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Enhanced bioactive components and repairing effects of *Tricholoma matsutake* co-fermented by *Saccharomyces cerevisiae*

Miaoxin Zheng[*1], Lu Hu[*1], Huixian Xu[1], Yanyan Chen[2], Dongli Zhang[2], Zhong Liu[2], Zhaodong Yuan[3], Chujie Huang[1]

1 R&D Department, SHE LOG (Guangzhou) Biotechnology Co., Ltd;

2 College of Life Science and Technology, Jinan University, Guangzhou;

3 School of Pharmacy and Food Engineering, Wuyi University, Jiangmen, China.

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1. Introduction

Environmental pollution, rising stress, and lifestyle changes contribute to an increasing prevalence of sensitive skin in both women and men. Sensitive skin is a clinical syndrome with stinging, burning, and itching sensations, primarily on the face. Recent research suggests a strong association between sensitive skin and dysfunctional neurogenic inflammation [1]. Neurogenic inflammation is characterized by four commonly observed signs of inflammation, namely redness, heat, swelling, and pain, accompanied by higher levels of inflammatory markers (IL-6, IL-1β, TNF-α, etc.) and key transcription factors (e.g., NF-κB, activator-1, and activator-2). Therefore, targeting these inflammatory factors provides new therapeutic approaches for sensitive skin. Driven by the demand of consumers for safe, effective, and environmentally sustainable cosmetics, natural-ingredient products have attracted increasing attention [2,3].

Tricholoma matsutake (*T. matsutake*) is a mycorrhizal fungus that grows in the outer layer of pine or oak trees [4]. It is a rare and valuable natural medicinal fungus in the world, known as the “king of fungi” [5]. Research indicates that *T. matsutake* contains a variety of active substances, including matsutake polysaccharides, matsutake polypeptides, matsutake alcohol, and other constituents, which exhibit biological activities such as anti-inflammatory, antioxidant, hypoglycemic, and immune-regulatory effects [6]. Li et al. discovered that the *T. matsutake* peptides reduce IL-1β and IL-6 secretion, decrease TNF-α, COX-2, and iNOS expression, and inhibit the activation of both the mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) pathways [6]. Deng et al. found that the polyphenols extracted from *T. matsutake* (TME) suppresses IL-1, IL-6, IL-8, and TNF-α expression; reduces UVB-induced p38 mitogen-activated protein kinase (p38 MAPK) phosphorylation and transcriptional factor NF-κB activity, thereby decreasing the cyclooxygenase-2 (COX-2) expression, an essential mediator of the inflammatory response [7]. Growing evidence suggests that *T. matsutake* is a promising ingredient for alleviating sensitive skin. However, traditional chemical extraction methods face multiple limitations, including low extraction efficiency, chemical residue risks, high energy consumption, and the

production of poorly absorbed large-molecular-weight compounds, which dramatically reduces the bioavailability of *T. matsutake* [8].

Biological fermentation technology leverages enzymatic reactions and metabolic pathways to convert active substances from various sources into more easily absorbed or bioactive forms, making it widely used in fields such as medicine, food, agriculture, and industry [9,10]. *Saccharomyces cerevisiae* (*S. cerevisiae*) can produce nutrients such as amino acids, vitamins and enzymes (glucanases, mannanases, amylases and proteases). It was found that solid-state fermentation of Ganoderma lucidum using yeast significantly increased the production of Ganoderma lucidum polysaccharides and triterpenoids, and that yeast metabolites, such as ethanol and esters, were able to promote degradation of Ganoderma lucidum cell walls, releasing more intracellular active components [11]. Recent yeast fermentation of cabbage has also confirmed the advantages of yeast in terms of active substance content and enhanced antioxidant and anti-inflammatory activity [12]. Therefore, using *S. cerevisiae* as a microbial agent represents a green biotransformation strategy, offering an eco-friendly alternative that circumvents the limitations of traditional extraction techniques.

Despite extensive research on the benefits of yeast in fermentation extraction, the co-fermentation of yeast with *T. matsutake* remains unexplored. This research pioneers to demonstrate successful co-fermentation between *S. cerevisiae* and *T. matsutake*. We investigated the *S. cerevisiae / T. matsutake* fermentation filtrate (STMFF) active constituents before and after fermentation. Moreover, the biological activities of STMFF, encompassing antioxidant, anti-inflammatory, soothing, and repair effects, were thoroughly examined, with anti-inflammatory mechanisms elucidated. This provides both a theoretical basis for *T. matsutake* fermentation and novel approaches for sensitive skin therapeutics.

2. Materials and Methods

2.1 Biological Materials and Reagents

Materials: *T. matsutake* comes from Shangri-La, Yunnan Province, China.

Strains: *S. cerevisiae* was purchased from Guangdong Microbial Culture Collection Center (GDMCC) and identified by BGI Sequencing Co., Ltd., Wuhan Branch.

Chemicals: LPS (Sigma L2880), NF-κB p65 antibody (Cell Signaling Technology #8242), p-p65 (CST #3033), HIF-1α (CST#D2U3T), IL-6 ELISA (Hangzhou Lianke Biotechnology Co. LTD#EK206), TNF-α ELISA (Hangzhou Lianke Biotechnology Co., LTD#EK282), All other chemicals and reagents used in this study were of analytical grade.

2.2 Samples Preparation

S. cerevisiae was inoculated to the flasks containing the fermentation medium with or without *T. matsutake* in a certain proportion. After fermenting for appropriate time, STMFF or the *Saccharomyces* fermentation filtrate (SFF) was collected by centrifugation and filtration. *Tricholoma matsutake* extract (TME) was prepared using water extraction under the same conditions.

2.3 UPLC-MS/MS and GPC analysis

STMFF, SFF, and TME were dissolved in 50% methanol and centrifuged (14000 rpm, 5 min) to extract supernatants for UPLC-MS/MS analysis. The 10 μL samples were subjected to gradient elution using ACQUITY UPLC HSS T3 column (2.1 mm × 100 mm, 1.8 μm) at a column oven temperature of 38 ℃. Data was collected using Q Exactive Orbitrap High Resolution Mass Spectrometry and analysed using Compound discover.

Then, the polysaccharide was tested by the phenol-sulfuric acid method. The changes in polysaccharide's molecular weight were further analyzed by Gel Permeation Chromatography (GPC). Waters Ultrahydrogel 500-250-120 A (7.8 × 300 mm) was employed for chromatographic analysis. 0.1 mol/L $NaNO_3$ in aqueous solution was used as the mobile phase with a flow rate of 1 mL/min and a column temperature of 40℃.

2.4 Measurement of ABTS+, DPPH, ·OH scavenging capacity

Different volume fractions of samples were added to the assay system, vitamin C solution was used as a positive control, and different solvent substrates were used to dilute the samples to determine the ABTS+, DPPH, ·OH free radical scavenging ability.

2.5 Cell culture

RAW264.7 cells (Mouse Monocytic Macrophage Leukemia Cell Line) and Human Keratinocytes Cells (HaCaT) were provided by the Type Culture Collection of the Chinese Academy of Sciences (Shanghai, China). Cells (passages 5-10) were seeded in DMEM containing 10% FBS and 1% P/S and incubated at 37℃ in a humidified atmosphere of 5% CO_2. Cells in stable growth and logarithmic growth phases were selected for subsequent experiments.

2.6 Cell wound scratch assay

The HaCaT cells were seeded under good growth conditions. After being attached to the wall, the samples were added. The wound was vertically scratched and washed with PBS, and images were taken under an inverted fluorescence microscope at 0h and 24h.

2.7 qPCR profiling of mRNA expression and protein secretion

After RAW264.7 cells were modelled with LPS (100 ng/mL, 6 h), they were subjected to various doses of the samples for detection. HaCaT cells were subjected to UVB irradiation for modelling (7.5 minutes, 400 mJ/cm²; pre-optimized dose with viability above 85%) and received samples of varying concentrations for treatment. qPCR analyzed LPS-induced IL-6, IL-1β, TNF-α, iNOS and COX-2 secretion in RAW264.7 cells and UVB-modulated AQP3/FLG expression in HaCaT cells.

2.8. Cytokine assay by ELISA

The contents of IL-6 and TNF-α in the culture medium supernatants were determined using ELISA kits according to the manufacturer's protocols.

2.9. Determination of intracellular ROS

RAW264.7 cells were treated with samples and 100 ng/mL LPS for 24 hours. The proportion of DCFH-DA fluorescence-positive cells was detected by flow cytometry after loading the DCFH-DA fluorescent probe in situ.

2.10. Western blotting

After the cells were treated as described above, they were lysed on ice for 10 minutes. The lysed proteins were collected, and the p65, p-p65, and HIF-1α protein expression were detected by the protein assay kits.

2.11 Statistical analysis

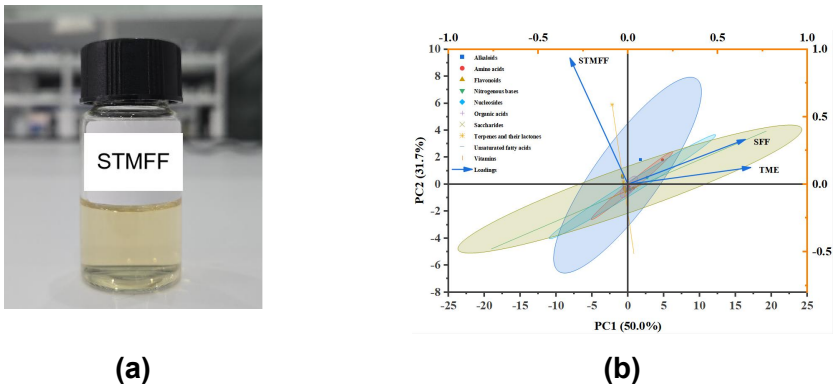
The data were analyzed using GraphPad Prism 8 software (GraphPad Software Inc., San Diego, California, USA). Each experiment was replicated at least three times in parallel, and data were expressed as means ± standard deviation (SD). One-way analysis of variance

(ANOVA) followed by Dunnett's multiple comparisons test was performed to compare the differences between groups, with a significant level was set at $p < 0.05$.

3. Results and Discussion

3.1 Composition analysis of active compounds

STMFF, a translucent light yellow liquid produced through controlled joint fermentation of *S. cerevisiae* and *T. matsutake* (Fig. 1a), demonstrates optimal cosmetic applicability due to its appearance. The composition of active compounds in SFF, TME, and STMFF was analyzed by UPLC-MS, respectively. The results showed significant differences in the variety and contents of active compounds in these three samples. STMFF were mainly composed of various sesquiterpenoids such as Curcumenol (35.67%), Arglabin (6.64%), and Dehydrocostus lactone (6.40%), as well as alkaloids such as (+)-Magnoflorine (6.45%), Stachydrine (5.94%), and Betaine (5.39%). In contrast, TME and SFF mainly consisted of various amino acids, nucleotides, and organic acids. These alterations in the types and contents of active compounds indicated that during the co-fermentation process, *Saccharomyces* not only utilized the nutritional components of *T. matsutake* for growth and reproduction, but also simultaneously converted different substances through internal biosynthesis, which finally could be metabolized and accumulate new chemical compositions. Combined with the inherent biological activity advantages of these active substances, this may be the direct cause of the synergistic effect of co-fermentation.



(a) **(b)**

Figure 1. The appearance of STMFF (a); Composition analysis results of chemical compounds on SFF, TME, and STMFF (b).

3.2 Polysaccharide analysis of content and composition

Many studies have found that polysaccharides from *T. matsutake* are one of the main active components in various biological activities such as antioxidants, whitening, and immune enhancement [13,14]. Therefore, it is essential to detect and analyse the content and composition of polysaccharides before and after fermentation.. The results showed that the polysaccharide content in STMFF was 481.9 μg/mL, which increased by 126% and 103%, respectively, compared to TME and SFF. Additionally, compared to TME and SFF, the polysaccharide of STMFF exhibited a broader range of molecular weight components and a higher proportion of lower molecular weight fractions. These findings demonstrated that *Saccharomyces* could continuously biosynthesize extracellular polysaccharides coupled with enzymolysis polysaccharides from *T. matsutake*, ultimately achieving an increase in content and a decrease in molecular weight of the polysaccharide of STMFF.

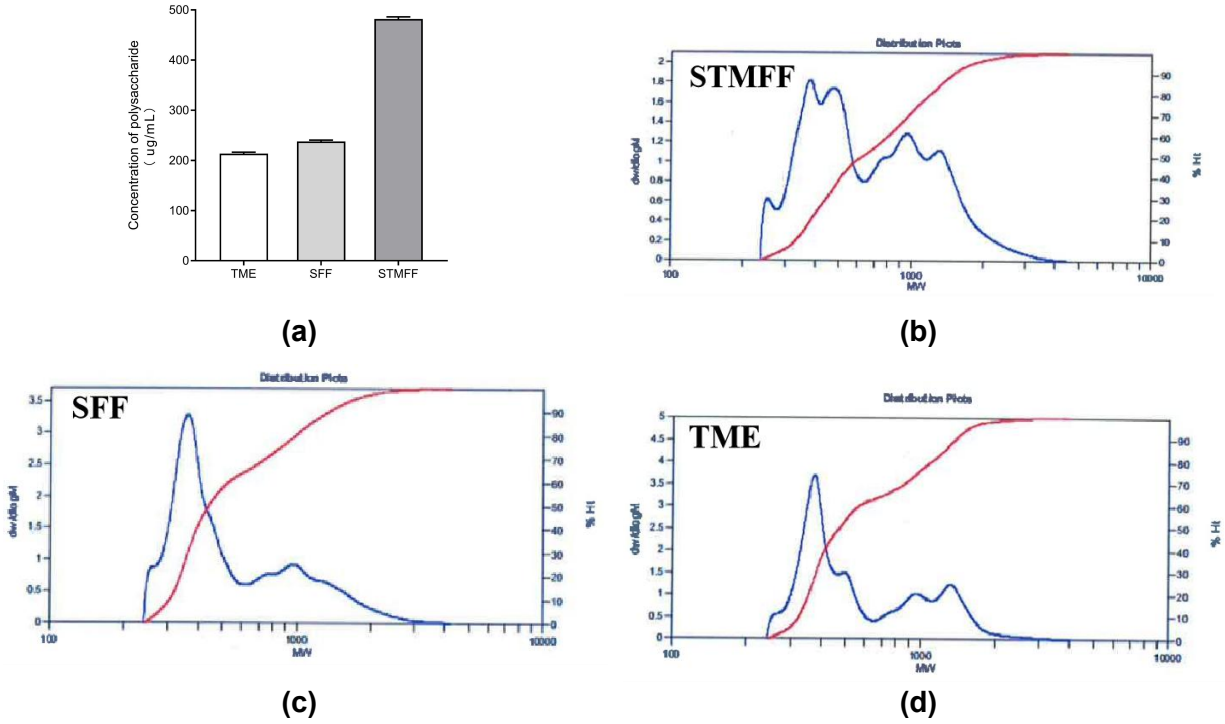


Figure 2. Polysaccharide content of TME, SFF and STMFF (a); The molecular weight distribution of polysaccharides of STMFF (b), SFF (c), and TME (d).

3.3 Efficacy Studies

3.3.1 Antioxidant activity

The in vitro antioxidant activity assay is a rapid evaluation of the antioxidant activity of an extract. As shown in Fig. 3, the results showed a dose-response relationship: the scavenging rate of free radicals increased with the increase of sample concentration. In the ABTS radical assay, at 2.5% concentration, the clearing rate of ABTS radicals of STMFF was enhanced by 34.7% compared to SFF, and by 253.6% compared to TME. In the DPPH radical assay, at a concentration of 12.5%, STMFF was elevated by 71.4% compared to SFF and 50.0% compared to TME. In the OH radical assay, at a concentration of 20%, the scavenging rate of STMFF was elevated by 137.4% compared to SFF, and 74.4% compared to TME.

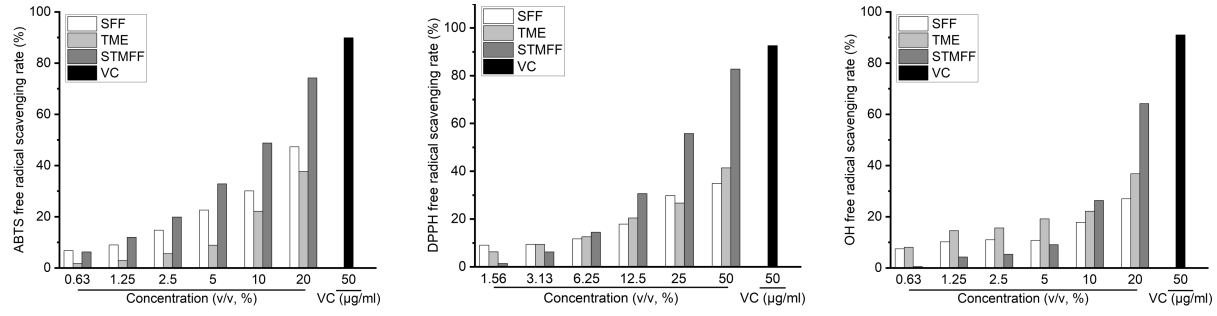


Figure 3. ABTS+ (a), DPPH (b), and · OH (c) scavenging capacity

3.3.2 Barrier repair activity

Zhu has shown that an increase in the concentration of *T. matsutake* remarkably promotes the proliferation of HaCaT cells [15]. As shown in Fig. 4a,4b, compared to the control, following a 24-h incubation period, a significant enhancement in wound closure was observed

in STMFF with the healing rate close to positive group and significantly better than SFF and TME, suggesting that STMFF had repairing efficacy.

Skin barrier damage leads to drying and dehydration of skin. FLG is known as a “natural moisturising factor” and essential for forming a functional skin barrier [16]. AQP3 provides a channel for moisture movement between the stratum basale and the stratum corneum to maintain constant moisture content within the epidermis [17]. As show in Fig. 4c and 4d, all samples showed different degrees of rebound after 48 h of treatment. Compared with SFF and TME, STMFF showed 307.5% and 251.5% higher FLG expression, along with 63.8% and 131.7% higher AQP3 levels.

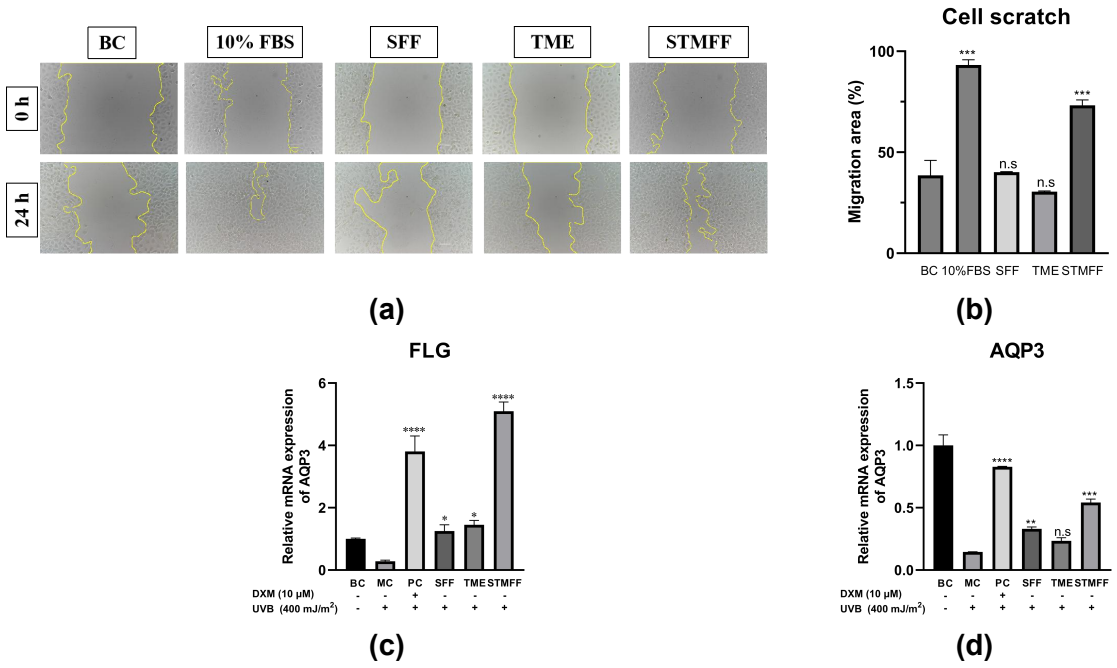


Figure 4. The scratch plot (a) and quantitative cell migration rates (b) of STMFF, SFF, and TME-treated HaCaT cells; The mRNA expression of FLG (c) and AQP3 (d).

3.3.3 Anti-inflammatory activity

NF-kB is crucial in coordinating cellular responses. Established activators of NF-kB activity include TNF-α, IL-1β, bacterial lipopolysaccharides (LPS), and ROS [18]. This work used LPS-stimulated RAW264.7 macrophages, a well-established *in vitro* inflammation model [19], to assess the anti-inflammatory ability of STMFF. Quantitative qPCR analysis revealed that STMFF significantly attenuated the LPS-induced upregulation of pro-inflammatory cytokines IL-1β, TNF-α, and IL-6 at the transcriptional level ($p < 0.05$) (Fig. 5). Compared to the model group, 2.5% STMFF therapy reduced IL-1β, IL-6, and TNF-α by 128.4%, 27.4%, and 323.4%, respectively, indicating greater anti-inflammatory potential (Fig. 5a, 5b, 5c). These findings support earlier research showing that decreasing early-phase cytokine transcription reduces inflammatory pathways. [20]. We performed additional investigations on the secretion of IL-6 and TNF-α. Consistent with transcriptional data, ELISA quantification confirmed that STMFF significantly inhibited LPS-induced secretion of IL-6 and TNF-α proteins ($p < 0.01$), achieving 66.51–70.43% suppression at 2.5% (Fig. 5a, 5b). This dual-phase inhibition, targeting both transcriptional and translational processes, strongly supports the anti-inflammatory efficacy of STMFF.

Given STMFF’s superior performance, its ability to modulate reactive oxygen species (ROS) generation was further examined. As Figures 5d and 5e illustrate, pretreatment with

STMFF (2.5%) reduced LPS-triggered ROS production by at least 90%, reaching levels statistically equivalent to dexamethasone ($p > 0.05$). As oxidative stress and inflammation are mutually reinforcing processes [21], this ROS-scavenging capacity likely contributes to STMFF's enhanced anti-inflammatory profile.

These findings demonstrate that STMFF possesses significant anti-inflammatory properties, mechanistically linked to suppression of cytokine signaling, downregulation of inflammatory enzymes, and attenuation of oxidative stress.

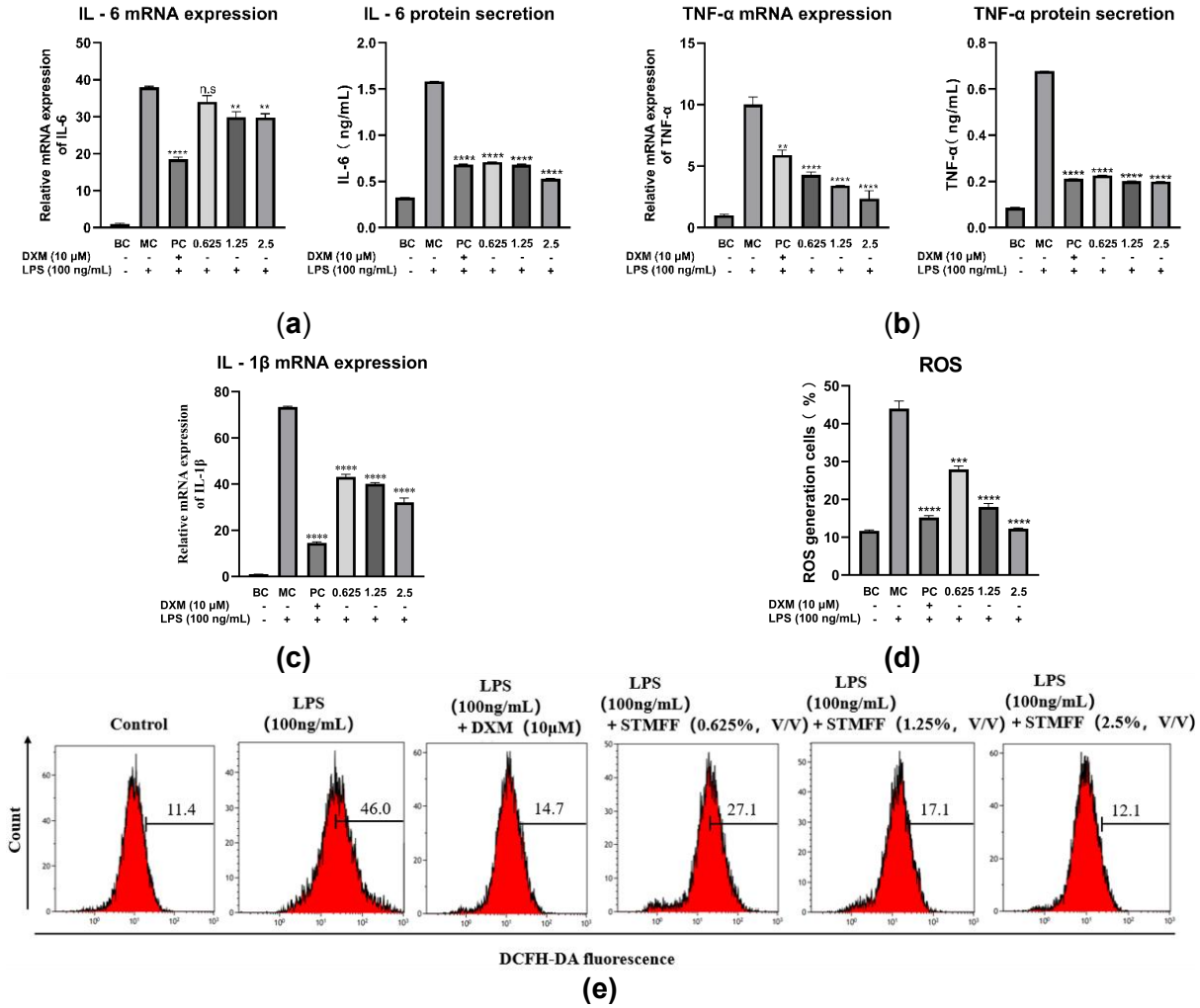


Figure 5. RAW264.7 cell ELISA assay results. Effects of STMFF samples on IL-6 (a), TNF-α (b), IL-1β (c), and ROS (d) levels with image (e)..

3.4 Mechanistic Elucidation of Anti-inflammatory Efficacy via NF-κB/HIF-1α Dual Modulation

NF-κB, iNOS and COX-2 are essential inflammation targets. Pro-inflammatory factors activate NF-κB and translocate it to the nucleus, thereby enhancing the expression of iNOS and COX-2 [22]. So, further investigation into downstream inflammatory mediators showed that STMFF dose-dependently suppressed the expression of iNOS and COX-2 (Fig. 6a, 6b), key enzymes responsible for nitric oxide and prostaglandin production during inflammation [23]. The activation of phosphorylated p65 is the core target for activating the NF-κB signaling pathway [24]. Western blot quantification demonstrated that STMFF dose-dependently inhibited LPS-induced phosphorylation of p65 (Fig. 6c, 6e). STMFF (2.5%) downregulated HIF-1α protein expression by 83.23% at six hours post-LPS challenge (Fig. 6d, 6f). Given HIF-1α's established role in amplifying MMP-9 production and inflammatory erythema in

compromised skin barriers [25], this suppression suggests dual therapeutic potential with both anti-inflammatory and barrier-protective effects.

The above results established that STMFF as a multifunctional active ingredient, mechanistically targeting acute inflammation via IKK/NF-κB pathway suppression while chronic inflammation perpetuation through HIF-1α-mediated hypoxia signaling as well as ROS scavenging of the oxidative-inflammatory cascade. This triple-action mechanism surpasses conventional cosmetic anti-inflammatory agents, focusing solely on COX-2 inhibition [26].

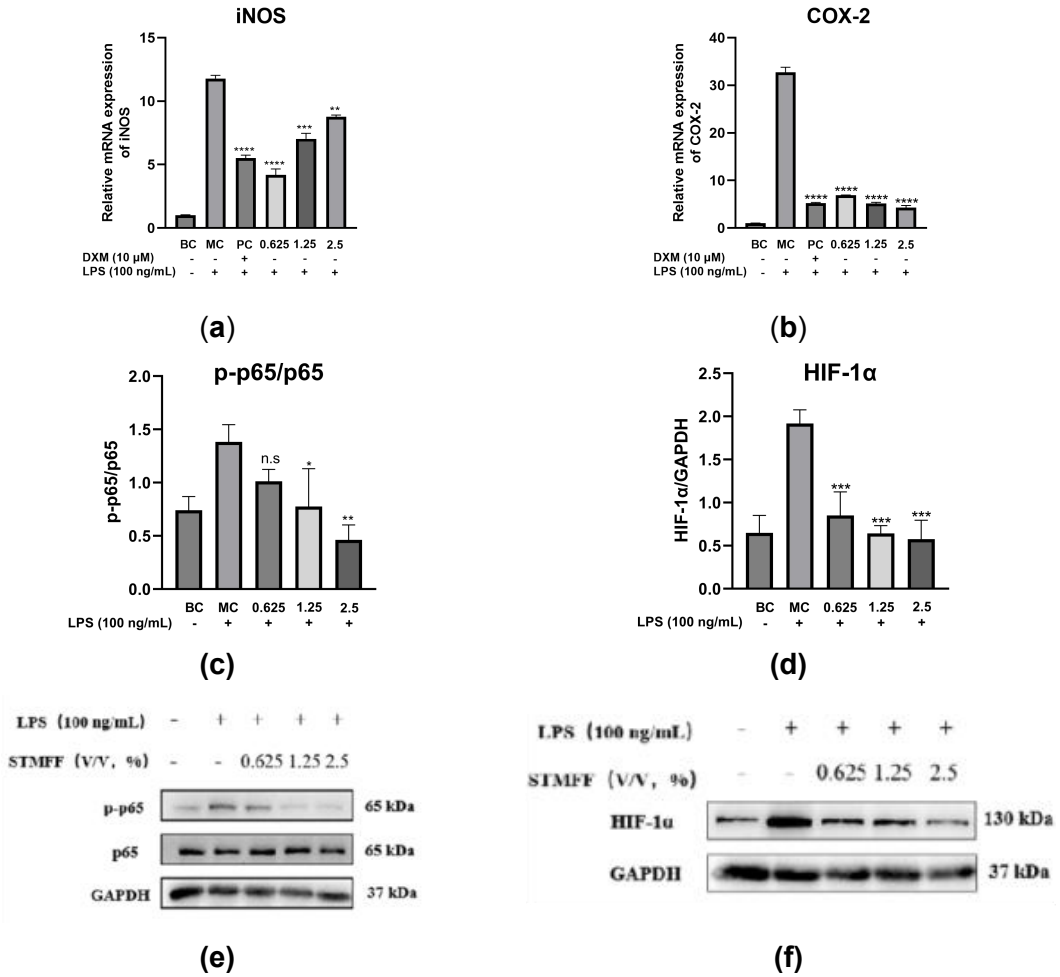


Figure 6. The assay results of iNOS (a) and COX-2 (b) in RAW264.7 cells. WB detection of p-p65 (c, e) and HIF-1α (d, f) expression in RAW264.7 cells.

4. Conclusion

This study developed STMFF through *S. cerevisiae* and *T. matsutake* co-fermentation, demonstrating enhanced immunomodulatory capacity via systematic bioactivity validation. We have validated three significant breakthroughs of STMFF by comparing data before and after fermentation: (1) Microbial bioconversion processes generated abundant yeast-derived secondary metabolites while enhancing the extraction efficiency and the diversity of active compounds of *T. matsutake*, as demonstrated by the elevated levels of polysaccharides and a broader array of active components. (2) Meanwhile, STMFF originates from natural sources, exhibiting markedly improved antioxidant and relaxing reparative qualities, which have been validated by results that reduce the levels of IL-6, TNF-α, and iNOS and promote cell healing and the expression of epidermal proteins. Notably, at a test concentration of 2.5%, STMFF

achieved an inhibition rate of 90.72% against IL-1β, comparable to synthetic anti-inflammatory drugs. (3) Furthermore, we verified that STMFF via NF-κB/HIF-1α dual modulation to exert anti-inflammatory efficacy that soothes the skin. These findings are expected to improve the *T. matsutake*'s biological activity and commercial value and foster research on prospective resources that aid ecological balance and stability.

5. Reference

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