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BANDOTAN LEAF EXTRACT THERAPY ON IL 6 PROFILE IN WISTAR RATS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Diabetes Mellitus (DM) is a non-communicable disease that has become a serious public health problem in Indonesia and the World. Indonesia ranks 7th in the world with 10.7 million diabetes sufferers in 2019 and this number is expected to increase to 13.7 million in 2030 and 16.6 million in 2045. Complications that occur in DM sufferers are due to cell damage and death caused by increased oxidative stress and the activity of inflammatory mediators including interleukin-6 (Il-6). Administration of oral hypoglycemic drugs to DM patients does not show improvement in oxidative stress. Additional therapy is needed for DM patients that can reduce oxidative stress and inflammatory mediators and support the work of endogenous antioxidants. Bandotan leaves are plants that contain antioxidants and are used as a traditional medicine for DM patients. The purpose of this study was to determine the profile of Il-6 as a marker of inflammation due to oxidative stress in DM patients after administration of bandotan leaf extract. The research revealed significant differences between the control, bandotan, and glimberclamide groups. The bandotan group had the lowest IL-6 levels at 1.63 pg/ml. Bandotan leaf extract caused the least inflammation compared to the control and glimberclamide groups.

Keywords: Bandotan Leaf Extract, IL 6 Profile, Therapy, Type 2 Diabetes Mellitus, Wistar Rats

INTRODUCTION

Diabetes Mellitus (DM) is a disease or health disorder in the form of a collection of symptoms caused by increased blood sugar (glucose) levels (Antoni, 2023). This chronic disease occurs when the pancreas does not produce enough insulin or when the body cannot use the insulin it produces effectively (Ganesan and Orgill, 2024). Diabetes Mellitus (DM) is one of the non-communicable diseases that has become a serious problem for public health in Indonesia and the world (Aldyno *et al.*, 2024). The World Health Organization (WHO) in 2014 stated that globally there were 422 million adults aged over 18 years suffering from diabetes, while according to the International Diabetes Federation (IDF) in 2019 there were 463 million people suffering from diabetes (Donatila Mano S *et al.*, 2023). Indonesia ranks 7th in the world with 10.7 million diabetes sufferers in 2019 and this number is expected to increase to 13.7 million in 2030 and 16.6 million in 2045 (Ismafillah, Rohana and Cahyana, 2023). Complications that occur in DM sufferers are due to cell damage and death caused by increased oxidative stress and the activity of inflammatory mediators including interleukin-6 (IL-6) (Pangestu *et al.*, 2025).

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Interleukin-6 is a pro-inflammatory cytokine produced by various cell types. High levels of IL-6 in people with type 2 diabetes can worsen insulin resistance, leading to endothelial dysfunction, which can lead to complications such as blindness, kidney damage, stroke, amputation, and others (Diniyah Nurud, 2020). Bandotan (Ageratum conyzoides) is a wild plant in Indonesia and is better known as a weed (Budianto *et al.*, 2022). Bandotan was chosen because it contains various active compounds (flavonoids, saponins, alkaloids) that simultaneously have antibacterial, antifungal, and immune-boosting properties, unlike other herbs that generally only have one or two functions. This weed is readily available and also effective in lowering blood glucose levels, making it an efficient and multi-beneficial herbal choice (Annas Tasya Pertiwi, Ratu Choesrina and Fetri Lestari, 2023).

Phytochemical studies conducted showed that bandotan extract contains several substances including steroids, sterols, triterpenoids, alkaloids, flavonoids, saponins, tannins, phenolics, carbohydrates and proteins (Rismawan, Handayani and Rahayuni, 2023). Alkaloids, flavonoids, and saponins show antibacterial, antifungal and can improve the immune system (Kartono, Setiawan and Astuti, 2020). In some areas, bandotan leaves are used as a traditional medicine which is also used to lower blood glucose levels.

Administration of oral hypoglycemic drugs to DM patients did not show improvement in oxidative stress (Herawati, Sa'pang and Harna, 2022). Therefore, additional therapy is needed for DM patients that can reduce oxidative stress and inflammatory mediators and support the activity of endogenous antioxidants. Previously studied substances that can reduce oxidative stress and inflammatory mediators include antioxidants, including flavonoids. Bandotan leaves are known to contain several antioxidants, including flavonoids. Research Natur, Damri and Agam (2022) stated that the hypoglycemic properties of Ageratum conyzoides leaves were seen from several doses of extract tested on diabetic rats, showing statistically significant hypoglycemic and antihyperglycemic activity (Hardianto, 2021). However, there is still limited research related to reducing oxidative stress, so this study was conducted to determine the IL 6 profile as a marker of inflammation due to oxidative stress in DM patients after being treated using bandotan leaf extract.

RESEARCH METHODS

This research is an experimental study with a quantitative approach using a post-test only control group design (Tenekedjiev et al., 2025). The aim of this study was to determine the effect of bandotan leaf extract on interleukin-6 (IL-6) levels in Wistar rats induced by diabetes mellitus, by comparing it to the control group and the group given glibenclamide. The independent variables in this study were the administration of bandotan leaf extract and glibenclamide, while the dependent variable was serum IL-6 levels measured using the ELISA method and expressed in pg/ml.

The subjects were 3-4 month old male Wistar rats weighing 250-350 grams that had been induced with streptozotocin (STZ) until they reached a hyperglycemic state (fasting blood glucose levels ≥200 mg/dl). A total of 30 rats were randomly divided into three groups, each consisting of 10 rats: a control group without treatment, treatment group 1 which was given bandotan leaf extract daily for 14 days, and treatment group 2 which was given glibenclamide daily for 14 days. After the treatment period was over, all rats were euthanized

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and their blood samples were taken for IL-6 level examination using ELISA procedure at the Animal Experiment Laboratory of Muhammadiyah University of Semarang. The IL-6 examination data were analyzed using SPSS software (Permata, Syaidatussalihah and Abdurahim, 2023). Data normality was tested using the Shapiro-Wilk test. If the data were normally distributed ($p>0.05$), the analysis was continued with one-way ANOVA and Tukey's post hoc test to determine differences between groups. If the data were not normally distributed ($p<0.05$), the Kruskal-Wallis test was used, followed by the Mann-Whitney test. This study is scheduled to run from April to September 2023.

RESULTS AND DISCUSSION

RESULTS

Wistar rats were divided into three groups: control, Bandotan, and Gimberclamide. Blood glucose levels in each group were examined after stz induction. The results of the examination on 30 samples can be seen, obtaining the highest glucose levels of 559 mg/dl in the control group, 589 mg/dL in the Bandotan group and 568 mg/dl in the Gimberclamide group. After glucose levels exceeded the normal limit of more than 200 mg/dl, Wistar rats were given treatment with Bandotan and Gimberclamide, while the control group was not treated. After 14 days, IL 6 levels were examined with the results in Table 1 below:

Table 1. Results of IL 6 Level Examination

	IL 6 levels (pg/ml)		
Sample	**Control**	**Bandotan**	**Gilbert Clamide**
1	1,98	1,65	1,80
2	1,78	1,66	1,93
3	1,80	1,67	1,74
4	1,77	1,62	1,73
5	1,74	1,65	1,72
6	1,81	1,62	1,77
7	1,79	1,61	1,76
8	1,70	1,58	1,87
9	1,83	1,60	1,98
10	1,89	1,59	1,70
Minimum	1,70	1,58	1,70
Maximum	1,98	1,67	1,98
Average	1,81	1,63	1,80

The data used in the study are classified as small scale (<50 data), so the normality test used is Shapiro-Wilk. The results of the normality test on all variables show a significance value (Sig.) greater than 0.050 (>0.050) as shown in Table 2., so it can be concluded that the data used in the study are normally distributed, therefore a parametric test using ANOVA can be performed.

Table 2. Results of the Normality Test for IL 6 Levels

Group	**Kolmogorov-Smirnov (Stat)**	**Sig.**	**Shapiro-Wilk (Stat)**	**Sig.**
Control	0,195	0,200	0,925	0,398

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Group	Kolmogorov-Smirnov (Stat)	Sig.	Shapiro-Wilk (Stat)	Sig.
Bandotan	0,190	0,200	0,942	0,581
Gilbert Clamide	0,224	0,170	0,877	0,120

Based on Table 2, the significance values (Sig.) in the Kolmogorov-Smirnov and Shapiro-Wilk tests for the three groups (Control, Bandotan, Glibenclamide) were all > 0.05. This indicates that the IL-6 levels in each group were normally distributed. Thus, parametric tests (such as ANOVA) can be used for further analysis. Table 3 below shows the results of the ANOVA test:

Table 3. ANOVA Test Results for IL 6 Levels

Sources of Variation	Sum of Squares (SS)	Mean Square (MS)	F	p-value (Sig.)
Between Groups	0,215	0,108	19,907	0,000
Within Groups	0,146	0,005	-	-
Total	0,361	-	-	-

Based on Table 3, the p-value = 0.000 (<0.05), so there is a significant difference in the average IL-6 levels between the Control, Bandotan, and Glibenclamide groups. In other words, the administration of bandotan leaf extract and glibenclamide has a different effect on IL-6 levels compared to the control. Table 4 below shows the results of further tests:

Table 4. ANOVA Test Results for IL 6 Levels

Treatment	Treatment	Average Difference	Std. Error	p-value
Control	Bandotan	0,18400*	0,03288	0,000
Control	Gilbert Clamide	0,00900	0,03288	0,960
Bandotan	Control	-0,18400*	0,03288	0,000
Bandotan	Gilbert Clamide	-0,17500*	0,03288	0,000
Gilbert Clamide	Control	-0,00900	0,03288	0,960
Gilbert Clamide	Bandotan	0,17500*	0,03288	0,000

The results of the post hoc test using Tukey HSD showed that the significance value between the control group and the Bandotan group was 0.000 and this value was smaller than 0.050 (0.000 < 0.050), so it can be concluded that there was a significant difference between the control group and the Bandotan group. The significance value between the control group and the gimberclamide group was 0.960 and this value was greater than 0.050 (0.960 > 0.050), so it can be concluded that there was no significant difference between the control group and the gimberclamide group. The significance value between the Bandotan group and the gimberclamide group was 0.000 and this value was smaller than 0.050 (0.000 < 0.050), so it can be concluded that there was a significant difference between the Bandotan group and the gimberclamide group.

DISCUSSION

Diabetes mellitus (DM) is a chronic disease that occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces (Imanudin, Kurniawan and Rohmayanti, 2022). Elevated blood glucose levels, or hyperglycemia, are a common effect of

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uncontrolled diabetes mellitus and can cause serious damage to many body systems, particularly the nervous and vascular systems. This disease is a leading cause of increased risk of death and a reduced quality of life due to various serious complications (Vas *et al.*, 2020). Type 1 diabetes is diabetes characterized by damage to pancreatic beta cells and type 2 diabetes is characterized by defects in insulin secretion or insulin function (Cahyani *et al.*, 2024).

Type 2 diabetes mellitus (type 2 DM) is a metabolic disorder characterized by elevated blood sugar (hyperglycemia) due to decreased insulin secretion by pancreatic beta cells or impaired insulin function. Type 2 DM can occur due to several factors, including genetic and environmental factors (Pecová *et al.*, 2023). Genetic factors include a family history of diabetes and ethnicity/race. The main environmental risk factors for diabetes include age, obesity and abdominal obesity, dietary/nutritional factors, and lack of physical activity (Wu *et al.*, 2025). Hyperglycemic conditions in cases of diabetes will increase the production of free radicals which can be in the form of reactive oxygen species (ROS) or reactive nitrogen species (RNS) (Islam *et al.*, 2023). The pathophysiology of diabetes mellitus is related to inflammatory mechanisms. Inflammation is caused by increased proinflammatory cytokines (Chen *et al.*, 2024).

The pathophysiology of diabetes mellitus is related to inflammatory mechanisms. Inflammation is caused by an increase in proinflammatory cytokines. Proinflammatory cytokines are secreted by immunocompetent cells in response to infection. Generally, type 1 and type 2 diabetes are characterized by increased levels of interleukins (ILs) IL-6, IL-8, IL-1, and TNF-α in the blood of DM sufferers (Yuan *et al.*, 2024). Type 2 diabetes is characterized by hyperglycemia, which can lead to inflammation, stimulating a non-specific immune response, activating macrophages to release the pro-inflammatory cytokine IL-6. High IL-6 levels in type 2 diabetes can worsen insulin resistance, leading to endothelial dysfunction, which can lead to complications such as blindness, kidney damage, stroke, amputation, and others (Su *et al.*, 2022).

Bandotan is a type of weed commonly found on roadsides, in forests, fields, and open areas. It is native to Southeast Asia, Central America, South America, the Caribbean, Florida, southern China, and Australia. It is known as an ornamental plant from the Americas and is commonly found in the South Pacific and other warm-climate countries (Calavul, 2024). Bandotan is a wild plant in Indonesia and is better known as a weed in gardens and fields. It grows up to 1 meter tall and is characterized by leaves with fine white hairs. The flowers are small, pale purplish white, sunflower-shaped, and measure 5-8 mm in diameter. The stems and leaves are covered in fine white hairs, and the leaves reach 7.5 cm in length. The fruit is easily dispersed, while the seeds are light and easily blown by the wind (Sharma *et al.*, 2015).

Phytochemical studies conducted showed that bandotan extract contains several ingredients, including steroids, sterols, triterpenoids, alkaloids, flavonoids, saponins, tannins, phenolics, carbohydrates and proteins (Sharma *et al.*, 2015). Alkaloids, flavonoids, and saponins show antibacterial, antifungal and can improve the immune system (Muntafiah, 2017). Hot water extract of the leaves is used orally to treat intestinal worms and as an antispasmodic, and to treat diabetes (Elsiana *et al.*, 2023).

The decrease in interleukin 6 (IL-6) levels following glibenclamide administration occurs because the drug stimulates the accelerated growth of

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damaged pancreatic beta cells. However, antidiabetic drugs generally carry several risks. Therefore, alternative traditional medicines for diabetes mellitus sufferers that are relatively safe in the long term have been developed (Faridah, Afiyanti and Ariska, 2025). Bandotan leaf extract contains antioxidants in the form of alkaloids and flavonoids, which act as antidiabetics by protecting pancreatic beta cells from oxidative stress and increasing antioxidant levels, thus triggering a decrease in the pro-inflammatory cytokine IL-6. The alkaloids and flavonoids in bandotan leaves reduce IL-6 levels by inhibiting the activation of the transcription factor NF-κB. Alkaloids suppress the JAK2/STAT3 pathway, while flavonoids block the TLR4/NF-κB pathway and reduce oxidative stress, thereby inhibiting the production of the pro-inflammatory cytokine IL-6.

IL-6 is an endogenous biochemical active during B cell maturation and is one of the cytokines that mediate inflammation and can induce the release of the acute-phase protein C-Reactive Protein (CRP). This cytokine promotes inflammatory defense processes and tissue damage. Interleukin 6 is produced in various tissues such as macrophages, adipocytes, and immune system cells. Circulating IL-6 levels correlate with Body Mass Index (BMI), insulin resistance, and carbohydrate and blood glucose intolerance. IL-6 also acts antagonistically on adiponectin secretion and increases gluconeogenesis.

CONCLUSION AND SUGGESTIONS

Based on the results of the research conducted, it can be concluded that administering bandotan leaf extract for 14 days to Wistar rats with type 2 diabetes mellitus reduced serum interleukin-6 (IL-6) levels better than glibenclamide or no treatment. This is demonstrated by the average IL-6 level in the group given bandotan leaf extract of 1.63 pg/ml, which is the lowest value compared to the glibenclamide group (1.80 pg/ml) and the untreated control group (1.81 pg/ml). These findings indicate that bandotan leaf extract has the potential to be a more effective anti-inflammatory agent in suppressing IL-6 levels in type 2 diabetes mellitus.

As a follow-up to this study, further research is recommended using different parameters to further explore the mechanism of action of bandotan leaf extract, as well as conducting trials with varying doses to determine the most effective optimal dose. In addition, research related to oxidative stress in the organs of Wistar rats after administration of bandotan leaf extract is also needed to complete scientific evidence regarding the protective effects of this plant against diabetes complications caused by oxidative stress and inflammation.

REFERENCES

Aldyno, A.F. *et al.* (2024) 'Pengembangan Sistem Pendukung Keputusan Untuk Prediksi Diabete', *Jurnal Riset Sistem Informasi Dan Teknik Informatika (JURASIK)*, 9(2), pp. 543–554.

Annas Tasya Pertiwi, Ratu Choesrina and Fetri Lestari (2023) 'Studi Kepatuhan Pengobatan Pasien Diabetes Melitus (Dm) Tipe 2 Di Rsud Al- Ihsan Kabupaten Bandung', *Bandung Conference Series: Pharmacy*, (Dm), pp. 120–127. Available at: https://doi.org/10.29313/bcsp.v3i2.8276.

Antoni, M. (2023) 'Terapi Diabetes Melitus Tipe 2 Berbasis Hormon Inkretin', *Jurnal Kedokteran Meditek*, 29(2), pp. 218–225. Available at: https://doi.org/10.36452/jkdoktmeditek.v29i2.2664.

Budianto, R.E. *et al.* (2022) 'Potensi Senyawa Fitokimia pada Tumbuhan dalam

Article History:
Received: December 11, 2025; Revised: May 4, 2026; Accepted: May 6, 2026

Menurunkan Kadar Glukosa Darah pada Diabetes Melitus', *Jurnal Sains dan Kesehatan*, 4(5), pp. 548–556. Available at: https://doi.org/10.25026/jsk.v4i5.1259.

Cahyani, P.A. *et al.* (2024) 'Pengaruh Kadar HbA1c Pada Penderita Diabetes Melitus Tipe 2 Dengan Komplikasi Makrovaskular dan Mikrovaskular di Rumah Sakit Ibnu Sina YW UMI Makassar', *Jurnal Kesehatan Masyarakat*, 8, pp. 4274–4281.

Calavul, A. (2024) 'Efficacy of Hyaluronic Acid/Collagenase Ointment in the Treatment of Chronic Wounds: A Retrospective Observational Study', *The International Journal of Lower Extremity Wounds*, 17(4). Available at: https://doi.org/10.1177/15347346241243102.

Chen, L. *et al.* (2024) 'Effect of hyaluronic acid on the formation of acellular dermal matrix-based interpenetrating network sponge scaffolds for accelerating diabetic wound healing through photothermal warm bath', *International Journal of Biological Macromolecules*, 283(1). Available at: https://doi.org/10.1016/j.ijbiomac.2024.137268.

Diniyah Nurud, S.-H.L. (2020) 'Komposisi Senyawa Fenol Dan Potensi Antioksidan Dari Kacang-Kacangan: Review', *Jurnal Agroteknologi*, 14(1), p. 91. Available at: https://doi.org/10.19184/j-agt.v14i01.17965.

Donatila Mano S *et al.* (2023) 'Kegiatan Pengabdian Masyarakat dalam Rangka Edukasi Masyarakat Terhadap Hipertensi serta Deteksi Dini Penyakit Gagal Ginjal Sebagai Komplikasi dari Hipertensi', *Jurnal Pengabdian Masyarakat Indonesia*, 2(2), pp. 34–45. Available at: https://doi.org/10.55606/jpmi.v2i2.1776.

Elsiana, I. *et al.* (2023) 'Article Review: Molecular Docking of Anti Diabetes Mellitus Drugs Review', *JOURNAL OF PHARMACEUTICAL AND SCIENCES*, 6(2), pp. 541–554.

Faridah, I., Afiyanti, Y. and Ariska, M. (2025) 'Pengaruh Aromaterapi Terhadap Kualitas Tidur, Kualitas Hidup, Kelelahan dan Kecemasan Pada Pasien Diabetes Melitus', *Jurnal Terpadu Ilmu Kesehatan*, 9(2), pp. 237–259.

Ganesan, O. and Orgill, D.P. (2024) 'An Overview of Recent Clinical Trials for Diabetic Foot Ulcer Therapies', *Journal of Clininical Medical*, 1(2), pp. 1–17.

Hardianto, D. (2021) 'Telaah Komprehensif Diabetes Melitus : Klasifikasi, Gejala, Diagnosis, Pencegahan, dan Pengobatan', *Jurnal Bioteknologi & Biosains Indonesia (JBBI)*, 7(2), pp. 304–317.

Herawati, N., Sa'pang, M. and Harna, H. (2022) 'Kepatuhan Diet Dan Aktivitas Fisik Pasien Diabetes Melitus Tipe 2 Yang Sudah Mengikuti Prolanis', *Nutrire Diaita*, 12(01), pp. 16–22. Available at: https://doi.org/10.47007/nut.v12i01.3154.

Imanudin, N., Kurniawan, M.F. and Rohmayanti, T. (2022) 'Potensi Senyawa Aktif Ekstrak Kayu Manis Padang (Cinnamomum burmanii) sebagai Inhibitor Enzim Aldose Reductase secara Moleculer Docking Potential', *Jurnal Riset Sains dan Teknologi*, 6(2), pp. 171–179.

Islam, R. *et al.* (2023) 'Clinical Decision Support System for Diabetic Patients by Predicting Type 2 Diabetes Using Machine Learning Algorithms', *Hindawi Journal of Healthcare Engineering*, 11(1), pp. 1–11.

Ismafillah, D., Rohana, T. and Cahyana, Y. (2023) 'Analisis algoritma pohon keputusan untuk memprediksi penyakit diabetes menggunakan oversampling smote', *INFOTECH: Jurnal Informatika Teknologi*, 4(1), pp.

Article History:
Received: April 14, 2026; Revised: April 30, 2026, Accepted: April 30, 2026

27–36.

Kartono, T.H., Setiawan, D. and Astuti, I.Y. (2020) 'Analisis Kepatuhan Minum Obat Anti Diabetik Terhadap Kadar Gula Darah Puasa Dan Nilai Hba1c Pada Pasien Diabetes Melitus', *Journal of Pharmacopolim*, 3(3), pp. 166–173.

Muntafiah, et al (2017) 'Pengaruh Ekstrak Jahe Merah (Zingiber Officinale) dan Madu Terhadap Kadar Kolesterol Total Tikus Model Diabetes Melitus', *Scripta Biologica*, 4(1).

Natur, S., Damri, O. and Agam, G. (2022) 'The Effect of Global Warming on Complex Disorders (Mental Disorders , Primary Hypertension , and Type 2 Diabetes)', *Int. J. Environ. Res. Public Health*, 19(15), pp. 1–9.

Pangestu, A.G. *et al.* (2025) 'DiabTrack: Sistem Prediksi Dini Diabetes Melitus Tipe 2 berbasis Web menggunakan Algoritma K-Nearest Neighbors', *Edumatic: Jurnal Pendidikan Informatika*, 9(1), pp. 284–293. Available at: https://doi.org/10.29408/edumatic.v9i1.29691.

Pecová, J. *et al.* (2023) 'Clinical Efficacy of Hyaluronic Acid with Iodine in Hard-to-Heal Wounds', *Pharmaceutics*. mdpi.com. Available at: https://doi.org/10.3390/pharmaceutics15092268.

Permata, R.A., Syaidatussalihah and Abdurahim (2023) 'Analisis Data Penelitian Kesehatan: Perbandingan Hasil antara SmartPLS, R dan IBM SPSS', *JSN: Jurnal Sains Natural*, 1(1), pp. 17–22.

Rismawan, M., Handayani, N.M.T. and Rahayuni, I.G.A.R. (2023) 'Hubungan Kepatuhan Minum Obat Terhadap Kadar Gula Darah Sewaktu Pada Penderita Diabetes Mellitus Tipe 2', *Jurnal Riset Media Keperawatan*, 6(1), pp. 23–30. Available at: https://doi.org/10.51851/jrmk.v6i1.373.

Sharma, S. *et al.* (2015) 'The role of melatonin in diabetes: Therapeutic implications', *Archives of Endocrinology and Metabolism*, 59(5), pp. 391–399. Available at: https://doi.org/10.1590/2359-3997000000098.

Su, N. *et al.* (2022) 'Heparin and Related Substances for Treating Diabetic Foot Ulcers: A Systematic Review and Meta-Analysis', *Frontiers in Endocrinology*. frontiersin.org. Available at: https://doi.org/10.3389/fendo.2022.749368.

Tenekedjiev, K. *et al.* (2025) 'Quasi-Experimental Design for Medical Studies with the Method of the Fuzzy Pseudo-Control Group', *Applied Sciences*, 15(3), pp. 1–45. Available at: https://doi.org/10.3390/app15031370.

Vas, P. *et al.* (2020) 'Effectiveness of interventions to enhance healing of chronic foot ulcers in diabetes: a systematic review', *Diabetes/Metabolism Research and Reviews*, 36(1). Available at: https://doi.org/10.1002/dmrr.3284.

Wu, S. *et al.* (2025) 'Wet healing and Chinese medicine cupping can be used to form collateral circulation in diabetic foot artery occlusion: a case report', *Front. Endocrinol.*, 16(4), pp. 1–9. Available at: https://doi.org/10.3389/fendo.2025.1583647.

Yuan, W. *et al.* (2024) 'Hyaluronic acid methacryloyl/chitosan methacryloyl/3-methacrylamidophenylboronic acid multifunctional hydrogel loading exosome for diabetic wound healing', *International Journal of Biological Macromolecules*, 280(3). Available at: https://doi.org/10.1016/j.ijbiomac.2024.135562.

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