Interdental Jurnal Kedokteran Gigi
Website: https://e-journal.unmas.ac.id/index.php/interdental
ISSN 1979-9144 (print), ISSN 2685-5208 (online)

Research Article

Comparative Effects of 50% and 100% *Pleurotus ostreatus* Gel on TNF-α in Traumatic Ulcer Healing in Wistar Rats

[1]Ni Nyoman Gemini Sari, [1]Raziv Ganesha, [2]Ni Nyoman Linda Pradnya Ningsih

[1]Department of Oral Medicine, Faculty of Dentistry, Universitas Mahasaraswati Denpasar, Indonesia
[2] Undergraduate Student, Bachelor of Dental Education Program, Faculty of Dentistry, Universitas Mahasaraswati Denpasar, Indonesia

Received date: August 10, 2025 **Accepted date: March 26, 2026** **Published date: April 30, 2026**

KEYWORDS

Male Wistar rat, Tumor Necrosis Factor-Alpha, traumatic ulcer, white oyster mushroom

ABSTRACT

Introduction: White oyster mushroom (Pleurotus ostreatus) is a natural ingredient with diverse benefits, including its ability to heal traumatic ulcers. In the healing process, TNF-α acts as an inflammatory mediator that promotes epithelial growth and neovascularization.
Material and Methods: This study was an in vivo laboratory experimental study using a post-test only control group approach, involving 32 samples randomly divided into eight treatment groups (n=4) based on variations in gel concentration (50%, 100%, negative control, and positive control) and observation time (days 3 and 7). TNF-α expression measurements were performed using an ELISA kit. Research data were analysed using the parametric One-Way ANOVA test, the non-parametric Kruskal-Wallis and Mann-Whitney tests, followed by the Tukey Post-Hoc test.
Results and Discussions: Statistical analysis results showed a p-value of 0.000 <0.05 between treatment groups. Tumor Necrosis Factor-Alpha (TNF-α) expression decreased significantly in the groups given 50% and 100% white oyster mushroom extract gel, with the lowest average found at a concentration of 50% on both days 3 and 7, namely 231.33 and 195.33, thus demonstrating more optimal effectiveness at that concentration.
Conclusion: White oyster mushroom (Pleurotus ostreatus) extract gel at a concentration of 50% was more effective than a concentration of 100% in reducing TNF-α expression in the healing of traumatic ulcers in male wistar rats. Further research with a concentration range of 50-100% and other immunological parameters is required for further confirmation.

DOI: 10.46862/interdental.v22i1.12362

Corresponding Author:
Ni Nyoman Gemini Sari
Department of Oral Medicine, Faculty of Dentistry
Universitas Mahasaraswati Denpasar, Indonesia
Email: geminisari@yahoo.com

How to cite this article: Sari NNG, Ganesha R, Ningsih NNLP. Comparative Effects of 50% and 100% Pleurotus ostreatus Gel on TNF-α in Traumatic Ulcer Healing in Wistar Rats. Interdental Jurnal Kedokteran Gigi. 2022;22(1):15-22. doi: 10.46862/interdental.v22i1.12362

INTRODUCTION

Oral wounds, commonly referred to as ulcers, are frequently encountered in the general population regardless of age or gender. Trauma is the primary triggering factor for the development of these lesions.[1] Traumatic ulcers are the most commonly observed lesions in the oral soft tissues, with simple mechanical trauma being the predominant cause.[2] pidemiological data indicate that the labial mucosa is the most frequent site of ulcer occurrence (43.1%), followed by the buccal mucosa (25%).[3]

Traditional medicine utilizing herbal remedies remains a widely chosen approach among communities to manage and prevent oral and dental problems.[4] Among natural resources, the white oyster mushroom is recognized as a promising material due to its high carbohydrate content, accounting for approximately 57.6–81.8% of its dry weight. A substantial portion of these carbohydrates is indigestible by human enzymes; however, they serve as important nutritional components, including trehalose (an oligosaccharide), as well as chitin, β-glucan, and Foods that belong to the polysaccharide group. The β-glucan content in these polysaccharides is highly abundant, even reaching more than 80% of the dry weight.[5] This content acts as an anti-inflammatory agent, with one mechanism being the protection of blood macrophages from free radical threats and facilitation of their migration to the wound site. Given this mechanism, the effectiveness of β-glucan in combating inflammation heavily depends on the immune cell response, particularly macrophages, which play a key anti-inflammatory role.[6]

TNF-α is an inflammatory mediator whose role in the wound healing process cannot be underestimated. Moreover, this inflammatory mediator can also counterbalance the adverse effects of reduced macrophage numbers, which directly affect the wound healing process.[7] However, excessive and uncontrolled TNF-α expression can instead delay the inflammatory healing process by hindering the transition to the proliferation and remodeling phases. Therefore, modulating TNF-α expression is necessary to identify potential therapeutic approaches that can optimally support wound healing. Findings by Sabban and Wahyuni[8] demonstrate that the use of 50% white oyster mushroom extract on traumatic ulcers yields far better results compared to untreated ulcers.[8]

Upon deeper investigation, white oyster mushroom contains diverse active compounds, including polyphenols, flavonoids, saponins, tannins, and terpenoids, as revealed in phytochemical screening.[9] Flavonoids, known for their anti-inflammatory properties, work by inhibiting cyclooxygenase activity, which subsequently blocks prostaglandin formation and proline hydroxylation. Consequently, the number of inflammatory cells in tissues decreases significantly. Flavonoids also play a role in regulating TNF-α activity during traumatic ulcer healing. Two flavonoids, *apigenin* and *luteolin*, possess specific abilities to control pro-inflammatory cytokine production.[10]

Research by Sabban and Wahyuni compared the effectiveness of white oyster mushroom (*Pleurotus ostreatus*) extract gel on the diameter of traumatic ulcers in male Wistar rats (*Rattus norvegicus*) at concentrations of 10%, 25%, 50%, and 100%. The results showed that the 50% concentration was the most effective. Based on these findings, this study specifically tests the 50% concentration as the proven optimal dose, supplemented by testing the 100% concentration as a high-dose comparator to confirm optimization and identify the ceiling effect—the point at which dose increases no longer yield better biological

responses and may even pose potential side effects.[11] In this study, the observed biological response is Tumor Necrosis Factor-Alpha (TNF-α) expression.

MATERIAL AND METHODS

This study employed an in vivo laboratory experimental approach using a post-test only control group design, with sample selection via simple random sampling and sample grouping using a completely randomized design (CRD). The research was conducted from June to July 2024, beginning with comprehensive permits including research implementation approval and ethical clearance from the Phytochemistry Laboratory of the Faculty of Mathematics and Natural Sciences, as well as the Histology Laboratory and Biochemistry Laboratory of the Faculty of Medicine, Udayana University, under letter No. K.525/A.17.01/FKG-Unmas/V/2024. The technical implementation began with white oyster mushroom extraction and gel preparation at the Phytochemistry Laboratory, while the in vivo laboratory experiments were performed at the Histology and Biochemistry Laboratories of the Faculty of Medicine, Udayana University.

The initial stage involved dividing the experimental animals into 8 different groups consisting of white oyster mushroom extract gel concentration treatments (negative control [2% CMC-Na], positive control [triamcinolone acetonide], 50% gel concentration, 100% gel concentration) as the main variable and treatment duration (3 days, 7 days) as the supporting factor. Each concentration treatment was grouped by duration, with each group having n = 4 samples. Each sample underwent a 7-day acclimatization period. The next step was preparing the white oyster mushroom extract, starting from washing to drying the mushrooms. After drying, the mushrooms were chopped into coarse powder. The coarse powder was then further ground using a grinder to form fine powder. The fine powder was subsequently sieved using a 60-mesh powder sieve to remove any coarse particles. 355 grams of fine white oyster mushroom powder was added to 1.5 liters of 96% ethanol and collected in a maceration vessel. It was stirred using a stirring rod for 20 minutes twice daily for 3 days. After 3 days, the filtrate was collected using a Büchner funnel, followed by evaporation with a rotary evaporator at 50 °C.

For the negative control, 2% CMC-Na gel was prepared by weighing 2 grams of CMC-Na and sprinkling it over 100 mL of hot distilled water, then grinding until homogeneous. This was followed by preparing 50% white oyster mushroom extract gel by weighing 10 grams of 2% CMC-Na gel, mixing it with 5 grams of white oyster mushroom extract solution, and stirring until homogeneous. For 100% white oyster mushroom extract gel, 10 grams of 2% CMC-Na gel was weighed, mixed with 10 grams of white oyster mushroom extract, and stirred until homogeneous.

Before starting the research, the experimental animals underwent a one-week acclimatization period in individual cages. The next stage involved injecting the rats with 0.2 mL ketamine HCl into the posterior thigh muscle for anesthesia. Traumatic ulcers were created using a round burnisher (±2 mm diameter) heated over a Bunsen flame until red-hot, then applied to the lower labial mucosa of the rats for approximately 3 seconds. After 24 hours, traumatic ulcers formed, characterized by round white lesions with yellowish fibrinous exudate in the center and red margins. Treatment was applied by administering white oyster mushroom extract gel to the ulcer area using a cotton bud twice daily (morning and evening). The positive

control group received triamcinolone acetonide, while the negative control received 2% CMC-Na. Tissue samples were preserved in PBS (pH 7.4), homogenized with an ultrasonicator, and centrifuged at 12,000 rpm for 10 minutes at 4 °C to obtain supernatant. Tumor Necrosis Factor-Alpha (TNF-α) expression was measured using an ELISA kit from Bioassay Technology Laboratory (Cat No. E0764Ra), with absorbance readings at 450 nm using a microplate reader. Quantitative TNF-α data were analyzed using Statistical Product and Service Solutions (SPSS) software.

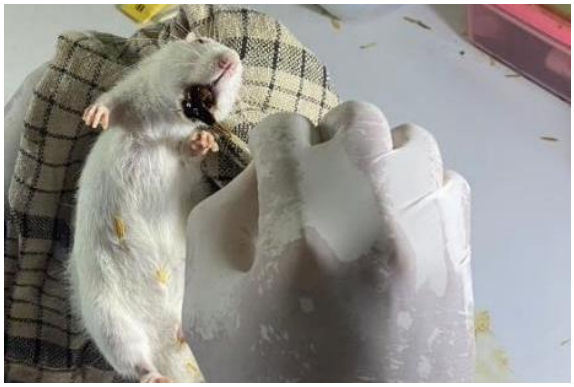

Figure 1. Process of applying white oyster mushroom extract gel on traumatic ulcers in male Wistar rats.

Figure 2. ELISA kit

RESULTS AND DISCUSSIONS

This study investigated the comparative effectiveness of two different concentrations of white oyster mushroom extract gel, namely 50% and 100%, in reducing TNF-α expression during the traumatic ulcer healing process in male Wistar rats. Thirty-two male Wistar rats were equally divided into eight distinct groups, with each group consisting of four rats. The groups received different treatments: four groups were given applications of white oyster mushroom extract gel (two groups with 50% concentration and two with 100% concentration, each applied twice daily for 3 and 7 days), two positive control groups received triamcinolone acetonide applications twice daily (for 3 and 7 days), and two negative control groups received 2% CMC-Na applications twice daily (for 3 and 7 days).

Before treatment, the white oyster mushroom extract was first tested for its phytochemical content to ensure the presence of bioactive compounds. Phytochemical analysis revealed the presence of polyphenols, tannins, saponins, flavonoids, and terpenoids.[9] Based on Fourier-Transform Infrared Spectroscopy (FTIR) identification results, the white oyster mushroom extract was confirmed to contain β-glucan, characterized by typical absorption peaks at wavenumbers 3750–3000 cm^{-1} (OH group), 3000–2700 cm^{-1} (–CH group), and 1260–1050 cm^{-1} (–C–O–C– group), indicating the presence of glycosidic bonds that are characteristic of β-glucan compounds. These compounds are responsible for modulating the inflammatory response during traumatic ulcer healing. After content testing, a series of statistical tests were conducted, beginning with the Kolmogorov-Smirnov test for data normality, which yielded p-values greater than 0.05 across all groups, indicating normally distributed data. Testing proceeded with Levene's test, which showed a Based on Mean value of 0.392 > 0.05, confirming homogeneity of variances between groups. Descriptive test results in Table 1 show that the highest TNF-α levels were in the negative control group (K-3) at 435.67 ± 4.63

pg/mL on day 3 and remained relatively high on day 7 (400.33 ± 5.51 pg/mL). In contrast, the lowest levels were found in the treatment group with 50% white oyster mushroom extract gel (P1), at 231.33 ± 4.93 pg/mL on day 3, decreasing to 195.33 ± 4.76 pg/mL on day 7. This pattern indicates that the 50% concentration was more effective in suppressing the inflammatory response compared to the 100% concentration (P2), which, although decreasing from 370.33 ± 6.90 pg/mL on day 3 to 308.67 ± 2.75 pg/mL on day 7, remained higher than P1. This pattern demonstrates that the 50% concentration was more effective in suppressing TNF-α levels compared to the 100% concentration.

Table 1. Descriptive test results

Group	TNF-α Level (Mean ± SD)
K-3	435.67 ± 4.63
K+3	241.67 ± 4.16
P13	231.33 ± 4.93
P23	370.33 ± 6.90
K-7	400.33 ± 5.51
K+7	215.00 ± 4.24
P17	195.33 ± 4.76
P27	308.67 ± 2.75

Note: K- = negative control; K+ = positive control; P1 = 50% extract gel; P2 = 100% extract gel; numbers 3 and 7 indicate treatment duration (day 3 and day 7)

Table 2. Results of hypothesis testing using One-Way ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	239166.951	7	34166.707	1396.621	0.000
Within Groups	587.132	24	24.464		
Total	239754.083	31			

Based on the One-Way ANOVA hypothesis test results (Table 2), an F-value of 1396.621 was obtained with a significance level of p = 0.000 < 0.05. These findings indicate significant differences between treatment and control groups in TNF-α expression during traumatic ulcer healing. The between-group Sum of Squares (239,166.951) was substantially larger than the within-group Sum of Squares (587.132), confirming that treatment variation dominated over internal group variation. Thus, white oyster mushroom extract gel at both 50% and 100% concentrations demonstrated significant effects in reducing TNF-α expression.

The final analysis employed Pearson correlation testing between white oyster mushroom extract gel concentration (%) and TNF-α expression (pg/mL). This supplementary Pearson correlation analysis examined the relationship between gel concentration and TNF-α expression, yielding a correlation coefficient (r) of -0.379 with p-value = 0.036 (p < 0.05).[12] The negative value indicates an inverse relationship, where higher gel concentrations paradoxically reduced effectiveness in suppressing TNF-α. Although this study's primary design was comparative, these correlation results align with findings that 50% concentration outperformed 100% and reinforce that dose-response relationships are not always linear.

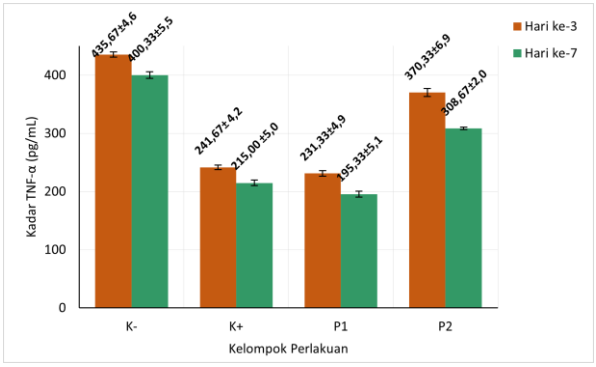

Figure 3. Diagram of TNF-α levels

The finding that the 50% concentration was more effective than 100% in reducing TNF-α levels contradicts the common assumption that higher doses yield better therapeutic effects. This phenomenon can be explained by the pharmacological

concept of the ceiling effect, where increasing the dose beyond a certain point no longer provides meaningful additional benefits to the pharmacological effect.[13] In other words, once a drug reaches its maximum effect, increasing the dose may instead potentially increase the risk of side effects.[14] In the context of this study, the 50% concentration represents the optimal dose that has achieved maximum effect in suppressing TNF-α expression. Increasing the concentration to 100% instead resulted in higher TNF-α levels (308.67 pg/mL) compared to the 50% concentration (195.33 pg/mL) on day 7. This aligns with the concept of hormesis or U-shaped dose-response, where bioactive compounds at low to medium doses provide beneficial effects, but at high doses may trigger stress responses or pro-inflammatory activity.[14]

The anti-inflammatory effectiveness of white oyster mushroom extract gel stems from its bioactive compounds, confirmed through phytochemical screening. Flavonoids play a dual role in this process, serving not only as antioxidants that prevent lipid peroxidation and neutralize triplet oxygen, but also as effective anti-inflammatory agents that alleviate swelling and pain in traumatic ulcers.[15] This aligns with the findings of García Mediavilla[17], who demonstrated that white oyster mushrooms reduce inflammation through modulation of pro-inflammatory cytokines in obese rats.[17] On the other hand, the saponin content in white oyster mushrooms significantly contributes to accelerating traumatic ulcer healing by enhancing type I collagen synthesis, which is an essential protein in the early healing phase. Saponins work through a mechanism that inhibits the cyclooxygenase enzyme, which catalyzes the conversion of arachidonic acid into endoperoxide compounds. This inhibition results in reduced prostaglandin synthesis and TNF-α expression, leading to a shorter inflammatory period and faster healing process.[16] Additionally, saponins also stimulate angiogenesis by enhancing Vascular Endothelial Growth Factor (VEGF) production, which plays a role in new blood vessel formation. β-glucan, as the primary polysaccharide in white oyster mushrooms, serves a central role in immune modulation. Through binding to specific receptors such as Dectin-1 and TLR-2/6 on macrophages, β-glucan activates immune cells in a controlled manner. At optimal concentrations (equivalent to 50% extract), β-glucan promotes macrophage polarization from the pro-inflammatory M1 phenotype to the pro-resolution M2 phenotype. M2 macrophages then release growth factors such as TGF-β1, PDGF, and VEGF, which stimulate fibroblast proliferation, collagen deposition, and angiogenesis.[4] However, when phytochemical compounds are present at high levels, they can exert the opposite effect (pro-inflammatory).

At 100% concentration, the bioactive compound content becomes excessively high and may potentially cause the opposite effect. Flavonoids at excessive concentrations can act as pro-oxidants and trigger oxidative stress through free radical formation. This oxidative stress condition instead activates NF-κB and increases pro-inflammatory cytokine production, including TNF-α. β-glucan at very high concentrations can excessively activate macrophages (over-activation), which paradoxically increases pro-inflammatory cytokine production.[17] These findings support previous research conducted by Sabban and Wahyuni in 2018, which investigated the efficacy of oyster mushroom extract in healing traumatic ulcers in rats. In that study, rats treated with 50% white oyster mushroom extract demonstrated a more effective reduction in ulcer diameter compared to untreated rats

as well as those treated with extract concentrations of 10%, 25%, and 100%.[8]

The selection of a 2% CMC-Na (Carboxymethyl Cellulose Sodium) base in this gel formulation is also appropriate, considering its characteristics of easy swelling, compatibility with active ingredients, the ability to produce a transparent gel, and its high viscosity, which allows the gel to adhere longer to the mucosa.[18] The finding that a 50% concentration is more effective than 100% has important clinical implications.

Using optimal concentration (50%) is not only more effective and cost-efficient, but also minimizes the risk of side effects from excessive concentrations. This aligns with the principles of phytopharmaceutical development, which emphasize the importance of determining optimal dosing.[19]

CONCLUSION

Based on the conducted study, it can be concluded that a 50% concentration of white oyster mushroom (*Pleurotus ostreatus*) extract gel is more effective than a 100% concentration in reducing TNF-α expression during the healing of traumatic ulcers in male Wistar rats. The 50% concentration was identified as the optimal dose, providing maximal anti-inflammatory effects, whereas increasing the concentration to 100% demonstrated a ceiling effect, resulting in decreased efficacy.

Further studies are recommended to explore concentration ranges between 50–100%, include additional immunological parameters such as IL-1β, IL-6, and IL-10, and conduct clinical trials in humans to confirm its efficacy and safety before development as a phytopharmaceutical product.

REFERENCES

1. Prehananto H, Purnamasari VD, Yuliastri N. Uji aktivitas ekstrak daun kemangi dalam meningkatkan jumlah fibroblas pada traumatik ulser. Bhakta Dent J 2023; 1(1): 1–8.
2. Regezi JA, Sciubba J, Jordan RCK. Oral Pathology: Clinical Pathologic Correlations. Elsevier Health Sciences; 2016.
3. Herawati E, Nur'aeny N. Etiologi, distribusi lokasi, dan terapi ulser traumatik pada pasien di Rumah Sakit Gigi dan Mulut Universitas Padjadjaran. B-Dent J Kedokt Gigi Univ Baiturrahmah 2021; 8(3): 313–9. Doi: 10.33854/jbd.v8i3.1022
4. Kristyanti Y, Lutsina NW. Penyuluhan dan edukasi tentang pemanfaatan tanaman herbal untuk kesehatan gigi dan gusi di jemaat GKII Filadelfia Family Alak. Maj Cendekia Mengabdi 2023; 1(4): 288–91. Doi: 10.63004/mcm.v1i4.266.
5. Jantaramanant P, Sermwittayawong D, Noipha K, Hutadilok-Towatana N, Wititsuwannakul R. [Beta]-glucan-containing polysaccharide extract from the grey oyster mushroom [Pleurotus sajor-caju (Fr.) Sing.] stimulates glucose uptake by the L6 myotubes. Int Food Res J. 2014;21(2):779.
6. Andrini N. Pengaruh beta-glukan dari ekstrak ragi roti (Saccharomyces cerevisiae) terhadap penyembuhan luka sayat pada mencit Wistar jantan. J Ilm Simantek 2021; 5(4): 35–44.
7. Wibowo E, Dharmana E, Maharani N, Budijitno S. Pengaruh kombinasi suplementasi omega 3 dengan kalori restriksi terhadap penyembuhan luka bakar pada tikus Sprague Dawley kajian pada: Tumor nekrosis faktor-alfa dan perbaikan luas luka bakar. Medica Hosp J Clin Med. 2020; 7(1): 75–81. Doi: 10.36408/mhjcm.v7i1.432.
8. Sabban If, Wahyuni In. Efektifitas Ekstrak Jamur Tiram (Pleurotus Ostreatus) Terhadap Penyembuhan Ulkus Traumatik Pada Tikus (Rattus Novergicus Berkenhout 1769). In: Prosiding Sintesis (Seminar Nasional Sains, Teknologi dan Analisis). 2018.
9. AlTasyah MH, Winahyu DA, Ulfa AM. Uji Toksisitas Ekstrak Etanol Jamur Tiram Putih (Pleurotus ostreatus) Dengan Metode BSLT (Brine Shrimp Lethality Test). JFM (Jurnal Farm Malahayati) 2022; 5(1): 98–107. Doi: 10.33024/jfm.v5i1.5707
10. Savira A, Mujayanto R, Amurwaningsih M. Bay leaf (Syzygium Polyanthum) extract gel effect on Tnf-A expression in traumatic ulcers healing process. ODONTO Dent J 2020; 7(1): 25. Doi: 10.30659/odj.7.1.25-30
11. Zahid S, Chinnam S, Ahmed A, Masaud SM, Khurshid B, Farman S, et al. RSM-based optimization of dose response and antibacterial potential of Cannabis sativa (L.) leaves using computational analysis. Dose Response 2025; 23(4): 15593258251404068. Doi: 10.1177/15593258251404067
12. Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. Anesth Analg. 2018; 126(5): 1763–8. Doi: 10.1213/ANE.0000000000002864
13. Sharifi-Rad J, Quispe C, Herrera-Bravo J, Martorell M, Sharopov F, Tumer TB, Taheri Y MN. Mushroom polysaccharides as potential anticancer agents: A mechanistic review. Int J Mol Sci. 2020; 21(2): 635.
14. Rahmadani N, Wahyukundari MA, Harmono H.

Efektivitas gel ekstrak biji kopi robusta (Coffea canephora) terhadap peningkatan jumlah fibroblas pada penyembuhan luka pasca gingivektomi. STOMATOGNATIC-Jurnal Kedokt Gigi 2022; 19(1): 13–8. Doi: 10.19184/stoma.v19i1.30694
15. Luo Z, Ming L, Ji J, Huang Q. U-Shaped dose-dependent modulation of macrophages by ginkgolide b mitigates systemic inflammation in septic rats. Dose-Response. 2025; 23(4): 15593258251406112. Doi: 10.1177/15593258251406112
16. Mendrofa AN, Mulawarmanti D. Ekstrak daun mangrove (A. marina) mempercepat kesembuhan ulkus traumatikus (Extract of mangrove leaf (A. marina) accelerates the healing of traumatic ulcer). J Dentomaxillofacial Sci. 2015; 14(1): 11–4.
17. García-Mediavilla MV, Crespo I, Collado PS, Esteller A, Sánchez-Campos S, Tuñón MJ G-GJ. Edible and medicinal mushrooms reduce inflammation in obese Wistar rats. Int J Mol Sci. 2023; 24(9): 7893.
18. Ningrum IS. Pengaruh ekstrak daun binahong (Anredera cordifolia (Ten.) Steenis) terhadap ekspresi tumor necrosis factor-α (tnf-α) pada ulkus mulut (penelitian in vivo). Karya Tulis Ilmiah. Semarang: Universitas Islam Sultan Agung; 2021.
19. Cladis DP, Weaver CM, Ferruzzi MG. (Poly) Phenol toxicity in vivo following oral administration: A targeted narrative review of (poly) phenols from green tea, grape, and anthocyanin-rich extracts. Phyther Res. 2022; 36(1): 323–35. Doi: 10.1002/ptr.7323
20. Siddique MF, Selim MYE, Ghannam MT, Huh J, Husain A. Enhancing the stability and rheological performance of date seed powder biomass-based slurry fuels: Influence of dispersants and temperature effects. Energy Convers Manag. 2025; 342: 120126. Doi: 10.1016/j.enconman.2025.120126
21. Karthikeyan M, Mehta A, Kumar SS, Mohan H, Usha B. Safety, Dosage, and Regulatory Aspects in the Use of Phytochemicals. In: Medicinal Plants and Their Bioactives in Human Diseases. Springer; 2025. p. 207–33.