



PIPER BETLE LINN (BETEL LEAF): A COMPREHENSIVE REVIEW OF ITS PHARMACOLOGICAL ACTIVITIES, THERAPEUTIC POTENTIAL AND CULTURAL SIGNIFICANCE

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ABSTRACT

Piper betle Linn., widely recognized as betel leaf, occupies a significant position in both traditional healing systems and socio-cultural practices across numerous communities worldwide. This plant's multidimensional relevance—spanning medicinal applications and cultural rituals—has generated considerable scientific interest globally. The present systematic review aims to provide a thorough examination of the pharmacological properties, therapeutic applications, and cultural dimensions of Piper betle Linn. From a pharmacological perspective, this plant has been revered as an auspicious species in Indian Ayurvedic traditions since antiquity, with documented bioactivities including antibacterial, antioxidant, anti-inflammatory, anticancer, antidiabetic, and neuroprotective effects. These activities are primarily attributed

to the presence of key phytochemicals such as flavonoids, phenolic compounds, alkaloids, and volatile essential oils. In the domain of traditional medicine, betel leaf has demonstrated efficacy in managing various health conditions, including oral disorders, gastrointestinal ailments, respiratory conditions, and dermatological diseases. Its therapeutic promise warrants continued scientific investigation to enable integration into contemporary medical practice while honoring its rich cultural legacy. This review presents Piper betle Linn. recognized as the 'leaf of prosperity' in Indian heritage—as a nature-derived therapeutic resource where ancestral knowledge converges with modern scientific inquiry, particularly

illuminating its significance within Ayurveda.

KEYWORDS: Piper betle Linn., Botanical Profile, Phytochemistry, Pharmacological Activities, Traditional Medicine, Ayurveda.

INTRODUCTION

Betel leaf (*Piper betle* Linn.) is a widely recognized medicinal plant native to Asia, classified under the family Piperaceae. The plant's leaves have long served as the basis for traditional medicinal preparations aimed at treating a spectrum of illnesses. Given its widespread availability and economic accessibility, both the food industry and pharmaceutical sector stand to gain substantially from further research into this plant's properties. Commonly referred to as the betel vine, this plant has established deep roots in the cultural and medicinal traditions of many Asian countries.

The practice of chewing betel leaves is prevalent across many nations, most notably India, where it is valued for its ability to freshen breath, strengthen the gums, and stimulate digestive function. In India, betel leaves serve as a natural mouthwash, while in Indonesia they are employed as a vaginal douche remedy. In Sri Lanka, the juice extracted from the leaves is applied topically to address skin conditions. When boiled, the leaves are also administered as a cough remedy due to their characteristic astringent properties.

Piper betle Linn., locally referred to as 'Paan', is a dioecious, perennial climber belonging to the Piperaceae family, capable of reaching approximately one meter in height via numerous short adventitious climbing roots. It thrives predominantly in warmer, more humid regions. The plant is distributed widely across India and several Southeast Asian nations including China and Vietnam, typically inhabiting moist forest environments. Within India, cultivation occurs in states such as Bengal, Orissa, Tamil Nadu, Andhra Pradesh, Uttar Pradesh, and Karnataka. In Tamil Nadu specifically, three major varieties are commonly available: Sirugamani, Karpoori, and Vellaikodi.

Among the most notable Ayurvedic formulations derived from this plant are Lokantha Rasa, Puspadhava Rasa, Brhat Sarwajwarahara, Laghusutashekhara Rasa, and Brhat Visamajwarantaka Rasa. Within the Ayurvedic system, betel leaf juice frequently functions as an adjuvant—combined with other therapeutic agents to enhance treatment outcomes. The *Susruta Samhita* describes tambola leaves as fragrant, pungent, heating, and astringent in

nature, with the capacity to pacify vata while increasing pitta.

1. CLASSIFICATION OF BETEL LEAF VARIETIES

Based on morphological features and essential oil composition, betel leaf cultivars are broadly classified into five primary groups: Bangla, Desawari, Kapoori, Sanchi, and Meetha.

- **Bangla:** Characterized by broad, heart-shaped leaves with nine midribs and oval laminae. Leaf blades are flat with short, pointed apices. The petiolar sinus is more pronounced compared to other varieties.
- **Desawari:** Features broad leaves with seven to nine veins and cordiform lamination. Leaves display a distinctive pink coloration, with curved, acuminate, and short leaf apices.
- **Kapoori:** Identifiable by elliptical leaves with small, smooth laminae. The leaf apex is sharply pointed and the petiolar sinus is not readily visible.
- **Meetha:** Recognized by large leaves with a broad, ovate lamina exhibiting a waxy texture and yellow spotting. Three to five veins are present, and the leaf tip is short and pointed with a distinct petiolar point.
- **Sanchi:** Distinguished by cordate leaf sheaths with multiple elliptical lamellae and elongated, tapering leaves. Typically displays seven prominent nerves.



Fig 1: Kapoori



Fig 2: Bangla



Fig 3: Desawari



Fig 4: Sanchi

Fig 2: Classification of Betel Leaf Varieties

2. PHARMACOLOGICAL ACTIVITIES

2.1 Antifungal Activity

Piper betle L. has been empirically employed in traditional medicine for centuries, and contemporary research has validated its antifungal efficacy. Studies have demonstrated that the essential oil derived from betel leaves exhibits significant inhibitory activity against multiple fungal species, including *Aspergillus niger*, *Trichophyton mentagrophytes*, and *Candida albicans*. The antifungal mechanism is attributed to the presence of active constituents such as eugenol, chavicol, and terpene compounds. Additionally, betel leaf extracts have been shown to suppress the proliferation of dermatophytes responsible for skin infections such as ringworm and athlete's foot. Synergistic interactions with conventional antifungal agents including fluconazole have also been reported, potentially enhancing therapeutic outcomes. These properties collectively position betel leaf as a candidate natural remedy for fungal infections, though further clinical evaluation is warranted.

2.2 Antimicrobial Activity

Betel leaf extracts have demonstrated broad-spectrum antimicrobial activity against several pathogenic organisms including *Streptococcus* species, *Staphylococcus aureus*, *Proteus vulgaris*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Activity has also been observed against urinary tract pathogens such as *Citrobacter koseri*, *Citrobacter freundii*, *Enterococcus faecalis*, and *Klebsiella* species. Additionally, the constituent allylpyrocatechol has been shown to exert both protective and curative effects against indomethacin-induced gastric ulceration in experimental rat models, underscoring the multifaceted antimicrobial and gastroprotective potential of the plant.

2.3 Analgesic and Anti-inflammatory Activity

Hydroalcoholic extract of betel leaf (HEPBL), prepared using Soxhlet extraction, has been evaluated for analgesic and anti-inflammatory properties in Wistar rats and Swiss albino mice. Analgesic activity was assessed using tail-flick and acetic acid-induced writhing methods, while anti-inflammatory activity was evaluated using cotton pellet granuloma and carrageenan-induced paw edema models. HEPBL exhibited significant analgesic activity at doses of 50, 100, and 200 mg/kg, and demonstrated notable anti-inflammatory activity at doses of 100 and 200 mg/kg. A subtherapeutic enhancement of conventional analgesic efficacy was also observed at 50 mg/kg. These effects are attributed to the presence of flavonoids, tannins, phenolic compounds, and glycosides within the extract.

2.4 Antioxidant Activity

Oxidative damage represents a critical consequence of free radical exposure in biological systems. Polyphenolic constituents of betel leaf—including catechol and allylpyrocatechol—effectively inhibit radiation-induced lipid peroxidation by scavenging free radicals involved in both the initiation and propagation phases of oxidative chain reactions. The extract demonstrates significant ferric ion (Fe^{3+}) reduction capacity and exhibits radical scavenging activity against hydroxyl radicals and superoxide anions, with potency comparable to established antioxidants such as ascorbic acid and butylated hydroxytoluene (BHT).

2.5 Gastroprotective Activity

Research has established that betel leaf preparations enhance mucus adhesion to the gastric lining when administered, particularly under thermal stimulation. This increased mucosal protective layer is considered central to the plant's gastroprotective mechanism, functioning by shielding the gastric mucosa from acidic damage and supporting the healing process. The gastroprotective effect appears to be mediated through modulation of inflammatory pathways rather than direct inhibition of acid secretion. Furthermore, the constituent allylpyrocatechol has shown potent antioxidant activity *in vitro* and significantly accelerates ulcer healing by promoting mucosal regeneration and protecting against gastric acid exposure.

2.6 Anticancer Activity

Extensive clinical and experimental evidence links chronic inflammation to the pathogenesis of numerous malignancies. Betel leaf has been investigated for its chemopreventive potential, particularly in the context of oral cancer—one of the most prevalent cancers in Southeast Asia. Experimental studies have demonstrated that application of betel leaf extract in animal models can suppress benzo(a)pyrene-induced oral carcinogenesis. Combinations of betel leaf with turmeric have shown additional chemopreventive benefits. Supplementation of drinking water with betel leaf preparations has also significantly reduced neoplasm formation in mice. The antiviral and chemopreventive properties of Piper betle constituents support its potential application in the management of cancers, including human lung cancer.

2.7 Cardioprotective Activity

Cardiovascular injury is fundamentally linked to oxidative stress resulting from ischemia-reperfusion imbalances. Pretreatment with Piper betle Linn. has been demonstrated to improve hemodynamic parameters and ventricular function in rat models of isoproterenol-

induced myocardial infarction.

The extract reduces cardiac lipid peroxidation while augmenting antioxidant enzyme levels including superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and glutathione peroxidase (GPx), thereby attenuating the release of cardiac biomarkers CK-MB and LDH into systemic circulation. Furthermore, compounds isolated from betel leaves—specifically piperbetol, ethyl piperbetol, piperole A, and piperole B—exhibit inhibitory activity against platelet-activating factor (PAF)-mediated platelet aggregation triggered by reactive oxygen species.

2.8 Antihypertensive and Lipid-Lowering Activity

Elevated lipid levels constitute a major cardiovascular risk factor. Research has demonstrated that betel leaf can effectively reduce total cholesterol, triglycerides, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) levels while simultaneously elevating high-density lipoprotein (HDL) cholesterol. This lipid-lowering effect is primarily mediated by eugenol—a natural antioxidant present in betel leaf—which neutralizes free radicals, inhibits hepatic cholesterol biosynthesis, and reduces intestinal cholesterol absorption. Additionally, eugenol accelerates the catabolism of LDL cholesterol and promotes the hepatic clearance of excess lipids through bile acid formation.

2.9 Wound Healing Activity

The wound-healing potential of *Piper betle* leaf and stem extracts was evaluated in experimental Wistar rat models. Wound healing involves a complex cascade of cellular and metabolic events aimed at restoring anatomical integrity and function. Application of an ointment formulation containing 10% *Piper betle* L. leaf and stem extract was shown to significantly accelerate wound closure compared to both untreated control and disease groups, with the wound area demonstrating complete coverage by a well-organized epidermis. These findings support the traditional use of betel leaf in wound management.

2.10 Anti-haemolytic Activity

The anti-haemolytic activity of betel leaf extracts has been investigated using erythrocyte membrane models. Erythrocytes are particularly susceptible to oxidative damage due to their high content of polyunsaturated fatty acids, constant exposure to elevated oxygen tensions, and the presence of haemoglobin—a potent oxidation catalyst. Oxidative damage to erythrocyte membranes leads to lipid and protein oxidation, ultimately causing haemolysis.

Treatment of erythrocytes with betel leaf extract in the presence of hydrogen peroxide has been shown to significantly reduce haemolysis, indicating a membrane-protective antioxidant effect mediated by the phenolic constituents of the extract.

3. RATIONAL OF WORK

1. Addressing limitations of current antifungal therapies:

Limited options and resistance: Current antifungal medications can be expensive, have side effects, and some fungal strains are developing resistance.

Delivery method drawbacks: Existing topical antifungal treatments often lack sustained efficacy or require inconvenient application methods like creams or ointments.

2. Potential benefits of betel leaf extract and film-forming spray:

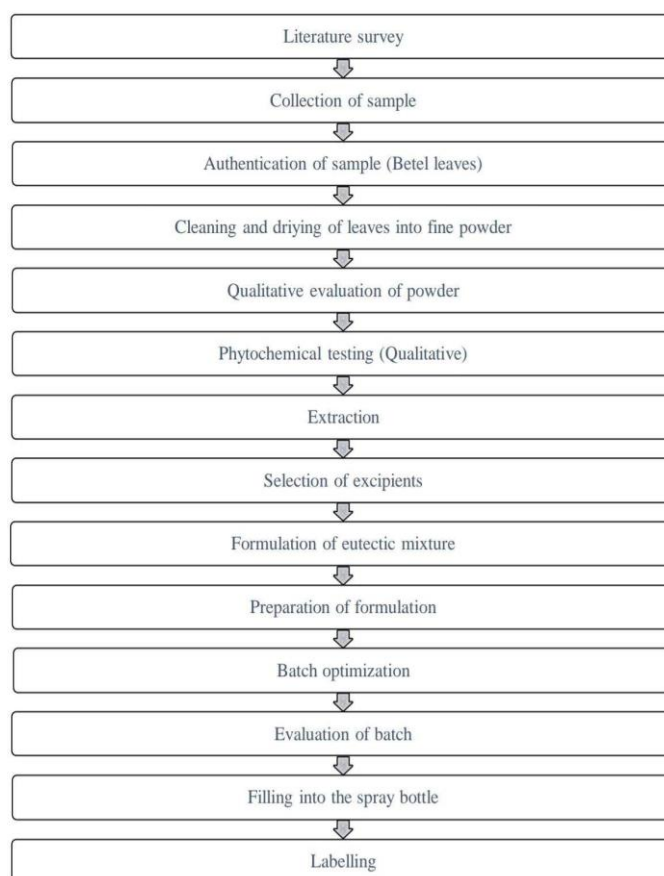
Natural source with antifungal properties: Betel leaf extract has a long history of traditional medicinal use and research suggests it possesses antifungal activity against various fungal pathogens.

Targeted delivery and patient compliance: A film-forming spray offers targeted application to the affected area, potentially improving efficacy and reducing side effects. Additionally, the spray format is convenient and user-friendly, promoting better patient compliance with the treatment regime.

3.1 Plan of work

The work started with a literature survey to collect information related to the formulation and use of betel leaves. After this, the sample of betel leaves was collected and authenticated to ensure the correct plant material was used. The collected leaves were then cleaned properly, dried, and converted into fine powder. The powdered sample was subjected to qualitative evaluation followed by qualitative phytochemical testing to identify the presence of different phytochemical constituents. After testing, the extraction process was carried out to obtain the active constituents from the leaves. Suitable excipients were selected for the formulation, and a eutectic mixture was prepared. The formulation was then prepared and optimized by batch optimization techniques. The optimized batch was evaluated for different parameters to check its quality and effectiveness. Finally, the prepared formulation was filled into spray bottles and labelled properly for further use and identification. The final product was checked for stability, appearance, and ease of application to ensure user convenience. Proper storage conditions were maintained to preserve the quality and effectiveness of the formulation. The

prepared spray formulation may be useful for further pharmaceutical and therapeutic applications after successful evaluation.



4. EXPERIMENTAL PROCEDURES

4.1. Sample collection

Piper betel leaves of the Calcutta variety were collected. The leaves were authenticated by Dr. Harshad

M. Pandit. The collected leaves were treated by washing thoroughly with distilled water, air-dried for 5 days at room temperature, and powdered.

4.2 Determination of Ash value and moisture content

4.2.1 Ash value: significance- determination of inorganic impurities in the powdered sample



Fig. 2 Ash Plate.

The % ash value for 1gm of Piper betel powder was found to be.

Table 1: Observation table (% ash value).

SR.NO	W1 Wt. of empty crucible	W2 Wt. of powder + crucible	W3 Wt. of ash + crucible	% Ash value
1	23.38	24.38	23.56	18%
2	22.93	23.93	23.13	17%
3	22.51	23.51	22.68	17%

Formula

$$\frac{W3-W1}{W2-W1} * 100$$

The % ash value of the powdered drug was calculated and was found to be 17%.

4.2.2 Moisture content: Significance- to determine the shelf-life, usability and quality of product.

Formula

$$\frac{W1-W2}{W1} * 100$$

Where, W1- Initial weight of powder. W2- Final weight of powder. Therefore, W1= 63.80; W2=62.864

$$\% \text{ Moisture content} = \frac{63.80-62.86}{63.80} * 100 = 1.4\%$$

4.3 Preparation of extract (betle leaf)

The dried leaf powder extracted by soxhlet and maceration extraction method by using ethanol as an solvent.

All the extractions were carried out from 25gm of the powdered leaf sample in 125 ml of ethanol as a solvent (50-60 temp) for 8 hrs. Maceration was carried out at the room temperature for 72 hrs with occasional stirring after completion of this process the product was filtered.



Fig.3 Betel leaf extract



Fig.4 Soxhlet extraction

4.4. Qualitative phytochemical analysis

Three grammes of powder were diluted in 20 millilitres of distilled water, heated, cooled, and filtered using Whatman No.1 filter paper. The extract underwent phytochemical analysis to identify carbohydrates, glycosides, fixed oils, protein, saponins, tannins, phenolic compounds, phytosterols, alkaloids, and flavonoids using the specified method.

4.4.1 Test for alkaloids

Solvent-free extract; 50 mg of plant material were mixed with 1 ml of diluted hydrochloric acid, then the mixture was filtered. The alkaloids in the filtrate were examined.

Mayer's Test

A drop of Mayer's reagent was applied to the filtrate along the test tube's sides. A white precipitate signifies a positive test result.



4.4.2 Tests for carbohydrates

2 ml of extract were diluted in 4 ml of distilled water and filtered. The filtrate was tested for carbs and glycosides using the methods listed below.

Molish test

After treating one ml of the filtrate with 2 to 3 drops of Molish reagent, 2 ml of concentrated sulfuric acid was poured along the edges of the test tube. A brown ring at the confluence of two liquids indicates the presence of carbohydrates.

4.4.3 Test for flavonoids

Alkaline reagent test

1 ml of a 10% ammonium hydroxide solution was added to 2 ml of aqueous extract. Yellow fluorescence shows the presence of flavonoids.



4.4.4 Test for steroids

Salkowski's test

Add equal amounts of chloroform and concentrated sulfuric acid to 1 ml of the extract. The presence of steroids is indicated by the formation of red precipitate.

Lliberman test

After adding equal amounts of chloroform and strong sulfuric acid to 1 ml of the extract, Check for acetic anhydride and saponins. The presence of steroids is indicated by the formation of a green precipitate.



4.4.5 Test for saponin

3 ml of distilled water were used to grind 50 ml of plant material, and the resulting 20 ml were diluted. The suspension within a graded cylinder was vibrated. A 2 cm layer of foam after 15 minutes suggests the presence of saponins.

4.4.6 Test for phenols

Ferric chloride test

5 ml of distilled water were used to dissolve about 50 mg of the sample. A few drops of a neutral 5% ferric chloride solution were added to this. When phenolic chemicals are present, a dark green color is present.



4.4.7 Test for glycosides

Keller-Kilani test

2 ml of glacial acetic acid containing 1-2 drops of a 2% FeCl_3 solution was combined with crude extract. After that, the mixture was transferred to a second test tube that included 2 ml of concentrated H_2SO_4 . The presence of cardiac glycosides was indicated by a brown ring at the interphase.



4.4.8 Test for reducing sugar

Add 1 ml of water and 5-8 drops of Fehling's solution to 0.5 ml of the plant sample's aqueous extract while it's heated and watch for brick red precipitate.



4.4.9 Test for tannins

1 ml of water, one or two drops of a ferric chloride solution, and 1 ml of the plant sample's aqueous extract were separated. Green-black color was noted for catecholic tannins and blue color for gallic tannins.

4.4.10 Test for phytosterols

0.5 ml of acetic anhydride and 0.5 ml of chloroform were applied to 4 mg of the plant sample. After adding strong sulfuric acid gradually, a greenish-blue hue indicative of steroids was noticed.

4.4.11 Test for terpenoids

Keller-Kilani test

0.5 ml of acetic anhydride and 0.5 ml of chloroform were added to 4 mg of the sample. Slowly, concentrated sulfuric acid was applied to the test tube's walls. Regarding terpenoids, a reddish-violet color was noted.

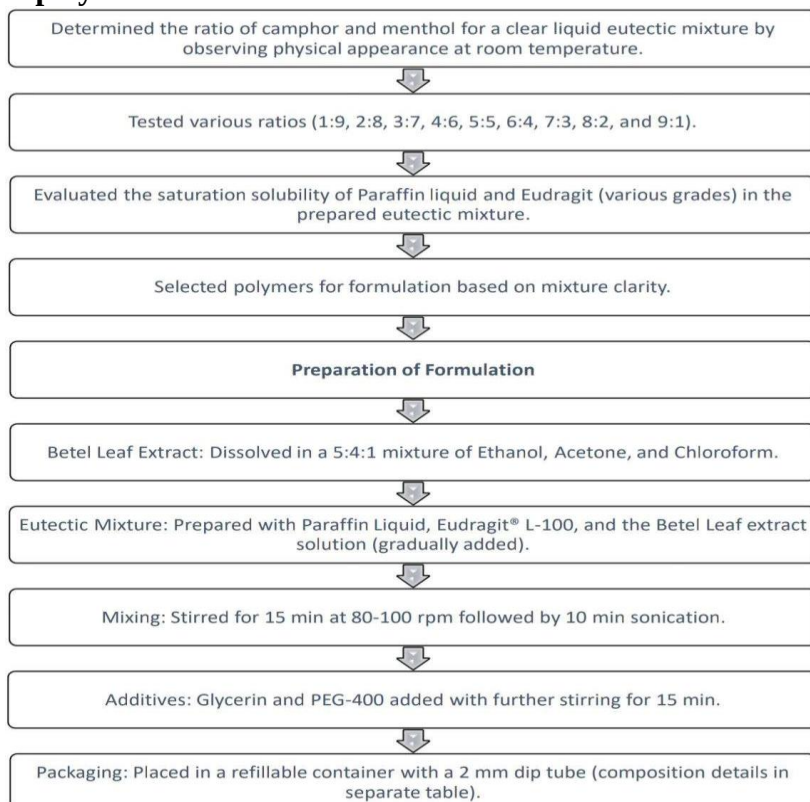
4.4.12 Test for proteins

To 1 ml of the extract few drops of Barfoed's reagent was added to give blue color products to indicate the presence of protein.



5. METHODOLOGY

5.1 Solubility of polymer in eutectic mixture



5.2 Formulae for the preparation of formulation

Table 3: Formulation table.

INGREDIENTS	F1	F2	F3	F4
Betel extract	2	2	2	2
Eudragit l 100	10	10	10	10
PEG 400	0.25	0.25	0.3	0.3
Eutectic Mixture	10	10	10	10
Paraffin liquid	4	5	4	4
Glycerine	1	1	1	1

6. EVALUATION TESTS

6.1 PH

The pH value is measured and adjusted to improve the stability of the active substance or make it suitable for the area of application. For skin pH ranging from 4-6. Adjusting the pH of

the preparation is to avoid irritation and changes in the physical form of fungal infections. In addition, the pH value of the dose depending on the degree of ionization K_a affects the penetration of the drug into the skin.

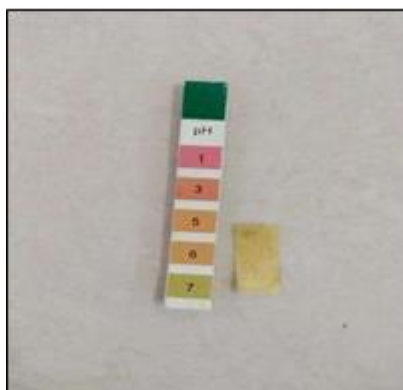


Fig. 5: PH value.

6.2 Drying time

The drying time of the film is measured to determine how quickly the film forms after the solution is sprayed. Under some conditions, the solution is sprayed on the surface of the skin and then allowed to dry at room temperature.

6.3 Water Washability

The ease of film wetting is assessed in the dried film. The film is washed with water and assessed in ordinal scale, i.e. easily washed, moderately washed, and poorly washed. The ease of sprinkling with water will be useful if the film-forming solutions contact with the sensitive areas in the body such as eyes and mouth.

6.4 Stickiness

The dry film is pressed gently using cotton wool. The viscosity of the film is assessed by the amount of cotton wool fibres attached to the film. The film adhesiveness is considered high if the attached fibre is thick, medium if the attached fibre is thin, and low if it is little or no attached fibre.^{20,34} Stickiness is tested to find out whether the film will become easily attached to clothing or other objects, so it needs attention when on the move.

6.5 The efficiency of the pump seal

The spray pump efficiency was estimated by the leak test. The spray bottle seal is tested by a pump seal test. The bottles of the same size and weight were tested for their weight variation. The bottles are balanced before and after the test stages and the leakages are tested.

6.7 Culture plate assay

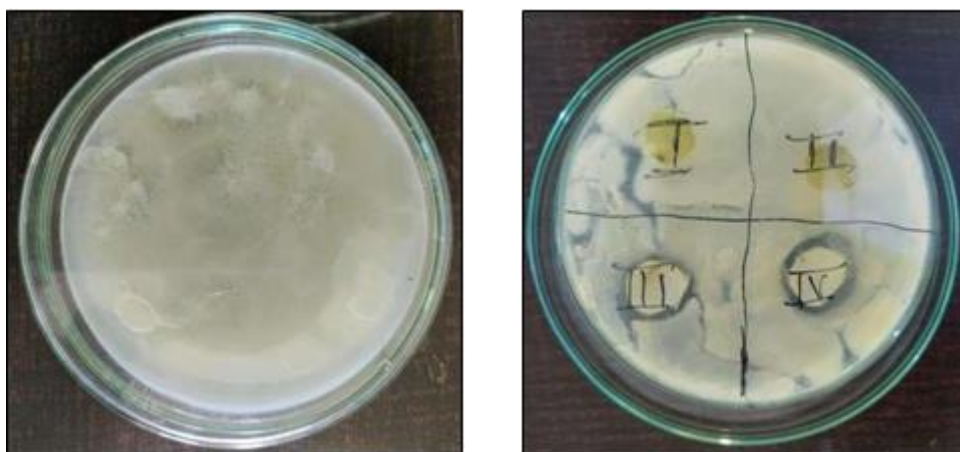


Fig. 6: Culture plates.

The well diffusion method is a common technique used to evaluate the antifungal activity of substances like your betel leaf herbal antifungal spray. Here's a brief overview

- Culture media: sabour dextrose agar.
- Bacterial strain used: yeast

Preparation of Agar Plates

Pour a molten sabour dextrose agar medium into sterile petri dishes and allow it to solidify. The medium is usually supplemented with a fungal inoculum to create a uniform lawn of the test organism.

Creating Wells

Use a sterile cork borer or a pipette tip to punch wells (small holes) into the solidified agar. These wells will serve as reservoirs for your test substance.

Adding the Test Substance

Dispense a specific volume of your betel leaf herbal antifungal spray into each well. Typically, multiple wells are used for replicates or different concentrations of the test substance.

Incubation

Incubate the plates at an appropriate temperature for fungal growth (usually around 28-30°C) for a specified period, typically 24-48 hours.

Observation and Measurement

After incubation, examine the plates for zones of inhibition (clear areas around the wells

where fungal growth has been prevented). Measure the diameter of these zones to assess the antifungal activity.

Control Wells

Include control wells with known antifungal agents (positive control) and solvent without active ingredients (negative control) to ensure the reliability of your results.

7. Observation table

Parameter	Observation (Formulation)
Color	Light green
Odour	Characteristic
Consistency	Smooth
pH	6
Loss on drying	41%
Drying time	Less than 1 min
Solubility	
1. Water	Soluble Insoluble
2. Alcohol	Soluble
3. Ether	
Washability	Poorly washable
stickiness	medium
Stability(37°C)	Stable at room temperature

8. RESULT AND DISCUSSION

The current study was conducted to formulate and evaluate herbal film forming antifungal spray. For this the herbal extract of piper betel leaves was prepared using Soxhlet extraction method. Prepared formulations were analyzed for various evaluation parameters.

Additionally, the presence of various Phyto constituents like alkaloids, flavonoids, reducing sugar, triterpinoids, phenol, saponins, proteins was confirmed. However, the negative results for the absence of tannins, phytosterols, anthroquinone, anthro-cyanides.

9. CONCLUSION

The comprehensive review of Piper betle Linn. presented herein constitutes an integrative documentation of the plant's cultural relevance and its wide-ranging medicinal applications across diverse scientific disciplines. The synthesis of phytochemical, pharmacological, and traditional perspectives provides a robust foundation for understanding the genuine therapeutic potential of this plant in clinical settings. Beyond its established antibacterial, antioxidant, and disease-specific therapeutic roles, Piper betle Linn. has demonstrated significant promise as an anticancer, antidiabetic, anti-inflammatory, and multi-target

medicinal agent, warranting expanded research and clinical validation. This review offers a systematic appraisal of the therapeutic potential of Piper betle Linn. and is intended to serve as a valuable reference for researchers, pharmaceutical scientists, clinicians, and those engaged in the preservation of traditional botanical knowledge.

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