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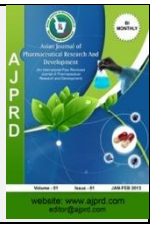

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Review Article

Drug Discovery of Griseofulvin : A Review

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A B S T R A C T

Background: Griseofulvin is a fungistatic antifungal drug used to treat dermatophytosis. Dermatophytes that are often found include *Trichophyton rubrum, Trichophyton mentagrophytes, Microsporum canis, Microsporum gypseum, Epidermophyton floccosum.*

Purpose: This review article aims to discuss the drug discovery review of griseofulvin.

Data Source: The author created this review article using the literature study method relevant to the purpose of the review. Sources of information from national journals and international journals that are accessed through online sites such as Google Scholar, Research Gate, Science Direct, Springer Link, and NCBI. Key words were used to find the journals, namely griseofulvin, dermatophyte, toxicity.

Conclusion: The conclusion of this article is that griseofulvin is used as an antifungal drug containing chlorine from *Penicillium griseofulvum* isolated against mycelium fungus. This drug is non-toxic, so it is effective and safe to fight various types of fungal infections of the skin such as tinea capitis and remains the drug of choice for dermatophytes.

Keywords: Griseofulvin, Dermatophyte, Toxicity**.**

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INTRODUCTION

Researchers in Indonesia and abroad have discovered a variety of new drugs. The discovery of new drugs is carried out to produce products that are useful in the world of health and also benefit the community. Traditionally, drug discovery relied on natural products as the main source of new drug entities, then shifted towards chemical-based *high-throughput* synthesis with combinatorial development[1]. Preclinical trials and clinical trials are important stages in drug discovery and development, which must meet various aspects such as sources of raw materials, drug targets, research and costs. A drug discovery program is initiated because there is a disease or clinical condition with an inappropriate medical product and a clinical need that cannot be met.

Common diseases that are often a complaint for the health of the body are skin infections caused by fungi. To overcome this, research on fungi has been carried out. The results showed that there are classes of drugs that inhibit or kill fungi, namely the antifungal group. Antifungal is an antifungal used to treat infections caused by fungi. Antifungal is the activity of a compound that can inhibit or kill certain fungi, so this antifungal is expected to cure a disease caused by a fungal infection[2]. Some discoveries of antifungal drugs that are usually used by the general public include griseofulvin.

Griseofulvin is an antifungal drug known as a fungistatic and not a fungicide. The antifungal drug griseofulvin has been used for a long time to treat dermatophyte infections. Dermatophytes are a group of fungi that can digest keratin such as the stratum corneum of the skin (epidermis), hair, nails and cause dermatophytosis[3]. Several species of fungi that cause dermatophytosis that commonly infect Indonesian people are *Trichophyton rubrum, Trichophyton mentagrophytes, Microsporum canis, Microsporum gypseum, and Epidermophyton floccosum*[3]. Griseofulvin is

considered to be a very effective drug against various types of these fungi.

It is necessary to know how the steps involved in identifying and developing griseofulvin drugs include testing the drug's action, followed by a determination that explains the process of the compound based on its chemical structure (in silico), then continued with preclinical testing (in vitro and in vivo) and clinical trials to see the reaction medicine to the human body. If the testing stage has been passed, then the registration stage is the final stage to obtain a distribution permit from the authorized party in order to strengthen the drug safety statement[4].

METHODS AND DATA COLLECTION

The author created this review article using the literature study method relevant to the purpose of the review. Sources of information from national journals and international journals that are accessed through online sites such as Google Scholar, Research Gate, Science Direct, Springer Link, and NCBI. Key words were used to find the journals, namely griseofulvin, dermatophyte, toxicity.

RESULTS AND DISCUSSION

GRISEOFULVIN LITERATURE REVIEW

In 1939 Oxford et al., observed the metabolic product of *Penicillium griseofulvum* containing chlorine by isolating it from mycelium fungus grown in a modified Czapek-dox solution named griseofulvin[5]. Apart from *Penicillium griseofulvum*, researchers also observed *Penicillium janczewskii* showing the existence of a "Curling-Factor" whose biological properties are identical to griseofulvin[6].

To determine the same activity of the 2 *Penicillium*, 100 g/ml solution of griseofulvin from *Penicillium griseofulvum* and "Curling-Factor" from *Penicillium janczewskii* were taken made in Weindling's solution[7], tested by extraction method. These two samples resulted in growth that was usually stunted and distorted and had the same activity[7].

Griseofulvin was isolated from 300 g mycelium and 50 g griseofulvin was isolated using 259 L of media, the culture was incubated for 65-85 days at 30°C. Extract the “Curling-Factor” *Penicillium janczewskii* for 11-14 days to obtain 150 mg/L or about 40g. Extract the “Curling-Factor” *Penicillium janczewskii* for 11-14 days to obtain 150 mg/L or about 40 g[7]. Griseofulvin with the chemical formula $C_{17}H_{17}O_6Cl$ has a structural formula that can be seen in Figure 1 below.

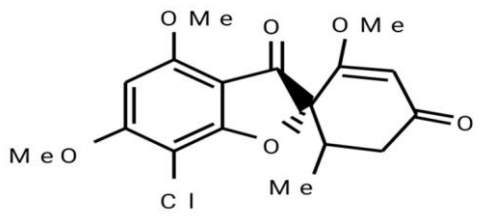

Figure 1: Structure of griseofulvin[8]

Griseofulvin ($C_{17}H_{17}O_6Cl$) is a colorless neutral compound, crystalline, does not give color to $FeCl_3$ and does not contain free hydroxyl or carboxyl groups. Griseofulvin when hydrolyzed with liquid alcohol by boiling N H_2SO_4, produces griseofulvic acid ($C_{16}H_{15}O_6Cl$).Then hydrolysis of griseofulvin acid by boiling liquid N/2 NaOH produces norgriseofulvic acid ($C_{15}H_{13}O_6Cl$). The color reaction of norgriseofulvic acid with alcoholic FeCl3 shows a brown color, when reacted with diazotized sulfanilic acid in Na_2CO_3 solution shows a dark orange brown color and the results are positive after Millon's test[5].

Catalytic reduction with palladium-charcoal-hydrogen, griseofulvin produces two reduction products namely dihydrogriseofulvin ($C_{17}H_{19}O_6Cl$) and tetrahydrogriseofulvin ($C_{17}H_{21}O_5Cl$). Dihydrogriseofulvin when tested with Brady's reagent still forms 2:4-dinitrophenylhydrazone indicating the presence of a CO group in griseofulvin. Tetrahydrogriseofulvin does not react with Brady's reagent because it has more hydrogen atoms and fewer oxygen atoms than dihydrogriseofulvin[5].

Oxidation of griseofulvin with KMnO4 in acetone at room temperature there are two degradation products isolated, first ($C_9H_9O_5Cl$) is a phenolic monobasic acid containing two methoxyl groups giving a dark purple color with FeCl3, so it is clearly a derivative of salicylic acid and secondly ($C_{14}H_{15}O_7Cl$) monobasic acid which does not give color with $FeCl_3$. Griseofulvin, in the fusion reaction KOH is added to produce orcinol (3:5- dihydroxytoluene) besides that the oxidation of griseofulvin with $KMnO_4$ at room temperature can also produce orcinol[5].

PRECLINICAL DEVELOPMENT

Pharmacology

Pharmacological processes that occur in experimental animals after being given griseofulvin: Griseofulvin is absorbed in the duodenum and jejunum, is evenly distributed in most tissues, at some concentrations occurs in the lungs after intravenous dosing[9]. The presence of blood samples from rabbits and mice showed griseofulvin at 65% in plasma, and the remainder in cells[10]. This drug is metabolized in the liver and excreted in the urine.

IN SILICO TEST

This test is a method that utilizes computing and database technology to develop further research, such as:

The results of research by Karuna Singh using a web server (T-Coffee, Bluues simulation and CASTp) and software (Autodock 4.0) showed griseofulvin with high affinity for the beta chain of the protein tubulin so that it was effective against *Cryptococcus neofarmans*[11].

IN VITRO TEST

This test is a preclinical test on isolated cell cultures or isolated organs, some of the research results are below:

a. Confocal microscope used to determine the effect of griseofulvin on individual microtubule dynamics in

MCF-7 cells indicating that griseofulvin or in combination with the drug vinblastine can be used as breast cancer chemotherapy[12].

b. Griseofulvin at a dose (15 g/ml) can inhibit the growth of K562 cells which have an average inhibitory concentration (SD) of 50% after being calculated by the MTT (methyl-thiazoldiphenyl tetrazolium) method[13].

IN VIVO TEST

This test is a preclinical test carried out on whole animals, some of the research results are below:

a. Griseofulvin at a dose of 450 g/day injected subcutaneously in mice can reduce tumor growth[14].

b. Oral dose of griseofulvin (125-250-500 mg/kg) in rats did not inhibit dextran-induced leg edema[15].

c. Griseofulvin with an oral dose of 20 mg/kg in rats showed that the longer the residence time of the drug in the intestine led to higher dissolution and absorption[16].

d. Griseofulvin can induce sister chromatid exchange (SCE) in rat bone marrow cells after a dose of 100 or 200 mg/kgBB[17].

TOXICITY TEST

This test is a test to detect the toxic effect of a substance on a biological system, some of the research results are below:

a. Griseofulvin given orally to experimental animals such as rats (dose of 1 mg/kg, 2 mg/kg, and 500 mg/kg) and dogs (dose of 1 mg/kg) did not cause toxic effects[18].

b. Gemcitabin-(C.4-amide)-[anti-HER2/neu] in double combination with griseofulvin by cell vitality stain-based method can increase anti-neoplastic cytotoxicity against breast cancer cells SKBr-3[19].

c. Ethosomal-assisted griseofulvin to enhance drug delivery to the skin showed no cytotoxicity in HaCaT cells for concentrations below 50 g/ml[20].

d. Griseofulvin mixed with peptides can reduce or eliminate drug toxicity to human erythrocytes[21].

HEPATOTOXICITY

Hepatotoxicity is a condition in which liver cells are damaged by toxic chemicals, such as the results of the griseofulvin study below:

Griseofulvin given orally to rats at a dose of 50 mg/kg using the cardiac puncture method showed that liver damage was less likely to occur[22].

TERATOGENICITY TEST

This test aims to obtain information on fetal abnormalities that occur due to the administration of griseofulvin during the formation of fetal organs (organogenesis period), such as : The results showed that griseofulvin at high doses affected embryonic development in pregnant rats[23].

STABILITY TEST

This test aims to determine the ability of a griseofulvin product to survive within the specified limits throughout the period of storage and use, some of the results of the research are below :

a. Griseofulvin containing vitamin E-TPGS (0.4 g) is stable at temperatures (4°C, 25°C, and 40°C) for 6 weeks[24].

b. Griseofulvin in a non-aqueous microemulsion system using the UV method is stable at 5°C and 25°C[25].

c. Griseofulvin which is formulated in microemulsion dosage form is stable at temperatures of 5 ± 3°C, 25 ± 2°C and 40 ± 2°C for a period of six months[26].

d. Mikroemulsi griseofulvin stabil pada pH kulit (4,2-7)[27].

e. Griseofulvin in LDE (Lyophilized Dry Emulsion) tablet dosage form is stable at 25°C after 6 months of storage[28].

FORMULATION

The formulation of griseofulvin from several research results :

a. The formulation of griseofulvin made in topical dosage forms is an effective, safe, stable, and efficacious alternative for the treatment of superficial fungal infections of the skin[24].

b. Griseofulvin via the topical route loaded in the form of lipid nanoparticles showed antifungal activity and better penetration into the skin[29].

c. The griseofulvin microemulsion formulation which was tested on the skin of male laca mice by Dunnet's method showed almost 3 times higher drug permeation compared to aqueous suspensions, oily solutions and conventional creams[26].

d. Griseofulvin at a dose of 8 mg/kgBB rats loaded in the form of a liposome formulation was able to increase the bioavailability of the drug[30].

e. The self-emulsifying formulation was able to increase the solubility of griseofulvin in water, drug release, and drug permeability through the rat intestine[31].

f. Nanovesicular formulation can enhance griseofulvin drug delivery[32].

g. Griseofulvin nanocrystals injected subcutaneously in rats at a dose of 500 mol/kg were able to increase drug bioavailability[33].

h. Lyophilized dry emulsion (LDE) griseofulvin tablets can increase the dissolution rate of the drug compared to ordinary drugs, but the drug release is

slightly slower[28].

i. Griseofulvin with β-cyclodextrin complexation using coprecipitation method showed a significant increase in drug dissolution and played an important role in its solubility[34].

j. The niosomal formulation can be used efficiently to increase the oral bioavailability of griseofulvin as well as faster drug absorption[35].

k. Amorphous solid dispersion (ASD) showed that griseofulvin-soluplus was able to mix well and the interaction was stronger than griseofulvin-hydroxypropyl cellulose[36].

CLINICAL TEST

Phase I

Phase I is the phase where the drug is tested on healthy volunteers to find out whether the properties observed in experimental animals are also seen in humans. The drug griseofulvin has gone through phase I involving 16 healthy volunteers. Healthy volunteers were induced with *Trichophyton mentagrophytes* infection and then treated with topical griseofulvin for 14 days, the trial showed that there were no side effects[37].

Phase II

Phase II is the phase where the drug is tested on about hundreds of patients, observed for efficacy in the disease being treated. Griseofulvin in phase II involved 100 patients who experienced tinea pedis caused by various dermatophytes where the drug was administered topically. The results of the trial showed a good response in clinical trials, a high cure rate and clinical improvement as well as mild side effects that are only temporary[37].

Phase III

Phase III involves large groups of patients of about thousands of people and compares their effects and safety against known comparison drugs. In this phase, griseofulvin and terbinafine involved 2163 subjects or patients with drug doses according to the patient's body weight. The results of the experiment showed that each drug had a good safety profile, low side effects but griseofulvin was efficacious in treating tinea capitis caused by *Microsporum* species, while terbinafine was more efficacious in treating tinea capitis caused by *Trichophyton* species[38].

Phase IV

After the drug is marketed, post-marketing surveillance studies are still being conducted which are observed in patients with various conditions, ages, and races. This study is carried out over a long period of time to see the therapeutic value of a drug. In this phase, laboratory data monitoring was carried out involving 321 patients, of which 225 were treated with griseofulvin and 96 were treated with terbinafine. The results obtained were abnormally rare but only one patient treated with griseofulvin revealed a significant increase in liver aminotransferase levels requiring discontinuation of treatment[39].

Biological Activity of Griseofulvin and its Analogues

Griseofulvin is active against infection with *Microspoum canis* and *Trichophyton mentagrophytes* in guinea pigs when given an oral dose reported by Gentles in 1985[40]. The antimitotic action of griseofulvin on plant and mammalian cells has been associated with colchicine-like disruption of microtubules[41]. Griseofulvin is able to bind tubulin[42], inhibits tubulin polymerization[43], and disrupt microtubule dynamics, but experiments show that binding to tubulin results in low affinity and often occurs at higher concentrations than fungistatic[44].

A large number of griseofulvin analogues can enhance the antifungal properties of natural products especially the efficacy of 3'benzyl-2'-demethoxy-2'ethoxygriseofulvin in vitro but has not been performed clinically. In 2006, Oda published the cytotoxic effect of griseofulvin on 2' and 3' modified analogues in Chinese hamster V79 cells, finding that the 2'- demethoxy-2'-propoxy analogue was the most potent, suggesting the anticancer[45] of griseofulvin can improved through structural modification of natural products.

Biological Test

Biological test or BioAssay is a step in drug discovery. Tests performed usually focus on drug targets such as cells, proteins, genes, or biopharmaceuticals. The results of research conducted by Roth and Blank showed that griseofulvin was detected at the base of the stratum corneum within 48 hours to 72 hours. Griseofulvin was initially transported through 25% of the basal stratum corneum for 6-12 days then to reach a depth of 50% (middle zone of the horny layer) for 12-19 days after the drug was administered to nine individuals at a daily oral dose of 1 mg[46].

Griseofulvin Biosynthesis

Biosynthesis is a chemical reaction that occurs when living organisms create new complex molecules from simpler and smaller precursors. Griseofulvin biosynthesis pathway through several processes, namely the introduction of chlorine atoms into the aromatic ring

and the incorporation of the phenol ring oxidation. Figure 2 below represents the biosynthetic pathway of griseofulvin.

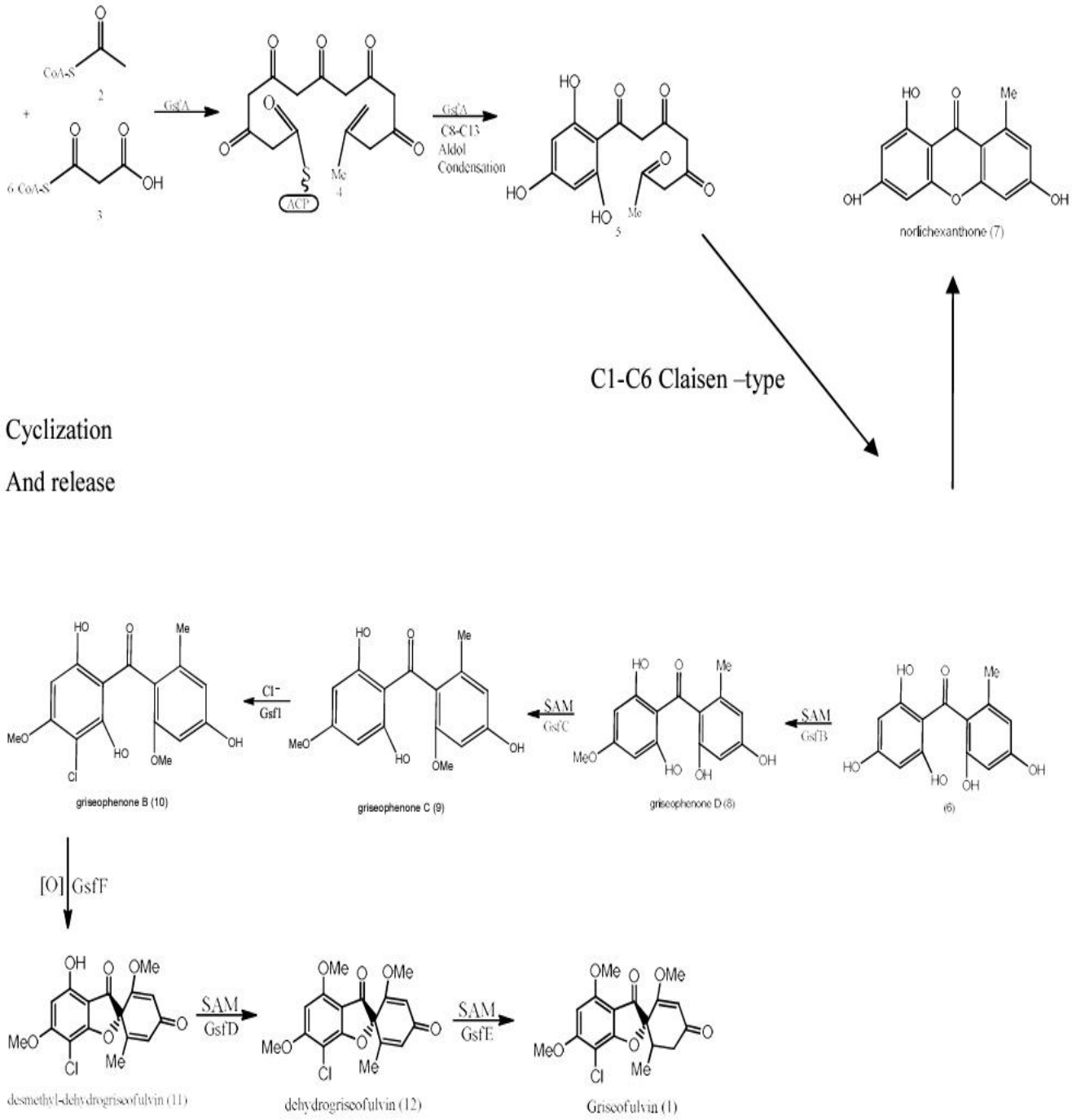

Figure 2: The griseofulvin biosynthetic pathway from Cacho et al.

ACP is an acyl carrier protein and SAM is S-adenosyl methionine [8].

Yi Tang's group conducted a study on *penicillium aethiopicum* on all single genes of the enzymatic event describing the biosynthesis of griseofulvin (1) using acetyl-CoA (2) as a starter and six malonyl-CoA (3) as extender units[8]. Intra-molecular Claisen-type reactions (4) and aldol condensation of the heptaketide backbone (5)[47], respectively yield (6) although neither thioesterase nor cyclase is part of GsfA[44]. GsfB deletion established that initial methylation (6) occurred at O-6 and norlichexanthone (7) formed as a shunt product, suggesting that O-6 methylation yielding griseophenone D (8) suppresses xanthone formation in the wild-type strain. The deletion of the GsfC methyl transferase explains that the second methylation occurs before the formation of the grisan ring. Deletion of the third metal-transferase gene encoding GsfD indicates that C-7 chlorination occurs before O-4 methylation due to accumulation of desmethyldehydrogriseofulvin (11)[48]. C-7 chlorination was also shown to occur prior to grisan ring formation as

griseophenone B (10) accumulates in the GsfF knockout strain. Oxidation of the phenol ring in spirocyclic grisan compounds by phenolic coupling is catalyzed by cytochrome P450 GsfF, in addition the mechanism can be through radical coupling or through arene oxide intermediates. Finally GsfE catalyzes the stereospecific reduction of dehydrogriseofulvin (12) to give griseofulvin (1)[44].

CONCLUSION

Griseofulvin is used as an antifungal drug containing chlorine from *Penicillium griseofulvum* isolated against mycelium fungus. This drug is non-toxic, so it is effective and safe to fight various types of fungal infections of the skin such as tinea capitis and remains the drug of choice for dermatophytes.

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