

Minimum Inhibitory Concentration and Minimum Fungicidal Concentration of Extract and Nanoparticles of Ethanol Extract of Golden Trumpet Leaves (*Allamanda cathartica* L.) Against *Malassezia furfur*

Konsentrasi Inhibitori Minimum dan Konsentrasi Fungisidal Minimum Ekstrak dan Nanopartikel Ekstrak Etanol Daun Terompet Emas (*Allamanda cathartica* L.) terhadap *Malassezia furfur*

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Abstract

Background: Fungal skin infections such as pityriasis versicolor caused by *Malassezia furfur* remain a common health problem in tropical regions. Limitations of conventional antifungal therapy have encouraged the development of alternative agents derived from natural products. Golden trumpet leaves (*Allamanda cathartica* L.) contain flavonoids and iridoids with potential antifungal activity, and nanoparticle formulations are being developed to enhance the extracts' effectiveness. **Objective:** To evaluate the improvement of antifungal efficacy of the nanoparticle formulation of the ethanolic extract of golden trumpet leaves against *Malassezia furfur* by comparing the Minimum Inhibitory Concentration (MIC), Minimum Fungicidal Concentration (MFC), and inhibition zone diameter with the conventional extract. **Methods:** This experimental study employed a posttest-only control group design. Treatment groups included ethanolic extract (6.25%, 12.5%, 25%, 50%) and nanoparticle extract (0.625%, 1.25%, 2.5%, 5%). Nanoparticles were prepared using a high-pressure homogenizer and characterized with a Particle Size Analyzer (PSA). MIC and MFC were determined using the broth dilution method, while antifungal activity was assessed using the disc diffusion method. Data were analyzed using one-way ANOVA at a 95% confidence level. **Results:** Nanoparticle characterization revealed a particle size of 367.51 nm. The MIC values for the extract and nanoparticles were 12.5% and 1.25%, respectively, while the MFC values were 50% and 5%, respectively. The highest inhibition zones for the extract and nanoparticles were 21.1 mm (50%) and 20.3 mm (5%), respectively. Statistical analysis showed significant differences ($p < 0.05$) in inhibition zone diameters across concentrations for both extract forms. **Conclusion:** The nanoparticle formulation of the ethanolic extract of golden trumpet leaves significantly enhances antifungal activity against *Malassezia furfur*, demonstrating equivalent inhibitory effects at concentrations ten times lower than the conventional extract. These findings indicate the potential of nanoparticle-based formulations as promising antifungal candidates.

Keywords: *Malassezia furfur*, Nanoparticles, MIC, MFC, Antifungal Activity.

Abstrak

Latar Belakang: Infeksi jamur kulit seperti pityriasis versicolor yang disebabkan oleh *Malassezia furfur* masih menjadi masalah kesehatan di negara-negara tropis. Keterbatasan terapi antijamur konvensional mendorong pengembangan alternatif dari bahan alam. Daun terompet emas (*Allamanda cathartica* L.) mengandung flavonoid dan iridoid yang berpotensi sebagai antijamur, dan formulasi nanopartikel dikembangkan untuk meningkatkan efektivitas ekstrak. **Tujuan:** Menganalisis peningkatan efektivitas antijamur formulasi nanopartikel ekstrak etanol daun terompet emas terhadap *Malassezia furfur* dengan membandingkan nilai Konsentrasi Hambat Minimum (KHM), Konsentrasi Fungisida Minimum (KFM), dan diameter zona hambat

dengan ekstrak konvensional. **Metode:** Penelitian eksperimental dengan desain *post-test only control group*. Kelompok perlakuan terdiri atas ekstrak etanol (6,25%; 12,5%; 25%; 50%) dan nanopartikel ekstrak (0,625%; 1,25%; 2,5%; 5%). Nanopartikel dibuat dengan metode *high pressure homogenizer* dan dikarakterisasi menggunakan *Particle Size Analyzer* (PSA). KHM dan KFM ditentukan dengan metode dilusi cair, sedangkan aktivitas antijamur diuji dengan metode difusi cakram. Data dianalisis menggunakan ANOVA satu arah pada taraf kepercayaan 95%. **Hasil:** Karakterisasi nanopartikel menunjukkan ukuran partikel 367,51 nm. Nilai KHM ekstrak dan nanopartikel masing-masing 12,5% dan 1,25%, sedangkan nilai KFM 50% dan 5%. Zona hambat tertinggi ekstrak dan nanopartikel masing-masing 21,1 mm (50%) dan 20,3 mm (5%). Terdapat perbedaan bermakna ($p < 0,05$) diameter zona hambat pada berbagai konsentrasi, baik pada ekstrak maupun nanopartikel. **Kesimpulan:** Formulasi nanopartikel ekstrak etanol daun terompet emas meningkatkan efektivitas antijamur terhadap *Malassezia furfur* dengan kemampuan penghambatan yang setara pada konsentrasi sepuluh kali lebih rendah dibandingkan ekstrak konvensional. Temuan ini menunjukkan bahwa nanopartikel ekstrak daun terompet emas berpotensi dikembangkan sebagai kandidat sediaan antijamur.

Kata Kunci: *Malassezia furfur*, Nanopartikel, MIC, MFC, Aktivitas Antijamur.



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Introduction

Malassezia furfur is an opportunistic fungus that can cause various skin disorders, including pityriasis versicolor, seborrheic dermatitis, and other conditions.[1]. This fungus attacks the outermost layer of the skin (*Stratum corneum*) of the epidermis, which is often affected in individuals who already experience increased sweating. *Malassezia furfur* fungus is very easy to infect the skin of people who have prolonged direct contact with water and lack awareness of personal and environmental hygiene [2].

The large number of fungal infections is also supported by the large number of Indonesian people who are still below the poverty line, so that environmental cleanliness, sanitation, and healthy lifestyles are less of a concern in the daily lives of Indonesian people. One of the diseases caused by fungi that attacks the skin is Pityriasis versicolor [1]. Pityriasis versicolor is a mild chronic superficial infection (infection limited to the outermost layer of the skin, nails, and hair) of the *Stratum corneum* (outermost layer of skin) caused by *Malassezia globosa*, *Malassezia restricta*, and other members of the *Malassezia furfur* complex [3–6].

One plant with potential antifungal properties is *Allamanda cathartica* L., also known as the golden trumpet leaf. The golden trumpet leaf (*Allamanda cathartica* L.) is a plant that contains flavonoids that can inhibit the growth of microbes such as fungi. Flavonoids, as antifungals, can hinder fungal growth by denaturing proteins and damaging fungal cells. This damage can kill the fungus. Another mechanism is that it can interfere with the diffusion process of fungal cell damage, thereby stopping fungal growth. The golden trumpet leaf (*Allamanda cathartica* L.) is part of the *Allamanda* plant that contains alkaloids, flavonoids, saponins, tannins, glycosides, and steroids/triterpenoids that can function as antifungals. In addition, trumpet flowers have broad pharmacological effects [7].

With advances in pharmaceutical technology, the manufacture of nanoparticles from plant extracts has become an attractive approach. Nanoparticles are solid colloidal particles with a diameter of 1-1000 nm. The shape and size of the particles affect the drug's effectiveness. Particle size has an essential Influence on the solubility, absorption, and distribution of drugs [8]. Nanoparticles enhance the effectiveness of bioactive compounds by increasing stability, solubility, and bioavailability.

The investigation into natural antifungal agents has gained considerable momentum, particularly for

the treatment of cutaneous mycoses prevalent in tropical regions. *Allamanda cathartica* L. (Apocynaceae) is a candidate of interest based on established ethnobotanical use and compelling phytochemical evidence. The species is renowned for its diverse secondary metabolites, including iridoids, flavonoids, and terpenoids, which are associated with a range of pharmacological activities [9].

Empirical validation of its antifungal potential is provided by Sitompul et al. (2016), who reported significant inhibitory activity of an ethanolic leaf extract against *Candida albicans* [10]. Further substantiating its mechanism of action, Souza et al. (2020) isolated the iridoid compound plumieridine from a congeneric species and identified it as a broad-spectrum chitinase inhibitor, demonstrating potent activity against *Cryptococcus neoformans* by disrupting cell wall integrity [11].

Given that the cell wall of *Malassezia furfur*, the etiological agent of Pityriasis Versicolor, is also composed of chitin, the demonstrated chitinase-inhibitory activity within the *Allamanda* genus provides a strong mechanistic rationale for hypothesizing efficacy against this pathogen. Therefore, the author is interested in studying the antifungal activity of ethanol extracts and nanoparticles from golden trumpet leaves by testing Minimum Inhibitory Concentration (MIC) and Minimum Fungicidal Concentration (MFC), as these extracts contain secondary metabolites that can confer antifungal activity and inhibit fungal growth.

Experimental Section

This research was conducted experimentally to determine the relationships between the independent and dependent variables, specifically the concentration of trumpet leaf extract gold and the concentration of nanoparticles from the ethanol extract of golden trumpet leaves, as an antifungal against *Malassezia furfur*.

Preparation of simplicia, characterization of simplicia, and preparation of extracts at the Pharmaceutical Botany Laboratory of Al-Washliyah Muslim Nusantara University, Medan. Preparation of nanoparticles and phytochemical screening at the Integrated Pharmaceutical Laboratory of Al-Washliyah Muslim Nusantara Medan. Particle Size Analyzer (PSA) test at the Integrated Research Laboratory of the University of North Sumatra, Medan. Antifungal test at the Microbiology Laboratory of Al-Washliyah Muslim Nusantara University, Medan. Plant determination was carried out by the Herbarium Medanense (MEDA) of the University of North Sumatra on the Golden Trumpet Leaves (*Allamanda cathartica* L.) studied.

The golden trumpet leaf samples used in this study were obtained from Perbaungan, Serdang Bedagai Regency, North Sumatra. The sampling method was purposive. Samples were taken from a single location without comparing them with other areas. Fresh samples of Golden Trumpet Leaves (*Allamanda cathartica* L.) were collected and wet-sorted to separate contaminants (dirt and other foreign materials) from the clean material, and weighed to a wet weight of 5 kg. The samples are then dried in a drying cabinet at 40°C-50°C, and dry sorting is performed, namely, removing any foreign objects left in the simplicia. Then the dry weight is weighed, ground with a blender, and stored in a tightly closed container [12,13].

Tools and materials

The equipment used in this study were digital scales, beaker glass, test tubes, blenders, petri dishes, porcelain dishes, glass funnels, hot plates, PH meters, aluminum foil, ose wire, gauze wire, bunsen lamps, autoclaves, laminar air flow, ovens, drying cabinets, sieves, stirring rods, spatulas, droppers, glass containers, measuring cups, micropipettes, Erlenmeyer flasks and temperature gauges, rotary evaporators, incubators, Particle size analyzers (PSA), Homogenizers 2000 rpm, centrifuges (centrifuge PLC series). The materials used for this study were trumpet flower extract, Aquadest, 96% Ethanol, DMSO (Dimethyl Sulfoxide), 0.9% NaCl Solution, 0.5% Mc Farland Standard Solution, Bouchardat, Dragendorf, Mayer, 2N Hydrochloric Acid, 2N Sulfuric Acid, 0.5N Nitric Acid, 10% Iron (III) Chloride, 0.4M Lead (II) Acetate, Molish, Lieberman-Bouchardard, 2N Sodium Hydroxide, Ketoconazole 2%, Potato Dextrose Agar (PDA), Potato Dextrose Broth (PDB) and *Malassezia furfur* fungal isolate.

Experimental Procedures

Examination of the characteristics of the simple drug includes macroscopic and microscopic examinations, determination of water content, determination of water-soluble extract content, determination of ethanol-soluble extract content, determination of total ash content, and determination of acid-insoluble ash content. Macroscopic examination is done by observing the external form of the golden trumpet flower leaves, namely, color, shape, taste, and size of the leaves [14]. At the same time, microscopic examination is done on

the golden trumpet leaf simplicia powder. The golden trumpet leaf simplicia powder is placed on a glass object, then dripped with chloral hydrate solution, then heated briefly over a Bunsen flame, covered with a glass cover, and observed under a microscope [14].

Toluene was placed in a round-bottom flask containing up to 200 mL of toluene and 2 mL of distilled water. Distillation was performed for 2 hours until all the water was removed, yielding saturated toluene. After that, the toluene was cooled and set aside for a bit to rinse. The volume of water in the receiver tube was read as the initial water volume with an accuracy of 0.05 mL. Then, 5 grams of trumpet flower simplicia powder, carefully weighed, were added to each flask containing saturated toluene, which was then heated for 15 minutes. After the toluene boiled, the drip rate was adjusted to approximately two drops per second until most of the water was distilled. The distillation rate was then increased to 4 drops per second. After all the water was filtered, the inside of the cooler was rinsed with saturated toluene. Distillation was continued for 5 minutes. The receiver tube was then allowed to cool to room temperature. After the water and toluene had separated, the water volume was measured as the final water volume with an accuracy of 0.05 mL. The difference between the two volumes is measured, and the water content of the material being examined is calculated as a percentage. This water content calculation uses the azeotropic method [15].

The preparation of golden trumpet leaf extract (*Allamanda cathartica* L.) is done by maceration. A total of 500 g of powdered simplicia is put into a vessel, poured with 75 parts of 96% ethanol solvent in a closed container, left for 5 days protected from light while stirring occasionally, filtered, squeezed, and washed the dregs with 96% ethanol to obtain 100 parts (5000 mL). Transferred into a tightly closed container, left in a cool place, and protected from light for 2 days, settled, poured, or filtered. Concentrated by evaporation on a rotary evaporator at a temperature of no more than 50 °C until a thick extract is obtained [14].

Phytochemical screening was carried out to determine the content of active compounds contained in the extract of golden trumpet leaves (*Allamanda cathartica* L.). The screening was carried out in several stages: examination of alkaloids, tannins, saponins, flavonoids, terpenoids/steroids, and glycosides.

In addition, nanoparticles of golden trumpet leaf extract were manufactured using a high-pressure homogenizer for unit operations such as crushing, mixing, and solid stabilization. Weigh 35 grams of thick extract of golden trumpet flower leaves, then homogenize in a homogenizer at 2000 rpm for 2 hours. After being homogenized, it was then placed in an ultrasonic cleaner for 1 hour. The principle of ultrasonication is to break down particles efficiently and homogeneously so they can be dispersed in a liquid. In general, ultrasonicators function for various purposes, such as dispersing nanoparticles into a base liquid, preventing clumping, reducing nanoparticle size in a liquid, and facilitating nanoparticle synthesis and surface functionalization [16].

The nanoparticle extract was characterized using a Particle Size Analyzer (PSA) to determine particle size. In characterizing particle size using PSA, the specimen was dissolved in 3 mL of ethanol. The solution was then inserted into a tube with a maximum solution height of 15 mm. The diameter distribution of the specimen was measured using the VASCO Nano Particle Analyzer. This examination was performed using the Dynamic Light Scattering (DLS) method on a Zetasizer Nano ZS (Malvern Instruments). The scale of one nanometer is equal to one thousandth of a micrometer ($1 \text{ nm} = 1/1,000 \text{ }\mu\text{L} = 1/1,000,000 \text{ mm} = 1/1,000,000,000 \text{ m}$). The comparison between one meter and one nanometer is the same as the comparison between the Earth's globe and a ping pong ball. It can be understood that one per 1,000,000,000 m is a tiny size [17].

The method used is the serial dilution method, also known as multilevel dilution. The test method uses turbidimetry. A total of 10 sterile test tubes were prepared. Each tube was filled with 3.5 mL of Potato Dextrose Broth (PDB) media and 0.5 mL of *Malassezia furfur* fungus equivalent to the McFarland 0.5 standard. Each test tube was labeled 1-8, and tube nine was labeled K (+), which served as a positive control: a tube containing media and fungi. Tube 10 was labeled K (-), which is a negative control: a tube containing media and extract. Tubes 1-8 were filled with golden trumpet leaf extract (*Allamanda cathartica* L.) with concentrations of 100%, 50%, 25%, 12.5%, 6.25%, 3.125%, 1.56%, and 0.78%. In comparison, nanoparticles of golden trumpet leaf extract (*Allamanda cathartica* L.) were prepared at concentrations of 10%, 5%, 2.5%, 1.25%, 0.625%, 0.3125%, 0.156%, and 0.078% each in 1 mL, and the absorbance was measured using UV-Vis spectrophotometry. Furthermore, the treatment tube media was incubated for 48 hours. Then the absorbance measurement was carried out again using uv-vis spectrophotometry, all tubes were visually checked for turbidity, if the turbidity of each tube was still equal to or more turbid than the K(+) tube containing the media and fungi, it meant that the fungi can still grow, but if the solution in the tube looks clearer than the K(-) tube, it means that fungal growth is starting to be inhibited. This is what indicates the minimum inhibitory concentration (MIC). The minimum inhibitory concentration is determined by the lowest concentration in the treatment tube that inhibits fungal growth [18].

The data from the antibacterial activity test were statistically analyzed using one-way ANOVA at the 95% confidence level in SPSS.

Results and Discussion

Minimum Inhibitory Concentration

The results of the MIC test of golden trumpet leaf extract against *Malassezia furfur* showed that the extract of 0.78% to 6.25% had an absorbance value that increased from before and after. Incubation, while the absorbance at a concentration of 12.5% up to 100% shows a decreasing absorbance value before and after incubation. Nanoparticles of golden trumpet leaf extract were obtained from *Malassezia furfur*, with an absorbance value ranging from 0.078% to 0.625%. The absorbance value increased before and after incubation, while it decreased at concentrations of 1.25% to 10%. The lowest concentration that does not show an increase in absorbance after incubation is the MIC. So that the MIC value is at a concentration of 12.5% in the golden trumpet flower leaf extract and 1.25% in the nanoparticles of the leaf extract golden trumpet, the minimum Inhibitory Concentration (MIC) needs to be known in a medicinal plant extract because it is the lowest antibiotic concentration that can still inhibit the growth of certain organisms. [19]. Here are the Absorbance Values of MIC Nanoparticles Golden Trumpet Leaf Extract Against *Malassezia furfur*.

Table 1. Absorbance Value of MIC of Golden Trumpet Leaf Extract Nanoparticles Against *Malassezia furfur*

Concentrated Extract of Golden Trumpet Flower (<i>Allamanda cathartica</i> L.)	Results						Average			Note	MIC
	Treatment I		Treatment II		Treatment III						
	T0	Yes	T0	Yes	Yes	T0	Yes	T0			
K (-)	0.126	0.126	0.126	0.126	0.126	0.126	0.126	0.126	Still	-	
0.78%	0.091	0.165	0.082	0.156	0.071	0.181	0.081	0.167	Go on	-	
1.56%	0.154	0.242	0.147	0.296	0.121	0.294	0.140	0.227	Go on	-	
3.125%	0.256	0.365	0.233	0.357	0.199	0.294	0.229	0.338	Go on	-	
6.25%	0.585	0.652	0.552	0.545	0.521	0.519	0.552	0.575	Go on	-	
12.5%	0.865	0.843	0.925	0.892	0.833	0.756	0.874	0.830	Down	MIC	
25%	0.941	0.899	0.896	0.843	0.975	0.950	0.937	0.897	Down	-	
50%	1,239	1,188	1,219	1,165	1,162	1,121	1,206	1,158	Down	-	
100%	1,235	1,225	1,241	1,196	1,278	1,259	1,251	1,126	Down	-	
K (+)	0.134	0.169	0.134	0.169	0.134	0.169	0.134	0.169	Go on	-	

In Figure 1 below, the percentage results of the minimum inhibitory concentration (MIC) are shown as follows:

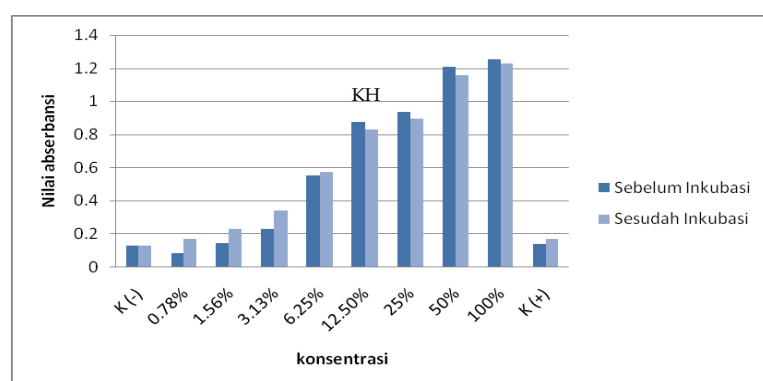


Figure 1. Percent of Minimum Inhibitory Concentration

Minimum Fungicidal Concentration (MFC)

The results of the Minimum Fungicidal Concentration (MFC) test showed that at a concentration of 50% in trumpet extract and 5% in trumpet extract nanoparticles, there was no growth of *Malassezia furfur* fungus. The MKC value was determined as the lowest killing concentration that prevented fungal growth on the agar

medium. Table 2 shows the results of the Minimum Fungicidal Concentration (MFC) of Ethanol Extract of Golden Trumpet Leaves Against *Malassezia furfur*.

Table 2. Minimum Fungicidal Concentration (MFC) of Ethanol Extract of Golden Trumpet Leaves Against *Malassezia furfur*

Concentration	Growth Colony	Information
6.25%	Grow	-
12.50%	Grow	-
25%	Grow	-
50%	No Grow	MFC

Antifungal Activity Test Results of Ethanol Extract and Nanoparticles of Golden Trumpet Leaf Extract (*Allamanda cathartica* L.) Against *Malassezia furfur*

The results of the antifungal activity test of golden trumpet leaf extract against *Malassezia furfur* obtained Zone of Inhibition (ZOI) values of 11.4 mm (concentration 6.25%), 14.5 mm (concentration 12.5%), 17.4 mm (concentration 25%), and 21.1 mm (concentration 50%). Meanwhile, the results of the antifungal activity test of nanoparticles of ethanol extract of golden trumpet leaves against *Malassezia furfur* obtained Zone of Inhibition (ZOI) values of 11.3 mm (concentration 0.625%), 14.3 mm (concentration 1.25%), 17.4 mm (concentration 2.5%), and 21.1 mm (concentration 5%). The antifungal results of the ethanol extract and nanoparticles of ethanol extract of golden trumpet leaves showed that the higher the concentration, the greater the inhibitory power obtained, as in the research conducted by Zanuury (2014) [20]. The following are the results of the Test Activity: Antifungal Extract and Nanoparticles Ethanol Extract of Golden Trumpet Leaves Against *Malassezia furfur*.

Table 3. Minimum Fungicidal Concentration (MFC) of Ethanol Extract of Golden Trumpet Leaves Against

Concentration		Flat - Average ZOI (mm)		Interpretation	
EDIT	NEDTE	EDIT	NEDTE	EDIT	NEDTE
Control(-)	Control(-)	0	0	R	R
6.25%	0.63%	11.4	11.3	R	R
12.50%	1.25%	14.5	14.3	I	I
25%	2.50%	17.4	17.6	I	I
50%	5%	21.1	20.3	S	S
Control (+)	Control (+)	22.3	22.8	S	S

The test results above show that *Malassezia furfur* is sensitive to the ethanol extract of golden trumpet leaves and to nanoparticles of its ethanol extract, with concentrations classified as sensitive and intermediate, respectively. Positive control using disc paper containing 20 µg of the ketoconazole antibiotic produced an inhibition zone diameter of 22.3 mm with the golden trumpet leaf extract against *Malassezia furfur* and 22.8 mm with the ethanol nanoparticles of golden trumpet leaves against *Malassezia furfur*. This shows that *Malassezia furfur* is classified as susceptible (sensitive) to the antibiotic ketoconazole (CLSI).

Nanoparticles of 5% ethanol extract of golden trumpet leaves have the same antifungal ability as 50% ethanol extract of golden trumpet leaves with a sensitive category against *Malassezia furfur* fungus so that it can be said that nanoparticles of 5% ethanol extract of golden trumpet leaves can reduce the concentration of antifungal compound doses up to one tenth of the ethanol extract of golden trumpet leaves 50% (1:10). Based on the research that has been done, it is known that the antifungal inhibitory power of ethanol extract of golden trumpet leaves and nanoparticles of ethanol extract of golden trumpet leaves are effective against *Malassezia furfur* with the formation of an inhibition zone.

This shows that the higher the concentration used, the wider the inhibition zone. The higher the concentration of golden trumpet leaf extract and golden trumpet leaf extract nanoparticles, the more antifungal content it contains, and it will have a greater ability to inhibit *Malassezia furfur*. The difference in the inhibition zone diameter between the golden trumpet leaf extract and the antibiotics used is due to the extract being a crude preparation that contains many other compounds, which affect its ability to inhibit fungal growth. Ethanol extract nanoparticles can reduce the dose of a drug because, at a small concentration, the

inhibition zone is almost equivalent to that of the ethanol extract with a higher concentration. The cause is the difference in particle size.

The negative control used was dimethyl sulfoxide (DMSO). DMSO is a solvent that can dissolve almost all compounds, both polar and non-polar. DMSO is a compound that has low toxicity and exhibits anti-inflammatory and analgesic effects. Data from solvent tests carried out using the disc paper method against *Malassezia furfur*. [21,22]. The positive control used was ketoconazole, which produced the largest inhibition zone because it is highly effective at inhibiting the growth of *Malassezia furfur*, making it suitable for use in the antifungal test using the disc diffusion method. Ketoconazole is an azole antifungal, which is a potent inhibitor of ergosterol biosynthesis by inhibiting 14- α -demethylase, a microsomal cytochrome P450 enzyme in the fungal membrane. Another target of the antifungal ketoconazole is the plasma membrane, and it can also interact with 3-ketosteroid reductase (an enzyme in the biosynthesis of methyl sterols). Ketoconazole works specifically to inhibit the microsomal cytochrome P450 enzyme in the fungal membrane that is responsible for the synthesis of ergosterol in fungal cells [23]. The ability to inhibit the antifungal activity of the ethanol extract and nanoparticles of the ethanol extract of golden trumpet leaves in this study depends on the type of fungus being tested and on the content of active compounds. Golden trumpet leaves (*Allamanda cathartica* L.) are among the plants that can be used as antifungals. The chemical content of golden trumpet leaves (*Allamanda cathartica* L.) includes alkaloids, flavonoids, steroids/triterpenoids, tannins, saponins, and glycosides.

Alkaloids are compounds that have antifungal activity by inhibiting DNA esterase and RNA polymerase. [24–27]. Alkaloid compounds, including anthraquinones, glycosides, and resins, can penetrate fungal cell walls, disrupting their metabolic processes. This disruption can lead to cell growth inhibition at specific concentrations, ultimately resulting in fungal cell death [28].

Flavonoids work by inhibiting fungal cell membrane disruption. They also denature cell proteins and shrink the cell wall, causing the fungal cell wall to lyse because flavonoids form a protein complex with cell membrane proteins [29,30]. This is in line with the results of research by Marsha et al. (2022), which found that flavonoids possess hydroxyl groups that can alter the organic components of microbial cells, disrupt nutrient transfer, and exert toxic effects on fungi. Saponins contribute as antifungals by reducing the surface tension of the sterol membrane of the *Malassezia furfur* cell wall, increasing its permeability [31]. Increased permeability draws more concentrated intracellular fluid out of the cell, allowing nutrients, metabolic substances, enzymes, and proteins to exit, and the fungus dies. Saponins are a group of compounds that can inhibit or kill microbes by interacting with the sterol membrane. The main effect of saponins on microbes is the release of proteins and enzymes from within the cell [32]. The mechanism of action of phenol is by increasing the permeability of the cytoplasmic membrane, causing leakage of intracellular components and coagulation of the cytoplasm, resulting in cell lysis [33]. Phenolic compounds are antimicrobial agents with bactericidal and fungicidal properties. They exhibit broad-spectrum activity against both gram-positive and gram-negative bacteria, as well as certain fungi, making them suitable for intensive use as disinfectants [34].

The mechanism of action of steroids as antibacterials involves lipid membranes and their sensitivity to steroid components, leading to leakage from fungal liposomes. Steroids can interact with cell phospholipid membranes that are permeable to lipophilic compounds, decreasing membrane integrity and altering cell membrane morphology, leading to fragile cells and lysis. The mechanism of action of tannins as antifungals is by inhibiting the biosynthesis of ergosterol, which is the principal sterol in fungal cell membranes. Sterols are both structural and regulatory components found in eukaryotic cell membranes.

Gunawan & Rahayu (2021) stated that the higher the concentration of plant extracts containing antibacterial compounds, the greater the inhibitory power of the antibacterial activity. [35]. Likewise, Rahayu et al. (2021) stated that the higher the concentration of the plant extract tested, the greater the diameter of the zone of antibacterial activity inhibition. [36]. According to Rahayu *et al.* (2022), the antibacterial ability of a plant extract depends on the type of plant, the content of metabolite compounds in the plant, and the type of bacteria to be tested [37].

According to Fahira *et al.* (2023), preparations in the form of plant extract nanoparticles can reduce the dose of a drug. Nanoparticle extracts can reduce the dose of a medication because, at small concentrations, the inhibition zone of antibacterial activity is almost equivalent to that of extracts with higher concentrations [38,39]. The cause is differences in particle size. Nanoparticles are tiny, so they are more effective in penetrating bacterial cell walls and inhibiting bacterial growth [40].

The definition of nanoparticles is ultrafine particles measuring in the order of nanometers. “Nano” is a prefix indicating the power of minus nine of ten, which is one millionth. Here, nanometer (nm) is used for

length. One nm is a minimal length equivalent to one millionth of 1 m, one millionth of 1 mm, or one thousandth of 1 μm . The definition of nanoparticles varies depending on the material, field, and application. In a narrower sense, nanoparticles are considered as particles smaller than 10-20 nm, where the physical properties of the solid material itself will change drastically. On the other hand, particles in the 1 nm to 1 μm range are called nanoparticles. In many cases, particles measuring 1 to 100 nm are generally referred to as nanoparticles. Still, here, nanoparticles will be considered as particles smaller than those conventionally referred to as "submicron particles," and concretely smaller than the wavelength of visible light (the lower limit of which is about 400 nm), as a size that needs to be treated differently from submicron particles [41]. A *Drug Delivery System (DDS) with nanoparticles delivers the appropriate amount of drug* to the relevant body area when needed. It is the targeting of drugs introduced into the body to a specific location. There are two targeting methods: active targeting, which utilizes particular affinity (e.g., antibodies) in the human body, and passive targeting, which prolongs the blood circulation time of intravenously administered drugs and increases the efficiency of drug accumulation in inflammatory areas or tumor cells. [41].

On the other hand, in considering the concept of DDS as an ideal drug formulation (DDS in a broad view), it is necessary to focus on drug delivery into the body by selecting the most appropriate route of administration. Since many water-insoluble drugs have been developed in recent years, it is an important task to find new delivery methods to obtain the efficacy of a particular drug.

Although some drugs are given as injections, patients should opt for less invasive routes such as oral administration. This will lead to good patient compliance. The demand for this type of dosage form has increased. In any aspect of drug delivery, nanoparticles are expected to play a vital role in complementing it. To design a dosage form using nanoparticles, it is necessary to understand their role and behavior precisely. For example, when drugs are incorporated into fine particles and administered intravenously, the particle diameter should be in the submicron range, around 100 nm. Particulate drug carriers may clog the very narrow sections of blood vessels. Externally administered particles are recognized as non-self in the body whenever they are fine enough [41].

The advent of nanotechnology has created unprecedented promise for addressing several unmet industrial and clinical issues, including the growing threat of so-called "antibiotic resistance" in medicine. Recent insights into the field of bacterial nanotechnology are explored that could substantially improve the fundamental understanding of nanoparticle-bacterial interactions. Nanotechnology-based approaches have been developed for bacterial detection and removal, as well as biofilm eradication. The challenges posed by nanotechnology to beneficial bacteria in the human body and the environment, and the mechanisms of bacterial resistance to nanotherapy, are reviewed. [42].

Bacterial infections are a growing health problem mainly due to the current imbalance between the discovery of new drugs and the rate of bacterial resistance. Therefore, there is an urgent need to develop new antibacterial therapies to address this growing problem. Over the last few decades, nanotechnology has been increasingly developed and used to address bacterial resistance, with promising results. Nanoparticles (NPs) can interact with bacterial membranes and disrupt efflux pumps and membrane integrity, along with the induction of oxidative stress [43–45]. Unlike conventional antibiotics, NPs can cross biological barriers and biofilms (e.g., by applying an external magnetic field to magnetic NPs) [46–48]. NPs are also able to kill bacteria effectively, before the growth and development of infection, by inhibiting density-dependent cell-to-cell signaling that drives bacterial growth, virulence, and resistance [49–51]. Therefore, the development of precision antibacterial therapy is a rational strategy to use lower concentrations of NPs with the highest therapeutic efficacy to kill bacteria in the shortest possible time [42].

Data Analysis Results

The results of the normality test on the extract of golden trumpet leaves against *Malassezia furfur* show a p-value (Sig.) of 0.637 (≥ 0.05), indicating that H_0 is accepted and that the data are typically distributed. The data in this study were normally distributed, allowing a parametric one-way ANOVA. The results of the homogeneity test for the ethanol extract of golden trumpet leaves show a Sig. The value of 0.014 is greater than 0.05. Based on the decision-making criteria in the homogeneity test above, H_0 is accepted, indicating that the group variances are not significantly different and that the variances of the compared groups are homogeneous. ANOVA data of the diameter of the inhibition zone of the ethanol extract of golden trumpet leaves against *Malassezia furfur* shows a Sig. Value of 0.000 < 0.05 , which means that there is a significant difference in the provision of ethanol extract concentration variants of golden trumpet leaves on the antifungal activity of *Malassezia furfur*. Furthermore, to assess the similarity in the effects of average ethanol extract

concentration variants on antifungal activity, a Duncan Post Hoc test was used. The results obtained at extract concentrations of 6.25%, 12.5%, 25%, and 50% are in different columns, so each treatment has a different (significant) effect on the dependent variable.

While the results of the normality test on the nanoparticles of the ethanol extract of golden trumpet leaves against *Malassezia furfur* show a p-value (Sig.) of 0.637 (> 0.05), the data are typically distributed. The data in this study follow a normal distribution, and one-way ANOVA can be used. The results of the homogeneity of the nanoparticles of the ethanol extract of the trumpet have a Sig value. $0.014 \geq 0.05$, then based on the decision-making criteria in the homogeneity test above, H_0 is accepted, which means that the group variances are not significantly different, so that it means that the variance of the compared data groups is homogeneous. ANOVA data on the diameter of the inhibition zone of nanoparticles from the ethanol extract of golden trumpet leaves against *Malassezia furfur* show a significant Sig value. Of $0.000 < 0.05$, which can be concluded that there is a substantial difference in the provision of variants of the concentration of nanoparticles of ethanol extract of golden trumpet leaves on the antifungal activity of *Malassezia furfur*. Furthermore, to assess the similarity in average nanoparticle concentration in the ethanol extract of golden trumpet leaves and their antifungal activity against *Malassezia furfur*, Duncan's Post Hoc test was used. The results from positive and negative controls and nanoparticle extract concentrations of 0.625%, 1.25%, 2.5%, and 5% are in different columns, so each treatment has a different (significant) effect on the dependent variable.

Conclusion

The minimum inhibitory concentration (MIC) value of 1.25% ethanol extract nanoparticles of golden trumpet leaves is better than that of 12.5% ethanol extract of golden trumpet leaves. The Minimum Fungicidal Concentration (MFC) value of 5% ethanol extract nanoparticles of golden trumpet leaves is better than 50% ethanol extract of golden trumpet leaves against *Malassezia furfur* fungus. Nanoparticles of 5% ethanol extract of golden trumpet leaves have the same antifungal ability as 50% ethanol extract of golden trumpet leaves with a sensitive category against *Malassezia furfur* fungus so that it can be said that nanoparticles of 5% ethanol extract of golden trumpet leaves can reduce the concentration of antifungal compound doses up to ten times compared to 50% ethanol extract of golden trumpet leaves (1:10).

Conflict of Interest

The authors State that there are no conflicts of interest with any person or organization related to the conduct of this study and the preparation of this manuscript. They also confirm that all materials were handled and presented with full accountability and conscientiousness.

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