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# Potential of orchid as antifungal agent resources: a scoping review

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**ABSTRACT**

In 2017, one billion people suffer from fungal diseases with 11.5 million people contracted life-threatening infection and 1.5 million death per year. Orchid is a plant that grows in tropical and sub-tropical countries, the same places where fungal infection occurrence is high. On previous studies reported that orchid contains alkaloids and polyphenols such as flavonoid, and phenol acid. The review aimed to identify the orchid as a potential antifungal resource. A scoping review was used. The type of articles reviewed were original articles obtained from five electronic journal databases published within 2012-2021. Three articles reported similar result which was that orchid extract has a significant antifungal activity although the part of plant used was different, ranging from the root, to the leaf. Two articles reported a specific antifungal activity against *Candida albicans* while the remaining one against *Trichophyton rubrum*. In conclusion, the root, leaf, branch, and flower extracts of orchid is potential antifungal resources.

**ABSTRAK**

Pada 2017, satu miliar orang terinfeksi jamur dengan 11,5 juta infeksi yang mengancam jiwa dan 1,5 juta menyebabkan kematian. Anggrek adalah tanaman yang tumbuh di negara tropis dan sub-tropis tempat kejadian infeksi jamur tinggi. Pada penelitian sebelumnya dilaporkan anggrek mengandung alkaloid dan polifenol seperti flavonoid dan asam fenolik. Tinjauan ini bertujuan mengidentifikasi anggrek sebagai sumber antijamur yang potensial. *Scoping review* digunakan dalam tinjauan ini. Jenis artikel yang ditelaah adalah artikel hasil penelitian yang diperoleh dari lima database jurnal elektronik yang dipublikasi 2012-2021. Tiga artikel melaporkan hasil yang sama yaitu anggrek mempunyai aktivitas antijamur meskipun bagian tanaman yang digunakan berbeda dari akar sampai daun. Dua artikel melaporkan aktivitas antijamur spesifik melawan *Candida albicans* sedangkan satunya melawan *Trichophyton rubrum*. Dapat disimpulkan, ekstrak akar, daun, batang dan bunga anggrek merupakan sumber antijamur potensial.

## INTRODUCTION

Fungi are heterotrophic and eukaryotic microorganisms in the form of cells or branched filaments with chitin and glucan in their cell walls.[1] Fungi are one of the causes of infectious diseases in tropical countries with high humidity. Indonesia is one of the tropical countries with a hot and humid climate favorable for fungal growth, increasing fungal infection diseases incidence.[2] Infection is a health problem that is difficult to eradicate.[3] In 2017, one billion people contracted a fungal infection, with 11.5 million people contracted life-threatening infection and 1.5 million death per year.[4] Incidence of fungal infection diseases is higher in men compared to a woman.[5] Fungal infection disease can be classified into two groups, superficial infection and systemic infection.[6]

Superficial fungal infection is a fungal infection that affects the surface of the body such as skin, hair, and nails.[7] The superficial fungal infection

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affects approximately 20-25% of the world's population and is one of the most common types of infection in humans.[8] Superficial fungal infection includes dermatophytosis, pityriasis versicolor, candidiasis superficialis, and otomycosis.[9] Based on ten-year research from 2008 to 2018 in North East China, there were three most common dermatophytosis which were tinea pedis (28.62%), tinea cruris (18.94%), and tinea corporis (17.45%) and three most common cause of human fungal infections were *Trichophyton rubrum* (48.65%), *T. mentagrophytes* (16.14%) and *Candida sp*. (17.40%).[5]

The most frequent infection sites of *T. rubrum* include foot, inguinal, axilla, scalp, and nail. This infection causes mild to moderate dermatological symptoms with a variety of severity. The variation of dermatological symptoms is due to the level of immune response towards the microorganism. *Trichophyton rubrum* causes diseases such as tinea pedis, tinea cruris, and tinea corporis. Around 80% of patients with acute dermatophytosis respond well to topical antifungal treatment, while the other 20% develop chronic dermatophytosis resistant to antifungal treatment. The occurrence of dermatophytosis is affected by many factors such as personal hygiene, tight clothing, socioeconomic status, and chronic illnesses (immunosuppression) like HIV.[10.] Clinically, *T. rubrum* is resistant to the most frequently used treatment for the infection, terbinafine. It is also known to be resistant to other modern antifungals like fluconazole, itraconazole, and ketoconazole. This fungus resists the therapies mentioned above by increasing the efflux of the drug.[11]

Systemic fungal infection is a fungal infection that affects deeper tissues and organs.[7] Systemic fungal infections, including Coccidioidomycosis, Blastomycosis, Talaromycosis, and Candidiasis, are clinical severe conditions.[12]invasive disease can occur in immunocompetent individuals if the exposure dose is high or with primary (dimorphic Coccidioidomycosis is caused by a pathogenic fungus, *Coccidioides immitis*. It affects the lungs and produces a pneumonia-like symptom similar to pneumonia caused by other etiologies, which is coughing with pleuritis.[12] Blastomycosis is a systemic fungal infection that affects the lungs, bones, and nervous system. The causes of blastomycosis are *Blastomyces dermatitidis* dan *B. brasieliensis*. The symptoms of blastomycosis is similar to that of tuberculosis.[13] Talaromycosis, caused by *Talaromyces marneffei* is one of the most common opportunistic infections in acquired immune deficiency syndrome (AIDS) patients.[14] Talaromycosis may also affect healthy people and is widely spread in South Asia and Southeast Asia, particularly in the north part of Thailand and the south part of China. This infection often manifests as a lung infection associated with skin lesions.[12] Candidiasis is a fungal infection that can affect both superficial and deep parts of the body, such as the heart, lungs, mucosal layer, and vagina,[15]

Fungal infections can also be classified based on the type of fungi which are opportunistic fungi and pathogenic fungi.[7] Opportunistic fungi cause a disease in the presence of predisposition factors like immune suppression, metabolic disorders, and drugs such as corticosteroid and antibiotic consumption. Some examples of opportunistic fungi are *Candida spp, Aspergillus spp*, and *Mucor spp*.[7]

Candida is naturally a normal flora of the human body. However, candidiasis may occur in the presence of predisposition factors such as immune suppression, HIV-AIDS, and endocrine system disorders. Morphologically, *C. albicans* has three forms which are blastospores/yeast, hyphae, and pseudohyphae. *Candida* albicans reproduce by blastospores which are spores emerging from the budding. *Candida albicans* is dimorphic, and aside from yeast and pseudohyphae, it is also able to produce true hyphae.[16] The growth of *C. albicans* is optimum at 37 $^{O}$C in both aerobic or anaerobic conditions. In aerobic conditions, *C.*

*albicans* require 98 min to grow and 248 min in anaerobic conditions. Acidic condition is more favorable for candida growth compared to neutral or caustic conditions.[17] Fluconazole is the most frequently prescribed treatment for oropharyngeal and vulvovaginitis caused by candida. Despite that, a research conducted by Peron *et al.*,[18] this study aimed to perform an antifungal susceptibility surveillance with the C.albicans bloodstream isolates and to characterize the fluconazole resistance in 2 non-blood C.albicans isolates by sequencing ERG11 gene. The study included 147 C. albicans bloodstream samples and 2 fluconazole resistant isolates: one from oral cavity (LIF 12560 fluconazole MIC: 8μg/mL*C. albicans* was shown to have developed resistance towards antifungal medications in the azole group. Long-term treatment with fluconazole can cause mutation, leading to treatment failure in candidiasis.

Pathogenic fungus is a type of fungi that cause diseases in healthy humans without any predisposition factor.[7] Some pathogenic fungi include *C. immitis, Histoplasma capsulatum, Sporothrix schenkii, Paracoccidioides brasiliensis, B. dermatiditis*, and *Cryptococcus neoformans.*[19] Histoplasmosis is caused by inhaling air that contains microscopic spores of *Histoplasma capsulatum*.[20] This fungus species lives on highly nitrogenous soil contaminated with bat or chicken droppings. Symptoms of histoplasmosis occur gradually within a few weeks. The symptoms include weight loss, malaise, mild fever, cough, and breathing difficulty. Within 2-6 months, the symptoms usually resolve by themselves. However, the symptom could progress into hemoptysis with a large quantity of blood. In this case, antifungal medication could be used to diminish the infecting fungi, but it could not repair the damaged tissues. Paracoccidioidomycosis and Cryptococcosis are caused by inhalation of *P. brasiliensis* spores and *C. neoformans,* respectively. It presents as a nonspecific clinical appearance in the lungs and may spread into other organs. This fungus species lives on highly nitrogenous soil contaminated with bat or chicken droppings and reproduces by budding or blastospores.[21]

The abundance of diseases caused by fungal infection have prompted people, especially those working in health field, to make developments in antifungal agents. Nowadays, there are many kinds of antifungal agent freely sold in the markets, however, that does not ensure that fungal infection diseases will be subdued. Pharmacological therapy for fungal infection is divided into five groups, azoles, allylamines, polyenes, echinocandins, and others.[22] They have some side effects, most frequently gastrointestinal problems such as dyspepsia, nausea, vomiting, and diarrhea.[23] Those side effects have caused several people to choose traditional remedies to fight antifungal infection diseases instead of the modern antifungal agents.[24]

Indonesia has excellent knowledge of using plants as health maintenance and disease treatment alternative.[25] One of the plants used for traditional medicine is the orchid.[26] The use of orchids as traditional medicine has been reported in China, Japan, Korea, Taiwan, and Tibet. The local people of India, Sri Lanka, Papua New Guinea, Malaysia, and Indonesia utilize parts of the orchid plant such as the root, rhizome, stem, or all parts of the plant as a treatment for cough, ear pain, ringworm, internal bleeding, and wounds caused by infection.[27] Some chemical components found in large quantities in an orchid are alkaloids, flavonoids, bibenzyl derivates, phenanthrenes, and terpenoids.[27]

Alkaloids can suppress the work of enzymes to synthesize cells protein, causing metabolism disruption of the fungal cell, leading to cell death due to damage in the fungal cell wall structure. Furthermore, alkaloids can damage mitochondria, depleting the fungal cells of energy, resulting in cell death. In other cases, alkaloids can play a role as an anticancer by producing reactive oxygen species (ROS) and induce apoptosis in cancerous cells.[28-30] Besides alkaloid, flavonoid exerts antifungal property by interacting with the DNA of the fungus, disrupting fatty acid synthesis. This mechanism is also the specific target of the development of antifungal agents. Besides that, the hydroxyl ion in flavonoids can change the distribution process of nutrition and organic components which causes toxicity to the fungal cell.[31,32] Meanwhile, bibenzyl (dihydrostilbenoid) is reported to have antimitotic and antileukemia activity. There is also ongoing research on the potential of bibenzyl as a cytotoxic agent on cancer cells.[33] The other component, phenanthrene, is found in vascular plants, particularly in *Orchidaceae* plants.[34] Phenanthrene has been proven to have biological activities such as anticancer, antimicrobe, spasmolytic, antiallergy, antifungal, and antiinflammation.[35] Terpenoid has almost similar effects with phenanthrene which are antitumor, antiinflammation, antibacterial, antivirus, antimalaria, increasing transdermal absorption, prevent and treat cardiovascular diseases, and hypoglycemic activities.[36]

An article by Gutiérrez[27]light intensity and growth parameters. Namely, net assimilation rate, relative growth rate, leaf weight ratio, leaf area ratio and specific leaf area for oregano (Origanum onites L. has discussed the potential of orchid plants as an antifungal. However, it discussed antifungal properties towards fungi that infect plants and not humans. Based on the findings above, we will investigate the potential of orchid plants as an antifungal agent. To the researchers' knowledge, there is currently no scoping review article discussing orchid plants' potential as an antifungal for human fungal infections. Therefore, this review aimed to evaluate some literature about the potential ability of orchid as potential antifungal recources.

## MATERIAL AND METHODS

### Article criteria

The articles included in this review were selected based on the inclusion and exclusion criteria. The inclusion criteria were 1) original article published between 2012 – 2021; 2) the article was written in English; 3) the subject of the research was fungi that infect humans; 4) the plants used in the research had been identified or determined; 5) the orchid plants used were within the family Orchidaceae; and 6). the main outcomes of the research were inhibition zone diameter, inhibition strength, minimum inhibitory concentration (MIC), or minimum fungicidal concentration (MFC). Incomplete articles and articles only containing abstracts were excluded.

### Information sources

The data for this research were accessed from PubMed, Science Direct, Springer Link, Wiley, dan Taylor and Francis. Those databases were chosen because of their easiness to access with no cost needed as they can be accessed using the researchers' Universitas Islam Indonesia accounts.

### Article searching strategy

The articles were searched using keywords that were under the formulation of this research problem. The keywords were obtained using the PICO method seen in TABLE 1.

TABLE 1. PICO Formulation

| Question part | Question Term | Synonyms |
|---|---|---|
| Population | Fungi | Fungal/fungi/fungus |
| Intervention | Orchid | Orchid/*Orchidaceae* |
| Comparison | - | - |
| Outcome | Antifungal | Antifungal/Antifungi |

### Article selection process

The articles were selected based on the inclusion criteria. The process were conducted according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews* (PRIMA-ScR) statement.[37]

The scoping review process based on PRIMA-ScR followed several steps, which were a) *identification*, article searching process using the pre-determined keywords in the aforesaid information sources; b) *screening,* exclusion process of identical articles obtained from different information sources; c) *eligibility*, exclusion process of articles that can not be fully accessed; and d) *included,* selection process to choose to-be-reviewed articles based on the pre-determined inclusion and exclusion criteria.[38]

### Data extraction

The data extraction process extended from identifying the articles to study the content of the articles to gain information according to the aim of this research.[39] The Components that were included in the data extraction TABLE were reference, plant species, parts of plant utilized, extraction method, fractionation method, compounds found in the plant, research method, the result of the research and conclusion.

### Data item

Data items used in this research were: (a) characteristics of obtained journals, including authors, publishing year, plant species, parts of plant utilized, extraction and fractionation method, fungus species, and methods used to determine antifungal activity; (b) main outcomes of the study, which were inhibition zone diameter, inhibition strength, MIC, MFC, and active compounds that have antifungal activities.

## RESULTS

### Selection result of sources of evidences

The article searching process was conducted by inputting the keywords based on PICO analysis into five databases: PubMed, Science Direct, Springer Link, Wiley, and Taylor and Francis. There were 712 articles obtained from the mentioned databases (TABLE 2).

TABLE 2. Article searching result by using keywords based on PICO analysis

| Databases | Result |
|---|---|
| PubMed | ((((((fungi) OR (fungal)) OR (fungus)) AND (orchid)) OR (orchidaceae)) AND (antifungal)) OR (antifungi)<br>= 63 articles |
| Springer Link | fungal or fungi or fungus and or orchid or orchidaceae and or antifungal or antifungi<br>= 189 articles |
| Wiley | ((((((fungi) OR (fungal)) OR (fungus)) AND (orchid)) OR (orchidaceae)) AND (antifungal)) OR (antifungi)<br>= 108 articles |
| Science Direct | fungal or fungi or fungus and or orchid or orchidaceae and or antifungal or antifungi<br>= 137 articles |
| Taylor and Francis | [All: fungal] OR [All: fungi] OR [[All: fungus] AND [All: orchid]] OR [[All: orchidaceae] AND [All: antifungal]] OR [All: antifungi] AND [in Journal]<br>= 215 articles |

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRIMA-ScR) statement, the obtained articles were then screened for duplicates. There were 20 duplicated articles excluded. Therefore only 692 articles were processed into the next step. On the screening for incomplete articles, 21 articles were excluded. There were 157 more articles excluded on the next process as those did not fall into the original article category. On the title and abstract selection process, 500 articles were excluded as those are not relevant to the aim of this research. Thus, 14 articles were analyzed entirely. Among the 14 articles, 9 of those discussed antifungal activity of orchid plants to fungi that infect plants instead of humans; thus, those articles were excluded. Another article was excluded as it does not discuss the compound with antifungal activity, and another article was excluded as it does not use inhibition zone, MIC, and MFC as the indicator of antifungal activity. In conclusion, there were three articles used in this scoping review.

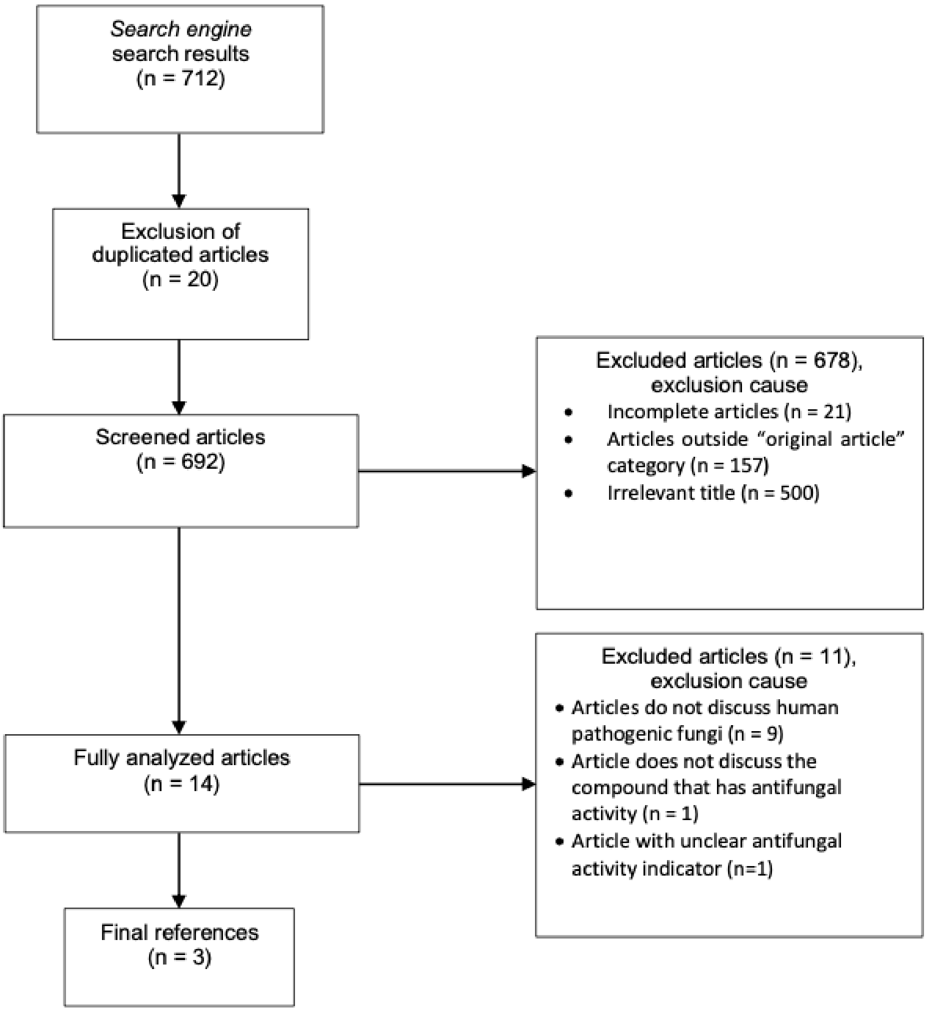


FIGURE 1. Flowchart diagram of article selection process

**Source of evidence characteristics**

Information obtained from the three analyzed articles is relevant to the research question and aim of this scoping review: plant species, part of the plant used, extraction and fractionation, the compound found in the plant, and the method to determine antifungal activities (TABLE 3).

TABLE 3. Result of source of evidence characteristics study

| Refrence | Species | Plant part | Extraction Method | Fractination Method | Compound | Research Method |
|---|---|---|---|---|---|---|
| Yoshikawa *et al.*[40] | *Cymbidium* Great Flower | Root | Maceration | Column chromatography | Ephemeranthoquinone C Marylaurencinol C Marylurencinol D 2,4,7,8-tetramethoxy-3-hydroxy-phenanthrene calaquinone A | Disk-diffuson |
| Cretton *et al.*[42] | *Gavilea lutea* | Aerial parts | Maceration | Flash chromatography | Kaempferol-3-7-di-o-glucoside kaempferol-3-O-glucoside batatasin III Gavilein Isohircinol | TLC plate |
| Fang *et al.*[41] | *Bulbopyllum ratusculum* | Roots | Soxhlet | Column chromatography | Ratusiussines A Ratusiuss-ines B<br><br>Ratusiussines C<br><br>Dihydroconyferyl dihydro-p-coumarate Methyl 3-(4-hydroxyphenyl) propionate 3-(4-hydroxyphenyl)-propionic acid dyhydroferulic acid methyl 3-(4-methoxyphenyl) propionate 3-(3,4-dime-thoxyphenyl)-2-propenal-Trans-p-coumaric acid Dihydroconyferyl alcohol | 96-well plates microdilotion |

**Result of each source of evidence**

Data extraction from the three selected articles showed a homogenous result which can be inferred that there are suitable antifungal activities of different kinds of orchid plants, as shown in TABLE 4.

TABLE 4. Result of each source of evidence

| Species | Active compound | Microorganism | Inhibition Zone (mm) | MIC (μg/mL) | MFC (μg/mL) | Reference |
|---|---|---|---|---|---|---|
| *C.* Great Flower | Ephemer anthoquinone C | *T. rubrum* | 12.7 | TD | TD | Yoshikawa *et al.*[40] |
| | Marylaurencinol C | *T. rubrum* | 15.7 | TD | TD | |
| *G. lutea* | Gavilein | *C. albicans* | TD | 50 | TD | Cretton *et al.*[42] |
| *B. retusculum* | Retusiusine B | *C. albicans* | TD | 16 | TD | Fang *et al.*[41] |

Notes: MIC (minimum inhibition concentration); MFC (minimum fungicidal concentration); TD (no data)

Yoshikawa *et al.*[40] isolated ephemeranthoquinone C dan marylaurencinol C from methanol extract of the root of *C.* Great Flower against *T. rubrum* fungi and reported their antifungal activity against *T. rubrum* with the diameter of inhibition zone of 12.7 mm and 15.7 mm in concentration of 10 μg/disk, respectively. The diameter of inhibition zone of ketoconazole as positive control in concentration of 10 μg/disk was 16.7 mm. Whereas, the methanol extract of the root of *C.* Great Flower had a low antibacterial effect against *B. subtilis* and high antibacterial activity against *K. pneumoniae* (Table 4).

Cretton *et al.*[42] reported antifungal activity of new bibenzyl derivative (gavilein) isolated from methanol extract of *G. lutea* against *C. albicans* with minimum inhibitory quantity (MIQ) of 50 μg (Table 4). This activity was better than miconazole as the positive control. Morover, gavilein exhibited a selective activity against *Leishmania donovani* with inhibitory concentration ($IC_{50}$) of 2.3 μg/mL.

Fang *et al.*[41] isolated 11 secondary metabolites form methanolic extract of *B. retusculum* and evaluated their activity against *C. albicans* and *Escherichia coli* and *Bacillus subtilis*. Among 11 the secondary metabolites, retusiusine B exhibited active against *C. albicans* with a MIC value of 16 μg/mL, whereas retusiusine C exhibited against *E. coli* and *B. subtilis* with a MIC value of 64 μg/mL.

**Result synthesis**

All three of the analyzed articles showed antifungal activity against the fungus studied. Two out of three articles used *C. albicans*. There is a heterogeneity in terms of the plant species and part of the plant used in the analyzed articles. These results showed that antifungal activity in orchid plants is not specifically found in a certain part of the plant. The extraction method used may influence the isolation of the compounds from the extract. This explains the reason of one extract is separated into five compounds while the other is separated into 11 compounds.

The three analyzed articles showed that different compounds are found in different plant species; however, all the plant extract exhibited antifungal activities. Yoshikawa *et al.*[40] used inhibition zone diameter as an indicator to determine antifungal activity, whereas Cretton *et al.*[42] used MIQ as the indicator, while Fang *et al.*[41] used MIC.

## DISCUSSION

The high prevalence of human fungal infection in tropical countries emerge the problems of the side effect and resistance of antifungal drugs leading to the need of new antifungal agents development. Medicinal plants are one of potential natural sources of new antifungal agents. In previous study, orchid plants have been investigated for their potential new antifungal agents. This scoping review was conducted to evaluate the potential of orchid plants as antifungal sources against human pathogenic fungi. Three reviewed articles showed different methods used to extract and isolate compounds from orchid plants. Two articles used silica gel chromatography, while the remaining used flash chromatography.[40,42]

Column chromatography is commonly used to separate natural active compounds due to its simplicity, high capacity, and low adsorbents like silica gel and macro resin cost. Silica gel is the most commonly used polar adsorbent in the phytochemical investigation, accounting for 90% of phytochemical separation. Compounds are retained by the silica gel via hydrogen bonds and dipole-dipole interactions. Therefore, polar compounds are retained longer in silica gel columns compared to nonpolar ones.[43] This column chromatography process starts with putting the sample on top of the column containing several adsorbents, most commonly silica gel. The remaining column is then filled with a solvent or solvent mixture, which flows via adsorbent by gravitational force. The various compounds that will be separated pass through the column with different velocities and are then collected separately when the compounds come out from below the column. Unfortunately, the solvent moves slowly. The velocity of the compound in passing through the column depends on how much the adsorbent absorbs the compound.[44] Yoshikawa *et al.*[40] used the column chromatography with silica gel to isolate phenolic acid i.e. phenanthrene and phenylpropanoid (cinnamic acid) from the root of *C.* Great Flower. Furthermore, Fang *et al.*[41] used the same method to isolate phenylpropanoid from *B. retusculum*.

Cretton *et al.*[42] used a different method, flash chromatography, to isolate an active compounds. Flash chromatography is also a column chromatography but uses pressure from nitrogen.[45] The pressure is used to speed up the solvent flow and decrease the time needed to purify the sample. Around ten to fifteen min is needed to conduct the method. Two differences of flash chromatography with the conventional method are 1) silica gel particles are smaller (250-400 mesh); 2) as the solvent flow is limited due to small particles of the gas, pressurized gas (10-15 psi) is used to move the solvent through the column. The final result is a rapid chromatography with high resolution.[44] Cretton *et al.*[42] isolated bibenzyl derivate, glycosylated flavonoid, batatasin III, and isorchinol phenanthrene.

Analysis of the three articles regarding the antifungal activity of orchid extract showed inhibitory activity against the fungi tested. The inhibitory activity is measured in different indicators. Yoshikawa *et al.*[40] showed that methanol extract of *C.* Great Flower contains new compounds, phenanthrene and marylaurencinols C which active against *T. rubrum*. New active compound belonging phenylpropanoid i.e. ephemeranthoquinone C was also reported. Phenanthrene, and its derivates have been found in vascular plants including orchid. The biological activities of these compounds have been reported such as antifungal and anti-inflammatory. However, the mechanism of action and structural activity relationship of these phenanthrene is rarely reported.

Antifungal activity against *C. albicans* of gavilein belonging bisbenzyl derivative isolated from G. lutea was reported by Cretton *et al.*[42] with MIQ of 50 μg. Some bibenzyl compounds are reported to have antimitotic, antileukemia and cytotoxic activities.[33] Fang *et al.*[41] reported the antifungal activity of phenylpropanoid i.e. retusine B isolated from *B. retusculum* extract against *C. albicans* with MIC of 16 μg/mL.

## CONCLUSION

In conclusion, orchid plants are sources of new potential antifungal agents. Further studies are needed to explore active compounds from orchid species which a lot of grow in tropical countries especially in Indonesia.


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