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Formulation Development and Evaluation of Herbal Based Antifungal Prepration: A Comprehensive Review

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Abstract

This study focuses on the formulation and evaluation of a polyherbal antifungal cream, designed to combat common dermatophyte infections. Utilizing a combination of traditional medicinal plants known for their antifungal properties, such as *Neem* (*Azadirachta indica*), garlic (allium sativum) turmeric (curcumalonga), etc we aimed to develop a safe, effective, and bioavailable topical treatment. The cream was formulated using a standardized extraction method to ensure consistency in active ingredient concentration. Physicochemical evaluations, including pH, viscosity, and spreadability, were conducted to assess the cream's stability and applicability. Antifungal efficacy was tested against common pathogens, including *Candida albicans* and *Trichophyton rubrum*, using in vitro methods. The results demonstrated significant antifungal activity, with minimal skin irritation observed during patch testing on human volunteers. Overall, this polyherbal cream shows promising potential as a natural alternative to conventional antifungal therapies, emphasizing the role of herbal formulations in contemporary medicine. Further clinical trials are recommended to establish long-term efficacy and safety profiles.

Keyword: Antifungal Activity, Polyherbal Formulation, Phytochemical Analysis, Synergistic Effect, In Vitro Studies**,** Herbal Extracts

Introduction

Plant matter is a valuable resource for combating a number of grave illnesses across the globe. traditional medical practices, particularly the application of medicinal herbs as pastes, powders, etc. In impoverished nations, medicinal herbs are crucial for meeting basic health demands [1]. Herbal medicine, sometimes referred to as herbalism or botanical medicine, is the practice of treating wounds or ailments with plants or plant components[2] . The plant parts—seeds, leaves, stems, bark, roots, flowers, and so on—as well as their extracts that are used to make topical applications, tablets, capsules, teas, tinctures, and other formulations in herbal therapy. A few of these conventional plants are extracted and sold as medicinal drugs [3].

- The usage of herbal medicine stems from improved patient acceptance and tolerance.
- In emerging nations with rich agroclimatic, cultural, and ethnic biodiversity, medicinal plant growth and processing are environmentally benign and do not pose an issue [4].

Because medicinal plants have the ability to tackle the issue of drug resistance in microorganisms, their usage as raw materials in the production of new medications is constantly growing [5].

The great majority of people on the planet use herbal medicines as ailment therapies. According to WHO estimates, almost 75% of people on the planet presently cure their illnesses with herbs and other traditional remedies. In India, both rural and urban communities use herbal formulations. A range of plant parts, including leaves, stems, roots, bark, and fruits, are used to produce herbal skin care medicines that include antibacterial and antifungal properties. To establish antimicrobial qualities, these can be applied as creams, lotions, soaps, saps, solvent extracts, and ointments. The idea of drug delivery through the skin has long been considered promising because to its huge-surface area, extensive exposure to the lymphatic and circulatory networks, and non-invasive treatment [6].

One of the oldest and most widely used forms of medicine is herbal medicine. Recently, there has been advancement in the administration of herbal medications aimed at

efficiently treating human illnesses. According to estimates from the World Health Organization (WHO), 80% of people on the planet currently receive their primary care from herbal medicine. Every country is turning to herbal treatments as a kind of self-medication in order to obtain healthcare beyond the confines of conventional contemporary medicine [7].

Polyherbal

Polyherbal compositions are combinations of two or more plants. In Ayurveda, the pharmacological formulation is based on two principles and is used as a single drug. Polyherbal formulation involves the use of many drugs. The "Sarangdhar Samhita" of Ayurveda discusses the idea of mutualism that underlies polyherbal formulations. Despite the fact that single-plant formulations do include active phytoconstituents, they frequently contain insufficient amounts to have the intended therapeutic effects. According to scientific studies, combining plants with different levels of potency produces better outcomes than doing so alone. Synergism is created by beneficial herb-herb interactions. Pharmacokinetic or pharmacodynamic synergisms are also possible [8].

Benefits of using herbal remedies:

1. A lower frequency of adverse consequences
2. Easily available
3. Effective in managing long-term health issues
4. Economical, which increases their allure
5. Strengthens the body's inherent detoxifying mechanisms

Drawbacks of the herbal medicine system:

1. The administration of significant amounts all at once.
2. Limited stability during hepatic metabolism and in acidic environments.
3. Large molecule size inhibits absorption.
4. High need for raw materials in the manufacture of medicines.
5. The medicinal efficacy of herbal extracts may be diminished or eliminated upon the isolation and purification of particular constituents.

These disadvantages cause the active plant ingredients to have a lower bioavailability and, as a result, a lower therapeutic efficacy. Herbal preparations frequently lose the

natural synergies that are inherent in chemically related componentsAs such, a lot of effort has gone into developing cutting-edge drug delivery strategies for herbal medicines [9].

Skin

The skin serves as the body's protective barrier. More physical and chemical harm is done to the skin than any other part of the body. An inflammatory skin condition is psoriasis. The primary anomaly in psoriasis is increased epidermal proliferation, which is brought on by excessive basal layer cell division and a shortened cell cycle. Keratocyte transit through the epidermis is sped up, and the epidermal turnover time decreases from 28 days to 5 or 6 days [10].

There are three main layers to the skin:

1. The epidermis, which is about 50 and 100 micrometers thick.
2. The dermis, which is between one and two millimeters thick.
3. The 1- to 2-millimeter-thick hypodermis.

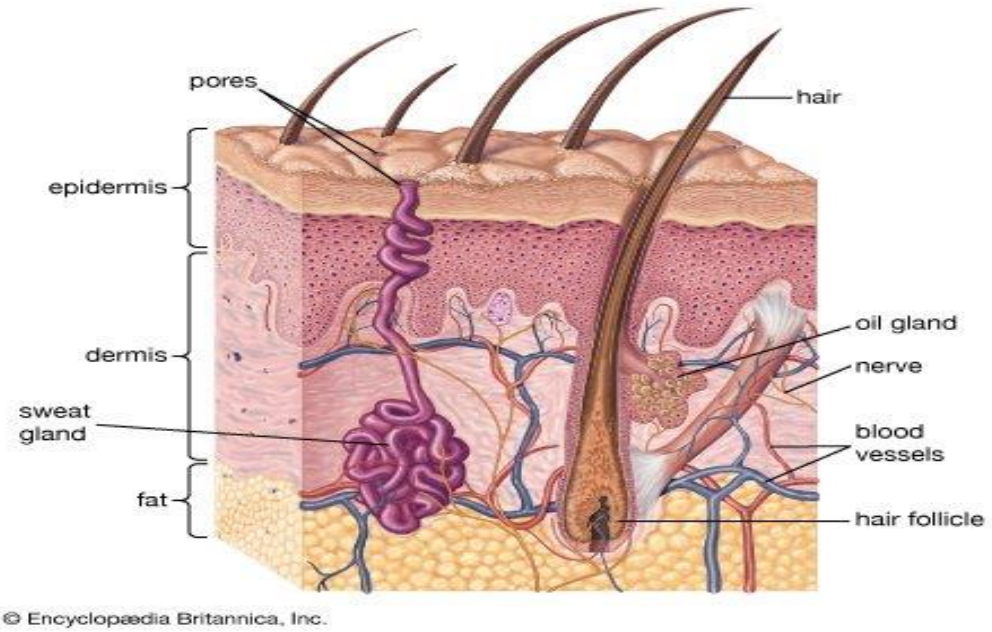

Figure 1 illustrates the anatomical layers of the cutaneous tissue

a) **The epidermis and its layers:**

The epidermis, which ranges in thickness from 0.1 to 1.4 mm, is the skin's outermost layer. The main cells in the epidermis that make keratin proteins are called keratinocytes. Other cells like Merkel, Langerhans, and Melanocyte cells are also included. Furthermore, it is estimated that during the course of a lifetime, skin will shed millions of cells every 40 minutes, culminating in around 18 kg of dead cells. We call this procedure "desquamation." It has been shown that the epidermis takes 28 to 30 days to [11]

b) Dermis

The thick network of connective tissue called the dermis provides the physical support and nourishment for the epidermis. Large organic molecules, protein fibers, and water (a mixture of the polysaccharides as complex carbohydrates and proteins) make up the field material known as connective tissue. This tissue mostly consists of glycosaminoglycans (GAGS), which are polysaccharides containing hyaluronic acid. But this tissue's matrix is known as the extracellular matrix [11].

c) Hypodermis or subcutaneous tissue:

The subcutaneous tissue, or hypodermis the purpose of this layer is to shield the dermis beneath it. Primarily composed of fat cells and connective tissue, the hypodermis shields the internal anatomy. This layer can serve as a heat-resistant barrier and trauma shield [11].

Delivery System for Topical Drugs:

In the past few decades, topical medicine delivery methods have attracted more interest for the care of different skin-related ailments. Topical distribution restricts the pharmacological effects of a medicine to the skin's surface or inside, making it an effective treatment for cutaneous conditions as well as the cutaneous manifestations of general disorders. Drug delivery methods, including material, nebuliser, medicine solid, mixture, and even treat cohesive group in the form of semi-solid formulations, are ideal choices for administering any medication topically [12].

Benefits:

1. First-pass metabolism prevention
2. Easy to use and convenient.

3. Steer clear of the dangers and side effects associated with several elements that can impact absorption, like pH variations, the presence of enzymes, the rate at which the stomach empties, etc.
4. Efficacy can be attained with a lower daily prescription dosage when drug input is continuous. Prevent drug levels from changing between and within patents [12].

Drawbacks:

1. Contact dermatitis or skin irritation may be brought on by the medication and/or excipients.
2. Some drugs have trouble getting through the skin.
3. The possibility of allergic responses.
4. Drug should only be used if it requires a very low plasma concentration to function; otherwise, the drug may be denatured by an enzyme in the skin.
5. Skin absorption of pharmaceuticals with bigger particle sizes is more challenging [13].

Skin diseases and their management:

Skin conditions are among the most prevalent wellness concerns in the world, affecting almost 900 million individuals. Common skin conditions include scabies, molluscum contagiosum/warts, eczema, impetigo, pruritus, and fungal infection.[14] Atopic dermatitis and acne vulgaris are two other skin conditions brought on by an overabundance of opportunistic bacteria that demand intensive therapy and have a major emotional toll [15]. A bacterial illness that affects the inner layers of the skin is called cellulitis.. It primarily affects the subcutaneous fat and dermis. It is a common infection of the skin and subcutaneous tissue. Teenage acne vulgaris is a common skin ailment that is thought to be brought on by an increase in male sex hormones after puberty. Sebaceous glands in the hair get blocked and infected, causing irritation and pustule formation. The most common skin infection is fungal infection that causes upper layer of the skin [16]. Surface situation were the second most common cause of nonfatal disease burden.Because skin disorders are stigmatized socially and emotionally, they have an impact on sufferers' quality of life. Skin problems are specifically impacted by a number of internal and external factors, including food, hormone imbalances, cleanliness, and climate. On the other hand, commensal bacteria

play a significant role in controlling skin defense mechanisms and immunological responses [17].

Fungi:

A complex kingdom of mostly multicellular eukaryotic creatures, fungi get resources heterotrophically and are important players in the nutrient cycling of ecosystems.

Characteristics of fungi:

The ability of fungus to exist as multicellular forms or as single-celled organisms known as yeast is one of its key properties. Similar to those found in plant and animal cells, fungal cells have nuclei and organelles. In contrast to plant cells, fungal cell walls are made of chitin, a hard material also present in the exoskeletons of insects and crustaceans, rather than cellulose.

Branched filaments known as hyphae, which are separated into compartments resembling cells by septa walls, make up multicellular fungi. A fungus's mycelium, or major body structure, is made up of a network of hyphae [18].

Types of Fungi:

- Chytridiomycota
- Zygomycota
- Glomeromycota
- Ascomycota

1. **Chytridiomycota:** Most chytrids in the phylum Chytridiomycota are asexual. They release spores that are driven by flagella and can pierce the skin of frogs to infect them.
2. **Zygomycota**: Mostly terrestrial, these fungi are known to cause problems by growing on a variety of food sources, including Rhizopus stolonifer, better known as bread mold.
3. **Glomeromycota**: Soil-dwelling fungus that work in symbiotic relationships with plants to harvest sugars while improving the availability of minerals in the soil through mycorrhizal connections. They have asexual reproduction.

4. **Ascomycota**: These pathogens can infect humans as well as plants and animals. They can cause ringworm, ergotism, and athlete's foot infections. Severe symptoms such as vomiting, seizures, hallucinations, and in severe cases, even death, can result from ergotism [18].

Fungal Infection:

A fungal infection is a term used to describe mycosis or zymosis, two medical terms for fungus-induced inflammation. Blastomyces fungal infections of the skin or mucous membranes are specifically referred to as blastomycosis. Infections by fungi are common in the natural world. These infections in humans happen when fungus get into a body component that the immune system cannot manage and spread. In addition to being present in plants, soil, water, and the air, certain fungi are naturally found in human bodies.

Fungal infections primarily come in two varieties:

1Superficial infections: These harm the skin and mucous membranes. Examples include ringworm infections, athlete's foot (tinea pedis), and tinea versicolor caused by dermatophytes, which break down the skin's keratin layer. Oral thrush, vulvovaginitis, and nail infections can all be brought on by yeast-like fungi that cause candidiasis.

Deep infections:

When they impact internal organs like the heart, brain, and lungs, they can result in diseases like pneumonia, endocarditis, and meningitis [19].

Overview of Fungal Skin Infections:

Fungal skin infections usually happen in moist places where skin surfaces come together, as under the breasts, in the vaginal area, and between toes. They are frequently brought on by yeasts such Malassezia furfur or Candida, and dermatophytes like Trichophyton, Microsporum, and Epidermophyton. These fungi typically live in the the outermost layer of skin, the yerstratum corneum. Because of their larger skinfolds, overweight people are more likely to get these infections, particularly if their skin becomes inflamed or breaks down (intertrigo). Individuals who have diabetes are also more vulnerable to fungal infections. It's interesting to note that rashes in unaffected sections of the body might occasionally result from fungal infections in one place. For

example, a fungal infection of the foot may result in a raised, itchy rash on the fingers [20].

The fungus is causing these breakouts as an allergic reaction. and are referred to as dermatophytids or id reactions. Direct contact with the diseased region is not the source of them.

Fig. 2: Fungal skin infection.

Symptoms:

These reactions might include skin alterations like redness as well as possible peeling or cracking of the skin along with itching.

Causes of fungal skin infection:

Fungal skin infections can be caused by an imbalance in the microorganisms in the body, which can happen for a number of reasons:

1. Antibiotic use
2. Changes in hormone levels
3. Unhealthy eating patterns

Diagnosis:

When a rash appears in one of the often-affected locations and is red, inflamed, or scaly, doctors may suspect a fungal infection. If a little piece of skin is scraped off and

inspected low a magnifier, or if it is located in a civilisation average where the particular flora may turn and be recognized, the diagnosis of a fungal skin infection can usually be confirmed [21].

Treatment:

1. Antifungal treatments, which can be taken orally or applied topically to the affected region (local dose like emollient, gelatin, application, mixture, or cleanser), are frequently used to treat fungal infections.
2. In addition to taking medicine, people can employ techniques like powder application or wearing open-toed shoes to keep the affected regions dry.
3. Doctors may give corticosteroids to treat specific infections by reducing inflammation and irritation [22].

Cream:

A cream is a water-based drug that is semi-solid and applied topically to the skin. It usually comprises of oil dissolved in water, either lanolin or petrolatum. Another topical medication with similar uses is an ointment. Yield is characterized as solid colloid of the water-in-oil (w/o) or oil-in-water (o/w) type that are meant to be practical externally [23]. Cream is divided into two phases: water-in-oil and oil-in-water. Cosmetics are used to improve one's beauty on the outside as well as one's health by lowering skin problems. Skincare products made from natural herbs hydrate, nourish, and moisturize the skin. The goal of the live work is to make over a flavourer cream that has multiple uses, such as reducing skin conditions like hyperpigmentation, wrinkles, and aging. Present a polyherbal cream containing medications such as papaya leaves, liquorice, and neem [23].

According to the function the cream can be classified as follows-

1. Ice creams and cleaning products.
2. Creams for disappearing and foundation.
3. Massage and night creams
4. Creams for hands and body.
5. General and all-purpose creams.

Antifungal cream:

An antifungal cream is a type of topical treatment used to either eradicate or inhibit the growth of fungi [24]

Advantages of Cream:

1. Able to lower inflammation.
2. Improves the tone of the skin.
3. Prevents acne and wrinkles.
4. Promotes blood flow and cell metabolism.
5. Easily removes with water and wipes away with ease.
6. Not as greasy as ointments.
7. Its skin is easily spread.
8. Ideal for fair, dry, and sensitive skin types.
9. Good at healing recently acquired skin lesions.

Disadvantages of Cream:

1. Ointments have greater stability than creams.
2. Compared to other semi-solid preparations, they absorb less moisture, which raises the possibility of contamination.
3. Their consistency is thinner than that of other semi-solid preparations.

Method of Preparation:

Cream formulations were semisolid substances meant to be applied topically. Different plant oils, extracts, and excipients were used to create the cream compositions. The two primary forms of cream formulations are the water in oil (W/O) and oil in water (O/W) types of colloid. The current formulation was an emulsion of the oil in water (O/W) type. The ointment preparation was divided into several classes, including cleansing, cooling, pain-relieving, antifungal, night and massage, head and body, disappearing, and shaving creams.One of the most significant medical systems that employs herbal plants and extracts for the management of a wide range of illnesses and diseased states is the Ayurvedic system

.Liquid in oil color emulsion-based ointment was developed. The emollient steric acid melted at 75 °C then add Cetyl alcohol and wait until. The oil phase (Part A) consist of herbal extract. Simultaneously prepare the water phase (Part B) by dissolving the KOH solution, Glycerine, methyl paraben, propyl paraben in water. Apply heating at a

temperature of 75 °C. Immediately after heating pour the oil phase into the trench mortar. Add the water phase in small portions into the oil color stage by continuously stirring with the help of a pestle [26].

S.NO.	INGREDIENTS	USES
1.	Clove Oil	Active Ingredient
2.	Neem Extract	Active Ingredient
3	Cinnamon oil	Active Ingredient
4	Tulsi oil	Active Ingredient
5	Oregano oil	Active Ingredient
6	Stearic Acid	Emollient
7.	Cetyl Alcohol	Emollient,co-emulsifier
8.	Potassium Hydroxide	Alkali Reagent,Emulsifier
9.	Glycerine	Moisturing Agent
10.	Propyl paraben	Preservative
11,	Methyl Paraben	Preservative
12.	Distilled Water	Vehicle

Evalution:

The following physical factors were used to further assess the herbal cream formulation: color, odor, consistency, and formulation state.

1. Color:

A visual inspection revealed the cream's color.

2. Odor:

It was discovered that cream has a distinct smell.

3. Consistency:

By manually rubbing cream on the hand, the formulation was evaluated.

4. State:

A visual inspection was conducted of the cream. The cream was only partially solid.

5. Homogeneity:

The homogeneity of the formulation was assessed by touch and appearance.

6.Removal:

Using tap water to wash the area where the cream was applied, the cream's ease of removal was assessed.

7.Irritancy Test:

The cream was applied to the dorsal surface of the left hand, marking a 1 sq. cm area, and the time was recorded. After a 24-hour period, the erythema, edema, and irritation were recorded [27].

8.Determination of pH:

The pH metre was calibrated initially, and a reading of zero was noted. The samples were placed in a beaker after being diluted with water to produce a suspension, and measurements were obtained using a calibrated electrode [28].

9.Determination of Moisturing:

Applying the prepared herbal cream to the skin's surface helped evaluate how moist it was [29].

10.Spreadability:

The cream's ability to spread was assessed by sandwiching a sample between two slides and compressing it to a consistent thickness for a predetermined amount of time using a specific weightiness. Spreadability was characterized as the quantity of clip required to dissension the two sheet glass into independent part. Better spreadability was demonstrated by a shorter separation period between the two plate glass. Spreadability was determined using the subsequent formula:

Transparency = **m × l/t**

where m is the standard weight that is over the upper slide or linked to it.

l is the glass slide's length.

t= amount of time in seconds [30].

11.Phase separation:

A suitable wide-mouth instrumentality was used to receive the factory-made cream. After 24 hours, the oil phase and aqueous phase separation were visible and were put aside for storage [31].

12.Viscosity:

Using spindle number LV-4(64), the brook field viscometer was used to activity the viscosity of the fitted-out cream at 20 rpm. The cream's viscosity ranged from 499990 to 30000cp, meaning that a small amount of shea butter can easily spread the cream [32].

13.Test for dye:

The beat is combined with the red dye. Apply a small amount of cream onto a tiny plate glass, cover it with a cover slip, then look at it nether a magnifier. The cream is of the o/w kind if the dispersed globules appear red against a backdrop that is colorless. In w/o type cream, the situation is the opposite; that is, the scattered globules seem colorless against the red background [33].

14.Patch Test:

Using a piece of cloth or a funnel, approximately 1-3 grams the most delicate spot on the skin—the area behind the ears, for example—was applied to the object to be evaluated. The cosmetic under evaluation was applied to one square meter of skin. Furthermore, control patches were employed, which belonged to a similar cosmetic brand. A day later, the patch site is investigated [34].

15.Accelerated stability testing:

After a seven-day study period, two of the most stable produced formulations were subjected to an accelerated stability test at area somatesthesia. For 20 days, they were formulations 4 and 5, maintained at 40 ºC ± 1 ºC. The formulations were examined on

the 0th, 5th, 10th, 15th, and 20th day for the various constant quantity. They were maintained at room temperature as well as increased temperature [35].

16.Antibacterial Activity:

After streaking with a loop, microorganisms were injected into nutritional broth and cultured for 12 hours at 35 oC. After making nutrient agar medium, it was put into Petri dishes and allowed to dry. Before putting the test sample disks, replace the plate top and give any surplus surface moisture three to five minutes, but no more than fifteen. Prior to this stage, disks were dipped in a sample concentration (10 mg/ml) and allowed to air dry in a laminar air flow to eliminate the solvent. Using sterile forceps, uniformly distribute the relevant discs around the agar plate's surface. Within fifteen minutes of applying the disks, invert the plate and put them in an incubator set at 35°C. After incubation for 12 hours the diameter of the disk was examined along with the zone of inhibition [36].

Conclusion

The assessment of herbal-based antifungal medications concludes by highlighting their potential as strong substitutes for traditional antifungal therapies. Numerous in vitro and in vivo investigations indicate the noteworthy antifungal capabilities of the varied bioactive components found in numerous herbs. To standardize formulations, establish ideal dosages, and evaluate long-term efficacy and safety, more study is necessary. Combining traditional wisdom with cutting-edge scientific techniques can improve our comprehension and application of herbal antifungals and open the door to novel therapeutic approaches for the management of fungal infections. It will also be essential to prioritize quality assurance and sustainable sourcing if they are to become effective medicinal agents.

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