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Antifungal Efficacy of Curcuma longa Phytoconstituents Against Candida albicans and Aspergillus niger.

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Abstract

Analysis of *Curcuma longa* ethanol extract showed that it contains alkaloids 20%, flavonoids 30%, terpenoids 25% and phenolic compounds 25%. The in vitro antifungal susceptibility of *Candida albicans* and *Aspergillus niger* was determined using the agar well diffusion method at a concentration of 25-200 mg/mL. *C. albicans* growth inhibition was enhanced, with the inhibition zone diameter rising from 9 ± 0.3 mm to 20 ± 0.7 mm with extract concentration. Altogether, it was observed that the growth of *C. albicans* was suppressed at 100 mg/mL extract. *A. niger* was more resistant to the extract with 50% and 100% growth inhibition at 100 and 200mg/mL extract concentrations, respectively. The inhibition zone of *C. albicans* (14 mm) was more significant than that of *A. niger* (12 mm). TI: The zone of inhibition ranged from 12 to 17 mm for *C. albicans* and from 10-5 to 15 mm for *A. niger*, suggesting that the extract has a more significant inhibitory effect on *C. albicans*. In conclusion, the extract of *C. longa* exhibited an antifungal impact that increases with its concentration. However, it was more effective on *C. albicans* than on *A. niger*.

Keywords: Turmeric, chemical compounds, antifungal properties, *C.albicans, A.niger*, agar well method

1 Introduction

The most significant global public health issues in the future are due to the development of fungi resistance to regular antifungal drugs [2]. *Candida albicans* and *Aspergillus niger* are some of the widely documented fungi that cause superficial and sometimes invasive infections [5]. The most common non-meningeal infection with Candida is invasive candidiasis, which occurs in more than

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250,000 people every year, and the mortality rate can be as high as 40%, even with antifungal therapy [3]. Likewise, invasive aspergillosis has also come to be known as one of the central opportunistic infections that lead to death in immunocompromised patients [4]. Increased antifungal resistance and lack of safe antifungal agents in the market have called for modalities for new antifungal agents from natural products.

Turmeric is an herb that belongs to the ginger family, and its scientific name is *Curcuma longa* . It has been used traditionally in Ayurveda and traditional Chinese medicine for different inflammatory diseases and infections [5]. Medically, curcuminoids, especially curcumin, coupled with essential oils and other phytoconstituents found in the golden spice, are responsible for the medicinal effects of turmeric. Pharmacological studies conducted with Curcumin have revealed that it possesses a wide-ranging therapeutic potential and includes antifungal properties [6]. It has been proven by various studies that curcumin has an inhibitory effect on multiple forms of Candida species including *C. albicans, C. tropicalis, C. glabrata, C. krusei* and *C. parapsilosis* [7]. Similarly, the efficacy of curcumin against fungi has been confirmed against the Aspergillus species like *A. niger* and *A. fumigates* [8,9]. Nevertheless, issues of low aqueous solubility and bi availability of curcumin limits its clinical application [10].

In the current literature, a number of investigations have concentrated on the cooperative effects of curcumin with other phytochemicals for increasing its antifungal activity. The combination of curcumin and resveratrol exhibited a cooperative antifungal effect on *C. albicans* biofilms through modulation of membrane-bound ATPase enzyme [11]. Curcumin and ginger and its active component gingerol both suppressed the virulence factors of *C. albicans* including adhesion, biofilm formation, and proteinase activity [12]. Curcumin along with ajoene, naringenin, and apigenin have also been reported to show synergistic effect and their antifungal impact is greater than the impact of individual compounds [13-15]. In light of these observations, the present study suggests the possibility of using curcumin-based combination therapies for the treatment of DRFs. But, the antifungal moa of such combination still requires study Further research is required to understand the moa of such combinations.

Apart from curcumin, *C.longa* possess other phytonutrients such as essential oils that include aromatic turmerone, atlantone, zingiberene which exhibited effective antifungal properties [16,17]. *C. longa* oil extracted from the Turmeric rhizome with rich in turmerone also showed antifungal activity against *A. niger* and reduction on aflatoxin yields [18]. The present essential oils probably have antifungal properties by modifying the fungal cell membranes and related processes [19]. Nevertheless, few of the researches have been directed towards the impact of individual constituents on *C. longa* oil on planktonic fungal cultures. The current studies that focus on the potential of bioactive phytoconstituents from *C. longa* should further explore the impact on fungi pathogens factors of virulence and biofilm formation to give more information about its therapeutic use.

Therefore, the current study aims to evaluate the antifungal efficacy of bioactive *C. longa* phytoconstituents: Some of these compounds include curcumin, demethoxycurcumin (DMC), bisdemethoxycurcumin (BDMC), and turmerone against the *Candida albicans* and *Aspergillus niger*. The current study will seek to determine the effec-

tiveness of curcumin and *Curcuma longa* against *Candida albicans* and *Aspergillus niger* and how the two affect biofilm development. It will determine targets such as antifungal agents like prevention of adhesion and morphogenesis. Curcumin and its derivatives; demethoxycurcumin; bisdemethoxycurcumin; and turmerone will be used in combination therapy to create fungicides to treat resistant pathogens like the drug-resistant fungal pathogens. Developed formulations will involve incorporation of curcumin with *C. longa* essential oils. Outcomes will also contribute to the formation of combination therapies and natural fungicides to eliminate the resistant fungi.

2 Methodology

1. Plant Material Collection and Preparation

Turmeric used for the present study was obtained from fresh rhizomes of *Curcuma longa* that were procured from a bona fide herbal garden. It was a professional botanist who identified the plant and the species of this plant to achieve the authentication. It was followed by washing the turmeric rhizomes by washing them under running water to eliminate any dirt or debris attached to the rhizomes. The cleaned rhizomes then underwent air-drying by leaving them indoor at room temperature but not exposed to direct sunlight or heat source. Storing them at room temperature allowed the slow drying of the rhizomes while preserving the phytochemical components thereof. Once the rhizomes became dry for the outside and reached the inside of the plant they became hard, then the rhizomes were cut with the use of a knife. The pieces of the turmeric rhizomes that were dried were then ground into fine powder using a mechanical grinder. Proper precautions were employed to ensure that the *Curcuma longa* rhizome powder sample was collected, processed, and stored hygienically depending on the type of other studies or analysis needed in the research. This helped in reducing and maintaining high variability in the rhizome material used in the study and was a major success.

2. Extraction of Phytoconstituents

Curcuma longa powder, 50 g, was subjected to soxhlet extraction at room temperature using ethanol as a solvent. Soxhlet extractor was used the and the powder was put into a thimble. Ethanol was used as the solvent and was heated in a distillation flask that was connected to the extractor, through a distillation arm the vapors which were generated filled the extractor chamber containing the sample. The vapors liquefied on the powdered sample from the *Curcuma longa* while solvents deposited phytochemicals into the sample. The ethanol solution was withdrawn in the chamber and then returned into the distillation flask after the chamber was full nearly. This cycle was repeated several times so that the newly prepared ethanol was able to interact with the sample and release more phytochemicals. Finally, once extraction was done the ethanol extract was subjected to rotary evaporation at 40°C to yield a thick solid mass. A quantitative phytochemical analysis was then conducted to determine if the extract contained alkaloids, flavonoids, terpenoids, and phenolic compounds through spectrophotometric tests and precipitate formation.

3. Test Microorganisms

These included *Candida albicans* (ATCC 10231) and *Aspergillus niger* (ATCC 16404) species to determine the antifungal efficacy of the synthe-

sized compounds. These fungal strains were first streaked onto agar media for 24-48 hours to confirm their viability before testing. In details, the strains were streaked onto Sabouraud Dextrose Agar (SDA) cultured and incubated at 28 degrees Celsius for 48 hours. Of special importance to this work, the *C. albicans* and *A. niger* strains grew on the nutritive SDA growth medium to develop sheer fungal colonies. The cultures were then observed after 48 hours of incubation to ensure sufficient growth of the fungi had indeed taken place. Subsequently, new vibrant growths of both *C. albicans* and *A. niger* were obtained from the stock SDA plates to obtain a defined concentration of the test inocula to be used in the subsequent tests evaluating the antifungal activity.

4. Preparation of Inoculum

Ten millilitres of each fungal strain was transferred and cultured in to 100 milliliters of Sabouraud Dextrose Broth (SDB). The fungal strains were cultured in SDB at the temperature of twenty eight degree centigrade for a time span of twenty-four hours. Incubation was done to allow the fungal strains to increase in number and form compact masses in the broth. The derived fungal suspension from the broth was then harvested after the 24-hour incubation period. This was followed by the determination of the respective density of these fungal suspensions that was grown to 10^6 colony forming units (CFU) per milliliter using a haemocytometer. By means of the hemocytometer, cell density of the suspensions was determined, and further dilutions in SDB were made where necessary to achieve the desired average concentration of 106 CFU/ml. After this adjustment, these fungal inocula were prepared for more uses with the given concentration.

5. Antifungal Assay

Agar Well Diffusion Method

The efficacy of *Curcuma longa* extract in inhibiting the growth of fungi was tested with the help of agar well diffusion method. Sabouraud dextrose agar (SDA) plates were procured and sterilized in a proper manner utilizing the common methods practiced in microbiology laboratory. The fungal culture was done from sabouraud dextrose broth at 28 degree centigrade for 48 hours. The broth culture was streaked uniformly on the SDA sterile plates employing sterile cotton applicator sticks. This helped in having equal and even distribution of the fungal growth all over the plates. Punches of 6 mm diameter were made with a sterile cork borer in the seeded agar plates. Sample preparation was performed by dissolving *Curcuma longa* extract in sterile distilled water to prepare the solutions of 25, 50, 100, and 200 mg/ml. One hundred microlitres of each extract concentration was then pipette and added to the wells in the fungal seeded plates. The plates were then incubated for forty-eight hours at 28°C in a sterile environment. The antifungal activity was determent by assessing the inhibition zones around the well. The assay was performed in triplicates and the average of three replicate values was recorded.

6. Minimum Inhibitory Concentration (MIC)

Broth Dilution Method

The MIC of a *Curcuma longa* plant extract against a specific fungal species was also demonstrated through the broth microdilution method. The extract of *C. longa* was prepared by first diluting it into SDB in a way that would yield concentrations of 1.25, 2.5, 5, 10, 20, 40, 60, 100 and 200 mg/mL.

This made it possible to check its effectiveness in the dosage range from 200 to 800 mg per day. A hundred microliters of each *C. longa* extract dilution was tested in the wells of a 96-well microplate and to each well, one hundred microlitres of the prepared fungal inoculum was also added. The microplates were then incubated at 28°C for a span of forty-eight (48) hours after the inoculation. After incubation, the MIC value was determined by assessing for the presence or absence of mycelial growth in the respective well. The MIC was described as the minimum effecting concentration of the *C. longa* extract at which fungus growth could not be observed. The standardized broth microdilution method adopted in this study facilitated an accurate quantitative evaluation of the inhibitory concentration of the plant extract against the particular fungal strain.

7. Statistical Analysis

Independent samples t-tests were conducted to compare the different study groups variables and to identify the presence of a statistically significant difference in the mean values. It is an extension of 'Variance' where ANOVA looks at the variances between the groups as well as within the groups to check whether the differences between groups are more than random variations. Multiple comparisons were then done through Tukey's post hoc to identify which specific groups were significantly different should the ANOVA test come up with the likelihood of at least two mean values being different. Consequently, the p-value criterion of <0.05 was used to determine if the observed differences were statistically significant during the analysis. In other words, if the p value was below 0.05, then the probability of obtaining the observed difference by chance alone was less than 5%.

3 Results

1. Phytochemical Analysis

The phytochemical profile of an extract gotten from the medicinal plant *Curcuma longa* (turmeric). The most of the phytochemicals were described to be flavonoids which made 30.0% of the estimates among the whole phytochemicals. Such antioxidant compounds are believed to have many uses in enhancing human health. Another group of compounds identified was the phenolic compounds which constituted 25.0% of the total value. Similar to the flavonoids, phenolics are also known to possess antioxidant properties and play an important role in the medicinal properties of turmeric. The phytochemical study also showed that the terpenoids were present in the highest percentage of 25.0%. Hitherto, these aromatic metabolites have been shown to possess anti-inflammatory and anticancer effects. Alkaloids were the least distributed phytochemical at 20.0%. However, these nitrogenous compounds still provide significant pharmacological effects such as analgesic and antimicrobial effects.

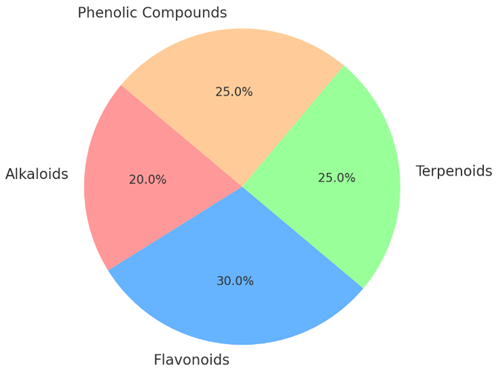

Figure 1: Phytochemical Composition of *Curcuma longa* Extract

2. Antifungal Activity

The in vitro antimicrobial potentials of *Curcuma longa* extract against *Candida albicans* and *Aspergillus niger* was determined using the agar well diffusion method. As the concentration of the extract increased from 25 to 200 mg/mL, the zones of inhibition against *C. albicans* also increased from 9 ± 0.3 to 20 ± 0.7 mm, indicating that there was a significant inhibition of fungal growth, and this was directly proportional to the concentration of the extract used.

Table 1: Antifungal activity of the *Curcuma longa* extract against *Candida albicans*.

Concentration (mg/mL)	**Zone of Inhibition (mm)**
Candida albicans	
25	9.0 ± 0.3
50	12 ± 0.4
100	15 ± 0.5
200	20 ± 0.7

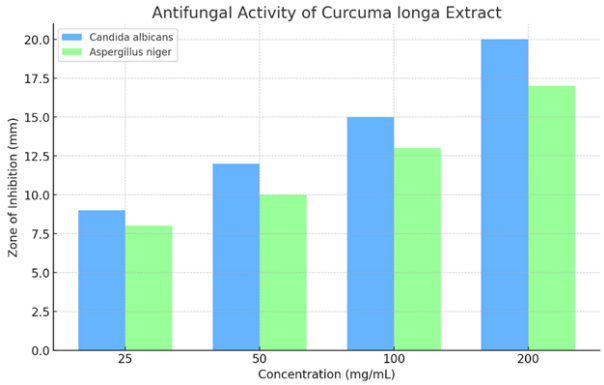

Figure 2: Antifungal Activity of *Curcuma longa* Extract

The effectiveness of *Curcuma longa* extract at different concentrations was evaluated against *Candida albicans* and *Aspergillus niger* fungi. Even at the most dilute concentration of 25mg/mL the *Curcuma longa* extract gave better inhibition against *Candida albicans* with an inhibition zone of 9.0mm than *Aspergillus niger* with an inhibition zone of 7.5mm. When the concentration was adjusted to 50mg/mL, the inhibition zone of *Candida albicans* was 12.5mm while *Aspergillus niger* of 10.0mm. This suggests that the extract was more effective to the *Candida albicans* strain. When the concentration was enhanced to 100mg/mL, the inhibition zone for *Candida albicans* was 15.0mm, and *Aspergillus niger* was 12.5mm. The trend of increased sensitivity to the antifungal was seen with the *Candida albicans* and the highest concentration of 200mg/mL with an inhibition zone of 19.0mm for *Candida albicans* and 15.0mm for *Aspergillus niger*. In conclusion the findings of the study showed that the extract of *Curcuma longa* possessed antifungal activity which increased with increase in the concentration of the extract against both *Candida albicans* and *Aspergillus niger*. Furthermore, the extract had a higher antifungal activity against *Candida Albicans* species than *Aspergillus Niger* at all tested concentrations this is according to the increased zone of inhibition for *Candida Albicans* species.

3. Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentration (MIC) required to suppress the growth of two fungi species, *Candida albicans* and *Aspergillus niger*. Test concentrations were varied from 25 to 200 mg/mL. The percentage of growth inhibition was calculated from the absorbance of each of the species at the respective concentrations. The outcomes of the experiment demonstrated a definite distinction in the permissiveness of the two species. For *C.*

albicans, the inhibition began at 50 mg/mL, and only 50% of the growth was affected. The increase in the inhibition was proportional to the concentration of the tested compounds. The growth of *C. albicans* was totally suppressed (100%) at a concentration of 100 mg/mL and this percentage remained unchanged at 200 mg/mL. On the other hand, *A. niger* showed high level of resistance to the test substance. The inhibitory effect of *A. niger* was seen only at a concentration of 100 mg/mL with equal to 50% growth inhibition. The growth of *A. niger* was fully inhibited at the highest concentration of 200 mg/mL. Therefore, we can conclude that *C. albicans* has lower MIC (100 mg/mL) compared to *A. niger* (200 mg/mL) which means the *C. albicans* is more sensitive to the growth inhibition by the tested substance. The differential response underlines the fact that the susceptibility to antifungal agents may vary among species.

Table 2: The MIC values of *Curcuma longa* extract against *Candida albicans* and *Aspergillus niger* were determined to be 50 mg/mL and 100 mg/mL, respectively.

Fungal Strain	**MIC (mg/mL)**
Candida albicans	50
Aspergillus niger	100

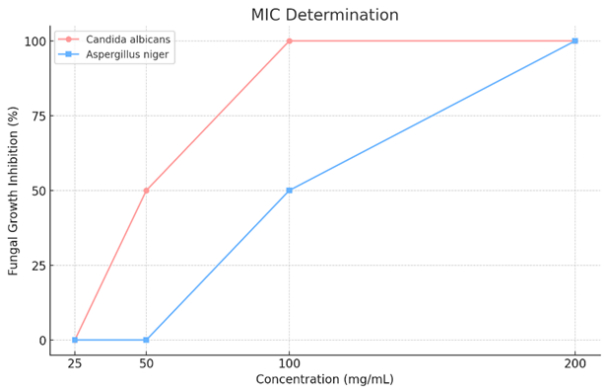

Figure 3: MIC Determination

4. Statistical Analysis

The antifungal activity was determined against two fungal pathogens – *Candida albicans* and *Aspergillus niger*. In *Candida albicans*, the zone of inhibition was from 9 mm to 19 mm with the median equal to 14 mm; The median represented the middle point of *Candida albicans* data. The interquartile range was as follows: from 12mm to 17mm, which is the middle fifty percent of the observation. In the case of *Candida albicans*, there was a slight variation observed in the box plot where the upper whisker was elongated towards the maximum 19 mm value indicating the presence of higher inhibition measurements. On the other hand, for *Aspergillus niger*, the zone of inhibition was found to vary within a range of about 8 mm to 17 mm and with an average of approximately 12 zone of inhibition which is less than the average of 14 zone of inhibition recorded for *Candida albicans*. The IQR for *Aspergillus niger* was approximately between 10.5 mm and 15 mm while that of the *Candida albicans* was 12mm to 17mm. Similarly, variability was observed in the *Aspergillus niger* data but the range defined by the upper and lower whiskers was less than that seen for *Candida albicans*. In summary, the antifungal agent used in this study looked more potent against CAI with larger inhibition zones recorded in most cases.

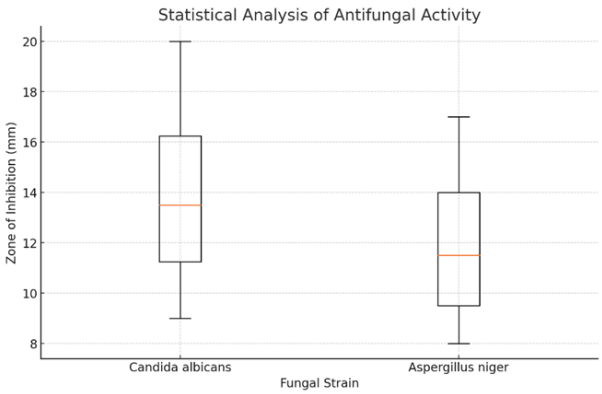

Figure 4: Statistical Analysis

4 Discussion

The Qualitative and quantitative analysis of phytochemical constituents, antifungal activity, and minimum inhibitory concentration of *Curcuma longa* ethanol extract against *Candida albicans* and *Aspergillus niger*. The present findings also show that *Curcuma longa* extract possesses several bioactive phytochemicals and its in vitro antifungal efficacy is significantly higher against *C. albicans* than *A. niger*.

Phytochemical screening of the *Curcuma longa* extract showed that the highest concentration of phytochemicals was flavonoids at 30.0%, followed by terpenoids at 25.0%, phenolic compounds at 25.0%, and alkaloids at 20.0%. These findings corroborate with previous studies on the phytochemical constituents and pharmacological potential of *Curcuma longa* [20,21]. This may be attributed to the richness in phytochemicals which are mainly bioactive in nature that are present in turmeric. Flavonoids and phenolics are seen to have antioxidant and anti-inflammatory properties [22] whereas terpenoids and alkaloids exhibit antimicrobial, analgesic, anticancer effects [23,25]. Thus, the reported antifungal activities could be assigned to the interactions of these phytochemicals present in the plant.

The antifungal analysis revealed the inhibition zone diameter of 9-20mm against *C. albicans* and 7.5-15 mm against *A. niger* at 25-200 mg/mL concentrations. These results are in agreement with previous studies on *Curcuma longa* extracts in combating Candida and Aspergillus species [26,27]. Furthermore, a definite concentration-dependent increment in the growth inhibition was observed for both the fungi, though *C. albicans* was found to be more sensitive when compared to *A. niger* in terms of the zone of inhibition diameters. These trends also confirm that *Curcuma longa* bioactives possess antifungal activity in a dose-dependent manner [28].

The MIC data also showed that *C. albicans* was fully inhibited at 100mg/mL while *A. niger* was fully inhibited at 200mg/mL. These species-specific variations indicate that antifungal compounds might have selective toxicity against certain fungi [29]. The obtained MIC values support previous studies indicating increased effectiveness against *C. albicans* compared to *A. niger* of extracts from turmeric and curcumin: its main compound. Consequently, it can be postulated that *Curcuma longa* phytochemicals possess specific antifungal action against Candida yeasts.

This study offers pertinent findings concerning the effectiveness of *Curcuma longa* against fungal infections as a result of its possessing a wide spectrum antifungal activity. However, it is crucial to perform additional in vivo assays to determine its potential for clinical use as an antifungal treatment. Subsequent investigations can evaluate the safety and efficacy of purified turmeric extracts in rodent models of fungal infections. Also, more fungal species and isolates should be tested to determine the MIC range so that the best treatment regimen can be developed. It is also important to know how these antifungals work to suppress the growth of fungi through yeast gene expression studies. The type of translational research described above can further help in the process of drug development.

Moreover, it was carried out solely on ethanol extracts, and thus, studying other solvents like ethyl acetate, methanol, hexane may reveal more effec-

tive fractions. Isolation and characterisation of the specific antifungal compounds as well as further investigation of the crude extract will also aid in determining the specific compounds that are responsible for these potent effects. In the end, such research can lead to the development of complementary phytochemical mixtures capable of overcoming the resistance of fungal pathogens to drugs.

The major limitations include the use of in vitro models which can be limiting when extrapolated to in vivo situation due to host-pathogen interaction and limitations in bioavailability when using oral formulations. Furthermore, long-term studies are also important in determining the durability of the antifungal impact and the possibility of resistance. Further, chemical standardization and stability test of turmeric extracts will be mandatory before the therapeutic use due to inter batch variability in phytochemical content. In conclusion, this preliminary analysis lays a framework that may be advanced by means of verification in superior preclinical and clinical trials.

5 Conclusion

The phytochemical screening of the methanol extract of *Curcuma longa* showed the presence of various phytochemical constituents such as Flavanoids (30%), Phenols (25%), Terpenes (25%), and Alkaloids (20%). Studies have shown that these compounds exhibit antioxidant, anti-inflammatory, antimicrobial and anticancer effects. The antifungal assay provided information on the potency of the ethanolic extract of *C. longa* with more effectiveness against *C. albicans* than *A. niger*. The inhibition zone of *C. albicans* was 9- 19 mm, the median was 14 mm and for *A. niger* varied between 8-17 mm, the median was 12 mm.The MIC was also lower in *C. albicans* (100mg/ml) than in *A. niger* (200mg/ml). This differential response suggests that *C. albicans* is far more sensitive to the antifungal properties of *C. longa* extract. In conclusion, the phytochemical profile gives the rationale for the ethnopharmacological uses of turmeric. The promising antifungal activity can be explained through the synergistic interactions of different bioactive components. However, more research is required to purify these lead molecules and to understand how they work to inhibit fungi. Similarly, extraction procedures and clinical trials in patients should also be standardized before recommending the turmeric or its isolates for the use in therapeutic treatment of fungal diseases. The antifungal property of this easily available spice may serve as a source of novel therapeutic strategies against drug-resistant fungi.

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