

Wood Vinegar Promote Wound Healing by Regulates p38 MAPK Signal Pathway

Zhongwei Lu¹, Huicong Shang², Zaoshi Wang¹, Wenhui Wu¹, Qing Dong¹, Jianqi Gu^{3,*}

¹ College of Oral Medicine, North China University of Science and Technology, Tangshan, Hebei, China

² College of Oral Medicine, Hebei Medical University, Shijiazhuang, Hebei, China

³ Hebei General Hospital, Shijiazhuang, Hebei, China

* Corresponding author: Jianqi Gu

Abstract: Objective: To investigate the mechanism by which wood vinegar regulates the expression of p38 MAPK signaling pathway and promote wound healing in diabetic rats. **Methods:** The wound model of diabetic rats was established, and different corresponding interventions were given to study the effect of wood vinegar on the wound healing of diabetic rats. **Results:** The healing rate of the wound was $24.12 \pm 1.01\%$ on the third day after operation, which was significantly higher than that of the model group ($8.21 \pm 0.69\%$ ($P < 0.05$)). On the 6th and 9th days, the healing rates of the wood vinegar group ($37.38 \pm 1.17\%$, $59.14 \pm 1.11\%$) continued to be higher than those of the other groups, which was statistically significant ($P < 0.05$). On the 12th day, the healing rate of wood vinegar group reached $88.84 \pm 1.60\%$, which was significantly higher than that of the model group ($P < 0.05$) of $58.36 \pm 1.85\%$. On the 15th day of the experimental endpoint, healing rate was $93.63 \pm 1.25\%$, while the aloe vera gel group was $87.77 \pm 1.51\%$, while the model group was only $68.21 \pm 0.53\%$ ($P < 0.05$); TNF- α content: The results of Elisa showed that the expression intensity of TNF- α , an inflammatory factor, in the four groups of rats showed an overall trend of the model group > blank group > AG group > WV group at 15 days; p38MAPK expression intensity: Western-blot Western blot showed that the expression intensity of p38 MAPK in the wound of the model group was the same as that of the wood vinegar group ($P < 0.05$) and the aloe vera gel group ($P < 0.001$), and the content of p38 MAPK was the lowest in the wood vinegar group. **Conclusion:** Plant-derived wood vinegar can reduce the inflammatory response of wounds and promote wound healing in diabetic rats by regulating the expression intensity of p38 MAPK signaling pathway.

Keywords: Plant Vinegar; p38 MAPK; Diabetic Wounds.

1. Introduction

Diabetes is a chronic disease caused by low insulin utilization or insufficient secretion, affecting multiple systems throughout the body. According to statistics, about 340 million people worldwide suffer from diabetes, and about 20% of them suffer from diabetic wounds [1]. Especially in acute skin trauma caused by various accidents, excessive blood sugar seriously affects the healing speed of wounds by affecting blood vessel formation, extending chronic inflammatory responses, continuously destroying immune defense barriers, promoting the formation of bacterial biofilms, and other mechanisms, and greatly increasing the risk of wound infection, and even turning acute wounds into chronic wounds with difficulty in healing, affecting the prognosis [2].

Wood vinegar is the product of purification and refining of wood or traditional medicinal materials, and the wood vinegar made by different production methods and raw materials has slightly different in compositions and proportions [3]. Usually phenols, aldehydes, and ketones are the main ingredients. Among them, 2-methoxyphenol (guaiacol) accounts for about 10% [4], and a related study by Patricia Verónica Aulestia-Viera [5] confirmed that the mixed preparation of guaiac has certain antibacterial, antioxidant stress, and the production of healing-related cytokines, and Theapparat et al. [5] showed that the wood vinegar extracted and concentrated from palm kernel shell biomass contains oxygen-containing compounds, can increasing expression of TGF- β and gene proteins related to the SMAD signaling pathway, significantly activates Akt and Fak phosphorylation, thereby promoting diabetic wound

healing. Ho CL et al. [6] showed that bamboo vinegar produced by a method similar to plant-derived wood vinegar has the effect of regulating the overexpression of MAPK signaling pathways, thereby controlling the inflammatory response. Therefore, it can be studied as a drug to promote diabetic wound healing and prevent postoperative or post-traumatic wound infection. The purpose of this study was to study the effect of plant-derived wood vinegar on the healing process of diabetic wounds, and to preliminarily explore its mechanism of promoting wound healing, in order to provide new treatment ideas for promoting diabetic wound healing and preventing wound infection caused by hyperglycemia.

2. Methods

2.1. Reagents and Instruments

0.78% wood vinegar (Tangshan Xinyano Biotechnology Co., Ltd.), streptozotocin (STZ), citric acid antigen repair solution (Siwega, batch number: ga2302052), isoflurane, saline, aloe vera gel, EGF antibody (bioworld), FGF antibody (Mitaka), PDGF antibody (affbiotech), secondary antibody Goat Anti-Rabbit IgG H&L (HRP) (abcam), BCA protein concentration determination kit (Shanghai Biyuntian Biotechnology Co., Ltd.), Elisa kit (Shanghai Biyuntian Biotechnology Co., Ltd.), electronic scale, centrifuge tube, centrifuge.

2.2. Experimental Animals

Seventy 6-week-old male SD rats (license number: SCXK (Beijing) 2024-0003) with a body weight of 200 ± 20 g were selected for the experiment, and the rats, corn cob bedding

and Co rat maintenance material were purchased from Beijing Huafukang Biotechnology Co., Ltd. The animal experiments have been reviewed and approved by the Medical Ethics Committee of Hebei Provincial People's Hospital (Ethics Review No.: 2024-DW-090).

2.3. Establishment of Animal Models

2.3.1. Animal Diabetes Modeling [7] [8]

Fifty-five male SD rats were selected and fasted for 6 hours, drinking normal water, and then configured with STZ solution, injecting STZ (65mg/kg) intraperitoneally with a 1 ml syringe, and placed back in the cage, providing normal food, and changing the drinking water to 10% sucrose water. Monitor the blood glucose and physiological status of the rats after 6 hours of fasting daily, and when the blood glucose value > 8.8mmol/L and remained stable after 5 days, the physiological behavior of polydipsia, polyphagia and polyuria was judged to be successful. Another 15 SD rats were selected to perform exactly the same procedure, replacing STZ injection with sodium citrate buffer as a blank group modeling.

2.3.2. Wound Modeling of Diabetic Rats

After the diagnosis of diabetes modeling, the wound modeling was started[9]. Isoflurane inhalation anesthesia was used and continued induction, and make an excision at about 2cm below the lower edge of the scapula on the back of the rat. In the surgical area, use a skin preparation knife to shave the hair, disinfected the skin, subcutaneous injection of 1% lidocaine for local anesthesia, the superficial layer of the skin was cut, and the entire layer of skin was cut. Finally, the entire layer of skin of 1.5cm*1.5cm was removed until the fascial layer.

2.4. Experimental Method:

After modeling, 47 of the 55 SD rats survived, and 45 diabetic rats were randomly divided into model group (normal saline dressing change), WV group (wood vinegar dressing), and AG group (aloe vera gel dressing). 15 non-diabetic rats were also selected as the blank group (normal saline dressing). All rats were dressed every other day, and the size of the wound was recorded for each dressing change, and photos were taken for keeping. Executed after 15 days, and the back wound tissue was cut and relevant indicators were tested.

2.5. Wound Healing Rate

Take photos every 3 days to measure the wound area and calculate the wound healing rate accordingly;

Calculation formula [10]:

$$\text{wound healing rate} = \frac{S_n - S_0}{S_0} \times 100\% *$$

* S_n : wound size on the n day; S_0 : wound size on the first day

2.6. Detection of TNF- α Inflammatory Factor Content

The content of TNF- α in the back wound tissue of rats was determined by Elisa method, aiming to determine the degree of inflammation, so that the wound healing of rats under different treatment methods was inferred.

After taking the skin of the rat's back wound, rinse with pre-cooled PBS, cut into pieces, mix with PBS and grind to obtain tissue homogenization, centrifuge 5000g for 10 minutes, take the supernatant, and test according to the

instructions of the Elisa kit.

2.7. Expression Intensity of p38 MAPK Signaling Pathway

Determine the protein potency of p38 MAPK to estimate the expression intensity of the p38 MAPK signaling pathway in the wound, and then the effect of wood vinegar on the activation process of the p38 MAPK pathway was obtained.

2.8. Data Processing

The obtained data were statistically tested using Prism, and the normally distributed data were analyzed using ANOVA, and the results were presented in the format of variance $\pm$ standard deviation.

3. Results

3.1. Rat Model Establishment

After STZ injection, the blood glucose, diet and water intake and mental state of the rats were monitored regularly every day. Diabetic rats lose weight, drink more, smell bad, have obvious lethargy, and reduce activity. Daily blood glucose higher than 8.3mmol/L. At 15 days, the body size of diabetic rats was significantly smaller than that of non-diabetic rats.

3.2. Wound Healing and Healing Rate

3.2.1. Assessment of Wound Healing

The wound was recorded by taking photos (Fig. 1), the area was calculated by ImageJ software, then evaluate the wound healing by comparing the differences between different groups, so that we can preliminarily evaluate the impact of significant differences in wound healing between different groups.

In longitudinal comparison, the wounds of the rats in each group were circular at 0d, then gradually became slender as the wound healed, which was presumed to be related to the direction of back muscle tension during exercise. The early wound (0d-3d) is dark red, soft, easy to bleed, obvious tenderness to the touch, bloody exudation. There is also yellowish-white pus and pseudomembrane partially or completely covers the wound, so that the wound is often adhered to the dressing. In the middle of healing (6D-9d), the color of the wound turns to red, the texture is slightly tough, a small amount of new granulation tissue is formed at the wound edge, the wound is still covered with yellowish-white pus or pseudomembrane, and the wound shrinks slowly. In the later stage of healing (12d-15d), the wound color becomes lighter, its area shrinks rapidly, the amount of pus is significantly reduced to disappear, a thin layer of blood scab is visible on the surface, there is basically no adhesion with the dressing, and a small amount of new hair can be seen on the surrounding skin.

In horizontal comparison, the wood vinegar group had the fastest healing speed, followed by the AG group, while the model group still had a darker wound at 15 days and struggled violently during dressing change, indicating that the tenderness was more obvious than that of the other groups. the healing speed of the blank group was between the model group and the AG group. From the perspective of the degree of wound infection, the model group could still see obvious yellow pseudomembrane in the wound at 12 days, and a small amount of pus could be seen at the wound edge, while the infection in the wood vinegar group and the AG group was

mild. There was no obvious pseudomembrane or obvious purulent secretion at 6 days. It was shown that wood vinegar could reduce the inflammatory response of the wound, shorten the duration of inflammation, and have a certain antibacterial effect on the wound.

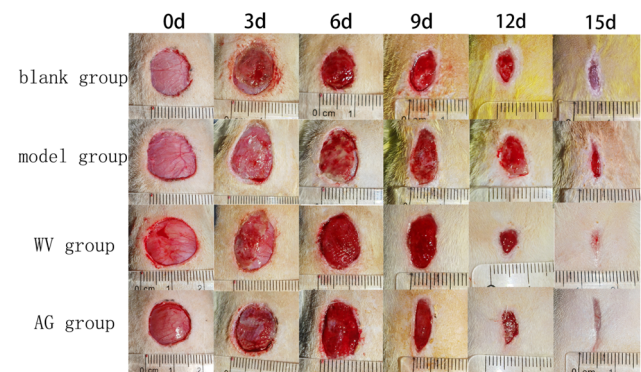


Fig 1. Comparison of each groups of wound healing in 15days

3.2.2. Determination of Wound Healing Rate

The wound healing rate of each rat at each time point is shown in Table 1. It can be seen from the table that the healing rates of WV group, AG group and blank group at each time point were significantly higher than those of the model group. At each observation time point, the wound healing rates of

WV group, AG group and blank group were significantly higher than those of the model group, indicating that each intervention had a certain healing effect. On the third day after surgery, the healing rate of WV group was $24.12\pm1.01\%$, which was significantly higher than that of the model group which indicates $8.21\pm0.69\%$ ($P<0.05$), suggesting that wood vinegar could play a positive role in the early healing stage. On the 6th and 9th days, the healing rates of the WV group ($37.38\pm1.17\%$, $59.14\pm1.11\%$) continued to be higher than those of the other groups, which was statistically significant ($P<0.05$). On the 12th day, the healing rate of WV group reached $88.84\pm1.60\%$, which was significantly higher than that of the model group ($P<0.05$) of $58.36\pm1.85\%$. On the 15th day of the experimental endpoint, the wound in the WV group was basically closed, and the healing rate was $93.63\pm1.25\%$, while the AG group was $87.77\pm1.51\%$, while the model group was only $68.21\pm0.53\%$, the difference was further widened ($P<0.05$).

Wood vinegar could effectively accelerate the healing process of wounds during the whole observation period, and its promotion effect was better than that of aloe vera gel. It still maintained certain repair advantages in the later stage of healing, which further confirmed the healing effect of wood vinegar on wound healing.

Table 1. Comparison of healing rate in each group

days/d	Blank	Model	WV	AG
3d	14.83 ± 1.05	8.21 ± 0.69	$24.12\pm1.01^{a)b)}$	$19.07\pm1.11^a)$
6d	26.42 ± 1.03	20.29 ± 1.43	$37.38\pm1.17^{a)b)}$	$32.06\pm1.63^a)$
9d	46.01 ± 1.50	37.44 ± 0.97	$59.14\pm1.11^{a)b)}$	$54.16\pm0.70^a)$
12d	67.22 ± 1.24	58.36 ± 1.85	$88.84\pm1.60^{a)b)}$	$83.26\pm0.60^a)$
15d	76.21 ± 1.08	68.21 ± 0.53	$93.63\pm1.25^{a)b)}$	$87.77\pm1.51^a)$

Note: At the same time point, the ^aP < 0.05 relative to the model group; ^bP < 0.05 relative to the AG group, n=3.

3.3. Wood Vinegar Reduced the Content of TNF-α in the Wound

Tumor necrosis factor (TNF-α) can activate a variety of MAPK signaling pathways, such as JNK and p38 signaling pathways, which are closely related to tissue inflammatory response [11]. By detecting the content of TNF-α in rat wound tissue, the molecular mechanism of local anti-inflammatory response of wood vinegar was preliminarily explored.

The results of ELISA showed that the expression intensity of TNF-α in the WV group was the weakest, slightly higher in the AG group than WV group, slightly higher in the blank group than in the control group, and the content of inflammatory factors in the model group was the highest, which was much higher than that of the WV group and the AG group. At 15 days, the wound inflammation degree of the rats in the four groups showed a trend of model group > blank group > AG group > WV group. At the same time, statistical analysis showed that there were significant differences between the model group and the WV group, the model group and the AG group, and the WV group and the AG group ($P<0.0001$), indicating that wood vinegar could reduce the content of TNF-α inflammatory factor in the wound area, thereby inhibiting the inflammatory response and promoting wound healing.

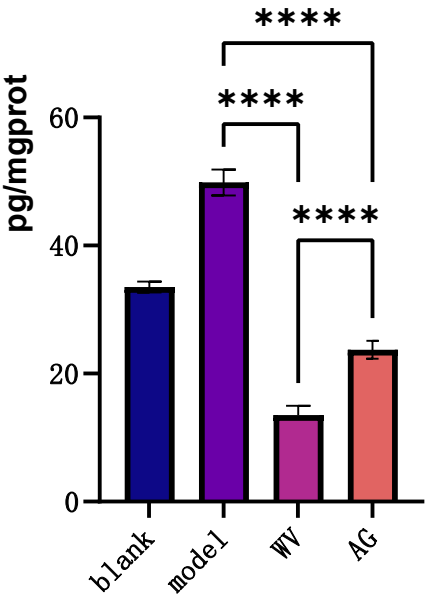


Fig 2. TNF-α concentration in 15-day rat wounds

3.4. Expression Intensity of p38 MAPK Signaling Pathway

The expression intensity of p38 MAPK signaling pathway in the wound of rats was detected by Western-blot Western

blotting (Fig. 3 and 4), and it was found that the content of p38 MAPK was the highest in the model group, indicating that there was still a certain degree of inflammation in the wound of the model group at 15 days, and it was the same as that of the wood vinegar group ($P < 0.05$) and the aloe vera gum group ($P < 0.001$), and the content of p38 MAPK was the lowest in the wood vinegar group. In line with the expected results, it was shown that wood vinegar had a certain regulatory effect on the p38 MAPK pathway, and could reduce the inflammatory response of the wound by reducing the expression intensity of the local p38 MAPK signaling pathway.

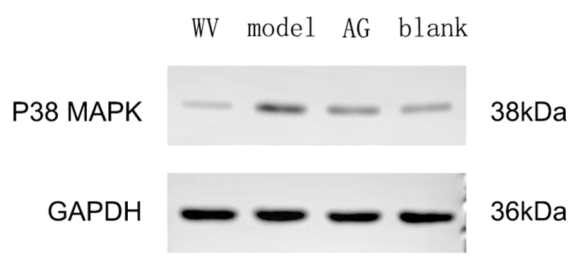


Fig 3. Western-blot Western blotting

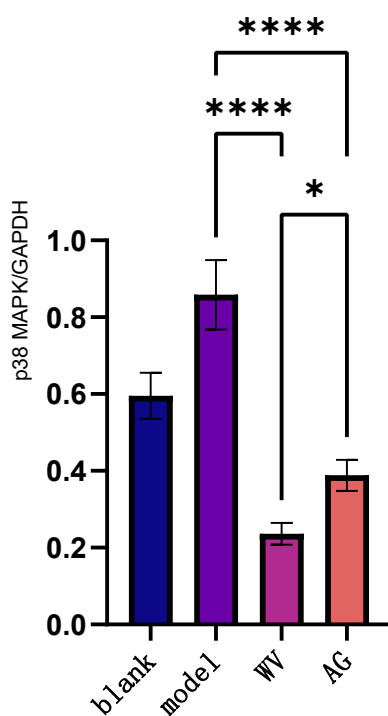


Fig 4. Content of p38 MAPK protein in the wound of 15d rats

4. Conclusion

Plant-derived wood vinegar can reduce the inflammatory response of wounds by reducing the content of TNF- α in tissues, thereby promoting wound healing. At the same time, it promotes tissue regeneration to a certain extent and accelerates the re-epithelialization of the wound. Judging from the changes in the wound within 15 days, plant-derived wood vinegar can reduce the degree of suppuration of the wound in rats, and to a certain extent plays an antibacterial role.

5. Discussion

Diabetes refractory wounds are one of the common serious

complications in diabetes management, with complex pathophysiological mechanisms involving multiple factors such as chronic inflammation, impaired angiogenesis, increased oxidative stress [12], impaired cell migration, and susceptibility to infection. This study focused on wood vinegar, systematically evaluated its effect on wound healing by establishing a wound model of diabetic rats, and preliminarily discussed its possible mechanism of action. The results showed that wood vinegar could significantly promote wound healing in diabetic rats, and its effects may be related to regulating the p38 MAPK signaling pathway, reducing the expression of the pro-inflammatory factor TNF- α , reducing local inflammatory response, and having certain antibacterial effects.

This study confirmed that topical application of plant-derived wood vinegar can effectively accelerate the healing process of wounds in diabetic rats. In terms of wound healing rate, the wood vinegar treatment group was significantly better than the diabetic model group (normal saline treatment) at all observation time points (3, 6, 9, 12, 15 days), and the healing rate was as high as 93.63% in the late healing period (15 days), even better than that of the positive control AG group (87.77%) and the non-diabetic blank group (76.21%). This suggests that wood vinegar is not only effective in promoting healing in diabetic pathological states, but may be more effective than some conventional dressings, and has the potential to reverse or partially counteract the delayed healing caused by diabetes.

Molecular biology results further reveal the underlying mechanisms of its healing effects. Result of ELISA showed that the content of TNF- α , a key pro-inflammatory factor in the wound tissue, was the lowest, and showed a gradient trend between the model group > blank group > AG group > WV group. TNF- α is one of the core cytokines that activate signaling pathways such as p38 MAPK and amplify inflammatory responses[13]. The significant reduction in TNF- α levels in this study suggests that wood vinegar may exert anti-inflammatory effects by regulating TNF- α content, thereby inhibiting overactivation of the p38 MAPK signaling pathway.

Mitogen-activated protein kinase signaling pathway (MAPK) is a widely existing signaling pathway in mammals, which is involved in various life activities such as inflammation and oxidative stress in organisms, and its subclasses can be divided into three types: JNK, ERK and p38 MAPK, and p38 MAPK α plays a major role in the inflammatory response. Studies have confirmed that not only does the high-glucose environment enhance the expression intensity of p38 MAPK[14], but the high-intensity expression of the p38 MAPK pathway also activates the secretion of pro-inflammatory cytokines and the intensity of oxidative stress[15], increasing the level of pro-inflammatory cytokines (PICs) such as TNF- α and COX-2, so that the inflammatory response continues and affects wound healing[16]. During oxidative stress, overexpression of p38 MAPK is also associated with upregulation of reactive oxygen species (ROS) content[17]. One consequence of hyperglycemia is the massive production of ROS[18]. A study from Osman showed that the use of inhibitors of p38 MAPK elicited an anti-inflammatory response in vascular smooth muscle in rats[19].

This study preliminarily correlates TNF- α reduction with possible inhibition of the p38 MAPK pathway, but there is a lack of direct detection of downstream effector molecules of this pathway (such as ATF-2), and there is a lack of practical

evidence on the overall effect of the MAPK signaling pathway. At the same time, although the observational description suggests that wood vinegar has antibacterial effects, quantitative analysis such as bacterial culture count or bacteriostatic zone experiment cannot be objectively evaluated without quantitative analysis. The first task in the follow-up study was to conduct a dose-effect relationship study. At the same time, it can extend the detection of other MAPK family members such as JNK and ERK, as well as other inflammatory pathways such as NF- κ B, and the determination of ROS content in wound tissue. In terms of dosage form, since wood vinegar is in liquid form, it is volatile and difficult to fix as a dressing, so it is possible to combine wood vinegar with other known healing materials (such as chitosan, hyaluronic acid, silver ions) to develop synergistic composite dressings to further enhance the curative effect.

Acknowledgments

Funded by: Hebei Provincial Department of Education (ZD2022144);

Hebei Provincial Department of Finance (ZF2024022).

References

- [1] Patel S, Srivastava S, Singh MR, Singh D. Mechanistic insight into diabetic wounds: Pathogenesis, molecular targets and treatment strategies to pace wound healing. *Biomed Pharmacother.* 2019 Apr;112:108615. doi: 10.1016/j.biopha.2019.108615. Epub 2019 Feb 20. PMID: 30784919.
- [2] Burgess JL, Wyant WA, Abdo Abujamra B, Kirsner RS, Jozic I. Diabetic Wound-Healing Science. *Medicina (Kaunas).* 2021 Oct 8;57(10):1072. doi: 10.3390/medicina57101072. PMID: 34684109; PMCID: PMC8539411.
- [3] Anggrayni D, Purnama I, Saidi B N, et al. Antifungal and phytotoxicity of wood vinegar from biomass waste against *Fusarium oxysporum* f. sp. *cubense* TR4 infecting banana plants[J]. *Discover Food*, 2025, 5(1):98-98. DOI: 10.1007/ S44187-025-00377-8.
- [4] Li Mengyuan, Li Zhanjun, Han Yue, et al. Analysis of wood vinegar components of three birch plants[J]. *Forest engineering*, 2021, 37(02):41-49. DOI:10.16270/j.cnki.slgc.2021.02.007.
- [5] Theapparath, Y., Khongthong, S., Roekngam, N., Suwandechea, T., Nopparat, J., & Farongsarn, D. (2024). Pyroligneous extract, a biomaterial derived from pyrolytic palm kernel shell wood vinegar, as a novel diabetic wound healing aid: an animal study. *Drug Development and Industrial Pharmacy*, 50(11), 907–916.
- [6] Ho CL, Lin CY, Ka SM, Chen A, Tasi YL, Liu ML, Chiu YC, Hua KF. Bamboo vinegar decreases inflammatory mediator expression and NLRP3 inflammasome activation by inhibiting reactive oxygen species generation and protein kinase C- α / δ activation. *PLoS One.* 2013 Oct 4;8(10): e75738. doi: 10.1371/journal.pone.0075738. PMID: 24124509; PMCID: PMC 3790849.
- [7] Furman BL. Streptozotocin-Induced Diabetic Models in Mice and Rats. *Curr Protoc.* 2021 Apr;1(4):e78. doi: 10.1002/cpz1.78. PMID: 33905609.
- [8] Kaczmarczyk-Sedlak I, Folwarczna J, Sedlak L, Zych M, Wojnar W, Szumińska I, Wyględowska-Promieńska D, Mrukwa-Kominek E. Effect of caffeine on biomarkers of oxidative stress in lenses of rats with streptozotocin-induced diabetes. *Arch Med Sci.* 2019 Jul;15(4):1073-1080. doi: 10.5114/aoms.2019.85461. Epub 2019 May 31. PMID: 31360202; PMCID: PMC6657250.
- [9] Tipton CD, Sanford NE, Everett JA, Gabriliska RA, Wolcott RD, Rumbaugh KP, Phillips CD. Chronic wound microbiome colonization on mouse model following cryogenic preservation. *PLoS One.* 2019 Aug 23;14(8):e0221565. doi: 10.1371/journal.pone.0221565. PMID: 31442275; PMCID: PMC6707584.
- [10] Ban E, Jeong S, Park M, Kwon H, Park J, Song EJ, Kim A. Accelerated wound healing in diabetic mice by miRNA-497 and its anti-inflammatory activity. *Biomed Pharmacother.* 2020 Jan; 121: 109613. doi: 10.1016/j.biopha.2019.109613. Epub 2019 Nov 7. PMID: 31707336.
- [11] Gültekin Tosun S, Balcioglu E, Arslan K, Yıldız G, Akyüz B. Molecular research: the effect of black fig (*Ficus carica* L.) leaf extract on inflammation in punch skin biopsy. *Inflammopharmacology.* 2025 Oct;33(10):6199-6209. doi: 10.1007/s10787-025-01798-8. Epub 2025 May 31. PMID: 40448818; PMCID: PMC12552302.
- [12] Peña OA, Martin P. Cellular and molecular mechanisms of skin wound healing. *Nat Rev Mol Cell Biol.* 2024 Aug;25(8):599-616. doi: 10.1038/s41580-024-00715-1. Epub 2024 Mar 25. PMID: 38528155.
- [13] Manohar SM. At the Crossroads of TNF α Signaling and Cancer. *Curr Mol Pharmacol.* 2024;17: e060923220758. doi: 10.2174/1874467217666230908111754. PMID: 37691196.
- [14] Li H, Zhao YC, Mo DS, Zhang YJ, Yang YZ, Huang JT, Kong P, Zhou T, Lu H, He ZX, Shu LP. The zebrafish caudal fin amputation model simulates the impact of hyperglycemia on inflammation and regeneration. *Am J Transl Res.* 2025 Oct 15;17(10):7659-7675. doi: 10.62347/OWYF1777. PMID: 41268230; PMCID: PMC12628199.
- [15] Cuenda A, Rousseau S. p38 MAP-kinases pathway regulation, function and role in human diseases. *Biochim Biophys Acta.* 2007 Aug;1773(8):1358-75. doi: 10.1016/j.bbamcr.2007.03.010. Epub 2007 Mar 24. PMID: 17481747.
- [16] Ma Dongmei, Zhang Xianggui. Progress of P38MAPK signaling pathway in diabetic nephropathy research[J]. *Journal of Clinical Nephrology*, 2021, 21(03):248-253.
- [17] Wang, S.; Ding, L.; Ji, H.; Xu, Z.; Liu, Q.; Zheng, Y. The Role of p38 MAPK in the Development of Diabetic Cardiomyopathy. *Int. J. Mol. Sci.* 2016, 17, 1037.
- [18] Coulthard LR, White DE, Jones DL, McDermott MF, Burchill SA. p38(MAPK): stress responses from molecular mechanisms to therapeutics. *Trends Mol Med.* 2009 Aug;15(8):369-79. doi: 10.1016/j.molmed.2009.06.005. Epub 2009 Aug 6. PMID: 19665431; PMCID: PMC3016890.
- [19] Osman, N. et al. (2008) p38 MAP kinase mediated proteoglycansynthesis as a target for the prevention of atherosclerosis. *Cardiovasc. Hematol. Disord. Drug Targets* 8, 287–292.