Proceeding International Conference Of Innovation Science, Technology, Education, Children And Health
Vol. 4 No. 1, 2024
e-ISSN : 2776-9062, page 154-163
Available online at: https://icistech.org/index.php/icistech

Icistech Literature Review: Fatty Acid Therapy Of Butternut Squash Seed Extract (*Cucurbita Moschata* Duchesnes) On Healing Of Type 2 Diabetes Mellitus Wounds

Suwanto Suwanto[1*], Slamet Widiyanto[2], Budi Setiadi Daryono[3], Bambang Retnoaji[4], Harto Widodo[5]
[2-4] Faculty of Biology, Gadjah Mada University, Yogyakarta, 55281, Yogyakarta, Indonesia
[1] STIKIP Catur Sakti, Yogyakarta, 55281, Yogyakarta, Indonesia
[5] Research Center for Medicinal Plants and Traditional Medicine, National Research and Innovation Agency, Karanganyar, 57792, Karanganyar, indonesia

*Corresponding Author: suwantofatima@gmail.com

Abstract. *Background, prevalence of diabetes mellitus (DM) has increased from year to year, the disease has characteristics of increased blood sugar levels, caused by insulin resistance and the inability of the pancreas to secrete insulin. DM can increase the risk of chronic hyperglycemia which results in DM complications in the form of wounds on the feet. Treatment of wound healing due to DM with butternut squash seed (Cucurbita moschata Duchesnes) contains fatty acids including: linoleic, oleic, lauric, and palmitic. The purpose of the review is to determine the effect of butternut squash seed extract (Cucurbita moschata Duchesnes) fatty acid therapy on healing type 2 diabetes mellitus wounds. The review method uses a narrative review method through literature searches, identification, searching, and downloading national and international journal references. Literature studies are conducted through several portals, such as Pubmed, Elseviewer, ScienceDirect, and Google Scholar. The references that have been found are in accordance with the inclusion criteria that have been set. Articles are not used if the topic is not relevant. Reference search in the form of research journals published on the internet in the last 10 years from 2014-2024. Results and discussion, fatty acids in butternut squash seeds have the potential for better wound healing. It is known that fatty acids can change the structure and immunology of the skin because they function as the stratum corneum and can change skin permeability. Fatty acids also inhibit proinflammatory eicosanoids, reactive species (ROS and RNS), and cytokines, thereby affecting inflammation and causing wound healing. Conclusion: therapy with fatty acids in butternut squash seed extract (Cucurbita moschata Duchesnes) can cause healing of type 2 diabetes mellitus wounds.*

Keywords: *fatty acids, butternut squash seed, type 2 diabetes mellitus, wound healing.*

1. INTRODUCTION

Type 2 diabetes mellitus is a disease characterized by disturbances in carbohydrate, fat, and protein metabolism caused by insulin resistance and insulin secretion in pancreatic beta cells [1][2]. The prevalence of type 2 diabetes mellitus increases every year. Based on the International Diabetes Federation (IDF), there were 424 million people with diabetes mellitus in 2017 predicted to increase to 686 million in 2045. The number of people with diabetes mellitus in Southeast Asia in 2017 was 82 million increasing to 151 million in 2045. Indonesia ranks 7th out of 10 countries predicted in 2045 to have 5.4 million people with diabetes mellitus [3]. Meanwhile, the World Health Organization (WHO) report in 2000 predicted the number of people with diabetes as many as 8.4 million increasing to 21.3 million in 2030 [4]. The impact of diabetes mellitus can have an impact on the quality and life expectancy. Long-term diabetes mellitus can cause acute complications due to

Received Agustus 15, 2024; Revised Agustus 30, 2024; Accepted September 15, 2024; Published September 18, 2024

uncontrolled high blood glucose levels (hyperglycemia), one of which is diabetic ulcers. Diabetic ulcers are chronic complications of diabetes mellitus indicated by tissue death and open wounds on the surface of the skin. Healing of diabetic ulcers with high blood glucose levels causes diabetes mellitus sufferers to experience a longer wound healing process. This is because the immune system response slows down so that blood plasma is not properly controlled and results in prolonged inflammation. Improper handling of diabetic ulcers will worsen the infection resulting in amputation.

Treatment for diabetes mellitus sufferers has so far used modern drugs, the types of modern drugs include: oral antidiabetic drugs (sulphonylureas, glinides, biguanides, thiazolidinediones (TZDs), alpha glucosidase inhibitors, DPP-IV inhibitors), and antidiabetic drugs used through injection (insulin, GLP analogs, and amylin analogs). These types of modern drugs cause side effects such as; diarrhea, allergies, nausea, bacterial resistance, liver and kidney disorders, and hypoglycemia. In addition to the side effects of modern drugs as a treatment for diabetes mellitus, the cost of treatment is also very expensive, therefore diabetes mellitus sufferers and their families switch to other alternative treatments by utilizing natural ingredients for faster healing of wounds due to diabetes mellitus without or with minimal side effects, the type of natural ingredients that have the potential for healing wounds due to diabetes mellitus is butternut squash seed which has a fatty acid content. The types of fatty acids in butternut squash seed oil include oleic acid, linoleic acid, palmitic acid, lauric acid, and stearic acid [5]. Based on the content of fatty acids in butternut squash seed, the highest found is oleic acid (36.08%). The high content of oleic acid in butternut squash seed is related to improved wound closure, this is due to the stabilization of fibronogen and fibroblast migration, thereby shortening bleeding time. Research conducted by Bardaa et al (2016) topical treatment of pumpkin seed oil has an effect on accelerating wound healing [6]. Research by Abbas & Alrekabi (2018) pumpkin seed oil plays a role in reducing wound inflammation and accelerating wound healing in diabetic model mice and non-diabetic mice compared to wound cream [7]. Based on previous studies, it has been proven that pumpkin seeds play a role in wound healing, so to understand it, pumpkin plants must be scientifically assessed based on the available literature. Literature review on butternut squash seed extract (*Cucurbita moschata* Duchesnes) fatty acid therapy for healing type 2 diabetes mellitus wounds needs to be made as a potential for future use in the treatment of diabetes mellitus. Literature reviews are used as reference standards to synthesize evidence and support the development of clinical practice guidelines for treatment because of their rigorous methodology.

2. RESEARCH METHODS

Article review method uses a narrative review method through literature review, identification, searching, and downloading national and international journal references. Literature studies are conducted through several portals, such as PubMed, Elsevier, ScienceDirect, and Google Scholar. This narrative review presents information about the effect of butternut squash seed extract (*Cucurbita moschata* Duchesnes) fatty acid therapy on the healing of type 2 diabetes mellitus wounds. Literature studies are conducted by summarizing material from journal article references into relevant publications, then presented in the form of a scientific literature study review. Reference searches use the PICO strategy such as: "buttenut squash", "*Cucurbita moschata* Duchesnes", "fatty acids", "hyperglycemic", "butternut squash seed oil", "wound healing", "fatty acids in butternut squash seeds" or combining keywords searched using boolean operators. The keywords use boolean operators such as: "effect of fatty acids in butternut squash seeds on the healing of diabetic wounds". References that have been found in full text according to the inclusion criteria that have been set, these inclusion criteria if the discussion is pumpkin seed oil and its role as a therapy for type 2 diabetes mellitus. Articles are not used if the topic is not relevant and full text is not available. Reference searches are in the form of research journals published on the internet in the last 10 years from 2014-2024.

3. RESULTS AND DISCUSSION

Description of butternut squash

Butternut squash is a species of Cucurbita moschata Duchesnes. Butternut squash has been cultivated for more than 5,000-6,000 BC, is an annual plant that has a creeping stem (herbaceous) [8]. The stem and leaves of this plant have hairs. The shape of the stem of the milk squash is round or blunt pentagon with twisted tendrils. The shape of the leaves is circular, kidney, heart, or triangular which juts inward at the base. The leaves of the milk squash can be seen wavy and toothed which can reach 10 cm in length with a width of 35 cm. The leaves are alternately arranged between the stems with a leaf stalk length of between 9-24 cm. The flowers are bell-shaped, large, yellow and five-lobed [9]. Flowers have actinomorphic or regular properties and in one individual there are male and hermaphrodite flowers [8]. The morphological characterization of butternut squash can be presented in Figure 1.

Figure 1. Morphological characterization of butternut squash [10]

Butternut squash fruit has various variations including; globular, flattened, cylindrical, turbinate, dumbbell, elongated, pyriform, or like a curved crooked neck [11][12]. The surface of the fruit is smooth and hard. The fruit stalk is hard, long five-angled covered with hairs. The length of the fruit is 13.21-91.99 cm, width 9.46-55.40 cm, thickness 0.58-6.95 cm. The flesh of the fruit is dark yellow, orange, pale green, or white. The middle part is hollow and has many seeds [9]. The weight of the pumpkin fruit ranges from 2-5 kg with a harvest period of 3-4 months and can be stored for up to 6 months or more at a temperature range of 10-16 °C with a humidity of 70% [8]. Variations in the shape of the fruit and butternut squash seeds are shown in Figure 2.

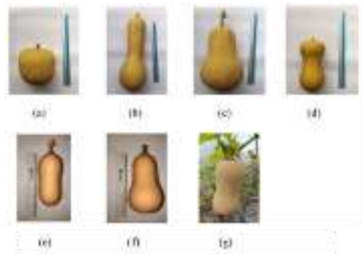


Figure 2. Variations in shape of butternut squash Note: a-d. Citara laga, e. Tiana, f. Waltham, g. Jacqueline. ((a) globular, (b,c,f) pyriform, (d) dumbbell, (e,g) blocky) [13]

Butternut squash seeds have a thin shell with an oval, flat, and irregular edge shape, are white to dark brown in color, and have a fleshy core [14]. The seed size is 8-22 mm long, 1-14 mm wide, 1.58-4.52 mm thick, and weighs 0.063-0.190 grams. Variations in the shape of butternut squash fruit and seeds are shown in Figure 3.

Figure 3. Variations in butternut squash seed shape [10]

Description of fatty acids

Fatty acids are carboxylic acids formed from hydrogen and carbon atoms. Based on the presence of double bonds, fatty acids are classified into saturated fatty acids and unsaturated fatty acids. Based on the double bond chain, unsaturated fatty acids can be divided into 2, namely monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). The chemical structure of fatty acids, saturated and unsaturated fatty acids can be presented in Figures 4 & 5 [15].

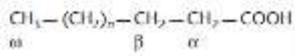


Figure 4. Chemical structure of fatty acids [16]

a

b

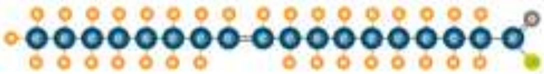
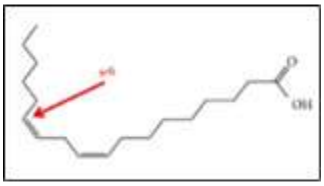
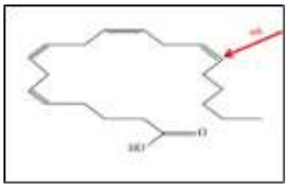


Figure 5. Chemical structure

a. saturated fatty acids; b. unsaturated fatty acids

PUFAs are classified based on the position of the first double bond counted from the methyl terminal. Then, when the first double bond is on the 6th carbon atom from the methyl terminal, PUFAs are called omega-6, ω-6, or n-6. PUFAs include linoleic acid (LA, C18 : 2 ω-6), an essential fatty acid because it cannot be synthesized by the human body. Linoleic acid can be "stretched" and desaturated into other ω-6 fatty acids, such as arachidonic acid (AA, 20 : 4 ω-6), while the chemical structure of n-6 PUFAs can be presented in Figure 6.





a b

Figure 6. Chemical structure of n-6 PUFA

a. linoleic acid; b. arachidonic acid [17]

Fatty acids alter the structural and immunological status of the skin by forming the stratum corneum, and can alter skin permeability. Fatty acids also interfere with the maturation and differentiation of the stratum corneum and inhibit the production of proinflammatory eicosanoids, reactive species (ROS and RNS), and cytokines, thus affecting the inflammatory response and leading to wound healing [18][19].

Diabetic wounds

Diabetic wounds are wounds that occur in diabetic patients due to peripheral and autonomic nerve damage caused by high blood glucose levels (hyperglycemic) [20][21]. Diabetic wounds are one form of diabetes complication that causes wounds to experience deeper tissue damage and experience a slower healing process. This condition increases the risk of wound infection due to decreased blood flow, immune response and nutrition in the wound area [22]. Diabetic wounds are influenced by impaired cytokine function, lack of collagen production accompanied by non-enzymatic glycation of collagen and keratin resulting in collagen stiffness that can damage tissue [23][24].

Improper treatment of diabetic wounds can cause rapid, widespread bacterial infections, and in more advanced cases, cause gangrene. Signs and symptoms of chronic diabetic wounds are inadequate growth factor formation, biofilm formation by bacteria, and other factors such as inappropriate treatment related to vasculopathy, immunopathy, and neuropathy [25]. Inadequate formation of growth factors results in increased proteolytic enzymes which result in disruption of the wound healing process.

Diabetes mellitus in uncontrolled conditions can cause morbidity and mortality in the form of microvascular and macrovascular complications to amputation of the lower leg [26]. Diabetes mellitus can cause the emergence of reactive oxygen species (ROS) in mitochondria to be produced excessively and activation of inflammatory mediators so that it can cause damage to the vascular endothelium, and cause tissue damage through the main mechanisms, namely, increased glucose and other types of blood sugar through the polyol pathway, formation of intracellular advanced glycation end products (AGEs), increased expression of AGEs receptors and ligands, activation of protein kinase C (PKC) isoforms, and excessive activity of the hexosamine pathway [27][20].

Wounds in diabetes mellitus can be influenced by several factors including age, ischemia, bacteria, nutrition, and immunity [28], in addition to these factors, wounds in diabetes mellitus can be specifically influenced by, among others; (a) macro and microcirculation dysfunction. Peripheral arterial disease impairs wound healing by affecting macrocirculation and blood flow to the lower limbs. In addition, neuropathy is associated with changes in microcirculation and causes decreased oxygen saturation in the feet. (b) Vascularization disorders. Vascularization is impaired in non-healing diabetic wounds. Reduced endothelial progenitor cells (EPCs) in diabetic patients are at risk for foot ulceration. Chronic hyperglycemia and inflammation are thought to be the main causes of EPC dysfunction and impaired EPC recruitment from the bone marrow in diabetic patients. It has also been suggested that non-enzymatic glycation of the vascular basement membrane results in disruption of EPCs and therefore impaired blood vessel regeneration [29]. (c) Impaired neuropeptide signal transmission. Nerve fibers in the skin immediately after injury release several neuropeptides into the wound microenvironment. Stimulation of c-nociceptive fibers results in further stimulation of adjacent fibers to release vasodilators such as substance P, neuropeptide Y (NPY), calcitonine-gene related peptide (CGRP), catecholamines, and hyperemia which cause vasodilation and hyperemia during wound injury. These neuropeptides are found to be reduced in patients with diabetes mellitus, thus having a negative impact on the wound healing process [30].

Healing of diabetic mellitus wounds

Wound healing is a complex physiological process in the form of a repair or reconstruction process of the human body as a general response to defects due to injury in tissue/organs, especially the skin. The normal wound healing process consists of 4 phases, namely; (1) hemostasis, vasoconstriction occurs, platelet aggregation, and recruitment of coagulation factors circulating in the wound; (2) inflammation, inflammatory cells gather and release inflammatory factors; matrix metalloproteinase (MMP)-9 is secreted by macrophages and neutrophil extracellular reticular traps (NETs) are secreted by neutrophils; (3) proliferation, inflammation subsides and skin cells, such as keratinocytes that release epidermal growth factor (EGF), proliferate and migrate to the wound bed; and (4) remodeling, new tissue is re-formed and stored through the extracellular matrix and neovascularization, involving fibroblasts that secrete fibroblast cytokines (FGF) and vascular endothelial cells that secrete vascular endothelial growth factor (VEGF) [31] (Raja et al, 2023). The stages of wound healing can be presented in Figure 7.

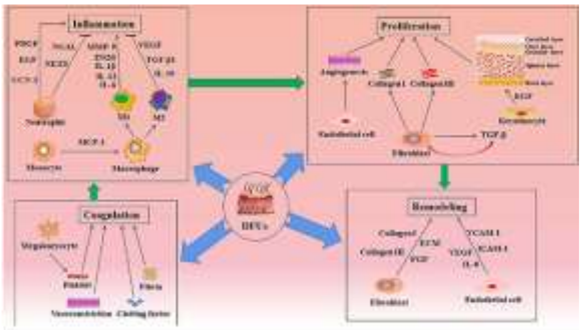


Figure 7. Stages of normal wounds [27]

Healing of diabetic wounds

Diabetic wounds, tissue ischemia, hypoxia, microorganisms, and hyperglycemia can interfere with wound healing so that wound healing is delayed and causes the impact of clinical complications. There are 8 main factors in the pathogenesis of diabetic foot ulcers, this can be presented in Figure 8.

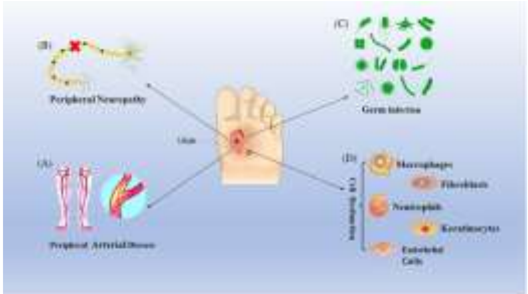


Figure 8. Pathogenesis of diabetic foot ulcers [27]

Based on Figure 8 shows that there are four main aspects of the formation of diabetic foot ulcers, including; peripheral arterial disease, peripheral neuropathy, bacterial infection, and cell dysfunction [32]. (1) peripheral arterial disease is the most important factor in the development of diabetic foot. Severe ischemia of the lower extremity skin causes ulcerated tissue to become necrotic due to insufficient blood supply. (2) peripheral neuropathy causes sensory, motor, and secretory dysfunction in the lower extremity skin. These pathological changes not only change the physical mechanics of the foot and cause loss of protective sensation but also cause dry skin, which does not support healing of diabetic wounds. (3) bacterial wound infection can delay wound healing, this is due to a decrease in beneficial inflammatory factors and an increase in harmful inflammatory factors, normal wound healing is delayed. (4) the functional status of wound cells directly determines the quality of healing. The specific microenvironment of diabetic wounds does not support the implementation of normal cell functions. For example, in the inflammatory phase, there is an imbalance between the proinflammatory and anti-inflammatory effects of macrophages and neutrophils. In the proliferation phase, endothelial cell proliferation and migration are disrupted. In the remodeling stage, fibroblasts differentiate and secrete collagen abnormally [27].

Fatty acids on diabetes mellitus wound healing

Fatty acids are associated with better wound healing, it is known that fatty acids can change the structure and immunology of the skin because fatty acids function as the stratum corneum and can change skin permeability. Fatty acids also inhibit proinflammatory eicosanoids, reactive species (ROS and RNS), and cytokines, thereby affecting inflammation and causing wound healing [33]. Based on the fatty acid profile in pumpkin seeds, it contains mostly polyunsaturated fatty acids (PUFAs), the types of unsaturated fatty acids such as oleic acid, linoleic acid, palmitic acid, lauric acid, and stearic acid [5].

Oleic acid has a pro-inflammatory effect on wound healing, such as the migration of enlarged leukocytes to the lesion, macromolecule and DNA content, in addition to stimulating the release of mediators by neutrophils such as VEGF-α (vascular endothelial growth factor) and IL-1, thus accelerating wound healing. Oral administration of oleic acid to mice with skin wounds can increase the activation of NF-kB (nuclear factor kappa light chain enhancer of activated B cells) and increase the production of tumor necrosis factor alpha 1 hour after tissue injury with a reduction in pro-inflammatory cytokines 24 hours later, indicating an acceleration of the inflammatory part of wound healing after oral administration of oleic acid. Therefore, oleic acid has a beneficial effect on wound closure [34].

Linoleic acid in pumpkin has an effect on wound healing, this is proven by a study using an animal model, namely BALB/c mice in a wounded condition given treatment using linoleic acid (30 μM) for 20 days, the results showed tissue repair [35]. These results are related to increased production of nitric oxide (NO). NO is a free radical derived from L-arginine oxidation through the activity of nitric oxide synthase (NOS). After inflammation occurs, inducible nitric oxide synthase (iNOS) is expressed in immune cells and produces large amounts of NO which will produce other free radicals, thereby expanding the inflammatory response [36]. NO plays important roles such as activation of macrophages and fibroblasts, induction of collagen synthesis, and proliferation of keratinocytes during wound healing, thereby accelerating reepithelialization [15].

4. CONCLUSION

Long-term diabetes mellitus can cause acute complications due to uncontrolled high blood glucose levels (hyperglycemia), one of which is diabetic ulcers or diabetic wounds. This condition increases the risk of wound infection due to decreased blood flow, immune response and nutrition in the wound area. Efforts to treat diabetes can use natural ingredients, one of which has been scientifically proven to use milk pumpkin which contains fatty acids. The types of fatty acids in milk pumpkin seeds include; oleic acid, linoleic acid, palmitic acid, lauric acid, and stearic acid. Fatty acids have the potential for better wound healing, it is known that fatty acids can change the structure and immunology of the skin because they function as the stratum corneum and can change skin permeability. Fatty acids also inhibit proinflammatory eicosanoids, reactive species (ROS and RNS), and cytokines, thereby affecting inflammation and causing wound healing.

REFERENCES

Abbas, N. F., & Alrekabi, F. M. K. (2018). The role of pumpkin seed oil in healing of wounds in diabetic mice. Indian Journal of Natural Sciences, 8(47), 13604-13614.

Alexander, J. W., & Supp, D. M. (2014). Role of arginine and omega-3 fatty acids in wound healing and infection. Advances in Wound Care, 3(11), 682-690.

Al-Hadi, H., & Zurriyani, A. S. (2020). Prevalensi diabetes melitus tipe 2 dengan kejadian hipertensi di Poliklinik Penyakit Dalam RS Pertamedika Ummi Rosnati. Jurnal Medika Malahayati, 4(4), 291-297.

Amin, M., Niaz, S., Sardar, S., Hussain, A., Korani, M. A., Burhan, M., et al. (2023). A novel study of pumpkin (Cucurbita moschata) on morphology and its yield attributing characters in Pakistan. Journal of Population Therapeutics, 30(17), 992-1000.

Andrejiova, A., Hegedusova, A., Matova, A., & Vargona, A. (2018). The possibility of butternut squash growing in conditions of Slovak Republic. International Journal of Agriculture, Forestry and Life Science, 2(2), 116-121.

Artha, I. M. J. R., Bhargah, A., Dharmawan, N. K., Pande, U. W., Triyana, K. A., Mahariski, P. A., et al. (2019). High level of individual lipid profile and lipid ratio as a predictive marker of poor glycemic control in type-2 diabetes mellitus. Vascular Health and Risk Management, 15, 149-157.

Baltziz, D., Eleftheriadou, I., & Veves, A. (2014). Pathogenesis and treatment of impaired wound healing in diabetes mellitus: New insights. Advances in Therapy, 31

Bardaa, S., Halima, N. B., Aloui, F., Mansour, R. B., Jabeour, H., Bouaziz, M., & Sahnoun, Z. (2016). Oil from pumpkin (Cucurbita pepo L.) seeds: Evaluation of its functional properties on wound healing in rats. Lipid in Health and Disease, 15(73), 2-12.

Dasari, N., Jiang, A., Skochdopole, A., Chung, J., Reece, E. D., Vorstenbosch, J., & Winocour, S. (2021). Updates in diabetic wound healing, inflammation, and scarring. Seminars in Plastic Surgery, 35(3), 153-158.

Deng, H., Li, B., Shen, Q., Zhang, C., Kuang, L., Chen, R., Wang, S., Ma, Z., & Li, G. (2023). Mechanisms of diabetic foot ulceration: A review. Journal of Diabetes, 15(4), 299-312.

Ezin, V., Gbemenou, U. H., & Ahanchede, A. (2022). Characterization of cultivated pumpkin

(Cucurbita moschata Duchesne) landraces for genotypic variance, heritability and agro-morphological traits. Saudi Journal of Biological Sciences, 29(5), 3661-3674.

Gbemenou, U. H., Ezin, V., & Ahanchede, A. (2022). Current state of knowledge on the potential and production of Cucurbita moschata (pumpkin) in Africa: A review. African Journal of Plant Science, 16(1), 8-21.

Genser, L., Rossario, J., Mariolo, C., Castagneto-Gissey, L., & Panagiotopoulos, S. (2016). Pathophysiologic relationships and guidelines for surgical intervention. Surgical Clinics of North America, 96(4), 681-701.

Hariono, M., Yuliani, S. H., Istyastono, E. P., Riswanto, F. D. O., & Adhipandito, C. F. (2018). Matrix metalloproteinase 9 (MMP9) in wound healing of diabetic foot ulcer: Molecular target and structure-based drug design. Wound Medicine, 22(1), 1-13.

Kim, J. (2023). The pathophysiology of diabetic foot: A narrative review. Journal of Yeungnam Medical Science, 40(4), 328-334.

Kim, K. A., Shin, Y. J., Kim, J. H., Lee, H., Noh, S. Y., Jang, S. H., & Bae, O. K. (2012). Dysfunction of endothelial progenitor cells under diabetic conditions and its underlying mechanisms. Archives of Pharmacal Research, 35(2), 223-234.

Mariadoss, A. V. A., Sivakumar, A. S., Lee, C., & Kim, S. J. (2022). Diabetes mellitus and diabetic foot ulcer: Etiology, biochemical and molecular based treatment strategies via gene and nanotherapy. Biomedicine & Pharmacotherapy, 151(1), 1-14.

Mariamenatu, A. H., & Abdu, E. M. (2021). Overconsumption of omega-6 polyunsaturated fatty acids (PUFAs) versus deficiency of omega-3 PUFAs in modern-day diets: The disturbing factor for their "balanced antagonistic metabolic functions" in the human body. Journal of Lipids, 1-15.

Mieczkowski, M., Rakowska, B. M., Kowara, M., Kleibert, M., & Czupryniak, L. (2022). The problem of wound healing in diabetes: From molecular pathways to the design of an animal model. International Journal of Molecular Sciences, 23(14), 1-21.

Nopianasanti, H., & Setiadi Daryono, B. (2018). Kestabilan fenotip tanaman labu susu (Cucurbita moschata (Duchesne) Poir “Butternut”) hasil budidaya di Sleman D.I Yogyakarta. Biogenesis: Jurnal Ilmiah Biologi, 6(2), 115-123.

Nurlian, S., Jafar, N., & Arman. (2024). Pengaruh pemberian ekstrak daun tembelekan (Lantana camara L.) terhadap penyembuhan luka diabetes melitus. Bina Generasi: Jurnal Kesehatan, 15(2), 41-51.

Okonkwo, U. A., & Dipietro, L. A. (2017). Diabetes and wound angiogenesis. International Journal of Molecular Sciences, 18(7), 1419.

Prayugo, B., Ikhwan, M., & Yamamoto, Z. (2021). Potensi ekstrak ikan gabus terhadap kesembuhan luka diabetes. Jurnal Kedokteran Syiah Kuala, 21(2), 172-183.

Purnomo, Daryono, B. S., & Sentori, M. B. (2015). Variability and intraspecies classification of pumpkin (Cucurbita moschata (Duch. ex Lam.) Duch. ex Poir.) based on morphological characters. KnE Life Sciences, 2(1), 286-293.

Putri, N. R. A., Kusnanda, P. S., Angellya, B. F., Sartika, D., & Purnomo, Daryono, B. S. (2023). Genetic variation of butternut squash (Cucurbita moschata Duchesne) based on inter-simple sequence repeat. Journal of Tropical Biodiversity and Biotechnology, 8(1), 1-8.

Rodrigues, H. G., Vinolo, M. A. R., Sato, F. T., et al. (2016). Oral administration of linoleic acid induces new vessel formation and improves skin wound healing in diabetic rats. PloS One, 1-19.

Rustan, A. C., & Drevon, C. A. (2005). Fatty acids: Structures and properties. Encyclopedia of Life Sciences, 1-7.

Sativa, A. R. (2019). Mekanisme diabetes melitus tipe 2 dalam meningkatkan risiko penyakit katarak. Jurnal Ilmu Kedokteran dan Kesehatan, 6(2), 160-165.

Shaban, A., & Sahu, R. P. (2017). Pumpkin seed oil: An alternative medicine. International Journal of Pharmacognosy and Phytochemical Research, 9(2), 2-8.

Silva, J. R., Burger, B., Kuhl, C. M. C., Candreva, T., Anjos, M. B. P., & Rodrigues, H. G. (2018). Wound healing and omega-6 fatty acids: From inflammation to repair. Mediators of Inflammation, 1-17.