays at a density of 1.5×10^5 cells.

Cells were treated with varying concentrations of *M. speciosa* extract (10–300 µg/mL) and aminoguanidine (10–100 µg/mL) as a positive control for NO assays, while indomethacin was used as a positive control for gene expression assays. Cells were stimulated with LPS (50 µg/mL). Results demonstrated a dose-dependent reduction in NO production, with an IC₅₀ of 147.79 ± 8.97 compared to 35.83 ± 3.33 for the positive control. Significant dose-dependent suppression of mRNA expression was also observed for pro-inflammatory genes (iNOS, COX-2, IL-1β, and IL-6), with IC₅₀ values of 182.71 ± 11.31 for iNOS, 275.82 ± 34.07 for COX-2, 286.29 ± 21.99 for IL-6, and 289.60 ± 43.51 for IL-1β. By contrast, positive control IC₅₀ values were 45.37 ± 8.0 for iNOS, 53.59 ± 6.40 for COX-2, 41.29 ± 1.68 for IL-6, and 53.24 ± 3.24 for IL-1β. These findings provide evidence of the anti-inflammatory effects of *M. speciosa* at the transcriptional level (Tuntiyawasdikul et al., 2024). Inflammatory gene expression plays a critical role in wound healing, with pro-inflammatory cytokines regulating gene expression to facilitate tissue repair and remodeling (Mahmoud et al., 2024). Salim et al. (2022) investigated the anti-inflammatory effects of *M. speciosa* using a carrageenan-induced paw edema model in mice. Animals were divided into a control group, a carrageenan-only group, and treatment groups receiving oral *M. speciosa* extract at doses of 75 mg/kg, 150 mg/kg, and 200 mg/kg. Results demonstrated reduced paw swelling at all doses, measured with a plethysmometer at 0, 1, 2, and 4 hours post-carrageenan injection. Histological examination showed restoration of skin thickness approaching normal, particularly at 150 mg/kg and 200 mg/kg. Oral administration of *M. speciosa* extract produced significant anti-inflammatory effects, including reduced vascular permeability, thereby limiting edema formation. The extract effectively suppressed early-phase edema by inhibiting synthesis, release, or activity of hyperalgesic mediators (Salim et al., 2022). Strong antioxidant activity of *M. speciosa* extracts was also highlighted in this study. Antioxidant capacity was evaluated using three assays: ABTS radical scavenging, Ferric Reducing Antioxidant Power (FRAP), and total phenolic content (TPC) via Folin-Ciocalteu reagent. Both crude and alkaloid extracts demonstrated strong ABTS radical scavenging, with 94% inhibition at 1000 ppm, indicating high antioxidant activity. In FRAP and TPC assays, crude extract was approximately 20 times more effective in reducing ferric ions compared to the alkaloid extract. TPC analysis

confirmed significantly higher total phenolic content in the crude extract (7224 ± 46.4 mg GAE g⁻¹) (Rahmawati et al., 2024). Antioxidants contribute to both anti-inflammatory and wound healing processes, as excessive ROS production or impaired detoxification leads to inflammation and oxidative stress-induced cellular damage—major factors delaying wound healing (Chaniad Id et al., 2020).

2. Potential for Wound Healing

Wound healing is closely associated with the inflammatory process, as wound repair consists of four overlapping phases, one of which is inflammation (Sjamsuhidajat et al., 2017; Zakaria et al., 2023). The study by Zakaria et al. (2020) demonstrated that the mechanism of wound healing extends beyond anti-inflammatory activity. The wound healing potential was attributed to two mechanisms: enhanced cell migration and the promotion of angiogenesis. Stimulation of cell migration was assessed by creating artificial wounds in fibroblast and HUVEC monolayer cultures, followed by treatment with various extract fractions (methanol crude extract, dichloromethane fraction, and ethyl acetate fraction) at concentrations of 1.56 µg/mL, 3.13 µg/mL, and 6.25 µg/mL. The extracts were evaluated for their ability to stimulate fibroblast and endothelial cell migration to close the artificial wound. Results indicated that all extracts contributed to accelerated cell migration compared to the control. Notably, the ethyl acetate and dichloromethane fractions exhibited the most rapid migration activity in fibroblasts, achieving 71.22–70.85% closure at 3.13 µg/mL. The ethyl acetate fraction also demonstrated the fastest closure in HUVEC cells. These findings provide evidence that *M. speciosa* extract can enhance wound healing processes (Zakaria et al., 2023). Angiogenesis plays a critical role in wound healing, as it ensures an adequate blood supply to the wound site and promotes tissue regeneration and repair (Nazarnezhad et al., 2022). The study by Zakaria et al. (2020) further evaluated the angiogenic potential of *M. speciosa* extract in HUVECs. Cells were cultured on a tissue-mimicking matrix (Matrigel®) and treated with varying extract concentrations (1.56, 3.13, and 6.25 µg/mL). The angiogenesis assay demonstrated significant stimulation of tube formation compared with the control group. Among the fractions, the ethyl acetate fraction was most effective, producing the greatest total branching length across all tested concentrations, with values of 9014.33, 7750, and 10,986 pixels, respectively. Chemical analysis (LC-MS/MS) identified multiple bioactive compounds within the extracts. The ethyl

acetate fraction contained the highest diversity of compounds, including flavonoids, phenols, and fatty acids, all of which are known to exert therapeutic effects such as anti-inflammatory, antioxidant, and antibacterial activities—properties that collectively support wound healing (Zakaria et al., 2023).

3. Safety Profile and Cytotoxicity

Overall, the five analyzed studies demonstrated that *M. speciosa* extracts exhibit a favorable safety profile at effective concentrations. In several assays, cytotoxicity testing was essential to confirm that the observed reduction in nitric oxide (NO) production reflected anti-inflammatory effects rather than cell death (Tohar et al., 2019). Determining a safe concentration range for cells is also important for evaluating the therapeutic potential of the extract. Zakaria et al. (2023) conducted cytotoxicity testing using 3T3 fibroblasts and HUVEC endothelial cells seeded in 96-well plates at a density of 1×10^4 cells/well. Extracts were tested at concentrations of 1.56, 3.13, 6.25, 12.5, 25, and 100 µg/mL. The crude ethanol extract, hexane fraction, and ethyl acetate fraction all demonstrated safety profiles with cell viability ranging between 50–150%. In contrast, the dichloromethane fraction exhibited slight cytotoxicity at higher concentrations (75.418 ± 5.286 µg/mL). In HUVEC cells, the hexane fraction was found to be the most cytotoxic, with a notably low IC₅₀ value of 21.323 ± 7.766 µg/mL. Extracts are generally considered non-toxic when their IC₅₀ values exceed 30 µg/mL (Zakaria et al., 2023). Rahmawati et al. (2024) also evaluated cytotoxicity using the MTT assay in RAW 264.7 macrophages. Cells were treated with either crude extract (25, 50, 100, and 200 ppm) or alkaloid extract at equivalent concentrations. The results revealed that the crude extract was safe and non-toxic to RAW 264.7 cells, with viability ranging from 91–100% across all tested concentrations, even at the highest dose. Conversely, the alkaloid extract exhibited concentration-dependent cytotoxicity. At 25 ppm, viability remained safe at 100%, but decreased to 46% at 50 ppm, 10% at 100 ppm, and reached complete cell death at 200 ppm. These findings suggest that the crude extract is considerably safer across a wider dose range compared to the alkaloid extract (Rahmawati et al., 2024).

Cytotoxicity testing was also conducted by Tohar et al. (2019) using RAW 264.7 macrophages with the MTT assay, involving 15 treatment groups and one control group. Cell viability was reported as a percentage, calculated by comparing the absorbance of treated cells with untreated controls.

For NO inhibition to be considered valid, cell viability was required to remain above 85%. Results showed that 9 of the 15 groups maintained viability above this threshold, while the remainder fell below (Tohar et al., 2019). Further cytotoxicity evaluation was performed by Tuntiyawasdikul et al. (2024), who applied the MTT assay across four skin-relevant cell lines: human fibroblasts (CRL-2522), human keratinocytes (HaCaT), mouse melanoma cells (B16F10), and murine macrophages (RAW 264.7). Cells were cultured in 96-well plates and treated with five extract concentrations, up to 2.5 mg/mL. Viability was measured spectrophotometrically at 570 nm. The IC₅₀ values obtained were: keratinocytes (1.29 ± 0.03 mg/mL), macrophages (1.40 ± 0.03 mg/mL), melanocytes (1.99 ± 0.06 mg/mL), and fibroblasts (2.46 ± 0.18 mg/mL). These results indicate a favorable safety profile, as IC₅₀ values exceeding 1 mg/mL are generally considered non-toxic (Tuntiyawasdikul et al., 2024).

Discussion

This systematic review synthesizes evidence from five experimental studies aimed at evaluating the role of *Mitragyna speciosa* (Korth) as an anti-inflammatory agent in the context of wound healing. Overall, the findings provide strong scientific support for the traditional use of this plant. Extracts of *M. speciosa* consistently suppress multiple inflammatory markers. Collectively, the analyzed studies demonstrate a reduction in the production of ROS, NO, and pro-inflammatory cytokines such as TNF- α and IL-6, as well as the inhibition of enzymatic pathways mediated by COX-2 and 5-LOX. However, it is important to note that inflammation is a critical component of the wound healing process, serving to cleanse wounds and combat pathogens. Prolonged inflammation, on the other hand, may hinder wound repair (Xu et al., 2021). The anti-inflammatory effects of *M. speciosa* are associated with its bioactive compounds. According to Tohar et al. (2020), extraction using Supercritical Fluid Extraction identified fraction M5S1 as the most potent extract, containing palmitic acid as the major compound (34.90%). Other compounds, such as tocopherol, were also shown to contribute to its anti-inflammatory effects (Tohar et al., 2019). *M. speciosa* exhibits multifactorial activity, reflecting the synergistic interaction of various bioactive compounds, including flavonoids, phenols, and fatty acids, in addition to its well-known alkaloids. Beyond anti-inflammatory activity, this review also highlights direct evidence of wound-healing

potential. Zakaria et al. (2023) reported that extracts specifically accelerated fibroblast and endothelial (HUVEC) cell migration and promoted angiogenesis. Such effects are crucial, as cell migration plays an essential role in wound closure, while angiogenesis ensures adequate nutrient and oxygen supply for tissue regeneration (Voza et al., 2024; Wang et al., 2024; Zakaria et al., 2023).

This systematic review is not without methodological limitations. The primary limitation lies in the reliance on narrative synthesis, due to substantial heterogeneity in study designs, interventions, and outcomes, which precluded quantitative meta-analysis. Consequently, conclusions were drawn qualitatively and did not provide a pooled systemic effect. The implications of these findings span clinical practice, policy, and future research. Clinically, it is still premature to recommend the broad use of *M. speciosa*. Nonetheless, the present findings offer a robust scientific foundation for the development of plant-derived therapeutic agents. From a policy perspective, *M. speciosa* and its main alkaloids, mitragynine and 7-OH mitragynine, are not yet approved by the FDA (Rahmawati et al., 2024). Current regulatory restrictions are largely based on concerns regarding the potential misuse of kratom, as higher doses may produce opioid-like effects and associated adverse outcomes. Therefore, a balanced regulatory framework is essential to facilitate research into its therapeutic compounds while tightly controlling its use (Davidson et al., 2021; Demick et al., 2020). Findings suggesting that crude extracts are safer than pure alkaloid fractions at higher concentrations may also provide important insights for regulatory bodies (Tohar et al., 2019).

Several critical directions are identified for future research. The foremost priority is to advance *in vivo* studies using clinically relevant wound models, such as excision, incision, or burn wounds in animals, to validate *in vitro* findings and assess all phases of wound healing. Standardization of extraction protocols and formulation is also necessary to ensure consistency and reproducibility of results. Further studies should focus on isolating and identifying the most active compounds responsible for anti-inflammatory and pro-regenerative effects, as well as clarifying the underlying molecular signaling pathways. Long-term toxicity evaluations, systemic safety studies, and comparative analyses examining the efficacy of *M. speciosa* extracts against standard wound care agents are essential steps before progressing to human clinical trials.

Conclusion

Mitragyna speciosa (Korth) is a plant long recognized in traditional medicine for its broad therapeutic effects, particularly in wound healing. Based on the systematic review conducted, this plant demonstrates clinically proven effects in regulating the suppression of inflammation, including modulation of NO, ROS, TNF- α , IL-6, and the enzymatic pathways of COX-2 and 5-LOX. Moreover, *M. speciosa* actively promotes the healing process by stimulating fibroblast and endothelial cell migration as well as angiogenesis, indicating its potential as a future therapeutic option for wound healing. Current wound-healing therapies commonly involve corticosteroids and NSAIDs, which are associated with various side effects, including cardiovascular and gastrointestinal complications, while excessive use of antibiotics has also led to resistance. Plant-based therapies such as *M. speciosa* are therefore expected to offer benefits by reducing adverse effects compared to conventional treatments. However, its utilization faces regulatory challenges due to the potential for misuse, leading to psychotropic effects and other harmful side effects. Thus, stronger scientific evidence is required to support its therapeutic claims. Controlled and evidence-based management of this plant may optimize its benefits and provide significant clinical advantages, although further research remains necessary before its application in humans. The findings of this study are expected to serve as a foundation for future research in developing plant-based therapies, particularly for wound healing.

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Ethics statement: This study is a systematic review that synthesizes data from previously published studies. As no new experiments involving human participants or animals were conducted, ethical approval and informed consent were not required. All data analyzed were obtained from publicly available sources in accordance with ethical publishing standards.

Conflict of Interest

No conflict of interest in this study

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