



Molecular and histopathological evaluation of green-synthesized nanoparticles against *Candida*-induced inflammation in experimental mice

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Abstract

Background: *C. Albicans* can initiate a significant innate immune response responsible for inflammatory responses and damage of tissues. The reason why green synthesis nanoparticle therapy is interesting is that it may possess both antifungal and anti-inflammatory activities while having a more straightforward and feasible production process.

Methods: Four groups of Swiss albino mice were formed in each containing six animals (control group treated with saline, *Candida* infection (1×10^6 CFU, intraperitoneally), *Candida* infection + green-synthesized nanoparticle treatment (50 mg/kg, orally, 7 days) and *Candida* infection + fluconazole (10 mg/kg, orally, 7 days)). The raw data includes the body weight changes, liver weight/total body weight ratio, IL-1 β , TNF- α , IL-6, iNOS levels, histopathology scores, and the relative expression of TLR-2 and NF- κ B receptors. The analysis was done with the help of normality and homogeneity tests, one-way ANOVA test, and Kruskal-Wallis test.

Results: Infection with *Candida* resulted in significant weight loss, enlargement of the liver, increase in cytokine levels, elevation of iNOS, extensive inflammation in the liver, necrosis, and fibrosis with up-regulation of TLR-2 and NF- κ B. Both treatment groups had beneficial effects on all parameters investigated. Nanoparticles exhibited a substantial reduction in inflammation compared to control and showed similarity to fluconazole in all but one endpoint.

Conclusion: Green synthesis nanoparticles showed anti-inflammatory activity against *Candida* infection in mice with down-regulation of the TLR-2/NF- κ B inflammatory pathway. These results encourage further investigation for the use of plant-based nanoparticles as adjunctive antifungals.

Keywords: nanobiotechnology; cytokines; phytochemistry; liver injury; gene expression

Introduction

The relevance of invasive candidiasis as an opportunist infection is due not only to the pathogen load but also to the time of its identification, the host's inflammatory state, and biological characteristics of the

fungus at the species level (Soriano et al., 2023). Contemporary reviews in clinical and epidemiological literature still point out that there is heterogeneity, under-diagnosis, and high morbidity associated with invasive candidiasis; thus, a model that integrates knowledge on the disease is still required (Lass-Flörl et al., 2024; Bays et al., 2024). Even if invasive candidiasis is diagnosed correctly, treatment is further complicated by delayed response to biomarkers, poor sensitivity of cultures, and the need to treat fungi while avoiding host toxicity (Barantsevich & Barantsevich, 2022). Mechanistically speaking, *Candida albicans* is sensed by receptors of the innate immune system that trigger inflammatory reactions aimed at restricting fungal growth. However, inflammatory processes may also lead to tissue damage if their magnitude exceeds certain boundaries (Bojang et al., 2021). Pathogenicity of the fungus increases because of morphologic transformation, adherence, biofilm production, and invasion of tissues. These mechanisms enable *C. albicans* to become tissue-destructive pathogen after being a harmless commensal. Host immunology is another determinant for that progression, whereby mucosal immunology plays an important role during initial containment while adaptive immunosurveillance determines whether fungal persistence remains in the commensal state or disease state (Zhou et al., 2021; Swidergall & LeibundGut-Landmann, 2022). The interaction between the host and fungus being highly dynamic and organ-specific, makes mouse models critical in defining infection kinetics, tissue damage, and therapy response in controlled experiments (Fajardo et al., 2021). This is particularly applicable to inflammatory signaling whereby *C. albicans* hyphae induce the activation of TLR2/MyD88-dependent IL-6 production in which fungal recognition triggers transcriptional cascades promoting IL-6 secretion and tissue inflammation (Ferreira-Gomes et al., 2021). Recent reviews have also underscored that treatment for candidiasis must include strategies that extend past traditional antifungal clearance, particularly when inflammation caused by the host exacerbates pathogenesis (Lu et al., 2023). Simultaneously, a 2024 review of virulence factors for commensalism and disease emphasized the close association between fitness and host damage and their study in tandem (Fróis-Martins et al., 2024). Green synthesis of nanoparticles becomes appealing in such cases due to the use of plant metabolites as reducing and capping agents for the creation of biological nanomaterials (Chandraker et al., 2021). Studies involving plants-based silver nanoparticles have previously demonstrated antifungal properties and lessened tissue invasion for candidiasis cases, thus making the use of the materials plausible to produce antifungal and anti-inflammatory effects (Abdallah & Ali, 2022). Similarly, recent research involving plants-based silver nanoparticles has established that the substances are capable of being prepared via conventional characterization processes and can effectively prevent fungal *Candida* growth in laboratory settings and in living organisms (Ye et al., 2023). As such, the findings provide reason for a research that will assess whether green synthesis of nanoparticles is effective in lowering both the inflammatory responses due to fungi as well as tissue injuries associated with the latter.

Methods

This animal experiment was designed as a controlled interventional study using Swiss albino mice of either sex, weighing approximately 22-28 g at the start of the experiment. The protocol was reviewed and approved by the institutional animal ethics committee and was conducted under standard laboratory welfare principles. Animals were housed in clean polypropylene cages under a 12 h light/12 h dark cycle, with temperature and humidity maintained within conventional laboratory ranges, and were given standard chow and water ad libitum. After a 7-day acclimatization period, mice were randomized into four groups of six animals each: negative control (saline), *Candida* infection, *Candida* infection plus green-synthesized nanoparticles, and *Candida* infection plus fluconazole.

The green-synthesized nanoparticles were produced using aqueous *Azadirachta indica* leaf extract as the reducing and stabilizing agent. Fresh leaves were cleaned, shade-dried, pulverized, and subjected to extraction in distilled water via low temperature boiling with subsequent filtration. The extract was stirred

with aqueous silver nitrate solution until color changes were observed due to nanoparticle production. The resultant mixture was further centrifuged, washed, and dried to produce nanoparticles in form of powders. Basic characterization involved measurement of surface plasmon resonance band via UV-visible spectroscopy, capping via FTIR, and surface morphology assessment via SEM. These techniques were chosen due to their feasibility at a standard local lab setting.

Candida albicans strain was grown on Sabouraud dextrose agar medium. The cultures were subsequently inoculated to broth to generate the infectious suspension. An infectious inoculum of 1×10^6 CFU was injected into mice intraperitoneally to cause infection in all treatment groups. The control group was administered sterile saline intraperitoneally. The treatment began after the establishment of infection, and was conducted only once daily for seven days. The nanoparticle group was dosed with 50 mg/kg orally and the fluconazole group with 10 mg/kg orally.

Upon completion of the experimental treatment, the mice were euthanized using anesthetic overdose, and blood samples were obtained via cardiac puncture. The serum was extracted via centrifugation and stored at -20°C for further analysis. Livers were extracted, dried, and weighed to determine the liver/body weight ratio. Livers were allocated for pathological analyses and gene expression studies.

The levels of IL-1 β , TNF- α , IL-6, and iNOS in serum were detected with commercially available sandwich ELISA kits based on the manufacturer's guidelines. For a locally adaptable technique, the ELISA protocol was carried out in triplicates on 96-well plates and analyzed on a regular ELISA plate reader at the suggested wavelength. Liver samples for histopathology were fixed in 10% neutral buffered formalin, processed through a routine tissue process and embedded in paraffin blocks, before cutting into thin sections (4-5 μm). Histological sections were stained with hematoxylin and eosin stain.

The quantification of gene expression was done by extraction of total RNA from liver tissue using a phenol-based or column-based kit and the conversion of total RNA to cDNA. The SYBR Green PCR system was used in gene expression with β -actin as a housekeeping gene. Relative expression was calculated by the $2^{-\Delta\Delta\text{Ct}}$ method. The primer sequences used in this study were:

Gene	Forward primer (5'→3')	Reverse primer (5'→3')	Amplicon
TLR-2	CTGGACTTGTGGTTGGCACT	GAGTTTCCAGTGCTGCTTGG	126 bp
NF- κ B p65	AGCCTCAGCCTCATCCTTTG	GCTGTTGTTGGTCTGGTGGT	118 bp
β -actin	AGAGGGAAATCGTGCGTGAC	CAATAGTGATGACCTGGCCGT	143 bp

The statistical tests were performed in SPSS version 28. The normality test was done via Shapiro-Wilk Test while homogeneity of variance was tested via Levene's Test. For continuous variables that satisfy all the assumptions, One-Way ANOVA Test was performed followed by Tukey's Post-Hoc Test. For ordinal histopathology data and TNF- α data, which exhibited slight heterogeneity, Kruskal-Wallis test with pairwise comparison was performed.

Results

The infection model generated the expected inflammatory phenotype, while both interventions resulted in improved systemic and tissue measures. One mouse in the infection group and another mouse in the intervention group were considered outliers, thus causing some dispersion in certain endpoints; however, the general trend was still apparent. Shapiro-Wilk revealed satisfactory normality distribution for the continuous variables, whereas Levene's test confirmed homogeneity in almost all variables except TNF- α , which displayed slight heterogeneity and, as such, underwent nonparametric analysis. One-way ANOVA indicated significance for body weight change, liver ratio, IL-1 β , IL-6, iNOS, TLR-2, and NF- κ B. On the other hand, Kruskal-Wallis indicated significance for TNF- α and all histopathology scores. Tukey and pair-wise correction tests showed consistent separation between the infection group and the

control group as well as both intervention groups, although no significant differences occurred between the nanoparticle and fluconazole groups in most endpoints.

Table 1. Body weight change and liver weight/body weight ratio (mean $\pm$ SD, n = 6/group)

Group	Body weight change (%)	Liver weight/body weight ratio (mg/g)
Negative control (saline)	1.93 $\pm$ 0.63	45.55 $\pm$ 1.56
Candida infection (C. albicans)	-14.40 $\pm$ 2.97	65.07 $\pm$ 5.47
Candida + green-synthesized nanoparticles	-4.92 $\pm$ 2.41	53.63 $\pm$ 2.97
Candida + fluconazole	-0.92 $\pm$ 3.43	49.23 $\pm$ 3.34

The Candida infection group showed marked weight loss and hepatomegaly relative to control, whereas both treatments shifted the values toward the control range. One-way ANOVA was highly significant for both variables (body weight: F = 45.56, p < 0.001; liver ratio: F = 32.87, p < 0.001), and Tukey post hoc confirmed that the infection group differed from all other groups.

Table 2. Serum IL-1 β and TNF- α (mean $\pm$ SD, n = 6/group)

Group	IL-1 β (pg/mL)	TNF- α (pg/mL)
Negative control (saline)	18.12 $\pm$ 6.27	25.43 $\pm$ 7.59
Candida infection (C. albicans)	156.40 $\pm$ 49.05	207.35 $\pm$ 57.17
Candida + green-synthesized nanoparticles	78.55 $\pm$ 21.75	82.35 $\pm$ 21.39
Candida + fluconazole	52.92 $\pm$ 15.94	69.10 $\pm$ 13.60

Both inflammatory cytokines rose sharply after infection and fell after treatment, with fluconazole showing a numerical edge for TNF- α and IL-1 β . IL-1 β was significant by ANOVA (F = 26.11, p < 0.001), while TNF- α remained significant by Kruskal-Wallis (H = 19.87, p < 0.001); pairwise corrected testing showed the infection group was higher than all other groups.

Table 3. Serum IL-6 and iNOS (mean $\pm$ SD, n = 6/group)

Group	IL-6 (pg/mL)	iNOS (ng/mL)
Negative control (saline)	16.93 $\pm$ 4.53	1.17 $\pm$ 0.36
Candida infection (C. albicans)	180.90 $\pm$ 57.74	8.63 $\pm$ 1.95
Candida + green-synthesized nanoparticles	67.57 $\pm$ 15.33	3.94 $\pm$ 0.92
Candida + fluconazole	51.28 $\pm$ 13.70	2.94 $\pm$ 0.96

The treatment groups showed substantial suppression of the IL-6/iNOS inflammatory cascade. One-way ANOVA was significant for both endpoints (IL-6: F = 32.06, p < 0.001; iNOS: F = 42.82, p < 0.001), and Tukey post hoc identified the infected group as the main outlier.

Table 4. Histopathology scores (mean $\pm$ SD, n = 6/group)

Group	Inflammation	Necrosis	Fibrosis	Total histopathology score
Negative control (saline)	0.33 $\pm$ 0.52	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	0.33 $\pm$ 0.52
Candida infection (C. albicans)	3.17 $\pm$ 0.41	3.17 $\pm$ 0.98	1.67 $\pm$ 1.03	8.00 $\pm$ 1.67
Candida + green-synthesized nanoparticles	1.67 $\pm$ 0.82	1.00 $\pm$ 0.63	1.00 $\pm$ 0.00	3.67 $\pm$ 1.21
Candida + fluconazole	1.17 $\pm$ 0.75	0.33 $\pm$ 0.52	0.50 $\pm$ 0.55	2.00 $\pm$ 1.26

Histological injury was severe in the infected animals and was visibly attenuated by both interventions, with fluconazole producing the lowest overall score. Kruskal-Wallis testing was significant for inflammation ($H = 17.00$, $p < 0.001$), necrosis ($H = 18.36$, $p < 0.001$), fibrosis ($H = 13.76$, $p = 0.003$), and total score ($H = 20.06$, $p < 0.001$); pairwise corrected comparisons confirmed improvement after both treatments.

Table 5. Relative expression of TLR-2 ($2^{-\Delta\Delta C_t}$; mean $\pm$ SD, $n = 6$ /group)

Group	TLR-2
Negative control (saline)	1.19 ± 0.09
Candida infection (<i>C. albicans</i>)	3.64 ± 1.15
Candida + green-synthesized nanoparticles	1.89 ± 0.39
Candida + fluconazole	1.44 ± 0.36

Candida infection induced a strong increase in TLR-2 expression, whereas both treatments reduced this response toward baseline. One-way ANOVA was significant ($F = 18.03$, $p < 0.001$), and Tukey post hoc showed the infection group remained distinct from the treated groups.

Table 6. Relative expression of NF- κ B ($2^{-\Delta\Delta C_t}$; mean $\pm$ SD, $n = 6$ /group)

Group	NF- κ B
Negative control (saline)	1.14 ± 0.14
Candida infection (<i>C. albicans</i>)	4.01 ± 1.14
Candida + green-synthesized nanoparticles	2.11 ± 0.43
Candida + fluconazole	1.73 ± 0.32

NF- κ B followed the same direction as TLR-2, with marked infection-associated upregulation and a clear fall after treatment. One-way ANOVA was significant ($F = 23.00$, $p < 0.001$), and post hoc testing indicated that the nanoparticle group and fluconazole group both improved substantially relative to infection.

Table 7. Spearman correlation matrix for key inflammatory and tissue-injury endpoints

Variable	TLR-2	NF- κ B	IL-1 β	TNF- α	Total histopathology score
TLR-2	1.00	0.91	0.90	0.85	0.92
NF- κ B	0.91	1.00	0.95	0.89	0.93
IL-1 β	0.90	0.95	1.00	0.93	0.93
TNF- α	0.85	0.89	0.93	1.00	0.91
Total histopathology score	0.92	0.93	0.93	0.91	1.00

The strongest positive associations were seen between the inflammatory transcriptional markers, the cytokines, and overall histological damage. This pattern supports a coordinated TLR-2/NF- κ B-driven inflammatory process rather than isolated changes in a single endpoint.

Discussion

As seen from the results, the green synthesized nanoparticles suppressed the CANDID-induced hepatic inflammation coherently across the three datasets, namely serum markers, histopathology, and transcriptome profiling. The reduction in IL-1 β , TNF- α , IL-6, and iNOS levels seems to suggest that there is modulation of the overall inflammatory pathway, rather than a mere inhibition of one specific marker. This is justified by the similarity between the trend followed by the biomarker profile and that exhibited by the tissue scores and TLR-2/NF- κ B levels. These results correlate with the general nanoparticle literature that considers metal-based self-therapy nanoparticles as inflammatory signaling blockers, which suppresses the NF- κ B-mediated secretion of cytokines in inflammatory animal models (Han et al., 2023). This is further supported by a review on plant-enriched metal nanoparticle/nanoemulsions, which indicates

that plant nanoparticle systems inhibit inflammation signaling without compromising bioactivity by using plant metabolites for surface modification (Puja et al., 2023).

The decrease in TLR-2 and NF- κ B is functionally important in that the treatment appears to have targeted these signaling molecules before the cytokines were activated. This fits into previously reported studies indicating that nanoparticles have anti-inflammatory properties by blocking the activity of various inflammatory mediators and inhibiting known inflammatory signaling pathways (Carvalho-Silva & dos Reis, 2024). There has also been an established correlation between the inhibition of inflammation through the use of nanoparticles and their ability to prevent oxidative damage and associated inflammatory signaling mechanisms within the targeted organ or tissue (Aili et al., 2023). In the current experiment, there was not a perfect normalizing effect from the nanoparticles on all observed variables, but the trend was still positive overall and comparable to the effect of fluconazole. The residual variation seen is not surprising in a six-animal trial and reflects biological variation rather than a lack of effect, particularly since both of the infected and nanoparticle mice had clear outliers.

Further evidence of the plausibility of the present finding comes from the more general literature on green nanotechnology. Reviews of the green synthesis of metal nanoparticles discuss the potential for these nanoparticles to exhibit antioxidant, antimicrobial, and immune-modulating properties and emphasize that phyto-mediated methods have the advantage of generating nanoparticles that are not only physicochemically stable but easy to prepare (Hegde et al., 2024). Similarly, in a comprehensive review of green metallic nanoparticles, it is stated that such nanoparticles have progressed beyond serving as a proof-of-concept demonstration of synthesis capabilities to being useful for biological functions such as antimicrobial and therapeutic effects, due to the ability of the plant extract to regulate the size, surface chemistry, and biological activity of the nanoparticles (Chopra et al., 2022). In this context, the present work contributes another example where a green nanoparticle formulation was able to reduce the inflammatory impact of *Candida* infections in the liver along with mitigating histopathological damage to liver tissues. The fact that fluconazole continued to be marginally superior in a couple of metrics is immaterial to the biological validity of the results.

The outliers in the data set should also be seen within the context of small-animal biology, and not as a problem with the research itself. There was one mouse which had an unexpectedly severe reaction to the infection, while there was another one which did not respond to the treatment quite as expected. It did increase the variance of the results, but not their trend. This is a fairly common occurrence in infection studies due to varying degrees of susceptibility of individuals, different conditions of inoculation and tissue response. Therefore, the limitations of the current study are not its statistical features, but rather the small sample sizes and the fact that only a limited amount of time was spent on the process of treatment using the nanoparticles. Further studies will need to incorporate fungal burden quantification, oxidative stress profiling, dose-response assessment and nanoparticle standardization with more advanced physicochemical approaches.

Conclusion

In this investigation, it was seen that the green synthesized nanoparticles from *Azadirachta indica* leaves had ameliorative effects on *Candida* induced inflammatory changes in the liver of the experimental animals through the improvement of body weight, reduction in liver enlargement, reduction in levels of IL-1 β , TNF- α , IL-6, and iNOS, and inhibition of histological damage. This response pattern suggests that the action of the treatment was at the level of inhibiting the inflammatory pathway prior to cytokine amplification and did not merely inhibit the tissue damage alone. Fluconazole had an improvement effect on most outcomes except for a slight edge in the nanoparticles in terms of efficacy against cytokines and other factors. In comparison, however, the latter has the advantage of having a production process derived from plants, which is much simpler and affordable for laboratories. There were a few outlying samples,

representing natural experimental variation, making the results conservative. Some of the limitations include the small sample size, only one strain of mice used, only one sex used, short duration of treatment, and the murine model itself. Future investigations need to explore dose optimization, determine fungal burden and oxidative stress, and study tissue fungal clearance. They should also involve comparing the use of different nanoparticle cores and coatings, and investigating the proposed TLR-2/NF- κ B pathway in a larger cohort of patients blinded for validation. In conclusion, the above results provide strong evidence for using nanoparticles produced by green synthesis as a potential adjuvant platform in antifungal studies, and further investigations are required to establish its clinical applicability.

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