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# Protective Efficacy with Purified β-glucan Against Systemic Candidiasis

Nada F. Abbas[1*], Wafaa S. Shani[2]

[1] Department of Biology, College of Science, University of Misan, Amarah 62001, Iraq
[2] Department of Biology, College of Science, University of Basrah, Basrah 61001, Iraq

Corresponding Author Email: nadafadhil@uomisan.edu.iq



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**ABSTRACT**

In an experimental rat model, the present study aimed to evaluate the immunological effectiveness of a β-glucan vaccine derived from Candida yeast. β-glucans are immunomodulatory polysaccharides that can be used as adjuvants in vaccines and as antifungal agents. In this study, β-glucan was extracted, purified, and administered subcutaneously on a weekly basis (10 µg/0.1 ml on day 0 and 20 µg/0.1 ml on day 7) to *Rattus norvegicus* albino Wistar rats. To assess both preventive and therapeutic effects, the animals were vaccinated and subsequently infected with *Candida albicans* cells. Prior to the Candida challenge, immunological evaluations revealed a significant increase in pro-inflammatory cytokines—IL-1β, IL-18, IL-17, and IL-23 ($P \leq 0.05$)—as well as in immunoglobulin G (IgG) antibody titers ($P \leq 0.05$) in the vaccinated groups compared to the control groups, indicating strong stimulation of both humoral and cellular immune responses. Interestingly, following the infection challenge, the concentrations of IgG, IL-1β, IL-18, and IL-17 decreased non-significantly in the vaccinated groups compared to controls, while IL-23 levels showed a significant reduction. These results suggest effective immune modulation and a less severe infection. Moreover, β-glucan vaccination appeared to serve dual functions: enhancing host immunity and regulating inflammatory responses during infection. Notably, fungal burden analysis demonstrated that liver tissues in vaccinated rats had significantly fewer colony-forming units (CFUs) than those in unvaccinated controls ($P \leq 0.05$), with a mean difference of 10.1, indicating better protection and reduced fungal load. In conclusion, Candida-derived β-glucan shows promise as a vaccine candidate capable of eliciting protective immune responses while minimizing immunopathology. This study supports further research into β-glucan-based vaccines as safe and effective strategies for combating fungal infections.

## 1. INTRODUCTION

Vaccines are biological preparations intended to confer protection against specific infectious diseases by enhancing the immune system's capacity to recognize and fight bacterial as well as viral infections. There exist several kinds of vaccines. Each type works differently in stimulating or eliciting an immune response. Vaccines are essential for increasing resistance to a variety of diseases. They provide one of the most reliable tools and affordable means of maintaining public health. Approximately 154 million deaths, or six deaths every minute, have been avoided over the previous 50 years thanks to vaccination [1, 2].

Vaccines against a variety of infections have saved hundreds of millions of lives over the past several decades [3]. And greater numbers of people are recognizing the tremendous promise of vaccines to halt disease outbreaks and provide protection for older individuals. Respiratory syncytial virus infection is a deadly disease caused by RSV, which usually infects children. People aged 65 and older should receive immunization for tetanus, diphtheria, influenza, herpes zoster, and pneumococcal disease [4].

Fingerprints of polysaccharides and, similarly, β-glucan, a component of the fungal cell wall, are regarded as potential diagnostic and therapeutic elements in invasive fungal infections (IFIs) [5]. These molecules' effects in regulating the immune system and their antimicrobial, anticancer, anti-inflammatory, and antiallergic properties have been proven [6, 7]. Also, Scientists have documented the synergistic effects of β-glucans as antioxidant, antigenotoxic, and antimutagenic properties [7, 8].

β-glucan is able to both stimulate and modulate the immune system. By binding to Dectin-1, complement receptor 3 (CR3), and Toll-like receptor 2 (TLR-2) expressed by dendritic cells, neutrophils, eosinophils, monocytes, and macrophages, this polysaccharide mediates the induction or priming of innate immune responses [9]. Receptor binding to β-glucan leads to two signal transduction pathways, involving nuclear factor kappa B (NF-κβ) and spleen tyrosine kinase (Syk). Then follows the expression of adhesion molecules and the synthesis and secretion of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 [7].

Beta-glucan activates B cells to produce IL-18, which induces neutrophil recruitment without the participation of T

cells. Beta-glucan causes the activation of B cells and the production of IgG immunoglobulins [10]. Some of the works identify the significance of isolation of beta-glucans on the cell wall of the yeast *S. cerevisiae* and *P. carini* as components of immunodrugs that trigger the activation of the immune cells [11].

Early in the 1990s, the impact of β-glucans and their application as adjuvants in vaccines was researched. β-glucan that includes Bacillus Calmette-Guerin (BCG)-like activity induces the tripartite motif family (TRIM) phenotype that is linked to the recognition of pathogens and the transcriptional regulation of the innate immune system [12].

Additionally, combined with other factors, there is an additive and synergistic effect of β-glucans [13]. As a result, there is a significant amount of studies devoted to the application of 2-glucans in vaccines against bacterial, viral, and parasitic diseases [9, 14]. They are vaccines against hepatitis B, *Toxoplasma gondii*, *Staphylococcus aureus*, and various types of fungi, such as *Candida* species and *Cryptococcus neoformans* [15, 16]. In a single study, complete β-glucan particles were used to produce a vaccination against coccidioidomycosis and systemic aspergillosis. The results disclosed that entire β-glucan particles were capable of producing a fungal vaccine [17].

Another study revealed that mice immunized against cryptococci were immunized against recombinant cryptococcal protein in β-glucan particles [17]. It enhances the immune response to vaccination since β-glucan is structurally similar and size-similar to natural pathogens. Nonetheless, it is now critical to develop antigen delivery systems for new vaccines with natural polymers. At the same time, fine-particle β-glucan may be an antigen carrier as well as an immunological stimulator [18, 19].

This study aims to evaluate the protective efficacy of the vaccine produced out of purified and extracted Candida specimen beta-glucan to elucidate the underlying immune responses by assessing the concentrations of immunoglobulin G and pro-inflammatory cytokines.

## 2. MATERIALS AND METHODS

### 2.1 Extraction and preparation of β-glucan vaccine

*Candida albicans* was cultured on SDA media for 72 hr at 37°C, from 50 petri dishes, and cells were harvested to collect about 48 g from colonies on the media. β-glucan was extracted from the *Candida albicans* cell wall using an alkaline-acid treatment method, modified from research [20]. 48 g of harvested yeast was mixed with 250 ml of 1M NaOH, and the mixture was incubated at 80°C in a magnetic stirrer for 2 hours. The pellet was collected by cooling the centrifuge at 6000 xg for 20 min. At 4°C and washed in 3-fold of distilled water. The step was repeated, and the supernatant was discarded. Then, the sediment was dissolved in 250 ml of 1M acetic acid ($CH_3COOH$). The mixture was incubated at 80°C in a magnetic stirrer for 2 hours. Then the pellet was collected by centrifugation at 6000 xg for 20 min. At 4°C, the cells were washed with distilled water 3 times and centrifuged at 6000 xg for 25 min at 4°C. The supernatant was discarded, and after that, the pellet was mixed with 600 mL of absolute ethanol with a magnetic stirrer for 1 hour, and the suspension was centrifuged at 6000 xg for 25 min. At 4°C, the pellet was dried in a glass Petri dish by a hot air oven at 60°C for 24 hr to be ready for diagnosis.

### 2.2 Diagnosis of β-glucan by high-performance liquid chromatography (HPLC)

An auto sampler high-performance liquid chromatography system (SYKAM–Germany), supplied with a C18-NH analytical column (250 mm × 4.6 mm, 5 µm), was used for the diagnosis of β-glucan. Mobile phase = D.W: MeOH (98:2). The flow rate was 0.7 mL/min, the injected volume was 100 µL, with Detector = RI (refractive index detector).

### 2.3 Vaccination schedule

To estimate the efficacy of the β-glucan vaccine in vaccination, forty rats (*Rattus norvegicus* albino strain Wister) aging 40 days were obtained from the animal house of the University of Babylon and maintained under controlled environmental conditions (temperature 22 ± 2°C, relative humidity 50–60%, and a 12h light/dark cycle). Standard laboratory chow and water were provided. Rats were divided into four groups: twenty rats were used for vaccination, and twenty rats were used as a control group. Each group comprised ten animals per cage in clean, sterilized cages and was housed for three weeks for adaptation.

Vaccines were emulsified with the same volume of Complete Freund's Adjuvant, and two booster injections were administered to rats. On Day 0, rats in the vaccinated group received a subcutaneous injection of 10 µg β-glucan (in 0.1 ml PBS), emulsified with an equal volume of Complete Freund's Adjuvant (CFA). On Day 7, a booster dose (10 µg/0.1 ml β-glucan in PBS) was administered subcutaneously, emulsified with an equal volume of Incomplete Freund's Adjuvant (IFA; Sigma, USA). On Day 14, a final booster dose of 20 µg β-glucan in 0.1 ml PBS (without adjuvant) was injected subcutaneously.

The control group received PBS mixed with the corresponding adjuvants on the same schedule. Seven days after the last injection, ten rats from each group were sacrificed for blood collection and serum separation at -20°C. while the other groups were challenged after 14 days with 0.2 ml of ($10^6$/0.1 ml) of viable colonies aged 72 hr. of the viable strain of *C. albicans*. On Day 49 (21 days post-challenge), rats were anesthetized by intraperitoneal injection of 0.2 ml of a ketamine–xylazine mixture (2:1 ratio) 15 minutes prior to sacrifice [21]. Blood was collected into gel tubes, and serum was separated and stored at -20°C for ELISA analysis.

Serum levels of IgG, IL-1β, IL-18, IL-17, and IL-23 were quantified using enzyme-linked immunosorbent assay (ELISA) kits (ELK Biotechnology Co., Cat. No. 80202, USA), following the manufacturer's instructions. Liver tissues were homogenized in PBS using a tissue homogenizer, and 0.1 ml of the homogenate was plated on Sabouraud Dextrose Agar (SDA). Plates were incubated at 37°C for 48 hours to determine colony-forming units (CFUs) of *Candida albicans*.

### 2.4 Preparation and viable cell count of *Candida albicans* for challenge inoculum

To prepare a cell suspension, *Candida albicans* was cultured in SDA media for 24-72 hr at 37°C. Then cells were collected by centrifugation and washed with 10 mL PBS, mixing well by shaking. The process was repeated. The Supernatant was discarded to collect the pellet. 50 µl of

*Candida albicans* cells were diluted with 950 µl of PBS to prepare a stock solution. After that, 50 µl of diluted cells was aspirated with 50 µl of trypan blue stain. Cell numbers were counted under a light microscope by a hemocytometer using the following formula [22]:

Total viable cells count (cells/ml) = (total cells counted × dilution factor × 10.000 cells/ml) /number of squares counted

### 2.5 Quantification of *Candida albicans* CFUs in liver tissue post-challenge

Rats were dissected and organs separated from the body, about 1 g from the liver, and were weighed in a balance, transferred to a sterile test tube, mixed, and crushed with PBS in the test tube using a tissue homogenizer. About 100µl of homogenized liver tissue was streaked on SDA petri dishes and incubated at 37°C for 24 hr. Growth was examined daily, and colonies of *Candida albicans* were counted to calculate colony-forming units per 1 ml. Colonies were counted in each petri dish after 24 hr [23].

### 2.6 Statistical analysis

All data of the present study were analyzed using SPSS (version 26), and the comparison between groups was done using one-way ANOVA followed by Tukey's post hoc test. Data was divided into four groups (vaccinated and non-vaccinated groups before and after challenge), each group comprises 10 rats. All data were expressed as mean, standard error, and standard deviation (SD). A probability value of $P < 0.05$ was considered statistically significant.

## 3. RESULTS

### 3.1 Extraction of β-glucan vaccine

In the current study, from about 48 g of *Candida albicans* growth, β-glucan particles extracted by the Alkaline-acidic extraction method, after drying, weighed almost 3.25 g, appeared in bright brownish color, sold as particles (Figure 1).

### 3.2 Analysis of β-glucan by high-performance liquid chromatography (HPLC) technique

Beta-glucan was analyzed using high-performance liquid chromatography (HPLC) to diagnose the active elements and compare them with the standard. The results revealed a clear similarity in retention time and absorbance values with the reference standard, verifying the identity and purity of the tested particle. Figure 2 shows the obtained chromatogram, while Table 1 summarizes the comparative data between the sample and the standard.

**Figure 1.** Crushed β-glucan particles from *Candida abicans*

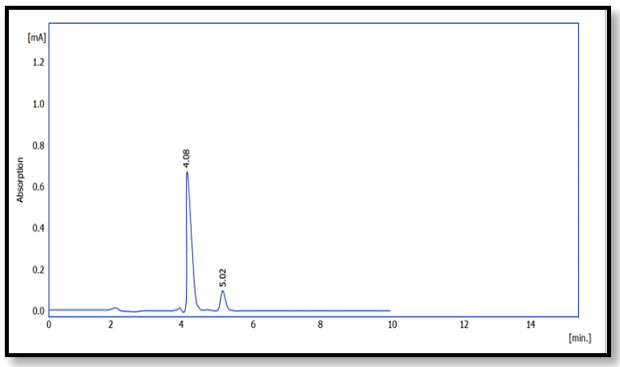


**Figure 2.** HPLC chromatogram of the β-glucan sample showing that the retention time matches the standard reference

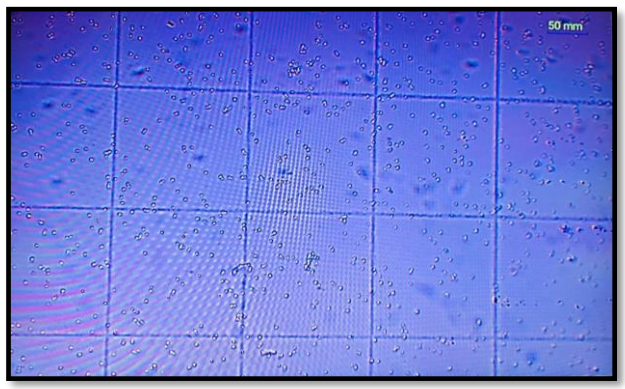


**Figure 3.** Viable cells of *Candida albicans* under a light microscope (10x)

**Table 1.** HPLC identification of β-glucan extracted from *Candida albicans*

| No. | Reten. Time, min | Area, mAU.s | Height, mAU | Area, % | Height, % | $W_{0.5}$, min |
|---|---|---|---|---|---|---|
| Sample | 4.08 | 69844.98 | 654.89 | 90.00 | 90.00 | 0.25 |
| | 5.02 | 854.00 | 88.45 | 10.00 | 10.00 | 0.02 |
| Standard β-glucan | 4.05 | 2001.89 | 592.61 | 100.00 | 100.00 | 0.25 |

### 3.3 Candida cells viability count

*Candida albicans* cells were grown on SDB with Tween 20 for 48-72 hr for challenge infection, and cells were counted to get $6 \times 10^5$ (Figure 3).

Signs were monitored in the vaccine-treated rats for 21 days. No mortalities appeared during this period, weight increased, and then the rats were dissected, while the control group showed white/creamy colonies of *Candida albicans* on the tissues (Figure 4).

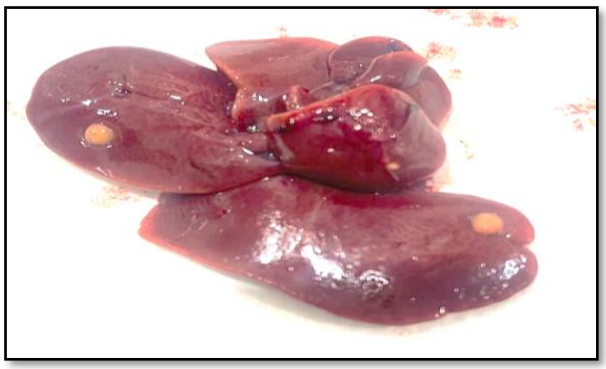

**Figure 4.** Liver from the control group showed regions with creamy colonies of Candida infection

### 3.4 Evaluation of vaccine efficacy

**-Determination of humoral and cellular immune response**

The concentrations of immunoglobulin G were measured in the sera of vaccinated and control rats. The results revealed that there were significant differences between concentrations in rats vaccinated with β-glucan vaccine (G1:10.737 µg/ml) compared with the control group (C1: 4.45 µg/ml) ($p \leq 0.05$). While the results after challenging infections showed that there was a non-significant elevation in rats vaccinated with β-glucan challenged with Candida cells (G2: 4.269 µg/ml) by comparing with control groups (C2: 5.052 µg/ml). Additionally, statistical analysis revealed that there was a significant difference in the concentration of immunoglobulin G in rats vaccinated with beta-glucan before challenge compared with those after challenge ($p \leq 0.05$) (Figure 5).

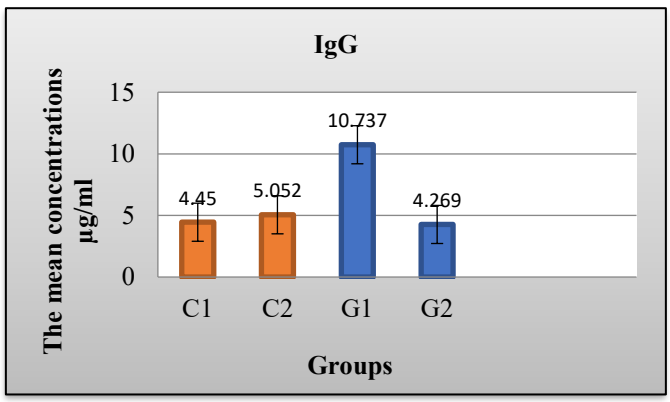


**Figure 5.** The mean concentration of IgG in vaccinated and control groups before and after challenge

C1 = control group before challenge, C2 = control group after challenge, G1 = β-glucan vaccinated group before challenge, and G2 = β-glucan vaccinated group after challenge

The concentrations of interlukine-1β measured in sera of vaccinated and control rats were measured by the ELISA technique. The statistical analysis revealed that the mean concentrations of IL-1β noticeably increased in rats vaccinated with β-glucan (G1: 64.342 pg/ml) compared with the control group (C1: 33.243 pg/ml) ($p \leq 0.05$). While the results after challenging infections showed that there were no significant differences in rats vaccinated with β-glucan challenged with Candida cells (G2: 66.188 pg/ml) by comparing with control groups (C2: 69.126 pg/ml) (Figure 6).

Also, statistical analysis showed a significant increase in the mean serum level of IL-18 in the β-glucan vaccinated group before challenge (185.544 pg/ml) compared with the control group (138.013 pg/ml) ($P \leq 0.05$). Moreover, the mean IL-18 concentrations in the β-glucan vaccinated group after challenging (142.525 pg/ml) also showed significant differences when compared with the control group (141.335 pg/ml) ($P \leq 0.05$) (Figure 7).

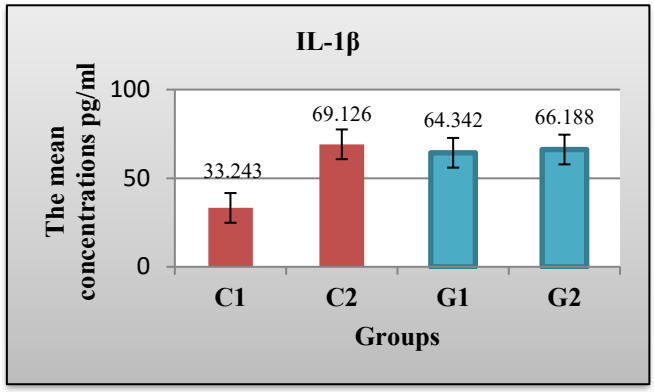


**Figure 6.** IL-1β concentrations in the vaccinated and control groups before and after challenge

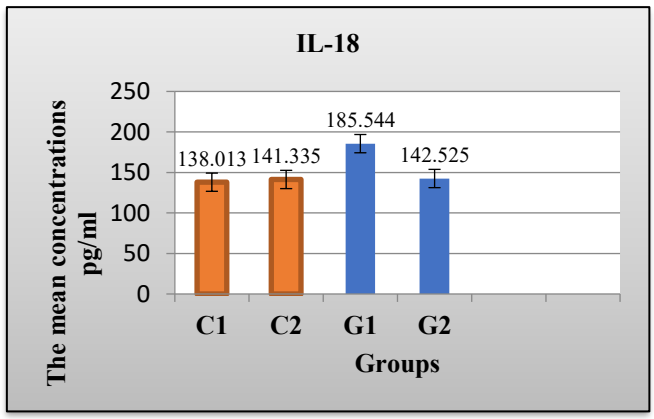


**Figure 7.** IL-18 concentrations in vaccinated and control groups before and after challenge

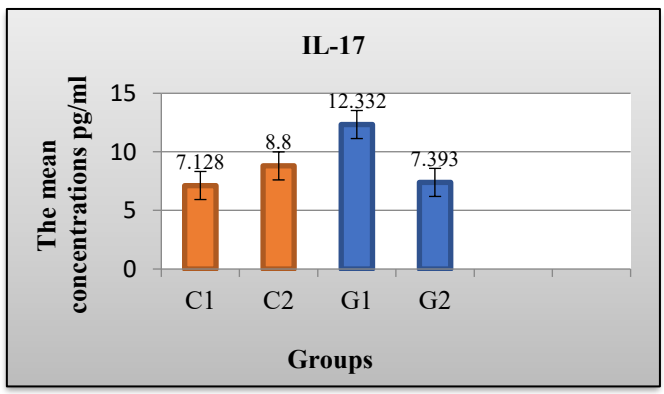


**Figure 8.** Mean concentration of IL-17 in vaccinated and control groups before and after challenge

Statistical analysis showed a significant difference in the mean concentrations of IL-17 in vaccinated rats with beta-glucan before challenge (G1: 12.332 pg/ml) compared with the control group (C1: 7.128 pg/ml) ($p < 0.05$). After challenge,

the mean level of IL-17 in rats vaccinated with beta-glucan (G2: 7.393 pg/ml) revealed a noticeable change compared with the non-vaccinated group (8.8 pg/ml) ($p < 0.05$) (Figure 8).

Moreover, statistical analysis results revealed a significant difference in the mean concentrations of IL-23 between the β-glucan-treated group before challenge (G1: 44.947 pg/ml) compared with the control group (C1: 39.164 pg/ml) ($p \leq 0.05$). After challenge, data analysis showed a noticeable decrease in IL-23 mean levels in rats vaccinated with β-glucan (G2: 35.504 pg/ml) compared with the control group (C2: 43.834 pg/ml) ($p \leq 0.05$) (Figure 9).

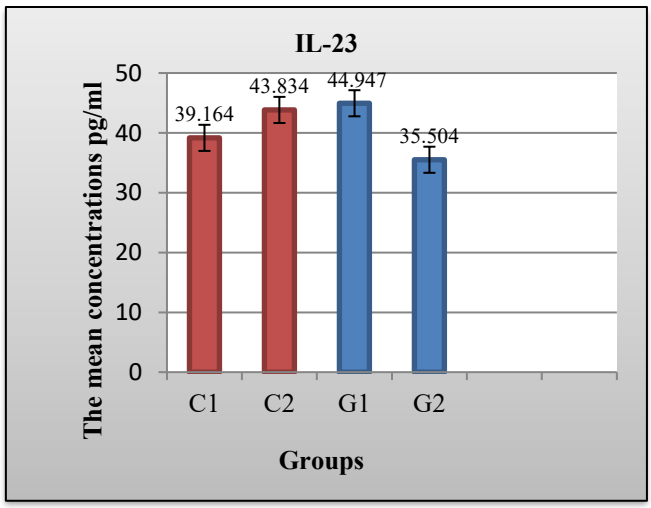


**Figure 9.** Mean concentration of IL-23 in vaccinated and control groups before and after challenge

**-Tissue burden evaluation by colony-forming unit (CFU)**

Colony-forming unit in the liver revealed a clear protective effect of β-glucan vaccination. The livers of vaccinated rats remained free of visible Candida colonies following challenge, whereas non-vaccinated rats developed multiple whitish lesions corresponding to fungal colonization (Figure 4). These observations indicated that β-glucan vaccination effectively reduced fungal burden in hepatic tissues compared with the control group.

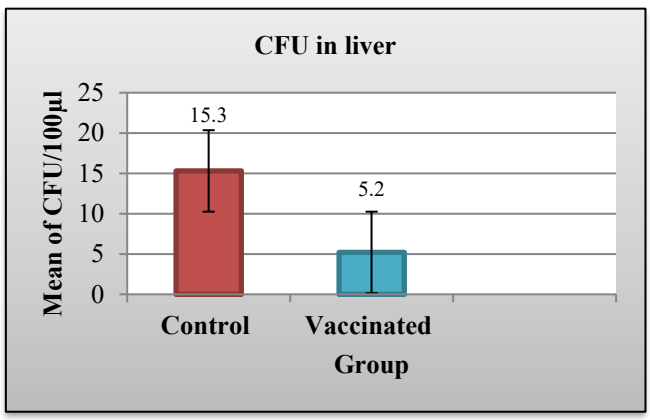


**Figure 10.** The mean of colony-forming units in the liver of vaccinated and control groups after challenge

A statistically significant reduction in the mean hepatic CFU counts was observed in the β-glucan vaccinated rats (5.2 CFU/100µl) compared to the unvaccinated controls (15.3 CFU/100µl) ($p \leq 0.05$). These findings indicated that β-glucan vaccination effectively decreased the fungal burden in the liver, reflecting its protective role against Candida colonization (Figure 10).

**-Correlation among the study parameters**

In the G1 group, correlation analysis between IgG and cytokines (IL-1β, IL-17, IL-18, and IL-23) revealed no statistically significant associations ($p > 0.05$). Although weak positive correlations were observed, such as between IgG and IL-17 ($r = 0.311$), and weak negative correlations with IL-18 ($r = -0.231$), these relationships did not reach statistical significance. Similarly, a moderate positive correlation was detected between IL-18 and IL-23 ($r = 0.568$, $p = 0.087$) and between IL-1β and IL-17 ($r = 0.494$, $p = 0.146$), but these also remained non-significant. These findings suggest that humoral immunity, as reflected by IgG levels, may act independently of the cytokine-mediated cellular immune responses within this sample. The non-significant positive trends among IL-17, IL-18, and IL-23 may indicate a potential activation of the Th17-related cytokine pathway, but the limited sample size ($n= 10$) likely reduced the statistical power to detect significant associations.

In the C1 group, the correlation analysis between IgG and the studied cytokines (IL-1β, IL-17, IL-18, IL-23) revealed no statistically significant relationships ($p > 0.05$). IgG showed weak negative correlations with IL-1β ($r = -0.268$) and IL-17 ($r = -0.251$), and nearly no correlation with IL-18 ($r = 0.062$) or IL-23 ($r = 0.001$). Similarly, inter-cytokine correlations such as between IL-17 and IL-18 ($r = 0.477$, $p = 0.163$) and between IL-17 and IL-23 ($r = -0.449$, $p = 0.193$) indicated moderate trends but did not reach statistical significance. These findings suggest that IgG-mediated humoral immunity is not directly associated with the cytokine profile within this sample. The observed, though non-significant, associations among IL-17, IL-18, and IL-23 may reflect partial involvement of the Th17 cytokine axis, but the limited sample size ($n = 10$) likely constrained the statistical power to detect significant correlations.

While in the G2 group, the correlation analysis demonstrated a strong and statistically significant positive association between IgG and IL-17 ($r = 0.862$, $p = 0.001$). This indicates that higher IgG levels were closely associated with increased IL-17 concentrations in the studied group. Such a strong correlation suggests a potential interaction between humoral immunity and Th17-mediated cellular responses. No significant correlations were detected between IgG and other cytokines (IL-1β, IL-18, IL-23), as all p-values exceeded 0.05. The observed IgG–IL-17 relationship may reflect the role of Th17-related cytokines in modulating B-cell responses and enhancing antibody production, consistent with previous reports linking IL-17 activity to humoral immune regulation. The lack of significant associations with IL-1β, IL-18, and IL-23 may be attributed to either independent regulatory mechanisms or the limited sample size ($n = 10$), which may have reduced statistical power.

Additionally, in the C2 group, correlation analysis demonstrated a strong and statistically significant positive association between IgG and IL-18 ($r = 0.794$, $p = 0.006$), indicating that higher IgG levels are closely associated with elevated IL-18 concentrations in the studied group. Moderate positive correlations were also observed between IgG and IL-1β ($r = 0.323$, $p = 0.363$) and between IgG and IL-17 ($r = 0.193$, $p = 0.594$), but these did not reach statistical significance. No

meaningful correlation was found between IgG and IL-23 ($r = -0.064$, $p = 0.860$). The strong IgG–IL-18 relationship suggests a potential link between humoral immunity and pro-inflammatory cytokine responses, highlighting a coordinated interaction between antibody production and IL-18-mediated immune activity. Other cytokines may be regulated independently or may not show detectable associations due to the limited sample size ($n = 10$).

## 4. DISCUSSION

### 4.1 Extraction and purification of β-glucan vaccine

The extraction and purification of β-glucan from yeast cell walls is a critical determinant of vaccine quality and immunogenicity. Crude yeast cell wall preparations contain a complex mixture of polysaccharides, proteins, lipids, and nucleic acids, which can mask antigenic epitopes or induce undesired immune responses. Therefore, effective purification protocols are essential to isolate β-glucan in a structurally intact and immunologically active form [24, 25].

In the current study, β-glucan purification was done using alkaline-acid treatment. It is commonly employed in yeast polysaccharide extraction, where mannoproteins and lipids are removed by alkaline hydrolysis and release of β-glucan in the complex cell wall matrix, which is removed by acid treatment that also simplifies the separation of any remaining impurities. It has been testified by numerous reports that β-glucan preparations of high purity, and with the triple-helix structure, both necessitate biological activity that is obtained by combined alkaline-acid extraction [18, 26].

According to the analysis of analytical HPLC of this investigation, high β-glucan concentrations were present in the purified fractions, and the elution patterns were very similar to the original reference standard. The distribution of molecular weight and conformational integrity of the β-glucan was not lost in the purification process, as the profile was very similar to the standard profile. These findings are aligned with other recent studies that indicate that when extraction steps are done correctly, β-glucan fractions can have chromatographic profiles that are almost identical to commercial standards [25, 27].

Crucially, the high-purity β-glucan offers a strong platform for immunological research. Branching patterns, solubility, and molecular weight alone can significantly alter the interaction between Dectin-1 and, consequently, immune activation, and thus provide a direct relationship between structural integrity and immunostimulatory ability. The current results support the effectiveness of the purification method and highlight its future applicability to vaccine production, as demonstrated by the achievement of both the increased concentration and compliance with the accepted reference values [9, 28].

Apparently, the whole procedure of the HPLC validation and alkaline-acid purification yielded high-quality β-glucan preparations that were of the set standards. These data support the fact that the method can be used in the pipeline of developing antifungal vaccines and support the idea that it can be reproducible and reliable.

The results of the present purification are consistent with the past research on the yeast β-glucan purification. Previous study showed that alkaline-acid extraction produced β-glucan with purity levels above 80%, but the remaining mannoprotein had to be removed through the use of enzymes. Conversely, the current procedure produced a high-purity product with the HPLC chromatogram being very similar to the industry standard, meaning that there was no need to add enzyme treatment to remove contaminants [24]. Similar to this, Chioru and Chirsanova [18] found that differences in extraction techniques had a significant impact on the molecular weight distribution and solubility of β-glucan. As it has been revealed through our inquiry, sequential treatments of the sample with acid and base did not cause the samples of the fraction to lose their triple-helical structure and immunologic capability.

The fact that the purified fractions and the reference profile were congruent is a strong indication that the conformational integrity was not lost during the extraction procedure, and this supports the existing results.

Our investigation has indicated that fractions that had undergone sequential acid-base treatment did not lose their triple helical structure and immunological property. The fact that the purified fractions matched the standard profile is a strong indication that the conformational integrity was not lost during the extraction, thus supporting the observed results. According to Zheng et al. [27], who highlighted the significance of HPLC as a gold-standard technique for evaluating β-glucan purity and structural consistency, the reproducibility of the chromatographic profile obtained in this study further solidifies its position. Strong confirmation that the purification procedure satisfied global standards for biochemical quality is thus provided by the close correspondence between our results and the reference standard.

In summary, by showing that β-glucan of a quality comparable to commercial standards can be obtained through acid-base purification and HPLC validation, the present result not only supports but also goes beyond earlier reports. These findings highlight the possibility of the translational application of the extraction method to develop antifungal vaccines and make it a reliable method to be used in further immunological testing [9, 28].

### 4.2 Determination of humoral and cellular immune response

The production of specific IgG antibodies after β-glucan vaccination is an important step of the adaptive immune response against *Candida albicans*. Earlier studies have proved that anti-β-glucan antibodies adsorb to the fungal cell walls, enhance the opsonophagocytosis process, and directly block the growth of fungi [28]. Given the fact that long-term protection requires humoral immunity and 1gG levels are supplemented by innate antifungal immunity, the increase of IgG levels in this study demonstrates that the vaccine preparation has been capable of stimulating humoral immunity [9]. The reduced levels of cytokines and the declined levels of antibody in vaccinated groups subsequent to the Candida challenge could be viewed as evidence of effective immune regulation rather than immune suppression. The significant rise in the pre-infection levels of antibodies and cytokines indicates that the β-glucan immunization was a strong stimulator of humoral and cellular response. The host could respond very fast and efficiently to the pathogen in case of exposure to the pathogen because of this immune priming [29, 30]. Therefore, the deterioration of the immune parameters after the challenge is a shift to an activated condition to a regulated balance, a hallmark of protective immunity and functional immunological memory [31, 32].

In contrast to the non-treated control group, as the present research has shown, the vaccination with β-glucan resulted in a significant increase in concentrations of IL-1β in successively vaccinated rats before the challenge. The initial increase states that β-glucan is a good inducer of the innate immune system and causes early activation of inflammatory cytokine cascades. This is pre-emptive of what could be termed trained immunity, whereby a phenotype of priming of β-glucans is said to restructure innate immune cells such as dendritic cells and macrophages that are subsequently able to respond with a greater degree of cytokine response to a subsequent stimulating occurrence of the identical antigen [33].

The vaccinated group's IL-1β levels decreased after the challenge infection, but the difference was not statistically significant compared to pre-challenge levels. This pattern might be the result of the immune system adjusting its regulation to prevent hyperinflammation. It has been demonstrated through previous studies that exposure to β-glucan can induce metabolic and epigenetic reprogramming and, consequently, limit excessive activation of the inflammasome to downregulate tissue damage and promote cytokine responses in parallel [33]. The observed downtrend in IL-1β may therefore indicate the establishment of a balanced inflammatory state, in which protective immunity is preserved without triggering harmful immunopathology.

According to the traditional activation of the NLRP3 inflammasome in response to infection, the non-treated control group, on the other hand, revealed a significant increase in IL-1β following the challenge infection in comparison to baseline values. This not-inspected increase in IL-1β in unvaccinated animals shows how β-glucan vaccination helps to regulate the cytokine environment and emphasizes the absence of immune priming. Recent studies have verified that β-glucan can serve as an immune adjuvant by boosting protective responses and diminishing the risk of an excessive inflammatory pathway [34].

All these findings suggest a biphasic immunologic outcome of β-glucan immunization, characterized by a priming phase enhancement in the production of IL-1β before the antigen challenge with immunologic effects, and then the active regulation phase that diminishes further increases in the production of cytokines on further exposure to pathogens. This dual action highlights β-glucan's function as a modulator of inflammatory homeostasis as well as an immune stimulant. In this regard, said features can have great ramifications on the development of vaccines, where the requirements of safety and efficacy are at loggerheads with a carefully-tuned generation of cytokine profiles [14].

Similarly, Inflammasome activation can be proven to play an antifungal defense role, as it leads to a rise in the levels of IL-18. The initial vaccination with β-glucan likely increased IL-18 because of activation of inflammasome pathways and enhanced signaling by receptors such as Dectin-1, which promote caspase-1-mediated maturation of IL-18 [35]. After challenge infection with *Candida albicans*, the observed decrease in systemic IL-18 may be due to rapid consumption of IL-18 at the site of infection, migration of IL-18-producing cells into tissues, or the engagement of regulatory feedback mechanisms that drop IL-18 release. Furthermore, IL-18 is known to raise both Th1 and Th17 responses (for example, via IFN-γ induction and modulation of γδT cells), and thus its decrease might signify transition from acute innate activation to a regulated adaptive phase [36]. Finally, the timing of sampling relative to peak IL-18 kinetics is critical; if sampling was taken after the initial surge, levels in the circulation could already have waned despite ongoing local immune action. Together, these mechanisms may explain the pattern of IL-18 increasing post-vaccination and reduction following fungal challenge. Growing evidence suggests that IL-18 and IL-12 are synergistic in boosting Th1-selected immunity and production of IFN-γ, and this leads to fungus clearance and macrophage activation [37]. According to the current study, the vaccination of β-glucan has a good prospect of training both cellular and adaptive immune cells, thereby enhancing host protection against candidiasis at the systemic level.

The early elevation in IL-17 levels after β-glucan vaccination can be attributed to the potent activation of Th17 differentiation via Dectin-1 and other pattern-recognition receptors, which are known to trigger IL-23/IL-6-dependent IL-17 secretion [38, 39]. After the infection with *Candida albicans*, the observed decline in systemic IL-17 concentrations may reflect migration of IL-17-producing cells from the circulation to the site of infected tissues, consumption of IL-17 at the mucosal site, or induction of regulatory feedback mechanisms such as IL-10/Tregs, which dampen Th17 responses [40, 41]. Furthermore, the dynamic remodeling of fungal cell-wall β-glucan exposure during infection could modulate dectin-1 signaling and thereby alter subsequent IL-17 output after the challenge [38]. Finally, the timing of sample collection relative to peak IL-17 kinetics is critical sampling occurred post-peak, the decrease may be attributed to the waning phase of IL-17 production rather than failure of the vaccine-induced response [42, 43]. Together, these mechanisms provide plausible explanations for the pattern of IL-17 elevation after immunization and decline following fungal infection.

The early increase in IL-23 in the β-glucan-treated group before the pathogen challenge is in line with the immunostimulatory effect of β-glucans through Dectin-1 engagement on macrophages and dendritic cells, which triggers IL-23/Th17 axis responses and activates Syk/NF-κB signaling [44, 45]. This finding supports the idea of trained immunity, which speculates that an individual becomes more susceptible to training through exposure to β-glucan, in which greater stimulations invoke a significant cytokine response among the previous exposure of the cell [46, 47]. There could be a number of causes for the subsequent decrease in IL-23 levels after the challenge infection. First, to protect the organs from tissue damage, negative immune regulation (such as the production of IL-10 or the activation of Treg cells) may suppress IL-23 [48]. Second, systemic cytokine concentrations may be temporarily dropped by functional exhaustion or the redistribution of IL-23-producing cells to infected tissues. Third, the IL-23/Th17 pathway may be downregulated by a shift in immune dominance toward Th1/IFN-γ responses, although some pathogens are also known to actively suppress IL-23 secretion as a means of immune evasion. Collectively, these results imply that β-glucan vaccination successfully primes the IL-23/Th17 pathway; however, its subsequent modulation is determined by post-challenge regulation and pathogen interactions.

The immunomodulatory function of β-glucan vaccination is approved by the decrease in IL-1β, IL-17, IL-23, and IL-18 concentrations seen in treated groups following Candida infection, in contrast to their distinct elevation in non-treated controls. Elevation in levels of IL-23 and IL-17, which are known to mediate mucosal immunity, can progress to too much inflammatory response and tissue damage when

dysregulated, which was a sign of a vigorous Th17-driven inflammatory reaction in control animals. This is due to the unchecked proliferation of fungi [33].

Conversely, the noted decline in the number of colony-forming units (CFU) in the hepatic tissue proves that prior immune priming of the body by β-glucan vaccination is what supports the quick fungal elimination is supported by. As a result, there is a reduced antigen load with resulting suppression of the sustenance stimulus of occurrences of prolonged cytokine generation, which portrays a success in suppressing the pathogen. Furthermore, β-glucan offers immunoregulatory properties that will suppress overinflamed hyperinflammation and promote a balanced immune reaction. Therefore, downregulation of IL-1β, IL-17, IL-23, and IL-18 indicates a controlled equilibrium state that reduces host immunopathology rather than immune suppression [49, 50].

According to recent research, β-glucan can stimulate both innate and adaptive immunity through "trained immunity" mechanisms, improving early pathogen control while also altering inflammatory pathways [51]. In addition, vaccine trials against Candida show that protective immunity depends on a balanced response that combines early Th17 activation with prompt inflammation resolution, rather than just persistent IL-17 overexpression [32].

The β-glucan-vaccinated rats exhibited a significant deficiency in hepatic CFU counts when compared with the non-immunized controls, suggesting that β-glucan may be protective against Candida infection. This effect is most likely mediated through the activation of innate immune mechanisms, specifically the stimulation of neutrophils, dendritic cells, and macrophages—key effectors in fungal clearance [50]. It has been demonstrated that β-glucan improves phagocytosis and oxidative killing of fungal pathogens, which lowers the fungal burden in target organs [51]. The observed decline in fungal colonization in vaccinated groups is in line with earlier research showing that β-glucan can act as an immunomodulatory factor that can improve host resistance to a Candida challenge by evoking trained immunity [52]. Thus, the present results supply strong evidence supporting the potential of β-glucan-based vaccines as promising candidates in antifungal immunotherapy.

After challenging, there was no mortality observed in the non-vaccinated groups and no dissemination of the fungal cells to all organs. This result may be attributed to different factors, including the overall good health status of the rats, the optimal environmental conditions maintained during the experiment duration, which collectively may strengthen their immune system. Additionally, the inoculum of Candida cells might have been relatively low and too little to evoke severe infection. Moreover, the innate immune cells may have played an important role in restricting the fungal infection and stopping the spread of fungal dissemination [53, 54].

The limitation of this study is that the structural characterization of the extracted β-glucan was primarily based on HPLC analysis. Future studies would benefit from more comprehensive techniques, such as Fourier-transform infrared spectroscopy (FTIR) for chemical bond confirmation and Congo red assay for verifying the triple-helix structure. Also, it is recommended to do histopathological micrograph studies that clarify the differences in tissue structure of the liver, kidney, or lymphoid organs in vaccinated and control groups.

Collectively, these results imply that β-glucan vaccination not only prepares the immune system for quick pathogen removal but also encourages immune homeostasis following infection, which is essential for reducing host pathology.

## 5. CONCLUSIONS

Considering the results provided in this research, it was observed that β-glucan vaccination has a significant induction of immunization, as evidenced by the increases in the concentrations of antibodies and pro-inflammatory cytokines before the occurrence of the infection. Following Candida challenge, a decrease in these immunological parameters indicated a controlled and balanced reaction that avoided hyperinflammation. Importantly, vaccinated groups also showed a significant decrease in liver yeast CFU counts, suggesting better protection against fungal growth. These results support the efficacy of β-glucan as a vaccine candidate or antigen that stimulates effective and regulated host defense.

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