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Review on Griseofulvin as Antifungal agent

[1]Mr.Kothare Nilesh,[2]Mrs.Pawar Madhuri,[3]Miss.Khandagale Shital

4Mr. Kambale Hemant 5 Mr. Waghmare Santosh

[1]Student,[2]Student,[3] Student
[1]Pharmacology,
[1]Loknete Dada patil Farate College of Pharmacy,

Abstract :
In India, dermatophyte infections have recently undergone unheard-of alterations.The effectiveness of the few primary oral antifungal medicines is not compared in any clinical studies. Dermatophytosis is treated with griseofulvin, a fungistatic antifungal drug.
The dermatophytes that are frequently recognised include fungal species including Trichophyton mentagrophytes, Fusarium oxysporum, Microsporumgypseum, and Epidermophyton floccosum.may improve vascular relaxation, enhance ACE2 activity, and raise capillary blood flow.Additionally, a molecular docking analysis revealed that the receptor-binding domain (RBD) of the spike protein may prevent SARS-CoV-2 entry and viral replication when used in combination with variants of griseofulvin and its major protease, RNA-dependent RNA polymerase (RdRp), and other proteins

Keywords - drug repurposing, dermatophytic fungal, gsf gene cluster, polyketide molecule, SARS-CoV-2, spindle microtubule, and griseofulvinderivatives

I. INTRODUCTION

The fungal kingdom includes a huge diversity of taxa, and each genus has a distinct morphology, life cycle, and ecological niche. Genuine variety within a Kingdom On the other hand, fungi are a little-known fact. (1).The estimated 1.5 million species that make up this kingdom have just 5% of them been formally categorised. Some fungus are parasites on other fungi, plants, animals, people, and even other fungi.(2)

Fungi are a class of heterotrophic creatures that historically have been compared to plants but lack chlorophyll. Although some are non-filamentous and unicellular, they are typically filamentous and multicellular. An organism known as a fungus is made up of filaments called hyphae (sing. hypha).(3)

Types of Fungus Organisms (5)

Fungi can be divided into four groups.

1. fungi:NeoformansCrypyococcus

2. Fungi that resemble yeast: Since they primarily spread as yeast and secondarily as filaments (hyphae), these fungi result in oral thrush. vaginal systemic candidiasis. An illustration of a specific kind of fungus is Candida albicans.

3. Moulds with two distinct morphologies. they expanded as yeast or filaments, causing histoplasmosis Coccidiomycosis Blastomycoses Sporotrichosis. One of the fungal species in this group is Histoplasma capsulatum. immitiscoccidioidesDeramtides Blastomyces

4. Moulds: For filamentous fungi, spores are the means of reproduction. This type of fungus led to infections of the skin and nails. Trichophyton sp., Microsporum sp., and Epidermophyton sp. are a few examples.

Classification of fungus infections (9)

Mycoses is a fungus disease that can affect animals, including humans. Mycoses are divided into groups based on the first tissue levels they invaded. The clinical nomenclatures for the mycoses have been devised based on the.

1. Classification Based on Site

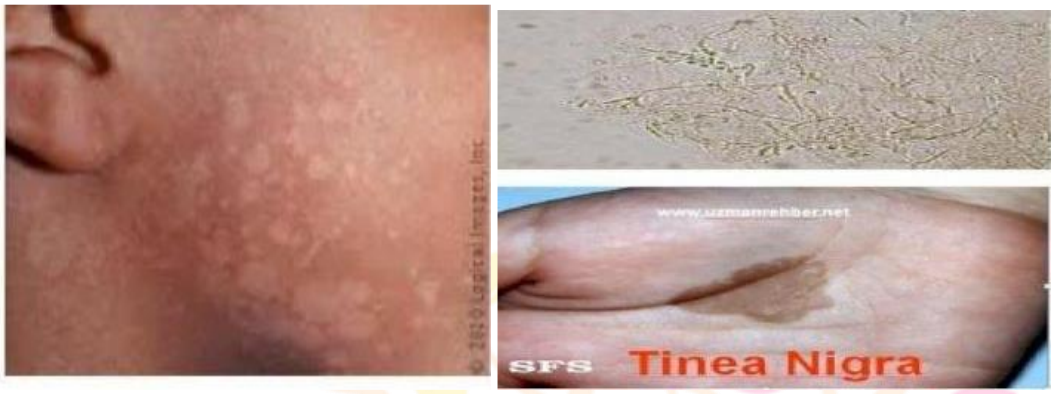
2. Classification Based On Acquisition Route

3. Distinguishing Groups Based on Virulence

1. Classification Based on Site

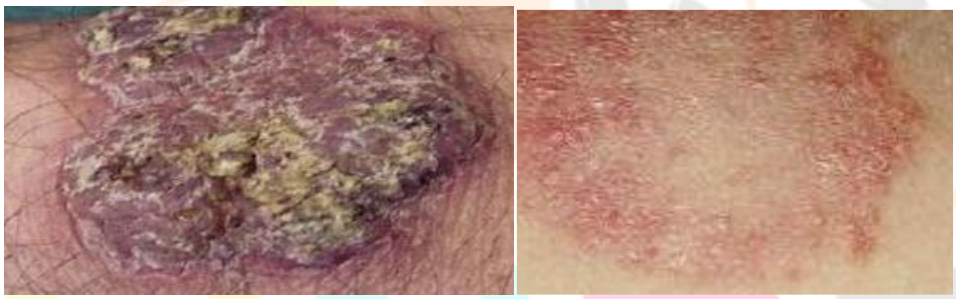
1.Extracellular mycoses

Only the outermost layers of the skin and hair are susceptible to superficial mycoses. One example of a fungus infection that regularly affects young people's skin is tinea versicolor, which usually affects the chest, back, upper arms, and legs. The etiology of tinea versicolor is a fungus that lives in the skin of some people.(12) Frequently, the face is unaffected. Blotches caused by this fungus are lighter or reddish brown in colour than the surrounding skin. This fungus comes in two varieties, and one of them causes observable patches. Immunological or hormonal issues, as well as high humidity levels, may amplify the fungus's presence. However, nearly everyone who suffers from this exceedingly prevalent condition is in good health.(15)



2.Cutaneous mycoses:

These invasive diseases of the hair and nails that pierce further into the epidermis are also referred to as cutaneous mycoses. These illnesses only affect the keratinized layers of the skin, hair, and nails. These illnesses are brought on by dermatophytes, often known as ringworm, dermatophytosis, or tinea.(18)



2. Classification Based On Acquisition Route

Normal hosts can become infected by primary infections. Opportunistic infections cause sickness in anyone whose host defenses mechanisms are inadequate.

Classification Based on the Chemical Structure, Action, and Source (22)

The antifungal agents can be divided into the following classes, based on their chemical structure, mechanism of action, and source:

I. Antibiotics: Amphotericin B, Nystatin, Griseofulvin

II. Azoles (imidazole, triazole derivates)

Triazoles—Fluconazole, Itraconzole, Terconazole

Imidazoles—Clotrimazole, Ketoconazole, Miconazole, Bifonazole, Butoconazole, and Zinoconazole

III. Fluorinated pyrimidines: Flucytosine

IV. Chitin synthetase inhibitors: Nikomycin Z

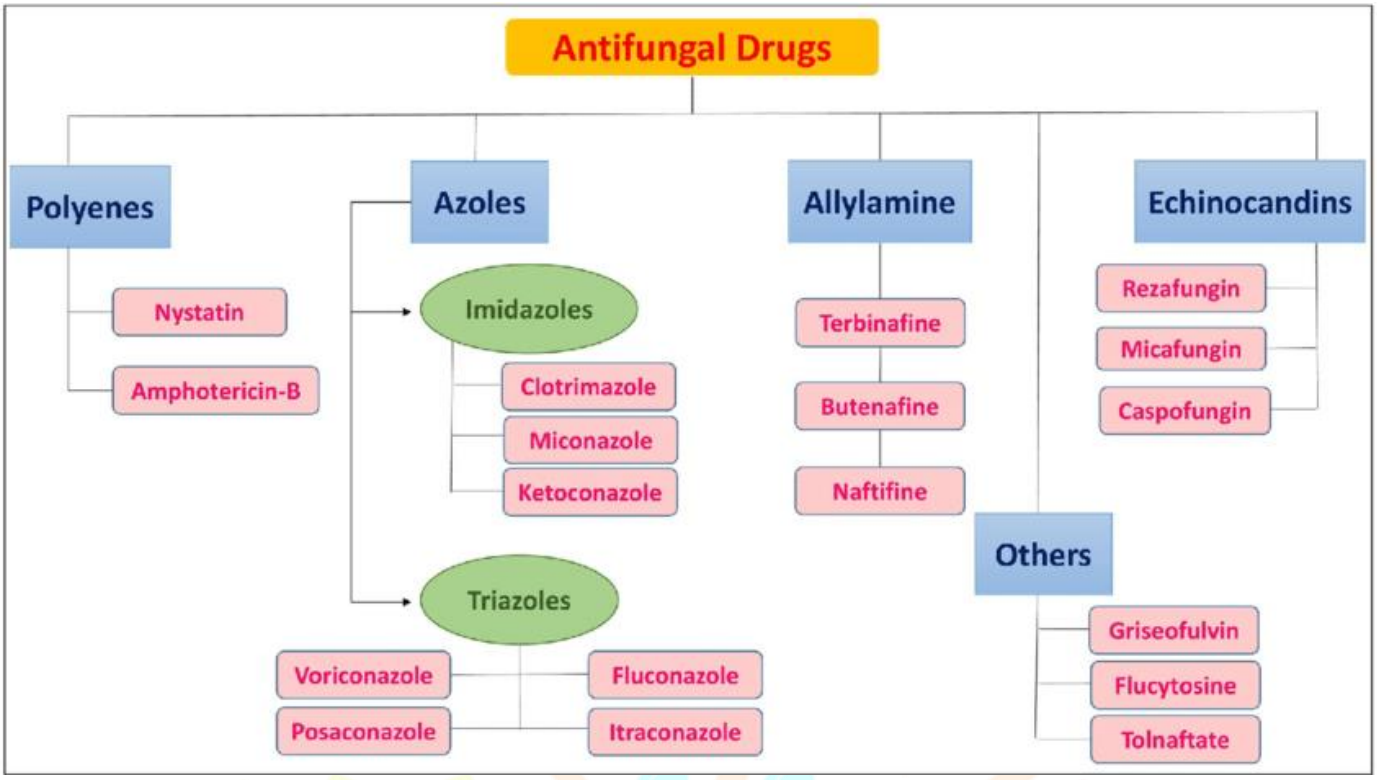
V. Peptides/proteins: Cispentacin

VI. Miscellaneous: Ciclopirox, Tolnaftate, Naftifine, and Terbinafine

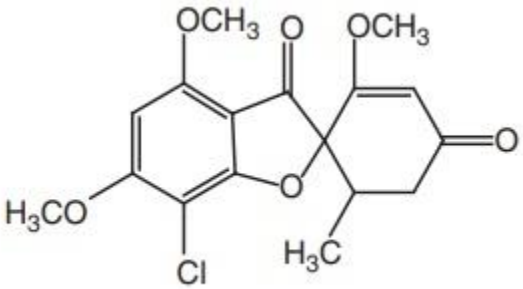
Classification Based on the Route of Administration

I. Drugs for subcutaneous and systemic mycoses: Amphotericin B, Fluconazole, Flucytosine, Itraconazole, Ketoconazole.

II. Drugs for superficial mycoses: Clotrimazole, Econazole



Griseofulvin (Fulvicin)(16)



Griseofulvin, a medication that inhibits the growth of fungi, disrupts the mitotic spindle by interacting with polymerized microtubules.

One of the first antibiotics made from Penicillium griseofulvum was this one. The clinical utility in dermatophytosis was only proven about 1960, however, due to the lack of antibacterial action, which attracted little attention.(20)

The majority of dermatophytes, such as Epidermophyton, Trichophyton, Microsporum, etc., are responsive to griseofulvin; however, Candida and other fungi that cause deep mycosis are not. Additionally, bacteria are unfeeling.(21) It is actively concentrated by dermatophytes, which is probably what causes its selective toxicity. In vitro resistance induction is possible, and this results in a reduction in mental acuity. Resistance seldom develops with clinical use, though.(18)

Fungal hyphae that are multinucleated and stunted are the result of griseofulvin's interference with mitosis. Additionally, it results in unusual metaphase configurations. Although it does not cause metaphase arrest like the traditional mitotic inhibitors (colchicine, vinca alkaloids), the daughter nuclei either fail to migrate apart or move very little.(21) It binds to polymerized

microtubules and somehow throws them off balance rather than preventing the polymerization of tubulin, a microtubular protein that pulls the chromosomes apart.

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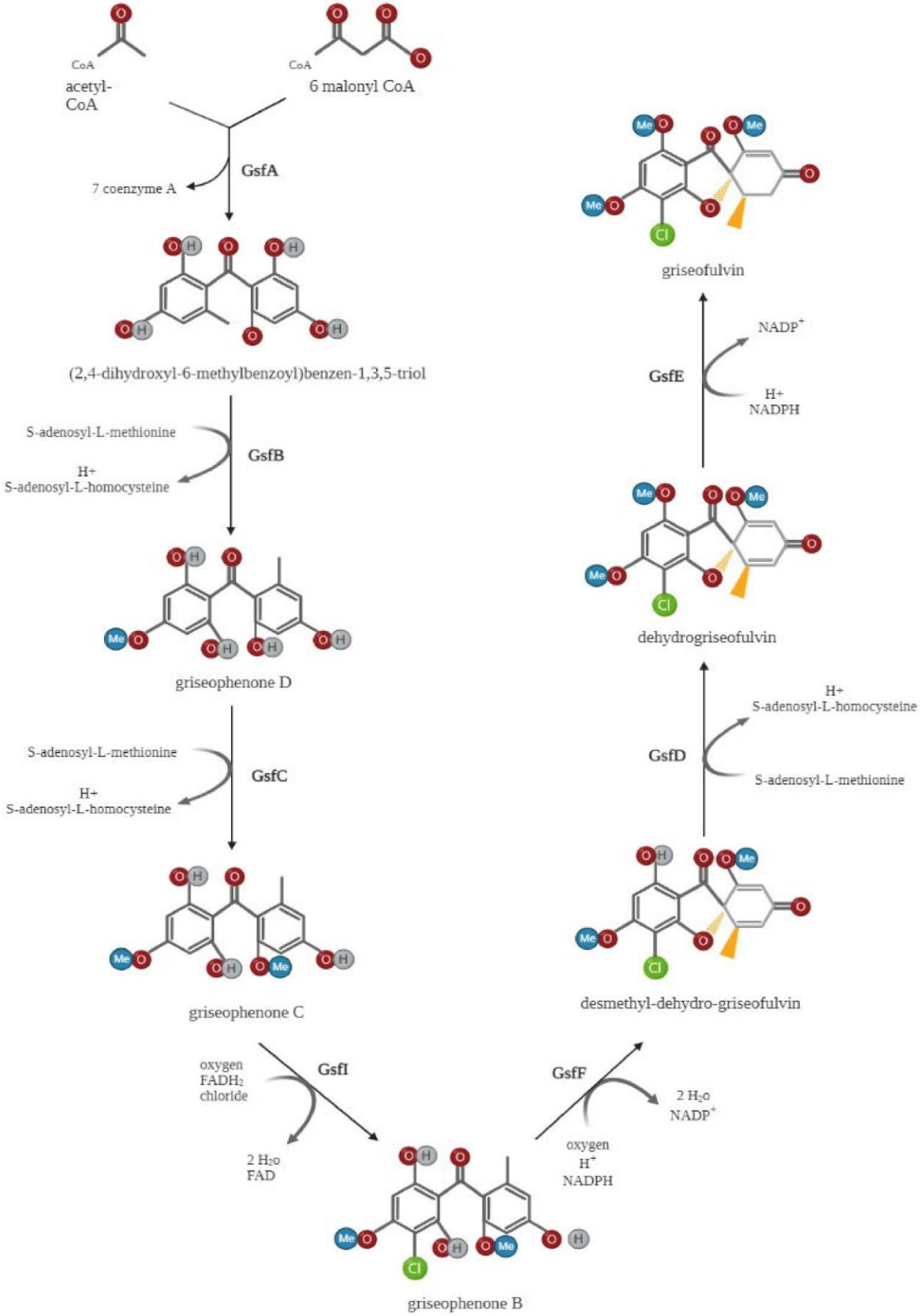
Properties and applications:

Griseofulvin is a microfine white or yellowish-white powder that is essentially insoluble in water, readily soluble in tetrachloroethane and dimethylformamide, and just marginally soluble in ethanol and methanol. utilised as an antifungal.(32)

Synthesis



Interactions between Cellular Components and Their Known Effects Alternatively, griseofulvin is delivered into the dermatophyte by energy-dependent transport pathways.(25)

Once that is done, it binds to the fungal microtubules and stops them from activating, thereby stopping mitosis. Grifofulvin suppresses spindle microtubule (MT) dynamics, which is the main way it prevents mitosis at metaphase.

It does this by acting directly at the plus end to increase stability and decrease the shortening rate at the MT plus ends.(27) According to docking studies, griseofulvin can bind to tubulin at two different locations, one of which is at the betatubulin H6-H7 hoop and overlaps with Taxol, a drug used to treat cancer, and the other is at the tubulin interface .

According to research, griseofulvin at concentrations of 30 to 60(28)

Griseofulvin

It is true that because griseofulvin is typically administered orally, low intestinal absorption could result in treatment failure. an investigation using spectrophotofluorometry, griseofulvin absorption.The effectiveness of a high-fat diet drastically rises.

The oral bioavailability of liposomes containing griseofulvin can really be greatly increased due to the high drug encapsulation efficiency and tiny liposome size.(30)

The duodenum and stomach both break down griseofulvin the slowest, while colon absorption is hardly noticeable.

The amount of griseofulvin was also observed to be larger in the lung after intravenous delivery than it was in the liver after oral treatment.(24)

Additionally, griseofulvin can be released by sweat glands and can be seen in the keratinized layer to inhibit four hours after a single dose is administered.

Pharmacodynamics

A mycotoxic metabolic byproduct of Penicillium spp. is griseofulvin. It has been in use for more than 40 years and was the first oral medication for the treatment of dermatophytoses. With in vitro action against several species of Microsporum Epidermophyton and Trichophyton, griseofulvin is fungistatic.(22)

Both bacteria and other genera of fungi are unaffected by it. Grifofulvin is deposited in the keratin precursor cells after oral dosing and has a stronger affinity for sick tissue.

The medication is firmly attached to the new keratin, increasing its resistance to fungus invasions. (28)The keratin-Griseofulvin combination alters fungal mitosis when it attaches to microtubules found in fungi (tubulin) at the skin's site of action.

Pharmacokinetics

Due of griseofulvin's extremely low water solubility, its absorption from the gut occurs rather erratically.

By micro-fining the drug's particles and eating it with lipids, absorption is improved; today, ultra-microfine particle preparations are available, and absorption is still better.

In the keratin-producing cells of the skin, hair, and nails, griseofulvin is deposited; it is particularly concentrated and maintained in cells with tinea infection.

The newly generated keratin is not infected by the fungus because it is fungistatic rather than cidal; however, the fungus survives in already infected keratin until it is shed off.

Therefore, the place of infection, the thickness of the infected keratin, and its turnover rate all affect how long the treatment will take.

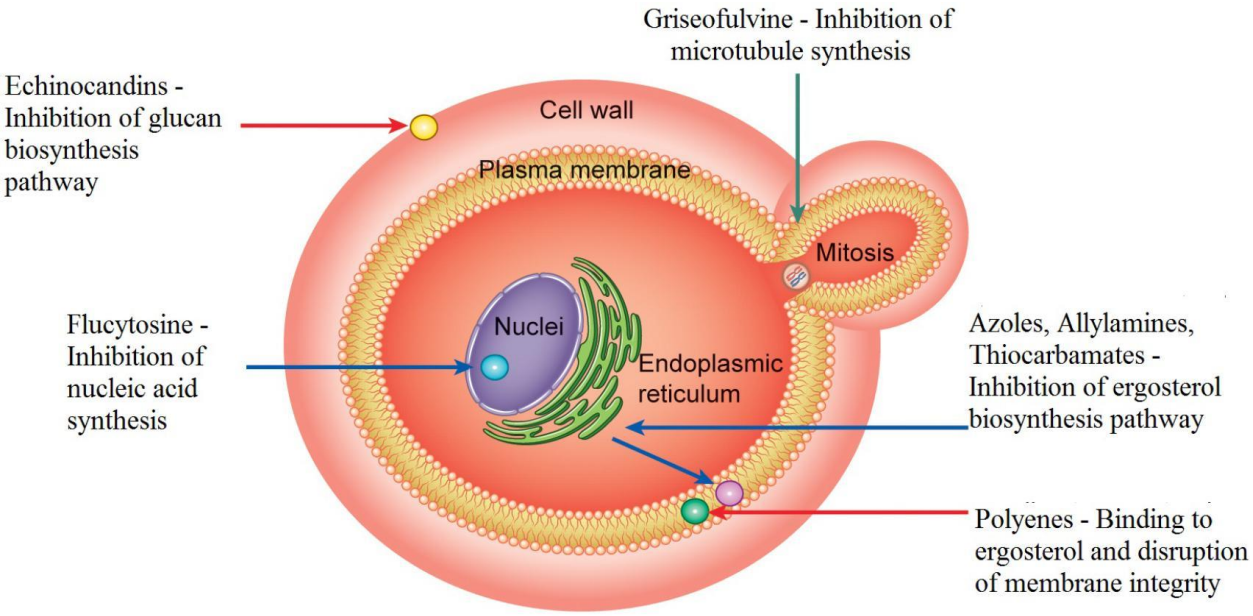
Mostly by methylation, griseofulvin is metabolised and eliminated in considerable amounts.

Griseofulvin's Physiochemical Characteristics

A secondary polyketide metabolite produced by fungi, griseofulvin is poorly soluble in water but is soluble in ethanol and methanol [6]. The capacity of griseofulvin to withstand heat stress and continue to function at a high temperature of 121 °C without losing functional characteristics is one noteworthy characteristic [4]. Because these characteristics have an impact on absorption, transit, excretion, and degradation, it is crucial to understand how they apply to medicine.

Mechanism of Action

Although gliseofulvin is fungistatic, it is unclear how exactly it prevents the growth of dermatophytes. It is believed to prevent nuclear acid production and fungal cell mitosis. Additionally, it binds to alpha and beta tubulin and interferes with the activity of spindle and cytoplasmic microtubules. When it reaches the fungal site of action, it first attaches to keratin in human cells before binding to fungal microtubes to change the mitotic process in fungi.(10,11)



Medical Applications

Since its approval by the U.S. Food and Drug Administration in 1962, griseofulvin has gained a place on the World Health Organization's list of essential medicines and belongs to the group of medications known as antifungal agents. This medication is used to treat a variety of skin diseases like ringworm, athletes foot, and other nail and skin fungus that don't react to creams or lotions, such as those that cause athletes' foot

By inhibiting fungal cells from splitting and proliferating, griseofulvin interferes with the process of fungal mitosis, ultimately causing the infection to disappear. Symptoms like itching, red, peeling, scaly skin, and discoloured nails will go away once the infections and fungus are removed.

The first documented application of griseofulvin in medicine was to treat ringworm infections in guinea pigs brought on by Microsporum canis . Further research found that it had an impact on Trichophyton and Epidermophyton in addition to the genus Microsporum . It is still in use today and is regarded as one of the most often used treatments for dermatophytes fungal infections in people and animals. Griseofulvin was given FDA approval in 1959.

Inflammatory Conditions That Aren't Fungal

Additional research revealed griseofulvin's efficacy in treating non-fungal skin inflammation conditions such lichen planus [8] and chronic purpuric dermatosis [5,9], indicating that it may potentially possess anti-inflammatory and immunomodulatory potential. The shoulder-hand syndrome [6,30], as well as a few other inflammatory, rheumatic disorders such posttraumatic reflex dystrophies and scapulohumeral periarthritis [11], have been successfully treated with griseofulvin, according to earlier research.

Conclusions

Practical clinical knowledge and uses have been well established in the literature since the discovery of the FDA-approved medication griseofulvin. Nevertheless, computational and bioinformatics analysis have sparked a revolution in scientific discovery, where the development of novel uses for medicines that have previously received approval has attracted a lot of attention in recent years. However, its potential to treat cancer, hepatitis C, and SARS-CoV-2 have been anticipated in principle and are currently the subject of experimental research. Griseofulvin has been shown to be a safe therapeutic treatment in treating and reducing dermatophyte infections. Our molecular docking investigation revealed that griseofulvin has the potential to bind to intermediate filament proteins in human, rat, and mouse keratin, which explains why rodents experience more severe liver issues than humans despite the fact that its interaction with spindle microtubules is widely known.

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