ORIGINAL ARTICLE

Efficient antidermatophytic agents to fight clinical *Tinea spp.* using *Salvia multicaulis* and *Hypericum scabrum*-based sustainable NCs

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Abstract: Increased problems associated with side effects and microbial resistance of chemical drugs have promoted the research focus of herbs and herbs-based medicines as renewed interest. The present study studied the antifungal potential of *Hypericum scabrum (H. scabrum), Salvia multicaulis (S. multicaulis)* plants and their derived sustainable NCs against dermayophyton species. These plants were used as free-toxic solvent media and phytogradiant reductants to fabricate nanoformulations as alternative antimycotic drugs. Analysis of antifungal activity showed a noticeable inhibition of the *trychophyton* mycelial growth when cultured on SDA mixed with different doses of the plant extract, particularly 50% *H. scabrum* that stopped mycelial growth of *T. mentagrophytes* and *T. verrcuosum* thoroughly after 10-day incubation by of 100 % MGI, followed by Ag@Fe_3O_4@SiO_2 with particle size around 20 to 60 nm, that record (67.64 and 63,.33 % of MGI) by 50 μg ml^{-1} application respectively. The lowest effect of *H. scabrum* and Ag@Fe_3O_4@SiO_2 at high concentrations was against *T. simii* (44.44 % and 16 % MGI). The maximum antifungal activity of 50 % *Salvia multicaulis* and 50 μg ml^{-1} CuO@SiO_2 NC with an average diameter of 60 nm was found against *T. mentagrophytes* and *T. verrcuosum* with (66.66 and 51.47 % MGI), respectively, while the minimum activity was found against *T. quinckeanum* and *T. simii* (33.33 and 13.33 % MGI), respectively. Thus, these plant extracts and NCs could be used to develop a new medication for dermatophytosis.

Keywords: *Salvia multicaulis; Hypericum sabrum;* CuO@SiO_2 NCs; Ag@Fe_3O_4@SiO_2 NCs; antifungal activity; dermatophytes.

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INTRODUCTION

Dermatophytes are a cluster of closely interconnected fungi that influence the human keratinous tissue (skin, hair, and nails), driving external infections and dermatophytosis, called ringworm or Tinea (Doughari *et al.*, 2009). fungal infections are severe health problems in patients with immune-compromised cases driven either by diseases like coronavirus or cancer therapies and long antibiotic medicines. The medications used to fight tinea show numerous side effects and are extremely expensive (Abid *et al.*, 2020; Santos *et al.*, 2013; Tocci *et al.*, 2018) Therefore, the alarming gap in the antifungal area calls for a strong request for unique categories of compounds has renewed the interest in screening medicinal plants and natural products (Saido, 2018). Possessing the ability to produce an unlimited variety of chemical compounds, plants have been a source of bioactive remedies for centuries (Durgeshlal *et al.,* 2019). Herbs of the *Salvia* genus are traditionally depleted in infection therapy, the *S. multicaulis* extract has a rich source of flavonoids, polyphenols, anthocyanins, diterpenes, triterpenoids, amides, and proteins (Rowshan & Najafian, 2020; Salimikia *et al.*, 2016; Wu *et al.*, 2012). Moreover, flavonoids have been focused interest because of their protective effect on DNA damage, antioxidant, anti-fungal, wound cleaning and certain kinds of cancer (Mallikarjuna *et al.,* 2013; Zakaria *et al.,* 2010). The other plant of *Hypericum* genus known as healing herbs has an antioxidant profile of plant flavonols, benzoates, and cinnamates, and of flavan-3-ols, employs the plant as a promising candidate species for novel antifungals activity with no cytotoxicity on human cells (Ayan *et al.*, 2009; Ghasemi Pirbalouti *et al.*, 2014).

Eco-Nanotechnology utilizes the plants as reducing, capping, and stabilizing agents, free-toxic solvent media to carry out the reaction, accumulation of plant phytochemicals on the surface of fabricated nanocomposites them a promising candidate in nanomedicine as next-generation antimicrobial agents (Al-Janabi & Bashi, 2022; Khan & Khan, 2023; Rabiee *et al.,* 2020; Shumaila & Al-Thulaia, 2019). In the present study, the antifungal potential of *Hypericum scabrum (H. scabrum), Salvia multicaulis (S. multicaulis)* plants and their derived sustainable nanocomposites was studied against dermayophyton species. Toward screening new candidates as novel alternative antimycotic drugs as natural-product inspired drugs entering medicine for clinical *tinea spp.* treatment.

METHOD

Plant material

Hypericum scabrum (Hypericaceae) was collected from Zreeza village (GPS coordinates: Latitude 37°13’34.3599”N and Longitude 43°27’4.1499”E), *Salvia multicaulis (Lamiaceae)* was harvested from Gara (Latitude 36°59’8.2099”N and Longitude 43°18’16.0499”E) in Duhok city, Kurdistan Region of Iraq in 2021, Fig.1. The aerial part of the plants was cleaned and air-dried at room temperature (20° ± 2°C) and then homogeneusly powdered and stored in glass bottles in the dark at room temperature for next steps.

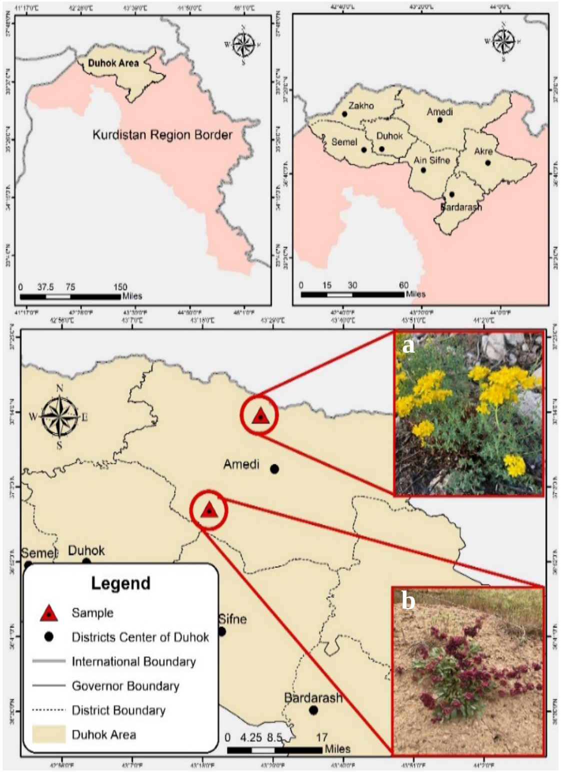


Figure 1. GIS map of: (a) *Hypericum scabrum,* and (b) *Salvia multicaulis* plants.

Phytochemical profile, synthesis and characterization of NCs

In continuation of our previous studies (Abduljabbar *et al.*, 2023; Omar *et al.*, 2022), Besides the full phytochemical profile of plants and assessment of their antioxidant activities, the green NCs were fabricated and structurally elucidated using spectroscopic and spectrophotometric analysis.

Screening for antifungal activities

Fungal isolates clinical samples (nails, skin scrapings and hair clippings) were gathered from patients attending the dermatology department of ALEmamain AL-Kadhumain Teaching Hospital and AL-Zahraa Consulting Center for Allergy and Asthma/ Baghdad between January 2021 and September 2021. The isolated dermatophyte caused ringworm diseases were diagnosed using the ITS region and its phylogenetic analysis (Hashoosh & AL-Araji, 2023). The *Tinea spp.* isolates employed for this study were: *Trichophyton mentagrophytes*, *Trichophyton simii*, *Trichophyton quinckeanum,* and *Trichophyton verrcuosum.* The fungus species were cultured on Sabouraud dextrose agar (SDA) at 29 °C and subcultured monthly during the study.

The poisoned food technique (PFT) was carried out for the antimycotic activity (Hussein *et al.*, 2021; Sardar *et al.*, 2022) with slight modifications. Briefly, 2 ml sterile distilled water contained the required amount of the dried plant extracts and $CuO@SiO_2$, $Ag@Fe_3O_4@SiO_2$ NCs, respectively, was sterilized by filtration through a 0.45-mm membrane filter, and then mixed with pre sterilized SDA medium required to give a final concentration of 10, 30 and 50% of (10g/100ml DW) crude plant materials and 10, 30, and 50 µg ml^{-1} for NCs (Rabiee *et al.*, 2020; Santos *et al.*, 2013). The same procedure was done with deionized water without treatment as a control. All of the Petri dishes solidified. Afterward, A mycelial disc 6 mm in diameter, was cut from the periphery of the 4-day-old cultures using a sterile 6 mm diameter cork borer and then aseptically inoculated (Rónavári *et al.*, 2018). And then incubated at 25 °C. The percentage of mycelial inhibition was calculated as follows: % mycelial inhibition = [(dc–dt)/dc] × 100; dc = the colony diameter in control, dt=colony diameter in treatment. The percent mycelium growth inhibition (MGI) was measured and recorded after 3, 7, and 10 days. Each treatment was replicated triplet.

Statistical analysis

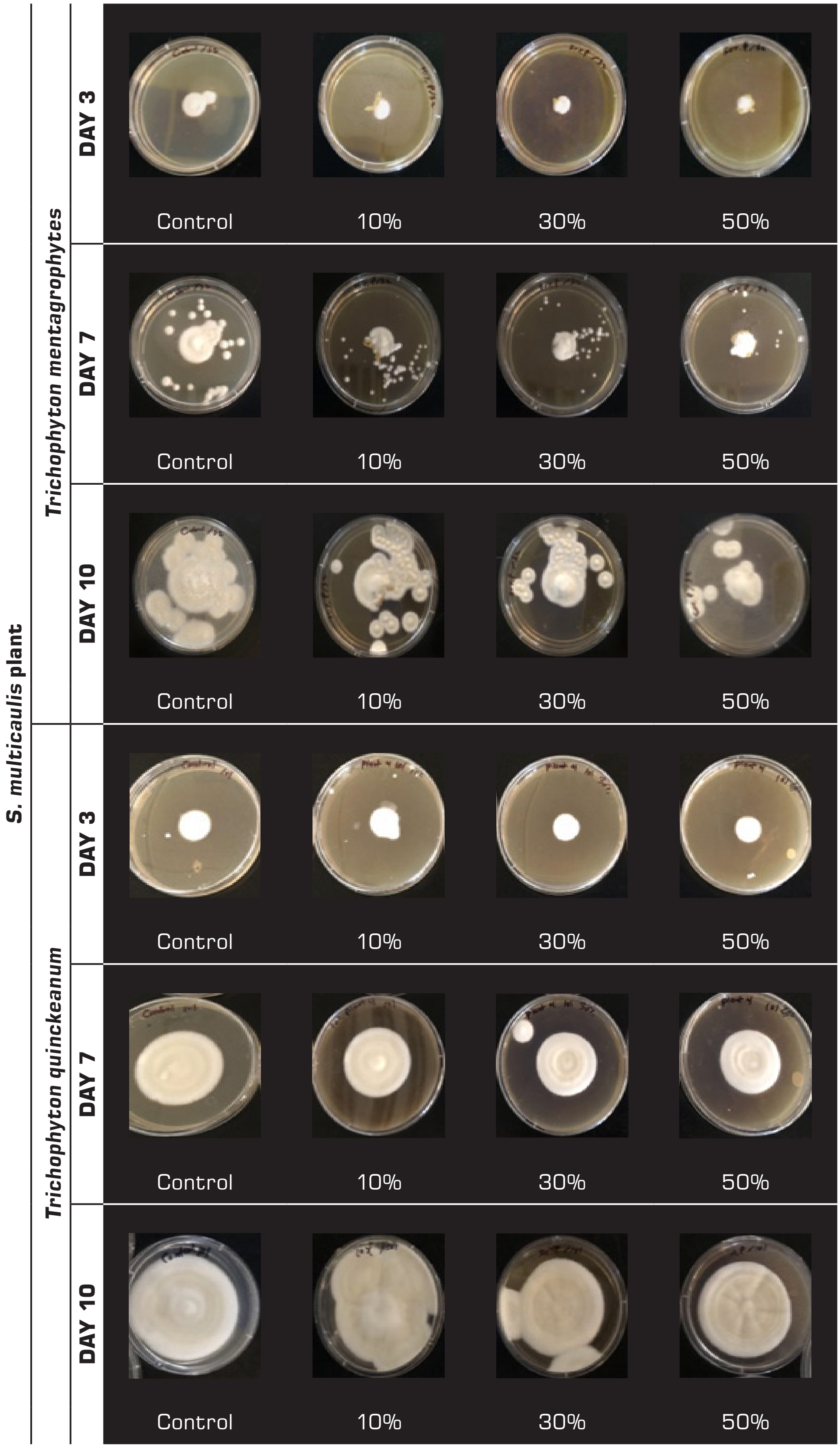
Experiments were conducted in triplicate; the obtained data are expressed as mean ± standard error of mean SEM.Data were analyzed according to one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test using GraphPad Prism software (version 9). In addition, 2way ANOVA multiple comparisons were used for multi-group comparison to compare doses of plants and synthesized nanocomposites with their control group using Dunnett's multiple comparisons tests. $P<0.05$ is considered statistically significant.

RESULT

For testing aqueous extracts of *S. multicaulis, H. scabrum* plants, and plant-based $CuO@SiO_2$, $Ag@Fe_3O_4@SiO_2$ NCs, the poisoned food technique is used. The MGI values were determined to evaluate antimycotic potential. The results were listed in Tables 1, 2, 3, 4 and Figures 2, 3, 4, and 5.

Tinea spp.	Mycelium growth inhibition (MGI%)											
	Plant extracts %						NCs µg ml^{-1}					
	S. multicaulis			*H. scabrum*			$CuO@SiO_2$			$Ag@Fe_3O_4@SiO_2$		
	10	30	50	10	30	50	10	30	50	10	30	50
T. mentagrophytes	46.66	41.66	66.66	54.86	72.19	100	25	25	33.33	41.66	53.33	63.33
T. simii	4	9.333	40	18.21	31.53	44.44	4	6.666	13.33	5.333	20	16
T. quinckeanum	6.666	26.66	33.33	45.33	74.21	85.81	6.666	20	33.33	2.666	6.66	9.33
T. verrcuosum	52.94	55.88	61.76	51.66	77.02	100	19.11	44.11	51.47	56	61.76	67.64

Table 1. The effect of plant extracts and their derived NCs on the percent mycelium growth inhibition of *Tinea spp.*



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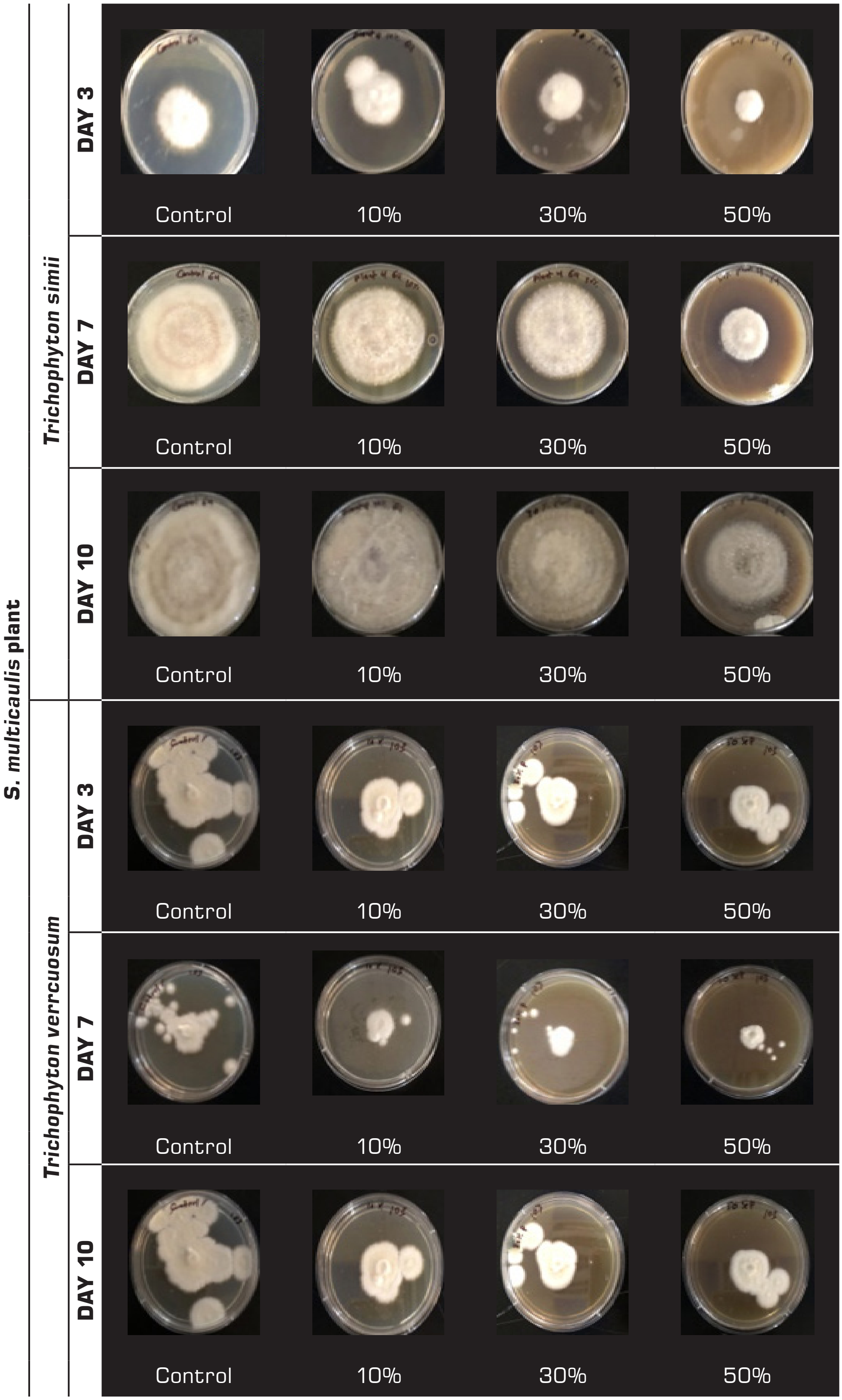


Table 2. Antidermatophytic activity of *S. multicaulis* plant extract against four *Tinea spp.* Trichophyton at different concentrations.

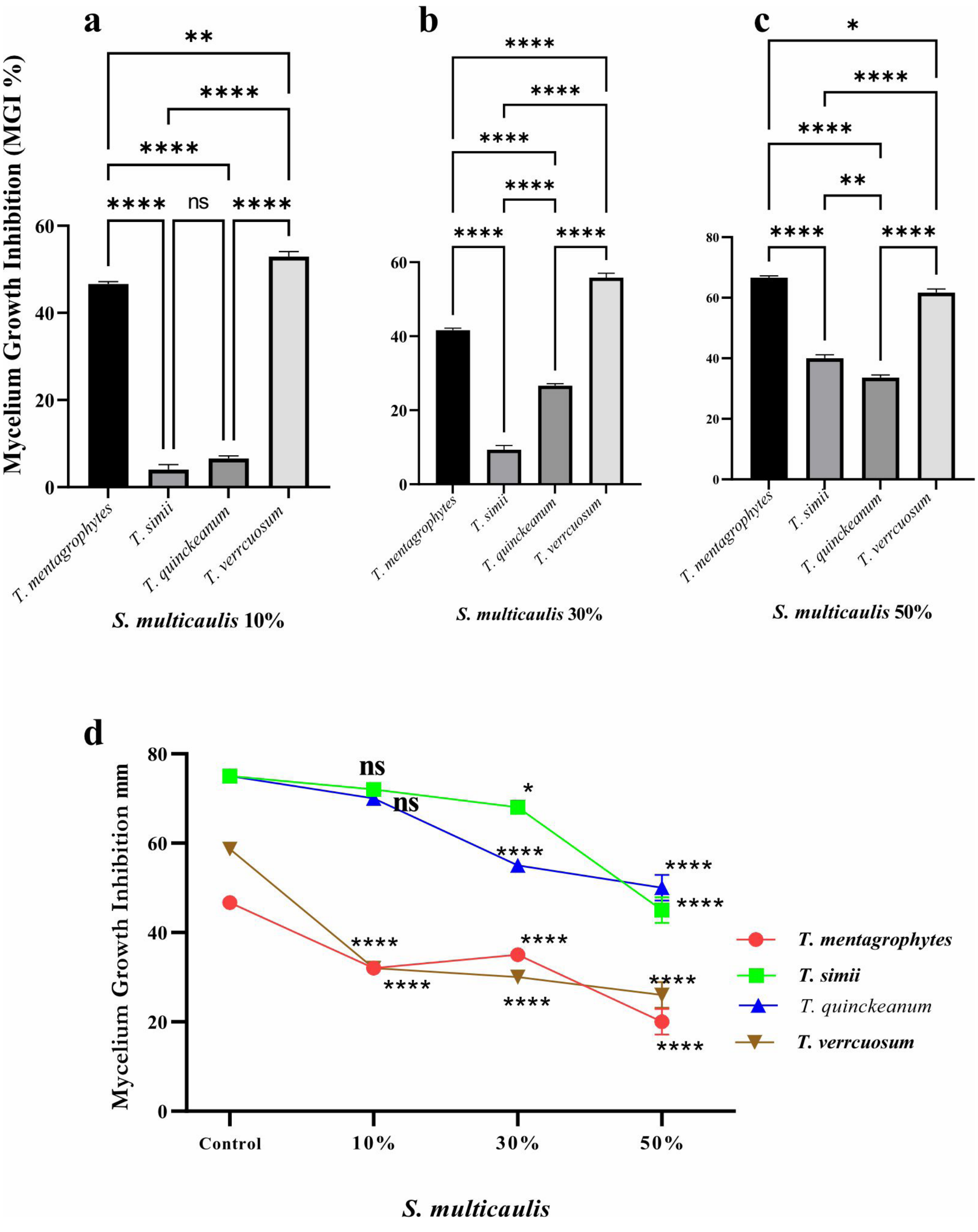
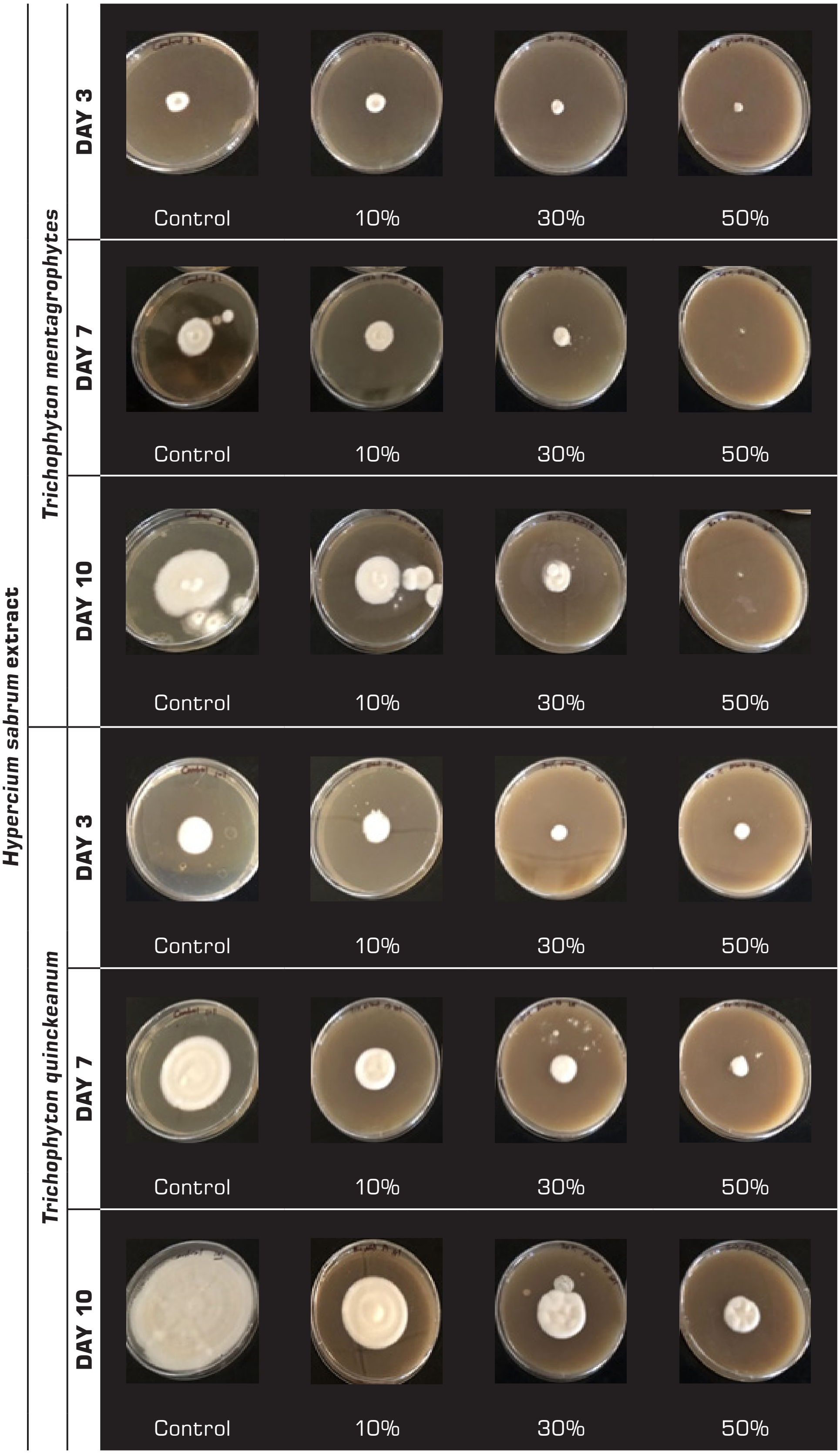


Figure 2. Quantitative measurement of *Tinea spp.*' percent mycelium growth inhibition (MGI) by PFT treated with *Salvia multicaulis* extract at: a. 10%, b. 30% and c. 50%, while d. represents mycelium growth inhibition diameter measurement of different doses of plant treatment compared with their fungus control group. Data are presented as mean ±SE of three biological replicas after 10-day incubation. All data were significant at P<0.05 (*), p<0.001 (**) and p<0.0001 (***).


Hypercium sabrum extract
Trichophyton mentagrophytes
DAY 3
Control
10%
30%
50%
DAY 7
Control
10%
30%
50%
DAY 10
Control
10%
30%
50%
Trichophyton quinckeanum
DAY 3
Control
10%
30%
50%
DAY 7
Control
10%
30%
50%
DAY 10
Control
10%
30%
50%

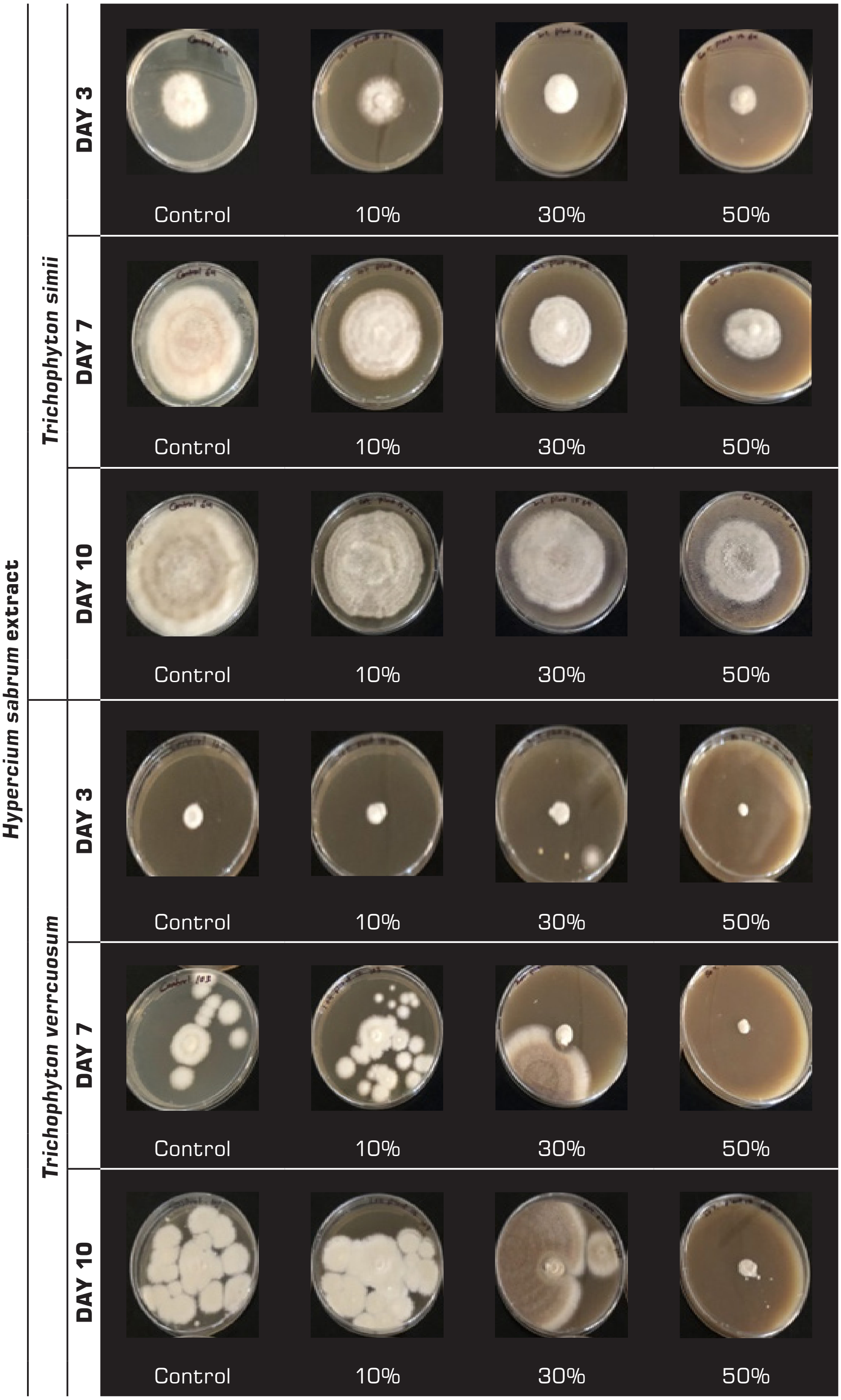


Table 3. Antidermatophytic activity of *H. scabrum* plant extract against four *Tinea spp.* Trichophyton at different concentrations.

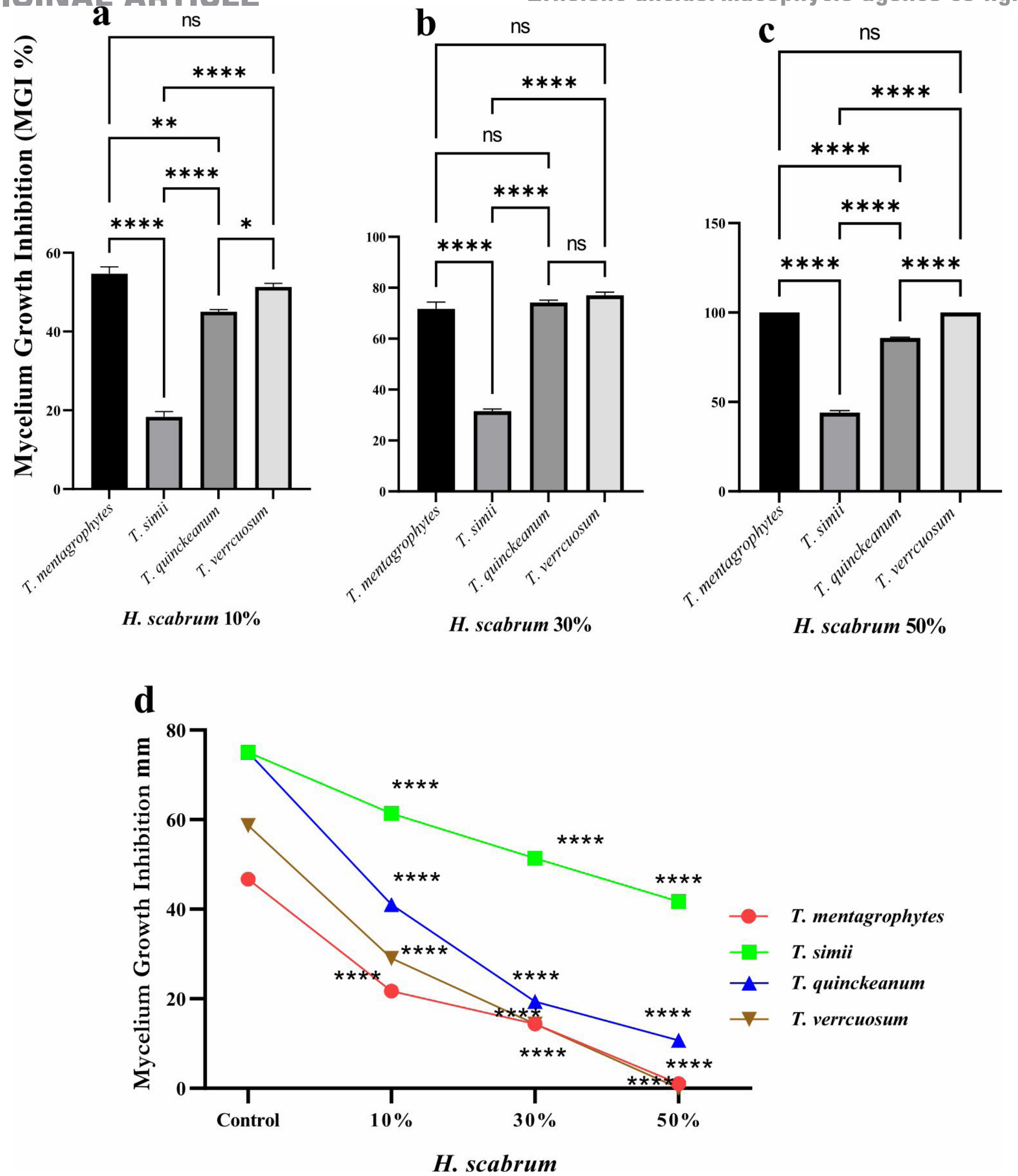


Figure 3. Quantitative measurement of *Tinea spp.*' percent mycelium growth inhibition (MGI) by PFT treated with *H. scabrum* extract at: a. 10%, b. 30% and c. 50%, while d. represents mycelium growth inhibition diameter measurement of different doses of plant treatment compared with their fungus control group. Data are presented as mean ±SE of three biological replicas after 10-day incubation. All data were significant at P<0.05 (*), p<0.001 (**) and p<0.0001 (***).

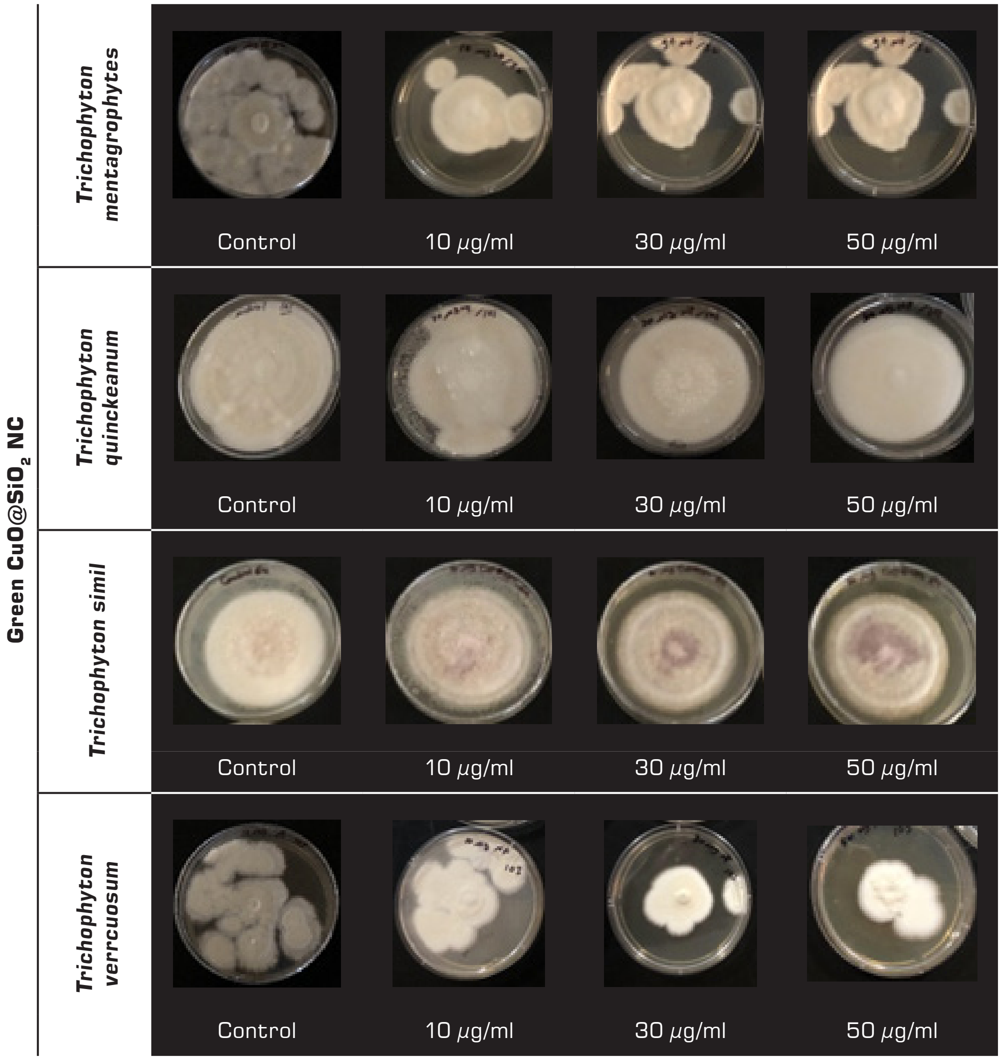


Table 4. Antidermatophytic activity of $CuO@SiO_2$ NCs against four *Tinea spp.* Trichophyton at different concentrations after 10 day incubation.

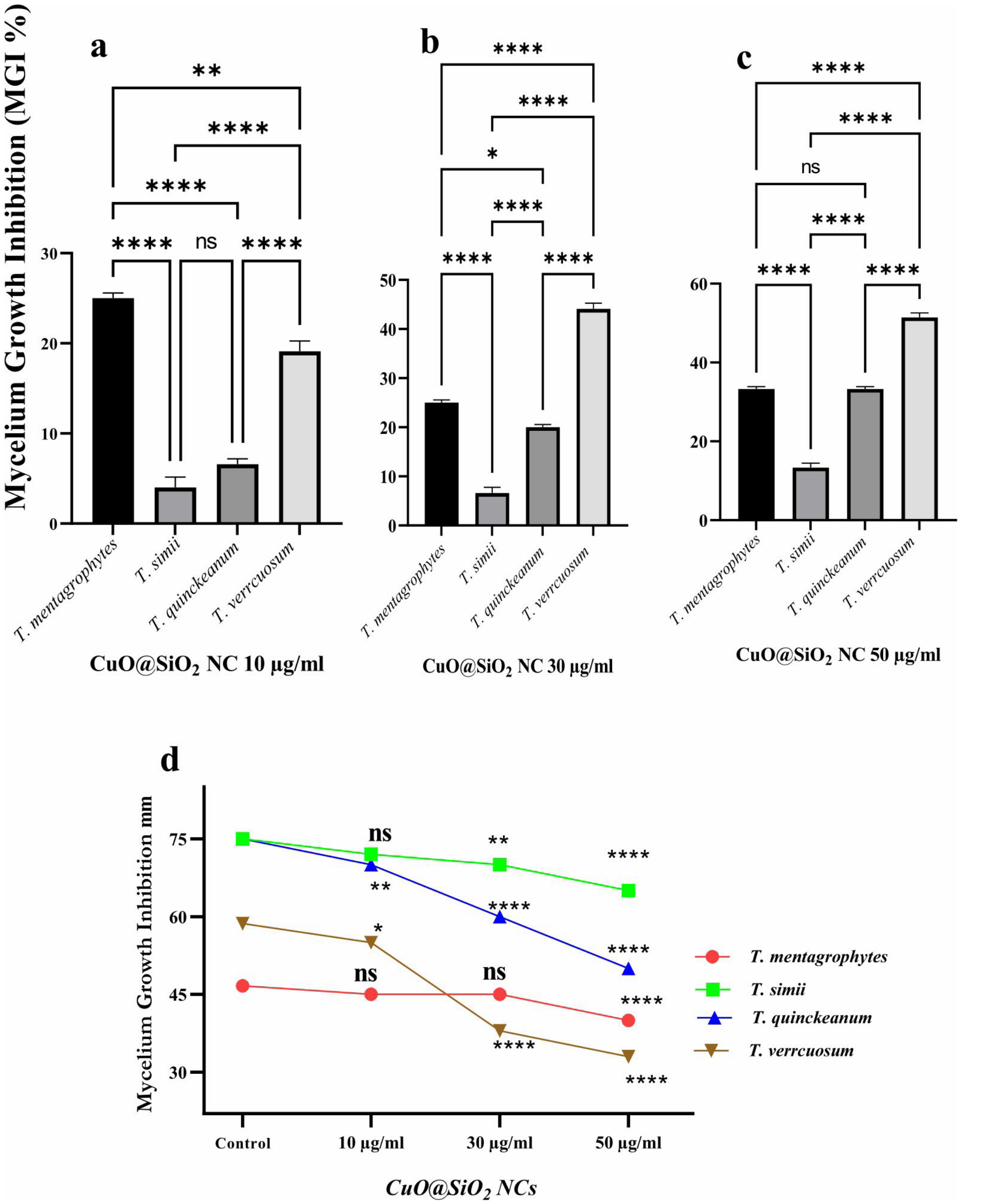


Figure 4. Quantitative measurement of *Tinea spp.*' percent mycelium growth inhibition (MGI) by PFT treated with $CuO@SiO_2$ NCs at a. 10, b. 30, and c .50 μg ml^{-1}, while d. represents mycelium growth inhibition diameter measurement of different doses of NCs treatment compared with their fungus control group. Data are presented as mean ±SE of three biological replicas after 10-day incubation. All data were significant at P<0.05 (*), p<0.001 (**) and p<0.0001 (***).

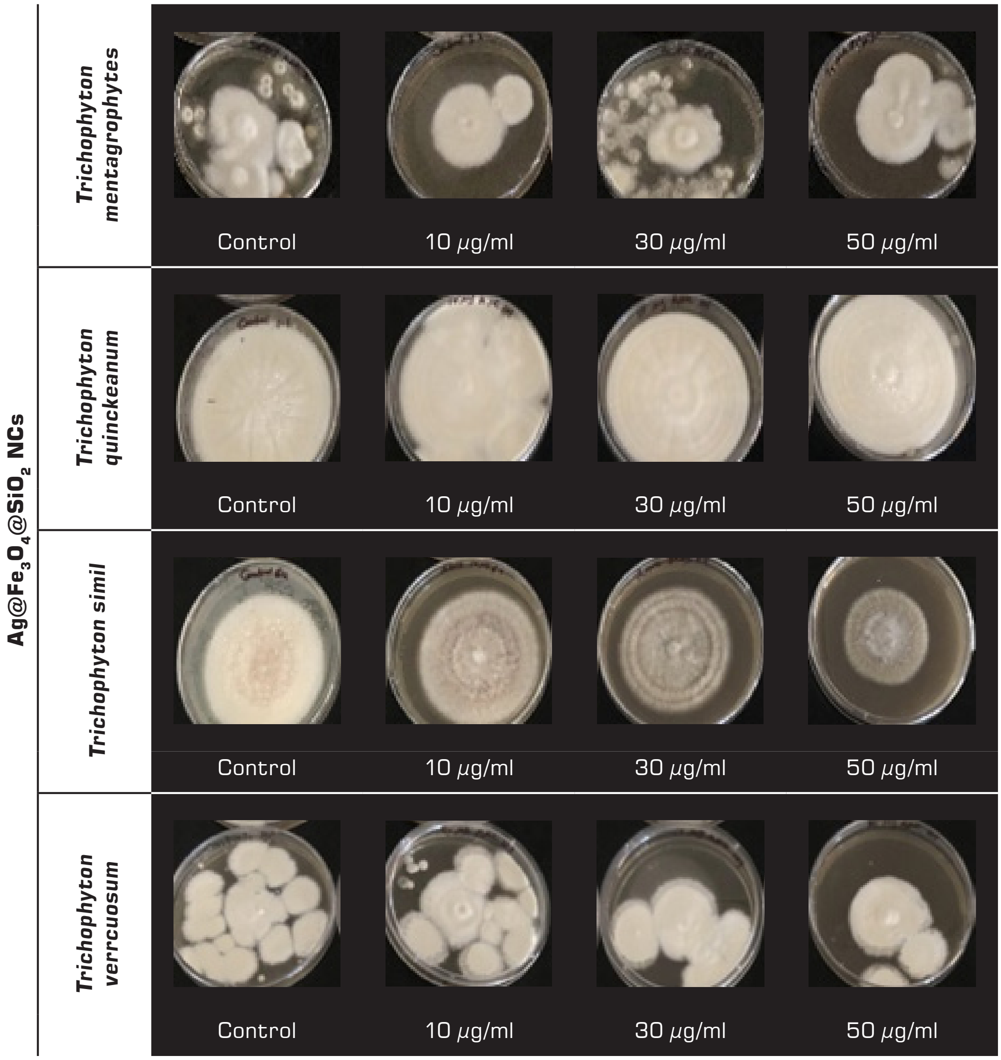


Table 5. Antidermatophytic activity of $Ag@Fe_3O_4@SiO_2$ NCs against four *Tinea spp.* Trichophyton at different concentrations after 10-day incubation.

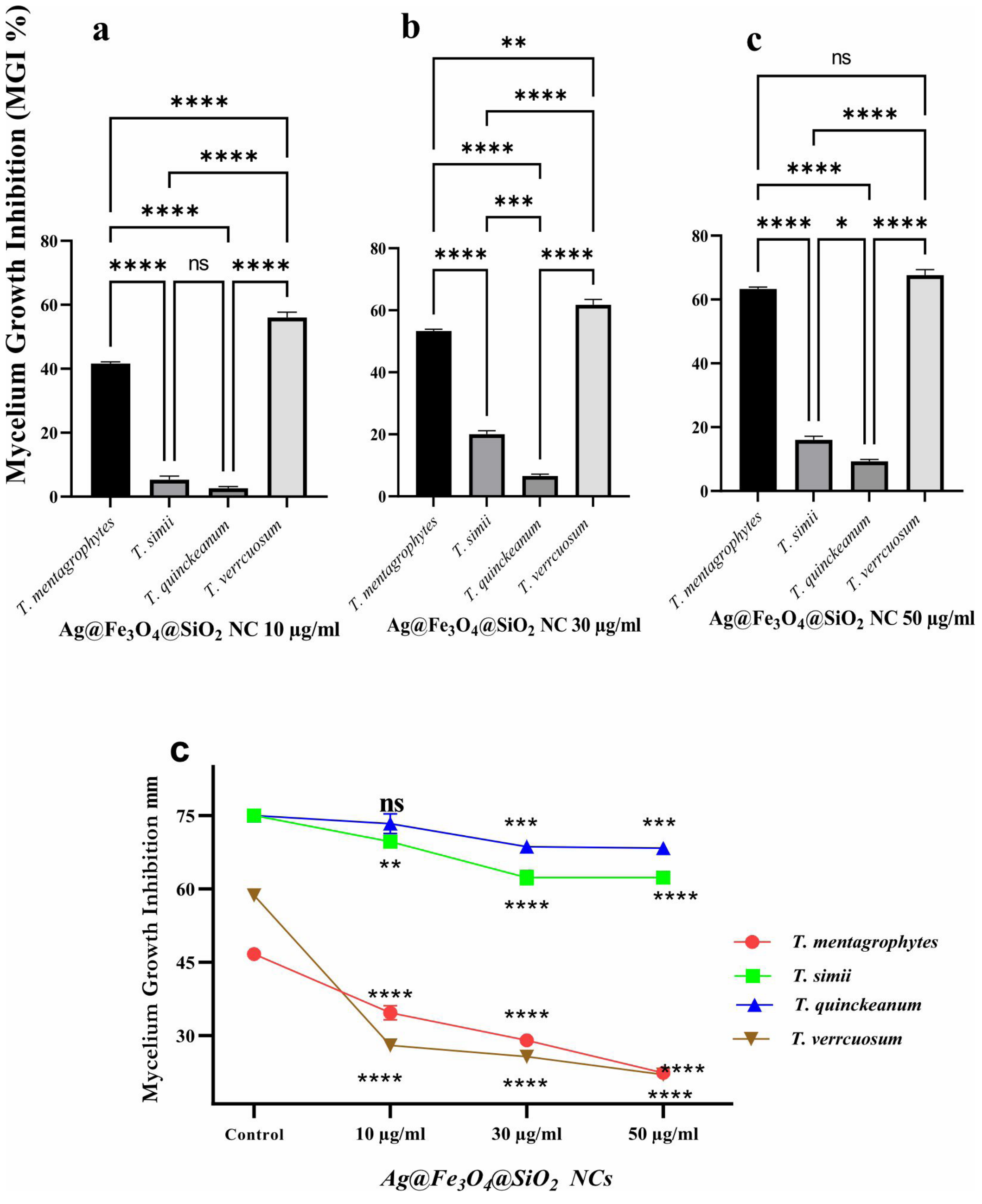


Figure 5. Quantitative measurement of the percent mycelium growth inhibition (MGI) of *Tinea spp.* by PFT treated with $Ag@Fe_3O_4@SiO_2$ NCs at: a. 10, b. 30, and c .50 μg ml^{-1}, while d. represents mycelium growth inhibition diameter measurement of different doses of NCs treatment compared with their fungus control group. Data are presented as mean ±SE of three biological replicas after 10-day incubation. All data were significant at $P<0.05$ (*), $p<0.001$ (**) and $p<0.0001$ (***).

The antifungal activity mechanism of metallic nanostructures was investigated previously by several scientists based on entering the metallic nanostructures into the cell membrane, leading to more impact on the respiratory chain and ceasing the cell divisions producing self-cell death. These metallic nanostructures can cause a potential interaction with the DNA of these fungi, leading to the destruction of protein replication leading to DNA mutations, which cause cell lysis in the process (B).

DISCUSSION

In general, both plant extract and green nanocomposites significantly show the growth inhibition of most tested species at different doses. while few species were moderate sensitive to the plant extracts and were significantly resistant to nanocomposites, especially T. simii.

In general, there are different mechanisms of fungal cell damage including membrane damage when fungus exposure to NPs causes changes in the fungal cell wall, including surface shrinkage, through microscopy, it has been detected that NPs may have direct contact and embedment within fungal cell walls during adsorption, which induces morphological change. Inner membranes also suffer distortion, with altered organelle disposition (such as increased intracellular vesicle and vacuole count) and decreased cytoplasmic content cell aggregation, pit and pore formation, and general deformation (Kim *et al.*, 2009), in addition exposure NPs caused alterations of phosphatidylcholine-to-phosphatidylethanolamine ratios in treated cells, causing a loss of membrane integrity and cell function (Slavin & Bach, 2022), ROS partake in lipid peroxidation, which can induce cell wall damage. metal NPs capture light and generate ROS, mainly hydroxyl radicals. These radicals attack the monomers of the cell wall, cleaving the glycosidic linkage and creating pores, leading to fungal death (Mukherjee, Acharya, Biswas, & Jana, 2020). Related to the fragmentation of DNA by NPs, which is enclosed in the nucleus, implies that the NPs should cross the nuclear membrane or produce significant damage in the intracellular membranes that would allow them to be in contact with the DNA. Moreover, it might also be the results of the ions released by the NPs that can affect the nuclear membrane at a distance, ion release has increased antimicrobial activity with an extended-release over time, improving results, studies have shown that ions are more toxic than their NPs counterparts (Pradhan *et al.*, 2015; Siddiqi & Husen, 2016), to account for ion activity, supernatants of NPs were tested, and studies found that SiO_2 NPs toxicity was due to NPs alone Ag NPs toxicity was due to a combination of NPs and ions, additional mechanisum of antifungal activity is related to hyphae and spores damage, NPs can have severe impacts on fungal hyphae and spores. Fungi treated with AgNPs, or CuNPs showed hyphae deformation, appearing distorted and shrunken (Slavin *et al.*, 2017). NPs change the growth patterns, clumping and thinning hyphal fibers Interestingly, even when CuNPs did not impact fungal growth, hyphae still appeared damaged, as a result of hyphal damage, NPs can inhibit mycelial growth, often dose-dependent manner (Ntow-Boahene *et al.*, 2021; Slavin *et al.*, 2017). Observations of the mycelia showed that it did not extend nor form around the presence of AgNPs, but untreated control had a healthy mycelial formation.

Over all, there are various theories on how NPs affect spores and what matters in the formulation. Spores possess an overall negative charge on their surface due to the presence of hydrophobins, or low molecular mass proteins secreted by fungi with the ability to self-assemble into amphipathic layers. the main antimicrobial mechanism attributed to cationic antimicrobial peptides is cell membrane disruption following electrostatic attraction interaction with anionic membranes. In addition, some Antimicrobial peptides can also act translocate across the membrane to act on intracellular targets for DNA and protein synthesis inhibition (Ntow-Boahene *et al.*, 2021). The global damages caused as a result of the exposure of the fungal cell to NPs is pictured in Figure 6.

From another perspective, Ergosterol is a sterol that resides on the cell membranes of fungi and acts to maintain cell membrane integrity, similar to mammalian cholesterol. And also, Ergosterol is an essential component of fungal cell membranes that determines the fluidity, permeability and activity of membrane-associated proteins (Jordá & Puig, 2020). Azole drugs inhibit ergosterol synthesis by targeting an enzyme called lanosterol 14α-demethylase, which is involved in the conversion of lanosterol to ergosterol. This enzyme is necessary for the production of ergosterol, and without ergosterol, the fungal cell membrane becomes structurally unstable (Bardal *et al.*, 2011). The specific mechanism of action of azole drugs involves binding to the active site of lanosterol 14α-demethylase and blocking its ability to convert lanosterol into ergosterol. As a result, the fungal cell accumulates sterol intermediates that are toxic to the cell and cannot properly function as a cell membrane component. This disruption ultimately leads to the death of the fungal cell (Bardal *et al.*, 2019).

In *S. multicaulis* plant extract, compared to the growth of fungus controls, among the different doses 50% (8mg/ml) show potent antifungual activity with significant inhibitory effects on the *trychophyton* spieces, while 10% (8mg/ml) of extract did not

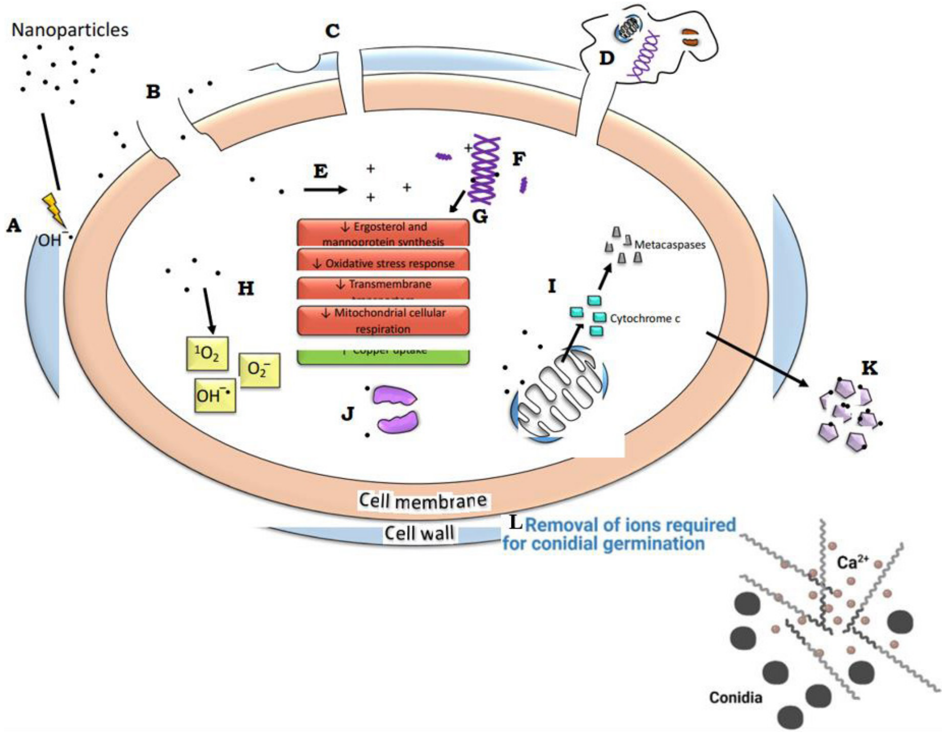


Figure 6. NPs mechanisms at the cellular level that lead to fungal cell damage include (A) ROS-inducing lipid peroxidation, (B) adsorption embedment and breakage of cell wall and membrane, (C) pit and pore formation, (D) leakage, releasing DNA and organelles from the cell, (E) ion release, (F) DNA intercalation, causing condensation and fragmentation, (G) gene expression changes, (H) ROS generation, (I) Mitochondrial release of cytochrome C into the cytosol, increasing metacaspase levels, leading to apoptosis cascade, (J) ribosome depolymerization, (K) adsorption onto EPS, and (L) removal of ions required for conidial germination, inhibiting biofilm formation, (reproduced with permission from reference(Slavin *et al.,* 2017))

reduce the growth of T. simii and T. quinckeanum (4 and 6% MGI), respectively, other species have moderate sensitivity toward the treatment. the results of mycelial growth inhibition in Tinea spp by *S. multicaulis* increased along with the concentration, Table 2. The phytoconstituents profile of *S. multicaulis* which grows naturally in Iraq confirmed the presence of biomolecules such as terpenes, flavonols, keto-enol compounds, aldehydes, proteins, vitamins, nitrogen-containing compounds, alkaloids, and tannins, this plant demonstrated as pontent antioxidants and antimicrobial activity (Rowshan & Najafian, 2020; Wu *et al.*, 2012).

Table 3, exhibited clearly the effective antimycotic potential of the aqueous *H. scabrum* extracts at all concentrations against the Trichophyton isolates, which caused Perniosis-like tinea corporis disease. These results were supported by in-vitro significant MGI, Fig. 3. Among the different concentrations, the application of 50% of the plant extract presented significant antidermatophytic action and stopped the growth of two fungus species, *T. mentagrophytes* and *T. verrcuosum* completely after 10-day incubation, followed by T. quinckeanum which show 85.81% of MGI compared to nontreated control after the same period. T. simii possesses a little sensitive to the drug with 44.44% of MGI. These findings are back to the phytochemical profile of the plant, numerous research reported the presence of bioactive compounds like quercetin glycosides, bisapigenin, catechin, and epicatechin in the aerial part of *H. scabrum* (Seyrekoğlu *et al.*, 2022). In addition, our results in excellent agreement with some previous studies, which efficiently show the metallocomplex of plant flavonoids has great potential as novel drugs or food supplements (Lewis *et al.*, 2016). Green NCs defined as the natural next generation of synthetic drugs, Because of fine-tuning in surface area, particle size, and surface activity, plant-based metal nanoparticles have attracted a lot of attention recently for their powerful antioxidant effects (Khan & Khan, 2023). For their antioxidant activity, metal nanoparticle-derived ROS that facilitates the damaging of the cell membrane of microorganisms, as well as cancerous cells, result in antimicrobial and anticancer effects as well as antifungal therapy. Because nanoparticles at low concentrations never enter into the fungal cells (Dauthal, Mukhopadhyay, & Research, 2016), none of the dermatophytes react sufficiently with nanocomposites when applied at low doses, like CuO@SiO_2 NC with an average diameter of 60 nm at 10 µg ml^{-1}, therefore NCs concentration was elevated up to 30 and 50µg ml^{-1}, a significant effect was detected to fight T. verrcuosum with (51.47 % of MGI) followed by *T. mentagrophytes* and *T. quinckeanum* which shows the moderate effect (33.33 % of MGI) while related to *T. simii*, still no inhibition was detected as obvious in Table 4 and Fig. 4.

On the other hand, Ag@Fe_3O_4@SiO_2 NCs mediated *H. scabrum* plant with a particle size of nanostructure around 20 to 60 nm, a combination of excellent magnetic properties, biocompatibilities, porosity, and silver plasmonic properties, in addition to accumulation of plant phytochemicals on their surface, results in a powerful antioxidants and promising composite for multiple applications (Flores, Torres, Popa, Crespo, & Calderón-Moreno, 2008). Therefore, their antifungal action reported in Table 5 and Fig. 5, observed significant activity to fight Trichophyton by application of different doses of Ag@Fe_3O_4@SiO_2 NCs, the percent mycelium growth inhibition of *T. mentagrophytes* and *T. verrcuosum* at 10, 30 and 50 µg ml^{-1} was (41.66, 53.33, and 63.33%), and (56, 61.76, and 67.64 %) respectively, after 10 day incubation, while *T. simii* show moderate sensitivity against the nanocomposite by application of various doses (5.333, 20, and 16 % MGI represents 10, 30 and 50 µg ml^{-1}), respectively. *T. quinckeanum* was resistant to all concentrations of nanocomposite after 10 days of incubation.

CONCLUSION

The extracts of *S. multicaulis, H. scabrum* plants, and plant-based CuO@SiO_2, Ag@Fe_3O_4@SiO_2 NCs, have strong fungicidal activity against Trichophyton species. Related to NCs, our data reinforce the importance of choosing the correct dose that can enter into the fungal cells, these plant extracts and nanoparticle formulations could be considered to treat various skin diseases caused by dermatophytosis as a new and natural alternative medication.

Acknowledgment

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Declaration of competing interest

The authors declare that they have no known competing financial and conflicts of interest or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

All authors contributed to searching, drafting, or revising the article, gave final approval of the manuscript to be submitted, and agreed to be accountable for all aspects of the work. ♦

REFERENCES

Abduljabbar, Rihan S, Sajadi, S Mohammad, & Al-Naqshabandi, Mohammed Ali. (2023). Salvia multicaulis for biosynthesis of antioxidant CuO/SiO2 NCs and assessment of its phytochemical profile. *Inorganic Chemistry Communications*. 110903.

Abid, M, Ali, Syed Salman, & Shivam, Najam Ali Khan. (2020). A small study of fungal disorders and its types of treatment. *Indian J Drugs. 8*, 54-59.

Al-Janabi, Ali Abdul Hussein S, & Bashi, Abas Matrood. (2022). Synthesis and antifungal activity of novel griseofulvin nanoparticles with zinc oxide against dermatophytic fungi: Trichophyton mentagrophytes and Trichophyton verrucosum: A primary study. *Current Medical Mycology. 8*(2), 40.

Ayan, Ali Kemal, Radušienė, Jolita, Çirak, Cüneyt, Ivanauskas, Liudas, & Janulis, Valdimaras (2009). Secondary metabolites of Hypericum scabrum and Hypericum bupleuroides. *Pharmaceutical Biology. 47*(9), 847-853.

Bardal, SK, Waechter, JE, & Martin, DS. (2011). Chapter 18 – Infectious Diseases. Applied Pharmacology; Saunders: Philadelphia, PA, USA, 233-291.

Dauthal, Preeti, Mukhopadhyay, Mausumi. (2016). Noble metal nanoparticles: plant-mediated synthesis, mechanistic aspects of synthesis, and applications. *Industrial, & Research, Engineering Chemistry, 55*(36), 9557-9577.

Dougari, James Hamuel, Human, Izanne Susan, Benadé, AJ, & Ndakidemi, Patrick Alois. (2009). Phytochemicals as chemotherapeutic agents and antioxidants: Possible solution to the control of antibiotic resistant verocytotoxin producing bacteria. *Journal of Medicinal Plants Research, 3*(11): 839-848.

Durgeshlal, Chaudhary, Khan, Mohammad Sahroj, Prabhat, Shah Aditya, Prasad, Yadav Aaditya. (2019). Antifungal activity of three different ethanolic extract against isolates from diseased rice plant. *Journal of Analytical Techniques, & Research, 1*(1), 47-63.

Flores, JC, Torres, V, Popa, M, Crespo, D, & Calderón-Moreno. (2008). Preparation of core-shell nanospheres of silica-silver: SiO2@ Ag. *JM Journal of Non-Crystalline Solids, 354*(52-54), 5435-5439.

Ghasemi Pirbalouti, Abdollah, Fatahi-Vanani, Maryam, Craker, Lyle, & Shirmardi, Hamzeali. (2014). Chemical composition and bioactivity of essential oils of Hypericum helianthemoides. Hypericum perforatum and Hypericum scabrum. *Pharmaceutical Biology, 52*(2), 175-181.

Hashoosh, Qadisiyah H, & AL-Araji, Alaa M. (2023). Molecular Identification of Tinea spp. Causing Tinea Disease using ITS Sequencing Analysis. *Iraqi Journal of Biotechnology, 22(*1).

Hussein, Hawkar M, Ghafoor, Dlzar D, & Omer, Khalid M. (2021). Room temperature and surfactant free synthesis of zinc peroxide (ZnO2) nanoparticles in methanol with highly efficient antimicrobials. *Arabian Journal of Chemistry, 14*(4), 103090.

Jordá, Tania, & Puig, Sergi. (2020). Regulation of ergosterol biosynthesis in Saccharomyces cerevisiae. *Genes, 11*(7), 795.

Khan, Mohammad Faheem, & Khan, Mohd Aamish. (2023). Plant-Derived Metal Nanoparticles (PDMNPs): Synthesis, Characterization, and Oxidative Stress-Mediated Therapeutic Actions. *Future Pharmacology, 3*(1), 252-295.

Kim, Keuk-Jun, Sung, Woo Sang, Suh, Bo Kyoung, Moon, Seok-Ki, Choi, Jong-Soo, Kim, Jong Guk, & Lee, Dong Gun. (2009). Antifungal activity and mode of action of silver nano-particles on Candida albicans. *Biometals, 22,* 235-242.

Lewis, Tyra, Wallace, William, Peterson, Finlay Dingman, Rafferty, Steven, & Martic, Sanela (2022). Reactivities of quercetin and metallo-quercetin with superoxide anion radical and molecular oxygen. *Electrochemical Science Advances, 2*(4), e2100054.

Mallikarjuna, K, Sushma, N John, Reddy, BV Subba, Narasimha, G, Raju, B Deva Prasad. (2013). Palladium nanoparticles: single-step plant-mediated green chemical procedure using Piper betle leaves broth and their anti-fungal studies. *International Journal of Chemical and Analytical Science, 4*(1), 14-18.

Marek, Cindy L, & Timmons, Sherry R. (2019). Antimicrobials in pediatric dentistry. *Pediatric Dentistry,* 128-141. e121: Elsevier.

Mukherjee, Khushi, Acharya, Krishnendu, Biswas, Aritra, & Jana, Nikhil R. (2020). TiO2 nanoparticles co-doped with nitrogen and fluorine as visible-light-activated antifungal agents. *ACS Applied Nano Materials, 3*(2), 2016-2025.

Ntow-Boahene, Winnie, Cook, David, & Good, Liam. (2021). Antifungal polymeric materials and nanocomposites, *Frontiers in Bioengineering and Biotechnology, 9,* 780328.

Omar, Zagros A, Abduljabar, Rihan S, Sajadi, S Mohammad, Mahmud, Sarbast A, Yahya, Rebaz Othman. (2022). Recent progress in eco-synthesis of essential oil-based nanoparticles and their possible mechanisms. *Industrial Crops, & Products, 187,* 115322.

Pradhan, Arunava, Seena, Sahadevan, Schlosser, Dietmar, Gerth, Katharina, Helm, Stefan, Dobritzsch, Melanie, *et al.* (2015). Fungi from metal-polluted streams may have high ability to cope with the oxidative stress induced by copper oxide nanoparticles. *Environmental Toxicology and Chemistry, 34*(4), 923-930.

Rabiee, Navid, Bagherzadeh, Mojtaba, Kiani, Mahsa, & Ghadiri, Amir Mohammad. (2020). Rosmarinus officinalis directed palladium nanoparticle synthesis: investigation of potential anti-bacterial, anti-fungal and Mizoroki-Heck catalytic activities. *Advanced Powder Technology, 31*(4), 1402-1411.

Raza, Aun, Xu, Xiuquan, Xia, Li, Xia, Changkun, Tang, Jian, & Ouyang, Zhen. (2016). Quercetin-iron complex: synthesis, characterization, antioxidant, DNA binding, DNA cleavage, and antibacterial activity studies. *Journal of Fluorescence, 26,* 2023-2031.

Rónavári, Andrea, Igaz, Nóra, Gopisetty, Mohana Krishna, Szerencsés, Bettina, Kovács, Dávid, Papp, Csaba, *et al.* (2018). Biosynthesized silver and gold nanoparticles are potent antimycotics against opportunistic pathogenic yeasts and dermatophytes. *International Journal of Nanomedicine*, 695-703.

Rowshan, Vahid, & Najafian, Sharareh, (2020). Polyphenolic contents and antioxidant activities of aerial parts of Salvia multicaulis from the Iran flora. *Natural Product Research, 34*(16), 2351-2353.

Saido, Khadeeja Ahmed. (2018). Effect of some plant leaves extracts on Fusarium culmorum that cause wheat damping-off disease. *Journal of Duhok University, 20*(1), 124-131.

Salimikia, Iraj, Monsef-Esfahani, Hamid Reza, Gohari, Ahmad Reza, & Salek, Mehrnoosh. (2016). Phytochemical analysis and antioxidant activity of Salvia chloroleuca aerial extracts. *Iranian Red Crescent Medical Journal, 18*(8).

Santos, Maximillan Leite, Magalhães, Chaiana Froés, Rosa, Marcelo Barcellos da, Santos, Daniel de Assis, Brasileiro, Beatriz Gonçalves, Carvalho, Leandro Machado de, *et al*. (2013). Antifungal activity of extracts from Piper aduncum leaves prepared by different solvents and extraction techniques against dermatophytes Trichophyton rubrum and Trichophyton interdigitale. *Brazilian Journal of Microbiology, 44,* 1275-1278.

Sardar, Momina, Ahmed, Waqas, Al Ayoubi, Samha, Nisa, Sobia, Bibi, Yamin, Sabir, Maimoona, *et al*. (2022). Fungicidal synergistic effect of biogenically synthesized zinc oxide and copper oxide nanoparticles against Alternaria citri causing citrus black rot disease. *Saudi Journal of Biological Sciences, 29*(1), 88-95.

Seyrekoğlu, Fadime, Temiz, Hasan, Ferda, ESER, & Yildirim, Cengiz. (2022). Usage of encapsulated Hypericum scabrum in ayran and determination of antioxidant, phenolic and sensory properties. *International Journal of Science Letters, 4*(1), 143-155.

Shumaila, Abdullah MA, & Al-Thulaia, Abdulsalam AN. (2019). Mini-review on the synthesis of Biginelli analogs using greener heterogeneous catalysis: Recent strategies with the support or direct catalyzing of inorganic catalysts. *Synthetic Communications, 49*(13), 1613-1632.

Siddiqi, Khwaja Salahuddin, & Husen, Azamal. (2016). Fabrication of metal nanoparticles from fungi and metal salts: scope and application. *Nanoscale Research Letters, 11,* 1-15.

Slavin, Yael N, Asnis, Jason, Hńfeli, Urs O, & Bach, Horacio. (2017). Metal nanoparticles: understanding the mechanisms behind antibacterial activity. *Journal of Nanobiotechnology, 15,* 1-20.

Slavin, Yael N, & Bach, Horacio. (2022). Mechanisms of Antifungal Properties of Metal Nanoparticles. *Nanomaterials, 12*(24), 4470.

Tocci, Noemi, Perenzoni, Daniele, Iamonico, Duilio, Fava, Francesca, Weil, Tobias, & Mattivi, Fulvio. (2018). Extracts From Hypericum hircinum subsp. majus Exert Antifungal Activity Against a Panel of Sensitive and Drug-Resistant Clinical Strains. *Frontiers in Pharmacology, 9,* 382.

Wu, Yi-Bing, Ni, Zhi-Yu, Shi, Qing-Wen, Dong, Mei, Kiyota, Hiromasa, Gu, Yu-Cheng, & Cong, Bin %J Chemical reviews. (2012). Constituents from Salvia species and their biological activities. *Chemical Reviews, 112*(11), 5967-6026.

Zakaria, ZA, Patahuddin, H, Mohamad, AS, Israf, DA, & Sulaiman, MR %J Journal of ethnopharmacology. (2010). In vivo anti-nociceptive and anti-inflammatory activities of the aqueous extract of the leaves of Piper sarmentosum. *Journal of Ethnopharmacology, 128*(1), 42-48.

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