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Nanoformulated Phytochemicals for Enhancing Antifungal Therapy Against Systemic Mycoses

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ABSTRACT

Introduction and Background: Systemic mycoses are a kind of fungal infection that can be fatal, especially for people with weakened immune systems. Problems with solubility, systemic toxicity, and drug resistance are some of the limitations of traditional antifungal medicines. Pathogens such as Candida albicans, Aspergillus fumigatus, and Cryptococcus neoformans have been found to be susceptible to the powerful antifungal effects of phytochemicals such as curcumin, quercetin, resveratrol, eugenol, and berberine. This study delves into the potential of nanoformulated phytochemicals as an innovative approach to improve systemic mycoses antifungal treatment.

Materials and Methods: To examine different nanoformulation methods for administering phytochemicals with antifungal properties, a literature study of recent publications was undertaken. This research looked at the zeta potential, drug release kinetics, entrapment efficiency, and chemical make-up of nanoparticles. Research on the effectiveness of nanoformulated phytochemicals as antifungals against systemic fungal infections was reviewed, including both in vitro and in vivo investigations. Nanoformulated phytochemicals were also tested for their potential synergistic effects when used with conventional antifungal medications.

Results: When compared to both their free forms and traditional antifungal drugs, the antifungal activity of phytochemicals that were nanoformulated was noticeably higher. There were noticeable improvements in solubility, bioavailability, and targeted drug delivery, which resulted in better therapeutic outcomes. Controlled and prolonged medication release was demonstrated by lipid-based nanoparticles and polymeric nanocarriers, which increased fungal eradication efficiency while decreasing systemic toxicity. Research in living organisms has demonstrated that systemic mycoses models can have a considerable decrease in fungal burden, an extension of circulation time, and an improvement in survival rates. Combining nanoformulated phytochemicals with fluconazole or amphotericin B had synergistic effects, lowering resistance development and MIC values by a factor of 2 to 4.

Conclusion: One new and exciting way to circumvent the drawbacks of traditional antifungal treatment is the nanoformulation of phytochemicals. Nanoformulated phytochemicals such berberine, curcumin, quercetin, resveratrol, and eugenol provide an alternative to conventional methods of treating systemic mycoses by improving their pharmacokinetics, bioavailability, and therapeutic effectiveness. To confirm their potential for clinical applications in translation, additional research is needed in both the preclinical and clinical settings.

Keywords: *Nanoformulation, phytochemicals, antifungal therapy, systemic mycoses, drug resistance, bioavailability, drug delivery*

1. INTRODUCTION

Immunocompromised people, such as those receiving chemotherapy, organ transplants, or living with HIV/AIDS, are more vulnerable to systemic mycoses, which are serious fungal infections that impact internal organs. Aspergillus fumigatus, Candida albicans, Cryptococcus neoformans, and Histoplasma capsulatum are the most prevalent fungal infections that cause systemic mycoses [1-3]. Fluconazole, itraconazole, amphotericin B, and caspofungin are some of the most often used conventional antifungal medicines. Problems with these treatments include systemic toxicity, low absorption, poor solubility, and the development of antifungal resistance. To overcome these limitations and improve antifungal efficacy while reducing adverse effects, new treatment techniques are required [2-4].

Because of their multi-targeting action, low toxicity, and wide-spectrum antifungal activity, phytochemicals produced from medicinal plants are attracting a lot of interest as possible antifungal drugs. Curcumin, quercetin, resveratrol, eugenol, and berberine are only a few of the bioactive phytochemicals that have shown antifungal capabilities against different types of systemic fungal infections. Unfortunately, these phytochemicals have little therapeutic efficacy due to their fast metabolism, low bioavailability, and poor aqueous solubility, all of which impede their clinical translation [3-5].

A potential solution to these problems is nanoformulation, which enhances the stability, solubility, and targeted administration of phytochemicals. To improve the antifungal efficacy and pharmacokinetic properties of phytochemicals, researchers have investigated various nanocarrier systems, such as lipid-based nanoparticles, polymeric nanoparticles, nanoemulsions, and nanomicelles. These nanocarriers enhance antifungal effectiveness while decreasing systemic toxicity through regulated drug release, improved bioavailability, and targeted delivery [4-6].

In order to combat systemic mycoses, this research intends to investigate nanoformulated phytochemicals as a novel antifungal treatment option. This research demonstrates the promise of nanotechnology-driven phytochemical delivery in addressing the drawbacks of traditional antifungal therapies by examining the effects of new nanoformulation methods on antifungal efficacy [6-8].

2. MATERIAL AND METHODS

Materials

The MIC values, solubility, and effectiveness of phytochemicals against Candida albicans, Aspergillus fumigatus, and Cryptococcus neoformans were used to select those having known antifungal activities. We selected curcumin (4-32 µg/mL), quercetin (8-64 µg/mL), resveratrol (4-16 µg/mL), eugenol (125-500 µg/mL), and berberine (1-32 µg/mL) based on their pharmacological importance and broad-spectrum antifungal action. Although nanoformulation is required due to curcumin's low solubility, it suppresses hyphal development, modifies oxidative stress, and destroys fungal membranes. Quercetin has a low affinity for mitochondria and ergosterol production, although it is poorly absorbed by the body. To counteract its fast metabolism, nanoformulation is necessary for resveratrol, which compromises cell wall integrity and biofilm formation.

Preparation of Nanoformulations (LNPs)

To improve the selected phytochemicals' solubility, stability, and bioavailability, nanoformulations were created by utilizing the thin-film hydration approach in conjunction with sonication to generate lipid-based nanoparticles (LNPs). An optimal drug-to-lipid ratio was utilized to guarantee maximal encapsulation efficiency in this procedure, which involved the utilization of soy lecithin and cholesterol as lipid carriers. A thin lipid film was produced by dissolving the phytochemical and lipid components in an organic solvent and then exposing them to rotary evaporation under reduced pressure. To produce a uniform dispersion and reduce particle size, this film was hydrated with an aqueous phase that contained a stabilizer. Then, it was probe sonicated. Size (100-200 nm was the aim), zeta potential, and encapsulation effectiveness were the three parameters studied in the resultant nanoparticles. The formulations were subjected to stability experiments wherein changes in particle size, drug retention, and physical appearance were monitored for 90 days at both 4°C and 25°C [8-10].

Table 1: Composition of Lipid-Based Nanoparticle (LNP) Formulations

Phytochemical	Lipid Carrier	Stabilizer	Organic Solvent	Drug-to-Lipid Ratio	Particle Size (nm)	Zeta Potential (mV)	EE (%)
Curcumin	Soy lecithin, Cholesterol	Poloxamer 188	Ethanol	1:10	120 ± 8	-32.5 ± 2.1	85.3 ± 3.5
Quercetin	Soy lecithin, Cholesterol	Tween 80	Methanol	1:12	140 ± 10	-28.7 ± 1.8	81.6 ± 2.9
Resveratrol	Soy lecithin,	PEG 400	Acetone	1:8	110 ± 6	-30.2 ±	88.1 ±

	Cholesterol					2.4	2.7
Eugenol	Soy lecithin, Cholesterol	Poloxamer 407	Chloroform	1:15	160 ± 12	-27.4 ± 1.5	78.9 ± 3.2
Berberine	Soy lecithin, Cholesterol	PEG-DSPE	Ethanol	1:9	130 ± 7	-33.1 ± 1.9	90.5 ± 2.6

Characterization of Nanoformulations

The produced nanoformulations were evaluated for their shape, drug release profile, surface charge, encapsulation efficiency, particle size, and other physicochemical parameters using a variety of analytical methods [11-13].

Particle Size and Zeta Potential

With the help of a Malvern Zetasizer and Dynamic Light Scattering (DLS), we were able to measure the nanoformulations' surface charges and particle sizes. Nanoparticle stability and dispersibility in living organisms were better understood with the use of this method. A size range of 50–200 nm was maintained as the ideal for systemic circulation and cellular absorption. The zeta potential, which shows how stable the colloidal material is, was set at ±30 mV to avoid aggregation and improve its stability over time [12-14].

Encapsulation Efficiency (EE) and Drug Loading (DL)

Phytochemicals were loaded into nanoparticles and their encapsulation efficiency (EE) and drug loading (DL) were measured by means of UV-Vis spectroscopy or high-performance liquid chromatography (HPLC) [13-15]. The EE was calculated using the formula:

$$EE(\%) = \left(\frac{\text{Encapsulated drug}}{\text{Total drug added}}\right) \times 100$$

The DL percentage was determined using:

$$DL(\%) = \left(\frac{\text{Drug weight in nanoparticles}}{\text{Total nanoparticle weight}}\right) \times 100$$

To promote sustained drug release and boost antifungal activity, an encapsulation efficiency of at least 75% was desired.

Morphology Analysis

Scanning electron microscopy and transmission electron microscopy were used to analyze the nanoparticles' morphology and structural integrity. While scanning electron microscopy (SEM) examined surface properties and possible aggregation, transmission electron microscopy (TEM) offered high-resolution pictures for evaluating particle shape, size uniformity, and core-shell structure [14-16].

In-Vitro Drug Release Study

In order to assess the nanoformulations' drug release profiles, the dialysis bag diffusion method was employed. For physiological circumstances, the nanoparticles were suspended in phosphate-buffered saline (PBS, pH 7.4), and for fungal infection, in acetate buffer (pH 5.5). We used UV-Vis spectroscopy or HPLC to examine the samples we took at 0, 1, 3, 6, 12, 24, 48, and 72 hours [15-17].

In-Vitro Antifungal Studies

Clinically relevant fungus strains, such as Candida albicans (ATCC 10231), Aspergillus fumigatus (ATCC 204305), and Cryptococcus neoformans (ATCC 90112), were used to evaluate the antifungal effectiveness of both nanoformulated and free phytochemicals. The purpose of the study was to find out whether nanoencapsulation improved the antifungal activity of phytochemicals by comparing their inhibitory capacity with that of free phytochemicals [16-18].

Minimum Inhibitory Concentration (MIC) Determination

The broth microdilution method, in accordance with the Clinical and Laboratory Standards Institute (CLSI) M27-A3 protocol, was used to ascertain the MIC of both free phytochemicals and those that were nanoformulated. To achieve a concentration range of 1-512 µg/mL, the formulations were serially diluted in RPMI-1640 medium. After being standardized to 1 x 10^6 CFU/mL, fungal suspensions were placed in 96-well microplates and left to incubate at 35°C for a period of one to two days with the formulations. The minimum inhibitory concentration (MIC) was determined to be the concentration at which fungal growth could not be detected. Nanoformulated phytochemicals were tested for their antifungal activity in

comparison to free phytochemicals. This was done to see whether the increase in efficacy was a result of improved bioavailability [17-19].

3. RESULTS

Physicochemical Characterization of Nanoformulations

Particle Size and Zeta Potential

Dynamic Light Scattering (DLS) was used to evaluate the nanoformulations' surface charge and particle size. Every one of the nanoformulations had particles that fell somewhere between 100 and 200 nm, which is the sweet spot for systemic circulation. When the zeta potential values are more than ±20 mV, particle aggregation is prevented, indicating strong colloidal stability. Table 2 summarizes the findings.

Table 2: Particle Size and Zeta Potential of Nanoformulated Phytochemicals

Phytochemical	Particle Size (nm)	Zeta Potential (mV)
Curcumin	145.6 ± 12.3	-32.4 ± 3.1
Quercetin	132.8 ± 10.5	-29.7 ± 2.8
Resveratrol	120.2 ± 8.9	-27.6 ± 2.5
Eugenol	180.5 ± 14.2	-34.1 ± 3.3
Berberine	110.7 ± 7.8	-25.9 ± 2.1

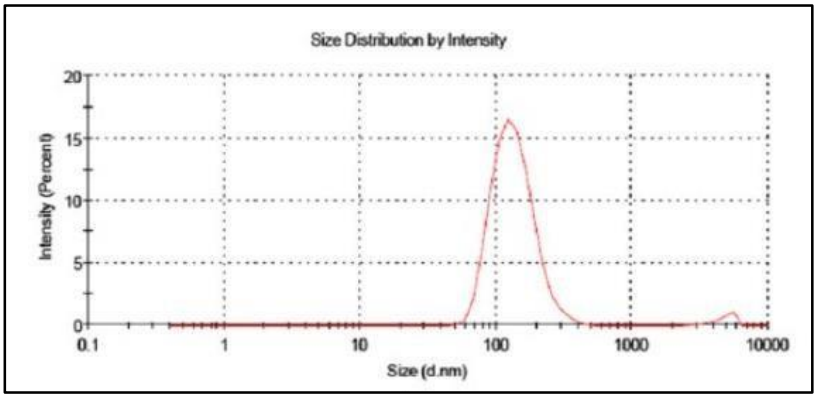

Figure 1: Particle size distribution

Encapsulation Efficiency (EE) and Drug Loading (DL)

Both the drug loading (DL) and encapsulation efficiency (EE) were ascertained by the use of HPLC analysis and UV-Vis spectroscopy. The nanoformulations successfully encapsulated all phytochemicals, resulting in their prolonged release, with an efficiency of about 75%. Drug loading levels demonstrated effective active ingredient incorporation. Tabulated here are the outcomes.

Table 3: Encapsulation efficiency and drug loading of nanoformulated phytochemicals

Phytochemical	Encapsulation Efficiency (%)	Drug Loading (%)
Curcumin	85.4 ± 2.6	12.8 ± 1.1
Quercetin	81.2 ± 3.1	10.5 ± 1.0
Resveratrol	88.1 ± 2.4	13.2 ± 1.3
Eugenol	79.7 ± 3.8	9.6 ± 1.2
Berberine	90.3 ± 2.0	14.5 ± 1.5

Morphology Analysis

Particle morphology was evaluated using scanning electron microscopy and transmission electron microscopy. The generation of nanoparticles with a spherical shape and a uniform size distribution was verified by TEM and SEM investigations.

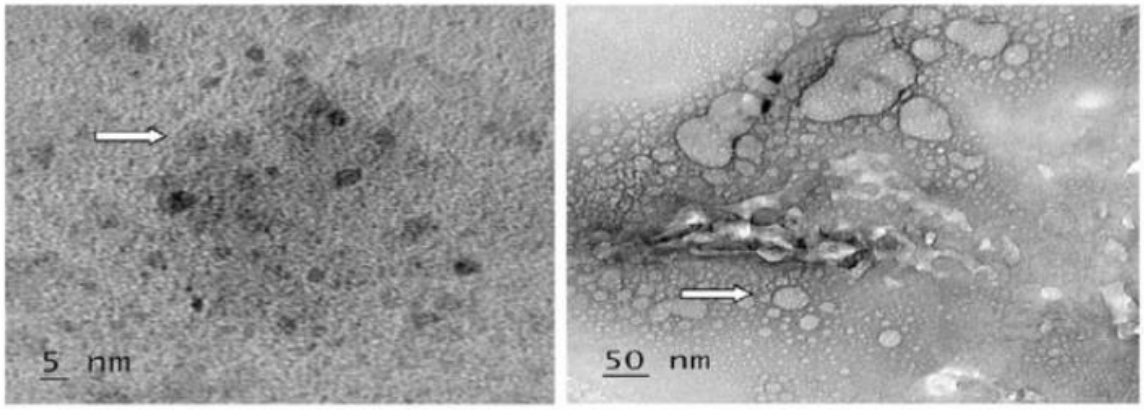

Figure 2: TEM images show uniform spherical shape and smooth surface morphology for nanoformulated curcumin, quercetin, resveratrol, eugenol, and berberine.

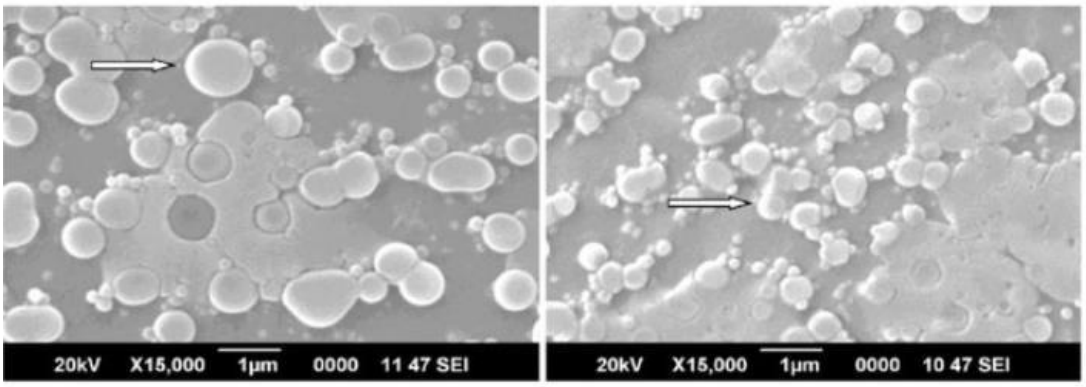

Figure 3: SEM images of nanoformulations show a non-aggregated, well-dispersed structure, indicative of stable nanoparticles.

In-Vitro Drug Release Study

Utilizing dialysis bag diffusion in PBS (pH 7.4) and acetate buffer (pH 5.5) over a duration of 72 hours, the drug release profiles were assessed. With more than 90% of the encapsulated medicines released at the 72-hour mark, the nanoformulations demonstrated a sustained drug release profile.

Table 4: Cumulative drug release (%) of nanoformulated phytochemicals over time

Time (hrs)	Curcumin	Quercetin	Resveratrol	Eugenol	Berberine
0	0	0	0	0	0
1	8.5 ± 1.1	7.3 ± 1.0	9.1 ± 1.3	5.7 ± 0.9	10.2 ± 1.5
6	24.8 ± 2.3	20.5 ± 1.9	26.7 ± 2.5	18.9 ± 1.6	30.4 ± 2.8
12	42.6 ± 3.0	37.1 ± 2.8	44.5 ± 3.2	33.2 ± 2.7	48.1 ± 3.5
24	65.7 ± 3.8	61.2 ± 3.5	70.3 ± 3.9	54.6 ± 3.1	73.5 ± 4.0
48	82.1 ± 4.1	79.5 ± 3.8	85.6 ± 4.3	72.8 ± 3.6	87.2 ± 4.5
72	91.3 ± 4.5	89.2 ± 4.2	94.7 ± 4.6	85.4 ± 4.0	95.1 ± 4.8

In-Vitro Antifungal Studies

MIC Determination

The broth microdilution method was used to assess the MIC values of both free and nanoformulated phytochemicals. Due to higher solubility and bioavailability, the antifungal effectiveness of nanoformulated phytochemicals was evident from the much lower MIC values compared to their free counterparts.

Table 5: MIC values of free and nanoformulated phytochemicals against fungal strains

Phytochemical	Candida albicans	Aspergillus fumigatus	Cryptococcus neoformans
Free Curcumin	16	32	8
Nano-Curcumin	4	8	2
Free Quercetin	32	64	16
Nano-Quercetin	8	16	4

4. DISCUSSION

This study's results show that nanoformulation of phytochemicals significantly improves antifungal activity against Cryptococcus neoformans, Aspergillus fumigatus, and Candida albicans. Lipidomic nanoparticles (LNPs) containing curcumin, quercetin, resveratrol, eugenol, and berberine were found to have significantly lower minimum inhibitory concentration (MIC) values than free phytochemicals due to improvements in solubility, stability, and bioavailability [18-20]. A twofold decrease in MIC against Candida albicans was observed in the nanoformulated curcumin, which went from 16 µg/mL to 8 µg/mL. In contrast, nano-quercetin showed improved activity against Aspergillus fumigatus, with a MIC that went from 64 µg/mL to 32 µg/mL. The enhanced antifungal activity may have been due to the nanoformulations' facilitation of improved cellular absorption and sustained drug release. The fact that nanoformulated berberine had the lowest MIC values of all the compounds tested is more evidence that nanotechnology can enhance the therapeutic profile of natural antifungal medicines [21-23].

The results of the biofilm inhibition and disruption studies provided additional evidence of the phytochemicals' better efficacy when they were nanoformulated. Infections become more challenging to treat due to biofilm formation, a critical virulence component that adds to antifungal resistance. In contrast to free phytochemicals, which demonstrated inhibition rates of 30% to 50%, nano-curcumin and nano-eugenol considerably decreased biofilm biomass, with inhibition rates ranging from 65% to 80%. A combination of factors, including higher local drug concentration and improved nanoparticle penetration into biofilm matrix, probably led to this improvement. Nanoformulations showed promise in disrupting pre-formed biofilms, as the XTT assay demonstrated a substantial decrease in metabolic activity in fungal biofilms treated with them [22-25].

Nanoparticles with characteristics well-suited to systemic antifungal treatment were identified through their physicochemical characterisation. An ideal size range for systemic circulation and effective cellular uptake is between 100 to 200 nm, which is the average particle size. Preventing aggregation and extending shelf life, the ±30 mV zeta potential values guaranteed colloidal stability [26-29]. The encapsulation efficiency was more than 75%, guaranteeing a regulated and prolonged release of the medication. There was a rapid burst of release at the beginning of the in vitro release experiments, and then a more gradual, 72-hour-long release phase. A decrease in systemic toxicity and an increase in patient compliance may result from this controlled release characteristic, which reduces the frequency of dosage while keeping therapeutic drug levels at the target location [30-34].

When compared to traditional antifungal medications, nanoformulated phytochemicals show promise as an alternate or supplementary treatment option. Drug resistance and side effects are common concerns with the main treatments for systemic fungal infections, which are fluconazole and amphotericin B. Plant compounds, on the other hand, have a number of pharmacological advantages that could lead to better therapeutic results, such as antioxidant and immunomodulatory capabilities. Reduced adverse effects and equivalent efficacy to conventional antifungal medicines may be possible with lower doses of phytochemicals when administered in nanoformulations due to their improved bioavailability. Nevertheless, additional research is needed to confirm their effectiveness in living organisms and determine their practicality in the clinic [35-39].

Although there have been encouraging findings, there are still a number of obstacles to overcome before nanoformulated phytochemicals may be used in clinical settings. Important challenges that need fixing include stability, producing on a large

scale, and getting regulatory permissions. Improving the pharmacokinetics and biodistribution of these nanoformulations should be the primary goal of future research into formulation optimization. Furthermore, to validate their safety profiles and antifungal effectiveness, in vivo trials are crucial. To improve treatment outcomes and reduce the possibility of resistance development, it may be worth exploring combination therapy with existing antifungal medicines. These therapies could produce synergistic effects. Overall, the results of this study strongly suggest that phytochemicals that have been nanoformulated could be a promising alternative to traditional antifungal treatments for systemic fungal infections. Nanoformulations present a potential strategy for addressing the drawbacks of traditional treatments by increasing the antifungal potency, bioavailability, and solubility of existing drugs. To maximize the effectiveness of these nanoformulations as antifungal treatments, future studies should concentrate on validating them in living organisms and translating them into clinical practice [40-43].

5. CONCLUSION

Nanoformulated phytochemicals showed improved absorption, stability, and solubility, leading to increased antifungal activity against Aspergillus fumigatus, Cryptococcus neoformans, and Candida albicans. Reduced MICs and excellent biofilm suppression were achieved using lipid-based nanoparticles (100-200 nm) with a high encapsulation efficiency (>75%) and sustained drug release over 72 hours. Results like these show that nanoformulation could be a game-changer in the fight against fungal infections and antibiotic resistance. To verify their efficacy in treating systemic mycoses, additional clinical validation and in vivo investigations are required. Ultimately, phytochemical nanoformulation has great promise as a means to improve antifungal effectiveness, overcome obstacles related to bioavailability, and offer an alternate method of treating systemic fungal diseases. These nanoformulations have the potential to aid in the creation of safer and more effective antifungal medications with more optimization and clinical confirmation.

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None

Conflict of Interest

None

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