Original Article

A Review on Oregano and Neem Leaves As Anti-fungal Agent In the treatment Of Athletes' Foot

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ABSTRACT:
Athlete's foot, also known as tinea pedis, is a common Dermatophyte illness that affects the skin on the feet. This review brings together current studies on the pathophysiology, diagnostic techniques, and management strategies for tinea pedis. Dermatophytes such as *Trichophyton rubrum*, *Trichophyton interdigitale*, and *Epidermophyton floccosum* are the primary causes of the infection. We look at the major risk factors, such as excessive sweating, weakened immunity, and environmental circumstances that promote fungal growth. The research also looks at several treatment options, including topical antifungals and systemic treatments, as well as their clinical outcomes. Preventive strategies and patient education are emphasized as important ways to reduce recurrence.

KEYWORDS: Athlete's foot, tinea pedis, Dermatophytes, diagnosis, antifungal treatment, prevention

1. INTRODUCTION:

1.1 INTRODUCTION TO ATHLETE'S FOOT:

Athlete's foot is a cutaneous fungal infection. Athlete's foot, also called tinea pedis, is the single most common Dermatophyte infection. This is one of the most prevalent superficial fungal Infections [1,2]. Tinea pedis is a common fungal infection that can lead to Dermatophyte diseases in other parts of the body. It often presents as itchy, red, and scaly skin between the toes or on the soles of the feet [3].

Dermatophytes are fungi belonging to three genera (*Microsporum*, *Epidermophyton*, and *Trichophyton*) that can cause skin disorders in people and animals. Dermatophyte fungus initially appeared after World War II, both in Europe and across the world[4].Antibiotic resistance is frequent in Dermatophytes .As a result, Dermatophyte infection is prone to recurring[16].An elderly population, close human-to-human or animal-to-human contact, sport and tourism activities, sharing of goods (socks, shoes, slippers, combs, pillows, etc.), communal living, or living in an endemic location are all considered possible risk factors for Dermatophytic infection[5].

Tinea pedis can cause Onychomycosis, a fungal nail infection more typically found in toe nails than fingernails [1]. Athlete's Foot generally occurs between the toes and soles of the feet [6]. Athlete's foot is often associated with warm, humid environments such as locker rooms and swimming pools, and it can spread through direct contact with contaminated surfaces [7].

Athlete's foot can also be referred to as ringworm of the foot, Tinea pedum, or moccasin foot [8]. It is more frequent in men aged 31-60 years than in women. The condition often affects the third, fourth, and fifth toes. The disease can cause scaling plaques and erythema on the soles, heels, and lateral aspects of one or both feet [17]. The prevention of athlete's foot is mostly concerned with keeping your feet clean and dry. Treatments for tinea pedis have changed throughout time. Initially, patients relied on plant extracts or minerals for treating tinea pedis [9].

1.2 SYMPTOMS: [12,14,19]

Athlete's foot, or tinea pedis, is a common Dermatophyte fungal illness that mostly affects the feet. The condition is characterized by white, macerated skin, fissuring, and scaling in the interdigital regions of the foot. This often happens between the third, fourth, and fifth toes. It is distinguished by a number of symptoms that vary in intensity. Understanding these symptoms is critical for timely diagnosis and treatment [10].

1. Itching and Burning Sensation: One of the most noticeable symptoms of athlete's foot is severing itching, which is frequently accompanied by a burning feeling. These symptoms are typically observed between the toes and on the soles of the feet. Itching is caused by the body's inflammatory response to the fungal infection, which may be extreme uncomfortable and irritating [11].

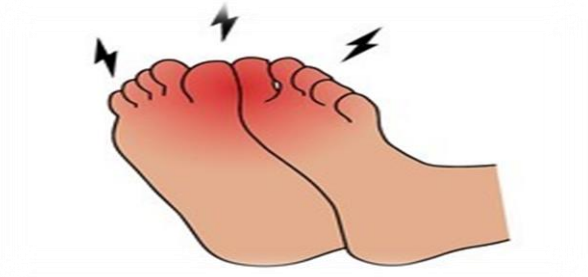

Figure 1: itching and burning between the toes

2. Redness and Inflammation: The suffering parts of the foot may get red and irritated. This erythema is commonly seen between the toes and on the soles. Inflammation happens by the fungal invasion and the body's immunological response, which is designed to treat the infection.[19]

Figure 2: Redness and Inflammation between the toes and on the soles

3. Peeling and Cracking of the Skin: Peeling and cracking of the skin is another common sign. This is most visible in the interdigital gaps (between the toes) and on the plantar surfaces (soles). The skin may seem dry and flaky, and peeling can range from mild to severe, frequently resulting in painful crakes [19].

Figure 3: Peeling and Cracking between the toes and soles

4. Blisters: Blistering is another symptom that can appear, especially in more severe instances of athlete's foot. Blisters are tiny, fluid-filled sacs that can be unpleasant and irritating. They usually form on the soles of the feet or between the toes and might eventually burst, resulting in raw, painful skin [19].

Figure 4: Blisters on the soles of the feet or between the toes

5. Odor: Infected feet may emit a distinctive, unpleasant odor. This odor is sometimes characterized as musty or nasty and is caused by a fungal infection reacting with perspiration and germs on the foot. The odor may be a major source of social discomfort and humiliation.

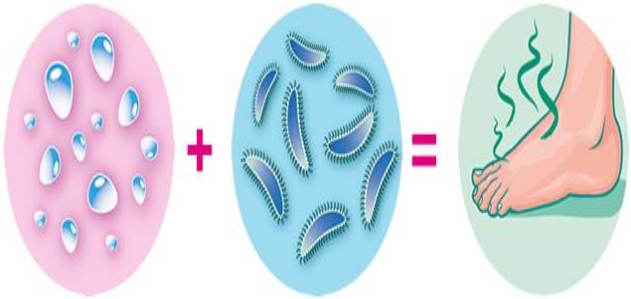

Figure 5: unpleasant odor

6. Sore and Ulcer Formation: In extreme circumstances, athlete's foot can cause sores and ulcers. These are more likely to arise if the infection is not treated or if there is too much scratching. The sores can get infected with germs, aggravating the situation and potentially leading to secondary illnesses.

7. Macerated skin: Maceration happens when the skin is exposed to high levels of moisture over a lengthy period of time. Moisture in athlete's foot is commonly caused by perspiration or the use of occlusive footwear that retains sweat. Excess moisture disturbs the natural skin barrier function, making it more susceptible to fungal invasion and subsequent disintegration [18].

Figure 6: Macerated skin

8. Additional Symptoms and Complications: In certain cases, athlete's foot can cause secondary fungal infections in other regions of the body, such as the toes (Onychomycosis) or the hands. Chronic athlete's foot can also worsen underlying dermatological problems such as eczema or psoriasis.

1.3 CAUSES:[15,20]

Dermatophytes, which are prevalent on floors, towels, and other surfaces, are the cause of athlete's foot. The fungus flourish in warm, damp environments, therefore the feet are a perfect breeding habitat [21].

Trichophyton rubrum is the most prevalent cause of athlete's foot, a fungal infection on the skin. *Trichophyton mentagrophytes* infection is more common in younger, active patients, according to research [21,22].

Athlete's foot has three clinical subtypes: interdigital, moccasin, and vesiculobullous. To comprehend these three categories, the accompanying table shows how they occur and their symptoms [23].

Type	Causes	Symptoms
Interdigital	*Trichophyton rubrum*	Symptoms include pruritic or asymptomatic erythema with macerated scales and elevated borders on the skin, generally starting in the fourth web gap.
Moccasin	*Trichophyton rubrum*	Symptoms involve erythematous plaques with hyperkeratotic scales on the heel and sole of the feet. The skin is dry and not inflamed, and the dorsum of the foot is unaffected.
vesiculobullous	*Trichophyton mentagrophytes*	Symptoms include an abrupt eruption of pruritic vesicles and bullae on the instep of the sole.

Table: 1 [Three clinical subtypes of athletes foot and its causes and symptoms][24,25]

1.4 FACTORS: [26,13]

There are certain factors which can raise the risk getting it. These include:

- wearing tight-fitting shoes that don't enable your feet to breathe
- Having a weakened immune system
- Excessive sweating
- Wearing socks for an extended time period
- Wearing synthetic/ rubber boots
- Walking barefoot in public places, such as locker room or showers
- Poor hygiene
- Existing skin condition
- More moisture

1.5 OCCURING:[27,28,29]

The physiological basis of the disease entails a succession of occurrences:

1. Fungal Invasion:

The Dermatophyte fungus, usually Trichophyton or Epidermophyton species, penetrates the skin via microscopic fissures or wounds. The fungus enters the keratinized layer of the epidermis (the skin's outermost layer).

2. Fungal Growth and Reproduction:

The fungus survives on keratin, a protein present in the skin, hair, and nails. As the fungus develops and multiplies, it creates enzymes that degrade keratin. This process produces athlete's foot characteristics such as itching, redness, scaling, and blistering.

3. Host Response:

The body's immune system responds to the fungal infection by directing white blood cells to the site. These white blood cells attempt to fight off the fungus, but the condition frequently persists. The inflammatory reaction might cause additional symptoms including pain and edema.

4. Spread of Infection:

The fungus can spread to other parts of the foot, as well as the hands and nails.
This is especially likely if the infected individual scratched the afflicted region before touching another portion of the body.

5. Chronic Infection:

Athlete's foot can sometimes develop into a chronic ailment that is difficult to cure.Poor cleanliness, wearing tight-fitting shoes, or having a weaker immune system are common causes.
Understanding the pathophysiology of athlete's foot can help healthcare practitioners establish successful therapeutic strategies and prevent the disease from spreading.

1.6 DIAGNOSIS:[30,31,32]

Tinea pedis can be diagnosed using several clinical approaches:

1. Clinical Examination:

Doctors look for characteristic symptoms such as,

- **Itching:** Often intense and localized to the affected areas.
- **Redness and Swelling:** Commonly observed on the feet and between toes.
- **Scaling and Peeling:** Particularly between the toes and on the soles.
- **Blisters and Ulcerations:** May be present in severe cases.

2. Patient History:

- **Previous Episodes:** The recurrence of symptoms may indicate a chronic or persistent infection.
- **Lifestyle Factors:** Activities that involve regular use of community baths or pools, as well as the wearing of non-breathable footwear.
- **Medical history:** Any diabetes or immune compromised diseases that may lead to fungal infections.

3. Laboratory Tests:

Microscopic Examination:

KOH Preparation: Skin scrapings from afflicted regions are treated with potassium hydroxide (KOH) and analyzed under a microscope to detect fungal hyphae and spores.

Fungal Culture:

Culture Methods: Skin samples are cultivated on specific medium (such as Sabouraud dextrose agar) to determine the causal fungus, which is often Trichophyton, Epidermophyton, or Microsporum species.

Polymerase Chain Reaction (PCR):

Molecular Diagnostics: PCR may be used for accurate fungal confirmation and is especially effective in circumstances when other tests produce unclear findings.

4. Differential Diagnosis:

Contact Dermatitis: Allergic reactions to substances that come into contact with the skin.
Psoriasis: Chronic skin condition that can present with scaling and redness.
Eczema: A condition causing inflammation, redness, and irritation of the skin.
These diagnostic tests aid in verifying the infection and distinguishing it from other conditions that present similar symptoms, such as eczema or psoriasis.

1.7 PREVENTION:[36,37,38]

To prevent the development of athlete's foot, follow beneficial foot care. This includes:

- Allow time for your feet to air out.
- Cleanse your feet with soap and water every day, giving specific attention to the area between your toes.
- Antifungal powder can be used to absorb extra moisture.
- Do not share your shoes or socks with others.
- Wear socks composed of moisture-absorbing materials.
- Wear flip-flops or slides in public restrooms, locker rooms, and swimming pools.

2. DETAILED PLANT STUDIES:

2.1 *Origanum vulgare* L.

Figure 7: Origanum vulgare L.

a) Taxonomical classification:[39,40]

Kingdom	Plantae
Class	Equisetopsida
Subclass	Magnoliidae
Superorder	Asteranae
Order:	Lamiales
Family	Lamiaceae
Genus	Origanum
Species	vulgare
Scientific name	Origanum vulgare L.

b) Vernacular Name of *Origanum vulgare* L.:

- Sanskrit name: Maruvaka
- Hindi name: Sathra, Maruga
- English name: Oregano, Wild Marjoram, Pot Marjoram
- Gujarati name: Jungli-marvo

c) Geographical Distribution:[42,43]

The regions of India, Jammu and Kashmir, Himachal Pradesh, Uttar Pradesh, and Sikkim. In the northern Himalayan area, Origanum vulgare is found in seven districts of Uttarakhand with varying geographical locations:

1. Nainital (1480–2240 m)
2. Uttar Akashi (2500–2800 m)
3. Rudrapryag (3555 m)
4. Chamoli (3260 m)
5. Bageshwar (2260 m)
6. Champawat (1840 m)
7. Almora (2220 m)

The species *Origanum vulgare* also occurs in Portugal, Spain, Afghanistan, China, Nepal, Pakistan, Denmark, and Europe, including sections of Russia.

d) Botanical Description:[56]

TREE: The plant Origanum vulgare is sometimes known as "common oregano" or "wild marjoram," is a compact and bushy perennial plant. It normally grows to a height of 20-80 cm(1-3feet). Plant Characteristics The stems are rectangular, and the leaves are tiny, oval in shape and kind of hairy *Origanum vulgare* blooms form thick, spherical heads at the top of the stalks and range in color from white to pink or purple.

LEAVES: Oregano leaves are oblong or elliptical in form and grow opposite one another on the stalk. They have a smooth, somewhat hairy texture and a deep green hue. The leaves are typically 2–4 cm (0.8–1.6 inches) long and 1–2 cm (0.4–0.8 inches) broad. Photosynthesis, the process by which plants convert sunlight into energy, takes place mostly on leaves. They also contain essential oils, which lend oregano its characteristic scent and flavor.

STEMS: Oregano stems have a triangular or angular cross-section and can become woody at the bottom as the plant ages. They are normally green, but can become brown as they mature. They're more fibrous and less fragrant than the leaves.

FLOWERS: Oregano flowers are short and tubular, generally pink, purple, or white, and form dense, spherical inflorescences called as terminal or axillary clusters. Each flower features a tubular corolla with five lobes. Flowers are plants' the reproductive organs. They attract pollinators, which aid in the process of fertilization and seed formation.

SEED: Oregano contains little, brown, dry seeds that are typically less than 1 mm in diameter. The seeds are found in tiny, rigid fruit capsules. They can be spread by wind, animals, or human action, resulting in the emergence of new plants. Oregano seeds are mostly utilized for reproduction.

e) Phytochemical profile:[57,58]

Carvacrol, an essential ingredient in oregano oil, has received much research. Carvacrol, the principal active ingredient, contributes to the oil's antibacterial capabilities. It effectively inhibits

bacteria, fungus, and Parasites. Carvacrol is a beneficial component of oregano oil due to its anti-inflammatory, antioxidant, and anticancer qualities. Thymol is another important ingredient discovered in oregano oil. Thymol, Carvacrol, has strong antibacterial action against a variety of pathogens. Along with Thymol and Carvacrol. Oregano oil contains further phenolic compounds, which improve its health benefits.
The compounds include p-cymene, Terpene, and γ-terpene. The combination of these chemical constituents in oregano oil gives it its unique therapeutic potential.

Plant parts	Chemical Constitution
Leaves	Essential Oils: Carvacrol, Thymol, Linalool. Phenolic Compounds
Steams	Carvacrol, Thymol, Rosmarinic Acid
Seeds	Carvacrol and thymol, Minor amounts of phenolic acids and flavonoids
Flowers	Essential Oils, Minor amounts of phenolic acids and flavonoids

f) Pharmacological Action:[41,55]

Antibacterial Activities:

Oregano has traditionally been used in herbal therapies to treat bacterial infections. Oregano oil is known for its strong antibacterial abilities, resulting in an effective natural therapy against many pathogens. The oil's antibacterial properties are linked to Carvacrol and Thymol, as well as other phenolic chemicals. [39]Oregano oil's antibacterial qualities originate from its ability to destroy microbial cell membranes. Carvacrol and Thymol may disrupt the lipid bilayer of bacterial and fungal cells, causing membrane instability. This disturbance leads to leaking of intracellular contents and ultimately microbial death [40].

Anti-inflammatory and analgesic effects:

The oil's active components, such as Carvacrol and thymol, and other chemicals, are responsible for these benefits. Oregano oil reduces inflammation by blocking pro-inflammatory chemicals and regulating inflammatory pathways. It efficiently reduces the release of cytokines and prostaglandins, which are major inflammatory mediators. Oregano oil reduces inflammation and promotes a healthy immune response by lowering the synthesis of these chemicals. Oregano oil has analgesic qualities that help with pain alleviation. Oregano oil's active components can reduce pain perception by interacting with pain receptors.

Anti-Cancer Activities:

A certain amount of the components in oregano can have anticancer effects. Extracts may protect cells from DNA damage caused by oxidative damage, sunlight, and mitochondria (proteins that trigger cell division). The study shows that Carvacrol and thymol can inhibit melanoma cell growth and spread in skin cancer.

Anti-diabetic Activities:

Components found in oregano could help treat type 2 diabetes. Enhance insulin resistance. Manage genetic activity for fat and carbohydrate metabolic processes.
Repair liver and renal tissues.

Antiviral Activities:

Oregano and its elements may defend in opposition to viruses as well as bacteria. Study demonstrates that the two chemicals in oregano have antiviral properties. They heal runny noses, sore throats, and battle colds and coughs. These two chemicals effectively inhibit 90% of the herpes simplex virus in approximately one hour.

Enhancing gastrointestinal:
Oregano has full of fiber. Fiber is a known component that improves digestion. Its advantages include adding weight to stools and stimulating peristaltic activity, which helps move food through the digestive tract and eliminate waste efficiently. Oregano oil can help cure digestive issues such as bloating, bowel dysfunction, and indigestion.

2.2 *Azadirachta indica:*

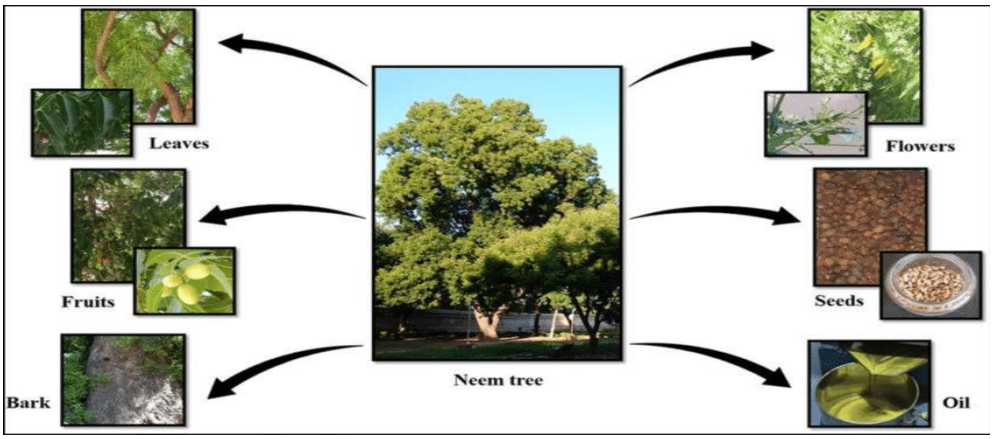

Figure 8: Azadirachta indica

a) Taxonomical classification:[44]

Kingdom	Plantae
Class	Magnoliopsida
Order	Sapindales
Family	Meliaceae
Genus	Azadirachta
Species	indica
Scientific name	Azadirachta indica

b) Vernacular Name of *Azadirachta indica:*[51]
- Sanskrit name: Picumarda, Arista, Nimba, Nimbah
- Hindi name: Nim and Nimb
- English name: Margosa tree, Neem tree, Indian lily
- Gujarati name: Danujhada, Limbado, Limbra, Limdo

c) Geographical Distribution:[45]
A. indica has been cultivated across Asia, including Bangladesh, Cambodia, India, Indonesia, Iran, Malaysia, Myanmar, Nepal, Pakistan, Sri Lanka, Thailand, and Vietnam. It has lately been introduced into Saudi Arabia, northern Yemen, and China's Hainan Island (NRC, 1992). In India, estimates range from 14 million (Ketkar, 1976) to 16-18 (Hegde, 1996), 15-25 (Rembold, 1996), and 15-20 million trees. Uttar Pradesh appears to have the most trees (53.4%), followed by Tamil Nadu (17.0%), Karnataka (5.3%), Madhya Pradesh (4.9%), Maharashtra (4.7%), Andhra Pradesh (4.4%), and Gujarat (4.2%). Neem is a common tree in Pakistan's arid regions.

d) Botanical Description:[52]

TREE: The Neem tree (*Azadirachta indica*) is a fast growing (up to twenty feet in three years) tropical evergreen related to mahogany. It will grow where rainfall is as little as 18 inches per year

and thrives in areas that experience extreme heat of up to 120 0F. They are reported to live for up to 200 years.

LEAVES: Compound, alternate, rachis 15-25 cm long, 0.1 cm thick; leaflets with oblique base, opposite, Exstipulate, lanceolate, acute, serrate, 7-8.5 cm long and 1.0-1.7 cm wide, slightly yellowish-green; odour, indistinct; taste, bitter.

STEM BARK: Bark varies much in thickness according to age and parts of tree from where it is taken; external surface rough, fissured and rusty-grey; laminated inner surface yellowish and foliaceous, fracture, fibrous; odour, characteristic; taste, bitter.

FLOWER, FRUITS AND SEEDS: The tree is often covered in delicate flowers in the early summer. The flowers (white and fragrant) are arranged axillary, normally more-or-less drooping panicles which are up to 25 cm long. It has a semi-sweet, olive-sized fruit. The seed inside is rich in oil with tremendous medicinal and botanical properties. The oil is easily obtained by pressing the kernels in a juicer. It generally begins bearing fruit at three to five years, and can produce up to 110 lbs. of fruit annually when mature.

e) Phytochemical profile:[46,47]

Neem has been a popular medicinal plant in India and adjacent countries for over 2000 years due to its diverse biological properties. Since ancient times, all parts of the tree have been employed as conventional therapies to treat numerous human illnesses.

Approximately 135 compounds have been extracted from various regions of Neem, with several studies published on their chemistry and structural variety.

The compounds are classified into two types: isoprenoids (diterpenoids and triterpenoids), which include protomeliacins, limonoids, azadirone, gedunin, vilasinin, and C-secomeliacins like Nimbin, salanin, and Azadirachtin, and non-isoprenoids, which include proteins (amino acids), carbohydrates (polysaccharides), sulfurous compounds, polyphenolics (flavonoids and glycosides), and dihydrochal. Neem oil fatty acids typically consist of linoleic acid (6-16%), oleic acid (25-54%), hexadecanoic acid (16-33%), octadecanoic acid (9-24%), alphaliolenic acid, and 9-hexadecenoic acid.

Plant parts	**Chemical Constitution**
Leaves[50]	Azadirachtin, Nimbin, Nimbolide, Quercetin, β-Sitosterol
Seeds[48]	Azadirachtin, NimbinFattyAcid, Glycosides
Bark[49]	Tannins**,** Saponins**,** Flavonoids
Flowers	Essential Oils, Flavonoids, Nimbin
Roots	Triterpenes, Alkaloids, Phenolic Compounds
Fruits	Azadirachtin, Fatty Acids, Nimbin

f) Pharmacological Action: [54]

Anti-fungal activities: [53]

Neem has wide-spectrum antibacterial action due to components such Azadirachtin, Nimbin, and Quercetin. These chemicals prevent microbial cell wall production, impair membrane permeability, and impede nucleic acid synthesis. Neem extracts have been demonstrated efficient against a wide range of diseases, including bacteria, fungus, and viruses. Neem oil, in particular, has demonstrated strong action against dermatophytes and other skin infections.

Anti-inflammatory Activity:

Neem chemicals, including Nimbin and Azadirachtin, prevent the generation of pro-inflammatory cytokines including TNF-α and IL-6. They also inhibit the action of cyclooxygenase (COX)

enzymes, which are involved in the production of prostaglandins that cause inflammation.Neem extracts and isolated chemicals have been shown in animal models and in vitro studies to alleviate the symptoms of inflammatory disorders. For example, Neem leaf extract has been demonstrated to significantly reduce paw edema in rats, demonstrating anti-inflammatory activity.

Anticancer Activity:
Neem chemicals like Nimbolide and Azadirachtin cause apoptosis (programmed cell death) in cancer cells via a variety of routes, including caspase activation and modification of the Bcl-2 protein family. They also prevent angiogenesis (the growth of new blood vessels) and cancer cell proliferation.Preclinical research has demonstrated that Neem extracts and compounds can decrease tumor development in a variety of cancer types, including breast, prostate, and colon malignancies. Clinical trials are still in early phases, but the findings are encouraging.

Antioxidant Activity:
Neem seeds and leaves include antioxidants such Quercetin and β-sitosterol, which aid in neutralizing free radicals and minimize oxidative stress. These antioxidants also boost the activity of naturally occurring antioxidant enzymes such as superoxide dismutase (SOD) and catalase.
In both animal and cellular models, Neem extracts have been shown to prevent oxidative damage. This activity can help avoid illnesses caused by oxidative stress, such as cardiovascular disease and neurological disorders.

Hypoglycemic Activity:
Neem chemicals can improve insulin sensitivity and lower blood glucose levels by increasing glucose absorption in cells and boosting pancreatic β-cell functionality.
Neem leaf extracts and Neem oil have been shown in studies to reduce blood sugar levels in diabetic animals and humans. This impact is caused in part by the presence of chemicals that regulate glucose metabolism.

Immune System Modulation:
Neem chemicals like Nimbin and Azadirachtin influence the immune system by increasing the activity of immune cells including macrophages and T lymphocytes and influencing cytokine synthesis. Neem has been demonstrated in animal studies to increase immune responses and improve infection resistance. It also aids in the treatment of autoimmune disorders by modulating immune cell activity.

Conclusion:
These two factors oregano and Neem leaves have strong antifungal qualities, making them useful for treating athlete's foot. Oregano's active components, Carvacrol and thymol, break fungal cell membranes and suppress fungal development. Neem leaves include Azadirachtin and Nimbin, which inhibit fungal metabolism and cell wall formation. These activities help to increase their efficacy in treating the fungal infection that causes athlete's foot. Oregano and Neem's medicinal properties are ascribed to phytochemical components. The Carvacrol and thymol in oregano affect membrane permeability and block fungal enzymes, whereas the Azadirachtin in Neem inhibits fungal cell activities. Both herbs treat symptoms by addressing the underlying causes of the fungal illness.

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