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Review

Active Ingredients and Natural Raw Materials Used in Foot Care in Diabetic Patients—A Literature Review

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Abstract: Diabetic foot syndrome is the leading cause of limb loss due to non-healing ulcers. Repeated injuries, abnormal foot loads, and ischemia lead to ulcers. Poor shoe selection and inadequate care worsen the situation. Lack of patient education contributes to bacterial infections, tissue necrosis, and amputation. Vigilant observation and regular care can reduce wound size and prevent new wounds. Cleansing, infection control, and pressure relief are crucial in diabetic foot treatment. In this review, the effect of selected active ingredients and natural raw materials used for topical application in the care of diabetic foot was analyzed. The main focus used was on ingredients of natural origin—research studies utilizing emollients, humectants, plant extracts, and animal-derived ingredients were discussed. In addition, research studies on the application of nanomaterials, ozone and stem cells are also discussed. The cosmetics industry and manufacturers of podiatric products play a vital role in diabetic care. They should prioritize proper formulation, optimal ingredient doses, and skin microbiome control. Educating diabetics and using cosmetic products with self-massage elements can reduce the risk of hard-to-heal ulcers.

Keywords: diabetes mellitus; diabetic foot; urea; emollients; nanosilver; nanocopper; ozone; herbals

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1. Introduction

Diabetes mellitus (DM), clinically characterized by hyperglycemia due to inadequate insulin release, is divided into two main types: type 1 diabetes and type 2 diabetes [1]. Other types have also been identified, including latent autoimmune diabetes in adults (LADA), maturity-onset diabetes of the young (MODY), steroid-induced diabetes, and gestational diabetes.

Type 1 diabetes (also known as insulin-dependent diabetes mellitus, IDDM) is characterized by a deficiency of insulin, resulting in hyperglycemia. This phenomenon occurs as a result of a complex disease process involving genetic and environmental factors that lead to an autoimmune response, in which beta cells in the islets of Langerhans are destroyed by an inflammatory response. The symptoms of IDDM are more severe in children than in adults. Type 1 diabetes develops suddenly and can cause symptoms such as increased thirst (polydipsia), polyuria, lack of energy, extreme fatigue, excessive hunger, rapid and unexplained weight loss, slow-healing wounds, blurred vision, severe dehydration, and diabetic ketoacidosis. Pharmacotherapy primarily involves the administration of exogenous insulin, often through modern pumps that allow precise dosing of the medication over time [2].

Type 2 diabetes, also known as noninsulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, accounts for approximately 85% of all diabetes cases. Its main causes are impaired insulin secretion by pancreatic beta cells and abnormalities in insulin utilization by tissues (insulin resistance). Skeletal muscles, the liver, and adipose tissue

exhibit the greatest reduction in insulin sensitivity. Peripheral insulin resistance can lead to excessive insulin secretion from pancreatic islets, resulting in a subsequent decline and eventual exhaustion of the islet's secretory function. Most individuals with type 2 diabetes, especially in the early stages of the disease, are not dependent on external insulin supplementation through injections since their endogenous insulin secretion is maintained, and insulin deficiency is rare. The treatment approach and the necessity of insulin administration are among the main differences between type 1 and type 2 diabetes [3,4].

During pregnancy, disturbances in carbohydrate tolerance are classified as either pregestational diabetes mellitus (PGDM) when a woman enters pregnancy with pre-existing diabetes or gestational hyperglycemia diagnosed during pregnancy. Gestational diabetes, which resolves after childbirth, and other types of diabetes (type 1, type 2) detected during pregnancy are referred to as diabetes in pregnancy. In this case, pre-existing carbohydrate metabolism disorders that were previously undetected are identified. Two subcategories of diabetes in pregnancy are recognized: diabetes diagnosed during pregnancy (DIP), when glucose values in pregnant women exceed clinically defined thresholds for overt diabetes, namely fasting plasma glucose $\geq$ 126 mg/dL (7.0 mmol/L), or 2-h plasma glucose during a 75 g oral glucose tolerance test (75 g OGTT) $\geq$ 200 mg/dL (11.1 mmol/L), or random plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L), accompanied by clinical symptoms of hyperglycemia, and gestational diabetes, when glucose values in pregnant women meet at least one of the diagnostic criteria: fasting plasma glucose 70–90 mg/dL (3.9–5.0 mmol/L), postprandial plasma glucose up to 140 mg/dL (7.8 mmol/L), or nocturnal plasma glucose between 2:00 and 4:00 a.m. above 70–90 mg/dL (3.9–5.0 mmol/L). Based on the treatment approach, two classes of gestational diabetes are distinguished: G1DM (dietary therapy is sufficient to achieve normoglycemia) and G2DM (pharmacotherapy is required to achieve normoglycemia) [5].

One of the complications of diabetes is diabetic foot, which significantly impairs the quality of life and increases treatment costs. It is caused by microvascular, neuropathic, and biomechanical changes in the tissues that make up the feet, leading to reduced blood flow to the extremities and delayed regenerative processes, ultimately increasing the risk of ulcer formation [6].

In light of the data presented above, the risk of patients developing a diabetes complication such as diabetic foot is high. Since this problem can be common in patients, and the care of a patient with diabetes requires the involvement of a number of specialists, appropriate skincare seems to be an important issue. Properly selected components of cosmetics used by patients for this purpose can have a prophylactic effect, which can prevent serious disease complications. This study focused on the analysis of the anatomy, complications, and recommendations regarding the treatment and care of diabetic foot. Ingredients used in the therapy of diabetic foot were identified and described. The literature analysis aimed to identify the existing ailments, their impact on the quality of life of individuals undergoing treatment, and the possibilities of alleviating them using cosmetic or podiatric preparations that mitigate the cutaneous symptoms of the disease.

2. Results

2.1. Diabetic Foot—Causes, Symptoms and Related Complications

Diabetic foot can be classified pathophysiologically and clinically into diabetic ischemic foot, neuropathic ischemic foot, and infected diabetic foot. However, such classification may appear too simplistic due to the possibility of more commonly occurring mixed clinical variants, such as neuropathic (with intact arteries) or neuro-ischemic diabetic foot [5]. To understand the role of care and treatment, it is necessary to familiarize oneself with the anatomy and physiological functioning of the diabetic foot. It significantly differs from the foot of a non-diabetic individual. Changes in the foot encompass etiological changes in the musculoskeletal, vascular, neurological, and dermatological systems (Figure 1).

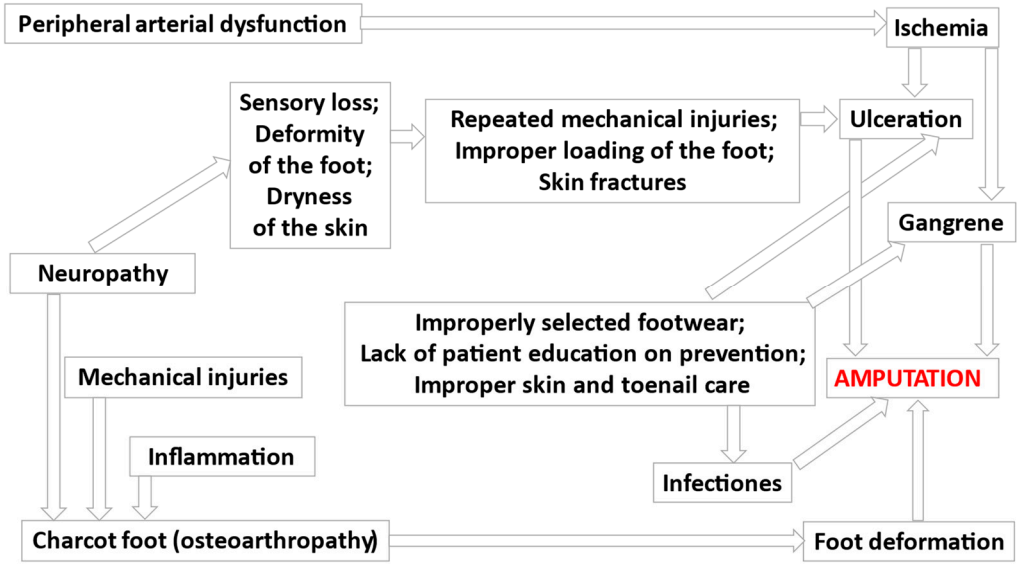

Figure 1. Pathogenetic factors associated with the development of diabetic foot and complications of the disease [1,4,5].

The musculoskeletal system is primarily affected, resulting in restricted joint mobility and foot deformities. Muscle tissue undergoes disorganization and is burdened by excess adipose tissue resulting from long-standing diabetes. Overloaded and weakened muscles contribute to the development of claw or hammer toes. Consequently, the weight distribution shifts from the distal to the proximal regions, potentially leading to the displacement of the distal fat pad. As toe deformities increase, pressure on the plantar head of the metatarsals intensifies. Due to increased forefoot pressure and tissue breakdown, diabetic patients have a high prevalence of equinus deformity of the ankle joint. The vascular structure of the lower limb plays a significant role in the morphology of the foot and ankle. The three major arteries and their branches supply six angiosomes of the foot and ankle. Due to the increased risk of peripheral arterial disease (PAD), patients may experience symptoms such as lower limb pain during both activity and rest, as well as tissue loss and gangrene in severe cases [5].

Diabetic neuropathy (DN) is defined as signs and symptoms of peripheral nerve dysfunction in a patient with diabetes, with other causes of peripheral nerve dysfunction excluded. It is one of the most common causes of peripheral neuropathy, leading to loss of pain sensation [7]. Hyperglycemia underlies diabetic neuropathy and disrupts various metabolic pathways, leading to an osmotic imbalance within the cells. Osmotic stress leads to the loss of myo-inositol, an essential component of the sodium–potassium ATPase, impairing the normal physiology of nerve cells [8].

Furthermore, increased aldose reductase activity reduces the level of NADPH, which is necessary for the production of nitric oxide (NO) and the regeneration of the antioxidant glutathione. This overload on the mitochondrial chain results in impaired electron transport and the excessive production of reactive oxygen species (ROS), ultimately leading to increased oxidative stress [5].

Increased glycolysis also leads to the accumulation of diacylglycerol (DAG), which activates protein kinase C (PKC). Activated PKC causes insulin resistance, impairs the function of the sodium–potassium ATPase, and alters the expression of vascular endothelial growth factor (VEGF) and transforming growth factor β (TGF-β), leading to vessel constriction, hypoxia, and neuronal damage [6,9]. These changes affect the rheological parameters of the blood, increasing endothelial vascular resistance, narrowing the vessels, reducing blood flow through the nerves, triggering inflammatory reactions, and causing a loss of neurotrophic support. Thus, activation of protein kinase C has been linked to vascular damage in DN. Hypoxia and further damage to capillaries result in metabolic

abnormalities within the neurons, their axonal parts, and Schwann cells. Impaired axonal transport and decreased activity of the sodium–potassium ATPase lead to axonal atrophy and impaired nerve conduction [7,10,11].

As a result of all the pathomechanisms described above, patients do not experience pain associated with minor or major injuries, which can go unnoticed. Neuropathy can develop in all patients with diabetes, regardless of their type. Diabetic neuropathic complications occur in insulin-dependent diabetes mellitus (IDDM), non-insulin-dependent diabetes mellitus (NIDDM), and secondary diabetes, with their frequency increasing with the duration of the disease [12]. According to the classification adopted at the San Antonio Conference on Diabetic Neuropathy in 1988, two types of diabetic neuropathy are distinguished: subclinical (without subjective symptoms) and clinically evident (symptomatic). Subclinical neuropathy is characterized by impaired sensations of vibration, temperature, light touch, weakened deep reflexes, and muscle strength. Symptomatic neuropathy includes generalized somatic neuropathy, autonomic neuropathy, and focal neuropathies. It affects about 40% of patients with diabetes for more than 25 years and clinically manifests as distal symmetric sensorimotor polyneuropathy. The course of this complication is chronic and progressive, with sensory symptoms predominating as well as less pronounced autonomic symptoms (often subclinical) and motor deficits [7].

Symptoms of diabetic autonomic neuropathy can be observed as early as one year after the diagnosis of diabetes. It affects various organs, causing disturbances in the cardiovascular, gastrointestinal, and urinary systems [10]. Sympathetic autonomic neuropathy leads to decreased sweating in the lower limbs, resulting in dryness of the foot skin, which becomes dry and prone to cracks, as well as increased blood flow and warming of the foot (when peripheral vascular disease is excluded) [11]. Changes in circulation allow for the investigation of thermography as a diagnostic tool and for monitoring the treatment of diabetic foot symptoms [13].

2.1.1. Ulcers

Neuropathies are considered the primary factors contributing to the development of ulcers. There is a significant correlation between the presence of somatic and autonomic neuropathy and foot ulcers. Patients with loss of sensation have a sevenfold increased risk of foot ulcers compared to individuals with diabetes but without neuropathy. Peripheral neuropathy symptoms, possibly secondary to proprioceptive loss, may contribute to this. Postural instability can have clinical significance and increase the risk of minor injuries and ulcers [14,15].

Ulceration (diabetic foot syndrome) is characterized by chronic tissue loss due to poor blood supply to the lower limbs. Vascular changes in individuals with diabetes include large artery atherosclerosis, arterial stiffness, and small vessel disease. Ulcers typically occur around the metatarsal heads, on the big toe, and on the hammer toes. They often occur at pressure points, where insufficient oxygen and energy supply can lead to the formation of a hematoma, which leaves a wound. This wound can be superficial (affecting only the skin) or deep (involving tendons and bones). Foot ulcers result from the interaction of two or more components, leading to foot damage. Neuropathic feet are prone to ulceration due to a combination of insensitivity and external factors (e.g., stepping on a sharp object barefoot, poorly fitting shoes) or internal factors (e.g., calluses, biomechanical dysfunction) [14].

In the case of bacterial infection and skin breakdown, damage to autonomic fibers occurs, leading to the opening of arteriovenous connections, microcirculation, and thermoregulation disturbances. This subsequently results in microcirculation insufficiency, making the foot vulnerable to damage and ulcer development [11].

Clinical assessment of diabetic foot ulcers should include a detailed description of size, depth, and location (Tables 1 and 2). Neuropathic ulcers typically occur in a warm, insensate foot, often at pressure points, and are surrounded by calluses. Ischemic ulcers, on the other hand, tend to occur in poorly perfused, cool feet, often in the lateral areas of the fifth metatarsal head or the medial areas of the first metatarsal head. Callus formation is

rare in ischemic ulcers. Proper identification of the degree of ischemia is crucial in wound assessment, and therefore, Doppler ultrasound examinations are recommended [11].

Table 1. Wagner classification of diabetic foot syndrome.

Grade	
0	High-risk foot, structurally abnormal without ulceration
1	Superficial ulceration
2	Deep ulceration with involvement of skin and subcutaneous tissues
3	Deep ulceration with osteomyelitis or abscess formation
4	Gangrene localized to the forefoot, treated conservatively or with wet gangrene
5	Extensive gangrene requiring amputation

Table 2. University of Texas diabetic foot classification system.

Stage	
A	No infection or ischemia present
B	Infection present
C	Ischemia present
D	Infection and ischemia present
Grade	
0	Intact skin with non-blanchable erythema
1	Superficial ulcer involving the dermis
2	Ulcer penetrating to tendon or joint capsule
3	Ulcer penetrating to bone or joint space

Ulcers in patients with diabetes mellitus (DM) are one of the main causes of hospitalization and foot amputations. Adequate care of the diabetic foot is a key aspect of limb preservation. Patients with diabetes and neuropathy have a 7–10% chance of developing foot ulcers each year, and the probability increases to 25–30% in individuals with additional risk factors such as peripheral arterial disease, foot deformities, or previous ulcers. It is estimated that 85% of amputations in diabetic patients are a consequence of foot ulcers. Furthermore, individuals with diabetes over the age of 45 are eight times more likely to undergo amputation; the risk increases to 12 times in those over the age of 65; and in the 65–74 age group, the incidence is 23 times higher [16].

In a patient with diagnosed neuropathy due to DM, inflammatory reactions (e.g., erythema) are significantly reduced, making it difficult to recognize them based on typical signs of infection. Therefore, obtaining a specimen for microbiological examination (after wound cleansing) is necessary, preferably through tissue biopsy, as swab results have limited value. Failure to examine the deeper layers of the wound can lead to bacterial infection and subsequent sepsis and amputation [11].

However, it should be noted that a positive result in a microbiological test does not necessarily indicate the presence of infection. Attention should be paid to the clinical presentation, such as the consequences of the ulcer. If a neuropathic ulcer does not show signs of connective tissue inflammation, secretion formation, or bone probing (indicating osteomyelitis) during the initial visit, wound cleansing with saline solution, application of dressings, and daily observation are sufficient. For neuroischemic and superficial ulcers, antibiotic therapy is recommended [17].

2.1.2. Arterial Diseases

Diabetic foot ulcers are an independent risk factor for peripheral artery disease (PAD). PAD occurs in half of the patients with diabetic foot syndrome and is characterized by the narrowing of the arteries below the renal arteries (arteriopathy), leading to reduced blood flow in the lower extremities. It is a common cause of walking impairment. Uneven weight distribution on the feet can result in wounds and lower limb amputation [16].

Diabetic arteriopathy is characterized by changes in the arterial walls, including arterial narrowing with increased thickness of the intima and media layers. The initial site of pathology is the vascular endothelium. The endothelium produces nitric oxide (NO), a potent vasodilator that also regulates platelet adhesion to the vessel wall, acting as an antiplatelet substance. Chronic hyperglycemia and insulin resistance disrupt NO production, impairing arterial vasodilation. Additionally, there is an overproduction of endothelin, a vasoconstrictive substance. Another underlying factor in atherosclerosis is inflammatory activation. Excessive production of inflammatory cell adhesion molecules leads to their penetration through the vessel walls and subsequent uptake by oxidized low-density lipoprotein (LDL) and foam cells. These components are significant in the formation of atherosclerotic fatty streaks, which represent an early marker of vascular disease [16].

Metabolic disturbances caused by arterial narrowing lead to various symptoms, the severity of which depends on the degree of arterial stenosis. Patients may experience pain during activity, pain at rest, or develop ulcers and tissue necrosis [5].

2.1.3. Charcot Foot

Charcot neuropathic osteoarthropathy is a destructive joint disease that is initiated by neuropathic injury to a limb. There are commonly two accepted theories used to describe the pathogenesis of this disease: neurotraumatic and neurovascular [14].

This disease occurs in the lower extremities. It is characterized by bone and joint fragmentation in the foot and ankle of individuals with various peripheral neuropathies. Diabetes, neuropathy, injuries, and metabolic bone abnormalities lead to a localized acute inflammatory state. The immune response can permanently disrupt the bone structure of the foot and result in foot deformities such as flatfoot, rocker-bottom foot, hammer toes, and ankle equinus. Improper pressure on the sole of the foot poses a risk of ulceration, infection, osteomyelitis, and amputation [18].

2.1.4. Gangrene

Gangrene is a clinical condition of ischemic and necrotic tissue. It is identified by discolored or black tissue and the sloughing of natural tissue planes. There are three types of gangrene: dry, wet, and gas [19].

Dry gangrene is dehydrated tissue that undergoes ischemia due to progressive distal arterial occlusion, often resulting from peripheral arterial disease. Risk factors for peripheral arterial disease overlap with those for coronary artery disease, including diabetes and hyperlipidemia. Worsening ischemia of the limbs may occur due to local infection and/or trauma, leading to an increased demand for blood. Dry gangrene is often aseptic due to the lack of bacterial viability in dry tissue [19].

Wet gangrene, complicated by secondary infection, is characterized by redness and swelling, but bone crepitus is not present. It occurs as a result of tissue infection with venous or arterial blood flow. This phenomenon is most commonly observed in individuals susceptible to lower limb and foot edema. Patients with diabetes are particularly prone to such infections due to impaired wound healing and hyperglycemia [19].

Gas gangrene is a type of necrotic infection with swelling, crepitus, and gas formation in the subcutaneous tissue (visible on X-rays). The infected necrotic soft tissues coincide with the infectious causes of gangrene and involve necrotic skin changes that can extend to subcutaneous, fascial, and muscular compartments. The infection is caused by *Clostridium perfringens*, a gas-producing bacterium, and due to the production of exotoxins, it can lead to the rapid development of local tissue necrosis and systemic symptoms [19].

2.2. Prevention and Care in Diabetic Foot Syndrome—General Assumptions

Patients with diabetes are susceptible to skin infections due to their tendency to develop skin injuries. Among bacterial infections, *Staphylococcus aureus* infections should be mentioned, which manifest as furuncles—nodules that form pustules with necrotic

cores—and Streptococcus infections causing erysipelas, characterized by well-defined swelling and acute inflammation of the subcutaneous tissue and skin [20].

Among fungal infections, candidiasis should be noted. The disease caused by Candida albicans occurs in the form of desquamating erythematous lesions with exudate in interdigital spaces, skin folds, as well as nail folds and plates. Symptoms indicative of a fungal infection include pain, itching, and a tendency for skin peeling and cracking. Coexisting with interdigital fungal infection is onychomycosis, which causes thickening, surface pitting, yellow discoloration, and brittleness of the nails [20].

As mentioned earlier, individuals with diabetes are at high risk of developing foot ulcers, which often become infected. These wounds, especially when infected, lead to significant morbidity. The treatment of wounds should aim to alleviate symptoms, accelerate healing, and prevent adverse effects, especially lower limb amputations. Dumville et al. conducted a review of components used for the treatment of diabetic foot ulcers, infected wounds, or for the prevention of infection in non-infected wounds [21]. The authors included randomized controlled trials conducted in hospitals or outpatient settings in their review. A total of 22 studies with a combined number of 2310 participants were identified. The included studies used various local antimicrobial treatments, including antimicrobial dressings (such as silver and iodine), aqueous solutions of oxidizing agents, zinc hyaluronate, silver sulfadiazine, tretinoin, pexiganan cream, and chloramine. The authors indicated that more wounds may heal after the use of antimicrobial dressings or a combination of dressings with antimicrobial agents compared to dressings without antimicrobial components.

The implementation of multidirectional care preparations can be extremely helpful in preventing or alleviating existing skin problems on the feet. The active ingredients in skincare products should be targeted at anti-inflammatory, antipruritic, keratoregulatory, superficial moisturizing, water-binding in the stratum corneum, and occlusive effects. Patients should be informed about which products can alleviate existing skin changes and what to pay particular attention to for preventive purposes.

Emollients

For preventive purposes, patients should be informed about the goal of daily foot skincare. Emollients play a crucial role in foot care. Research suggests that they can not only improve the condition of the skin but also act as a preventive measure for early diabetic foot changes. By improving the flexibility of the stratum corneum, emollients enhance the skin's resistance to irritants and external factors, soften the skin, and increase moisture levels.

Emollients are mixtures composed of a lipid base (fat, wax, or oil) and water. In the form of ointments, which have a higher lipid content than water, they appear to be the most effective in preventing water evaporation from the stratum corneum. On the other hand, lighter and less occlusive balms provide relatively weaker protection against transepidermal water loss (TEWL) for the user [22].

2.3. Plant Raw Materials Used in Diabetic Foot Care

2.3.1. Plant Emollients Used in the Skincare of Feet of Diabetic Patients

Plant oils are used as emollient ingredients. Some of them, due to additional phytochemical components, exhibit additional beneficial effects and can be successfully used for the skincare of diabetic patients' feet or to alleviate changes in diabetic foot skin.

Olive oil, thanks to its phenolic and polyphenolic compounds, exhibits antioxidant properties. It has been proven that oleuropein, tyrosol, hydroxytyrosol, verbascoside, ligustroside, and demethyloleuropein provide protection against coronary heart disease or cancer. They also show antimicrobial and antiviral activity [23].

Hydroxytyrosol (HT) is a polyphenol found in olives. Its health benefits are strongly correlated with the compounds' ability to scavenge free radicals and reactive oxygen/nitrogen species, as well as activate endogenous antioxidant systems in the body [23]. Oleuropein belongs to the group of coumarin derivatives, known as secoiridoids. It has been found

to be effective against various strains of bacteria, viruses, fungi, molds, and parasites. It also inhibits platelet aggregation and is the main ingredient in a patented endothelial proliferation inhibitor preparation. Oral treatment with oleuropein leads to a reduction in the number of blood vessels, indicating strong anti-angiogenic properties. It has also been shown that phenolic compounds (oleuropein, protocatechuic acid) from extra virgin olive oil inhibit LDL oxidation through macrophages. Extracts from olive leaves and fruits containing oleuropein protect insulin-producing pancreatic beta cell lines (INS-1) from the harmful effects of cytokines [23]. The evaluation of extra virgin olive oil can be of significant importance in the care of diabetic foot wounds due to its substantial antioxidant activity provided by the polyphenols present in the raw material.

Refined olive oil was evaluated in a clinical study involving 30 patients with diabetic foot syndrome. In addition to conventional therapy, patients were instructed to apply olive oil topically for 4 weeks. The results of the study indicated a reduction in wound surface area and depth. Importantly, 73.3% of patients treated with olive oil achieved complete wound healing, compared to 13.3% in the control group. The research results clearly suggest that olive oil, in combination with routine care, is more effective than routine care alone and has no side effects [24].

First-pressed coconut oil is obtained from mature coconuts. Its significance for various skincare and therapeutic purposes has been indicated for centuries [25]. It contains vitamins and antioxidants, exhibits antimicrobial and antiviral activity, and finds application in cases of atopic dermatitis in humans. The results of studies [26] demonstrated a significant impact of coconut oil on the wound healing process in diabetic foot wounds by promoting collagen synthesis and re-epithelialization. Furthermore, coconut oil was found to be more effective than silver sulfadiazine cream. Due to the limited amount of research regarding the use of coconut oil in this indication, it should be used with caution. However, it is worth noting that this ingredient has no adverse effects, is well-tolerated, and does not cause allergies [25].

2.3.2. Urea

To enhance the effectiveness of emollients, adjuvant ingredients are added to them. Among these ingredients is urea, a natural moisturizing factor found in human skin. Urea-based emollients are available in various concentrations. The selection of the appropriate preparation should be based on the individual's skin condition, age, and type of dermatosis. Reports indicate that a high concentration of urea effectively prevents skin keratinization, but to maintain moisturizing properties, its concentration should not exceed 20–25% [27]. It has been proven that daily application of a 25% urea-containing preparation on the soles of the feet of diabetic individuals significantly improves the function of the skin barrier and the integrity of the epidermis. For patients with diabetic foot syndrome, the keratoplastic, anti-itch, and moisturizing properties of urea are essential. This allows for the improvement of foot appearance, skin smoothness, and overall quality of life [27].

Individuals with diabetes who experience hyperkeratosis, peripheral arterial disease, and peripheral neuropathy should use urea-based skincare products daily. Such action allows for the fastest prevention of ulceration progression and helps avoid further consequences resulting from it [27]. The properties of urea are also utilized in combination products. In a study by Federici et al., the effectiveness of a combination of urea (5%), arginine, and carnitine in reducing skin dryness in diabetic patients was demonstrated [28]. For comparison, a local softening product based on glycerol was used. Over 28 days, DM patients applied the tested preparations twice daily.

2.3.3. Liquorice (*Glycyrrhiza glabra* L.)

Glycyrrhiza glabra, commonly known as licorice, is cultivated in Eurasia. The dried roots, collected in autumn, are the parts of the plant used. Licorice contains flavonoids such as liquiritigenin and liquiritin, as well as triterpenoids such as glycyrrhetic acid and glycyrrhizin. Licorice has anti-inflammatory and anti-allergic properties. It inhibits the process

of antibody formation caused by an increase in cortisol levels. Moreover, it shows antimicrobial activity against *Staphylococcus aureus*, *Streptococcus mutans*, *Mycobacterium smegmatis*, and *Candida albicans* [29]. Licorice extract has been used in the treatment of inflammatory skin conditions of various etiologies, including eczema, skin irritations, itching, and cysts [29,30]. Therefore, foot care products containing licorice should significantly accelerate wound healing in individuals with diabetic foot syndrome and provide relief within a relatively short time. However, this effect has never been analyzed in the form of randomized placebo-controlled trials or comparative studies, and the indication regarding the use of licorice in this context is based on its traditional use in various traditional and folk medicine procedures [31].

2.3.4. Curcumin

Curcumin is a yellow pigment isolated from the rhizome of *Curcuma longa* L., commonly known as turmeric. Research confirms the impact of curcumin on wound healing, attributed to its antioxidant, anti-inflammatory, and antimicrobial properties [32,33]. Curcumin inhibits the activity of matrix metalloproteinases and pro-inflammatory cytokines, reduces inflammation, inhibits mitogen-activated protein kinases, and increases the levels of antioxidant enzymes [34]. These findings demonstrate that curcumin enhances wound healing and, when developed as a pharmacological agent, can significantly influence the prevention and improvement of diabetic foot conditions [35]. Due to the formulation challenges associated with incorporating curcumin into cosmetic formulations, different carrier forms for this active compound are being investigated [36]. Research is also being conducted on specialized dressings that contain curcumin [37]. All of these approaches yield beneficial effects and confirm the usefulness of curcumin in prevention and treatment. Supplementation with curcumin is also being studied regarding its impact on disease management through dietary supplementation [32].

2.3.5. Banana (*Musa paradisica* L.)

Musa paradisiaca, commonly known as plantain or banana, is widely distributed in tropical regions. In folk medicine, plantain is used for the treatment of conditions such as diabetes, ulcers, and slow-healing wounds due to its hypoglycemic, anti-ulcer, and analgesic properties. Phytochemical studies of plantain stem juice have shown the presence of tannins and alkaloids, which are pharmacologically active compounds that have been experimentally confirmed [38–40]. There is a significant correlation between the phenolic content of the plant and its anti-diabetic effects. Furthermore, tannins, flavonoids, vitamin C, and vitamin E enhance the functions of pancreatic β-cells and prevent the excessive formation of free radicals [41,42]. This plant is being investigated as an oral supplementation agent, and galenic preparations from *M. paradisiaca* are also used for topical applications.

2.3.6. Aloe (*Aloe vera* L.)

Aloe vera has been used for centuries due to its skincare, health, beauty-enhancing, and healing properties. Its anti-inflammatory effects are particularly significant in the treatment of diabetic foot, as it inhibits the cyclooxygenase pathway, reducing the production of prostaglandin E2 from arachidonic acid [43]. The mucopolysaccharides present in the raw material help retain moisture in the epidermis. Additionally, aloe vera stimulates fibroblasts involved in the production of collagen and elastin fibers, making the skin more elastic [44]. It also acts as a binder for epidermal cells, softening the skin [45]. Aloe vera has some antibacterial properties [46]. The raw material is sometimes used by patients who have not responded positively to antibiotics, and its use is believed not to lead to antibiotic resistance. In the form of a gel, it supports wound healing due to the presence of anthraquinones and phytohormones, which have antibacterial, antifungal, and antiviral properties. In vitro studies described by Banu et al. [47] showed that fresh Aloe vera gel exhibited high activity against Gram-negative bacteria and slightly lower activity against all tested Gram-positive

bacteria. It was confirmed that the gel has inhibitory effects on Pseudomonas aeruginosa and Staphylococcus aureus, which are pathogens often involved in infections occurring at sites where the skin barrier is disrupted [47]. Based on the traditional use of this plant, experimental studies have identified the mechanisms and active ingredients responsible for its clinical effects. This effect has also been confirmed in clinical research [48]. The latest research focuses on combining aloe vera with other active ingredients (such as chitosan or extracts from algae) or developing modern formulations for topical use [49].

2.3.7. Kiwi Fruit (*Actinidia deliciosa* Planch.)

Kiwi fruits are exceptionally rich in vitamin C and contain a variety of nutrients, especially potassium, vitamin E, and folic acid, as well as bioactive components. These components, particularly relevant for individuals dealing with diabetic foot, include a wide range of antioxidants and enzymes that improve the metabolic functions of cells [50]. An important component of the fruit is the enzyme actinidin, a cysteine protease responsible for its cleansing properties.

In a clinical study involving 37 patients with diabetic foot syndrome, in addition to standard treatment, dressings with a thickness of 3 mm made from kiwi fruits were applied twice daily. After 21 days of treatment, the intervention group showed a significant reduction in ulceration and faster wound healing compared to the control group. Improved vascularization and granulation were also observed. Patients treated with kiwi exhibited faster tissue remodeling of scar tissue, which is likely due to the presence of ascorbic acid and actinidin—a proteolytic enzyme. It is also hypothesized that kiwi fruits may be rich in angiogenesis modulators, which are essential for the proper healing process of wounds [51].

2.3.8. Other Plant Raw Materials

The effect of *Plantago major* L. (common plantain) leaves on wound healing has been demonstrated in numerous animal studies. However, the quality of these studies has recently been negatively evaluated by Cardoso et al. [52]. Nonetheless, this traditionally recognized herb served as the basis for a clinical study. The work by Ghanadian et al. [53] aimed to evaluate the clinical efficacy of the water-alcohol extract of *P. major* in the treatment of diabetic foot syndrome. In the experimental group, patients were administered a 10% gel with *P. major* extract on the wound once a day for two weeks. The gel with plantain extract significantly reduced the wound size compared to the control group, and the number of patients with complete wound healing in the group using the preparation with common plantain was significantly higher.

Another plant originating from folk medicine (Iran) to consider when planning a preparation for diabetic patients is *Teucrium polium* L. (gray sage). Its usefulness has been verified in a clinical study [54]. A significant reduction in ulcer size and a significantly higher rate of complete remission of skin lesions were observed. The study included 70 patients with diabetes with grade 1 or 2 foot ulcers according to the Wagner scale. The patients were randomly divided into two groups, both receiving standard treatment for diabetic foot ulcers. Additionally, group 1 received a topical ointment with *T. polium* extract, while group 2 received a placebo. The preparations were applied twice a day, and the observation period lasted for four weeks.

In another form, the use of henna (derived from the plant *Lawsonia inermis* L.) is proposed as a plant-based ingredient recommended for diabetic patients. The difference here is that this component is intended for preventive rather than therapeutic purposes [55]. The authors of the study indicating the usefulness of henna point out that the main cause of infection is often damage to the integrity of the skin. The interdigital area is critical, as it usually serves as the entry point for infectious agents. It is a relatively closed environment that may be exposed to more moisture than any other part of the foot. Excess moisture can lead to maceration, increasing the likelihood of skin damage and intensified microbial colonization. This can be confirmed by examining the skin pH between the toes, which is significantly higher in diabetics than in the general population [56]. It should be noted

that henna has some antimicrobial properties [57]. However, the authors indicate that the most important preventive action for diabetic patients is to protect against maceration and skin damage in the interdigital area. This allows for the development of interesting and innovative foot care preparations.

2.4. Animal Derived Cosmetic and Therapeutic Ingredients

2.4.1. Raw Materials of Bee Origin

Treatment of wounds with honey has been used by ancient Egyptians, Assyrians, Chinese, Greeks, and Romans. Aristotle wrote about using honey for sunburns and for treating "all foul and deep ulcers." Honey therapy is still practiced in folk medicine in many parts of the world. In Ghana, for example, honey is used on ulcerated legs because of its antibiotic properties. Due to the increasing antibiotic resistance of bacterial strains, there has been a partial return to traditional methods.

Studies show that honey has a broad spectrum of antibacterial activity, but the research is not detailed enough to consider which type of honey exhibits the greatest antibacterial effects. It is known that the antibacterial action of most honeys is due to the production of hydrogen peroxide by an enzyme secreted by bees into the collected flower nectar. Some honeys have high photochemical antibacterial activity due to components derived from certain Leptospermum species (*L. scoparium*, *L. polygalifolium*, and possibly others).

It has been demonstrated that honey is able to absorb water from the interstitial tissue due to its increased osmolality, which can improve local lymphatic drainage and blood circulation. Honey dressings effectively reduce swelling and unpleasant odors in wounds. The use of honey dressings is more comfortable for patients due to their lack of adhesion to the granulating surface and moisture retention. Removing the dressings multiple times is easier and less painful. Moisture-retentive dressings currently available on the market are relatively expensive. Honey dressings are an economical and practical option for the treatment of ulcers in patients with diabetes mellitus [58].

Propolis is a resinous product composed of plant materials that is collected by bees and then modified by bee saliva enzymes during chewing. Flavonoids and caffeic acid esters are considered its most active biological fractions, which have a strong inhibitory effect on pro-inflammatory protease (MMP-9—matrix metalloproteinase-9), whose levels increase in diabetic foot ulcers. In addition, propolis exhibits antioxidant, antimicrobial, and antibacterial properties [59]. A 2019 study indicated that changes in patients with diabetic foot syndrome who received local propolis treatment healed better than those untreated [60]. It was reported that propolis reduced the ulcer surface area by an average of 41% compared to 16% in the control group, and after 4 weeks, it reduced the size of grade 1 and 2 ulcers on the Wagner scale, proving that local propolis can improve wound closure. Patients treated locally with propolis showed a 25% reduction in wound area after 8 weeks. Local administration of propolis allowed for better deposition of connective tissue with a favorable tendency for regeneration compared to the untreated group [60].

2.4.2. Cow's Milk

Another animal-derived substance studied was cow's milk [61]. In a randomized, controlled placebo clinical trial, patients with grade 1 or 2 ulcers participated. In the experimental group, 20% cow's milk ointment was applied topically to the wounds once a day for two weeks. Both groups (experimental and placebo) received standard wound care. The percentage change in ulcer size was recorded in both groups. The percentage reduction in wound size was significantly higher in the experimental group compared to the control group. Moreover, a significantly higher rate of complete healing of the ulcer was observed in this group.

2.5. Ozone Therapy

Ozone therapy (OT) is a non-pharmacological method that involves the use of an ozone-oxygen mixture and materials treated with it for medical purposes. The application

of ozone therapy allows for faster clinical effects, which result from the specific biological action of ozone. Ozone exhibits a priority reaction with unsaturated fatty acids, free amino acids, amino acids in peptide bonds, and nicotinamide. OT improves cellular oxygen utilization processes, possesses bactericidal, fungicidal, and virucidal properties, and stimulates the antioxidant defense system. Small doses of ozone stimulate the immune functions of the body, while high doses suppress them [62]. Patients can receive ozone through the use of ozonized oils, such as ozonized sunflower oil or olive oil [63]. Studies have been conducted using a spray preparation containing ozonized vegetable oil and α-bisabolol. It was compared to a control cream (containing vitamin A, E, talc, and zinc oxide), and its effectiveness was evaluated on days 0, 7, 14, and 30. At the end of the therapy, the percentage of patients with complete healing of the ulcer was higher when using ozonized oil and α-bisabolol (25% vs. 0%). Additionally, a significant and progressive reduction in wound size was observed on subsequent treatment days [64]. This is a promising therapeutic option that can contribute significantly as an adjunct therapy for ulcers. However, the number of studies confirming its effectiveness and safety is currently very limited.

2.6. Nantechnology for the Skincare Needs of Diabetics

Nanotechnology is an emerging field that focuses on the development and study of materials with unique properties at the nanoscale dimension. The distinctive properties of nanocarriers allow for better transport and controlled release of drugs to the wound surface compared to conventional dressings. This advantage arises from the versatility and potential changes in physicochemical properties such as hydrophobicity, size, surface functionalization of biomaterials, shape, surface charge, and colloidal stability. Due to these unique physicochemical and biological properties, the application of nanotechnology has gained popularity and increased demand for its use in the biomedical and pharmaceutical sectors [65].

In addition to nanocarriers, nanometals are obtained for the needs of the cosmetics industry. The most important ones are nanosilver, nanogold, nanocopper, and nanoplatinum. Silver plays a significant role in medicine, as it possesses antibacterial and immunostimulatory properties. In the context of wound healing, the therapeutic strategy aims to remove necrotic tissue and enhance defense mechanisms. This can be achieved through the use of dressings with silver cations or other preparations containing nanosilver. Silver ions do not exhibit toxicity towards human cells, but they inhibit bacterial respiration, interfere with electron transfer, and damage replication by binding to bacterial DNA [65]. Studies confirm that local administration of an AgNPs solution (silver concentration = 1.2 mg/mL) with a 24 h repetition for 12 days significantly influences wound healing. Regular use of a solution containing silver nanoparticles leads to improvement in less than 2 months [66].

The action of copper in medicine is directed, among other things, towards supporting wound healing due to its ability to induce endothelial growth factor, angiogenesis, expression, and stabilization of keratin and collagen. Copper ions, either alone or in complexes, exhibit strong antibacterial, antifungal, and antiviral effects [67]. As an essential trace element, copper is involved in numerous physiological and metabolic processes in humans, including wound healing. This is because copper acts as a cofactor for copper-dependent enzymes and polysaccharides such as lysyl oxidase, glycosaminoglycans, and metalloproteinases, which are necessary for the reconstruction of the epithelium and extracellular matrix proteins. Moreover, it has been shown that copper stimulates angiogenesis and modulates integrin expression by keratinocytes. Copper-impregnated products have a broad spectrum of antibacterial and antifungal activity, which is why the idea of creating socks impregnated with copper oxide was conceived, especially for diabetic patients. The in situ release of copper ions from dressings on wounds induces factors involved in angiogenesis, skin regeneration, and wound healing [68]. It is hypothesized that, besides acting as a biocide to reduce the risk of infection in diabetic foot ulcers, copper ions improve the overall skin condition by inducing angiogenesis and promoting keratin and collagen

expression and stabilization. Copper's ability to regenerate skin reduces the risk of cracks and secondary infections [68].

2.7. Stem Cells

An innovation in the treatment of diabetic foot ulcers is the use of stem cells. The study by Sun et al. aimed to evaluate the effectiveness of stem cells in treating diabetic foot ulcers [69]. The review summarized results that included the rate of ulcer or wound healing, amputation rate, new blood vessels, and other indicators. The study included a total of 14 trials with 683 participants. The meta-analysis conducted by Sun et al. demonstrated that stem cell therapy was more effective than conventional therapy in terms of the ulcer or wound healing rate, improvement of lower limb ischemia, pain-free walking distance, and resting pain score. Importantly, the amputation rate was significantly reduced. These results clearly indicate that this direction is an important and promising avenue for research in therapeutic approaches dedicated to diabetic patients.

3. Limitations

A limitation of this review is that the use of all these ingredients was brief, which may not fully capture the long-term effects of these interventions on diabetic neuropathy progression. The main risk factors for diabetic foot are the duration of diabetes and poor glycemic control. Patients should be informed that the effectiveness of active ingredients depends on rigorous glycemic control and may also be reduced in patients with a longer duration of DM. The indicated ingredients and natural raw materials added to cosmetic products can be used by people who do not yet have skin lesions involving deeper tissues that require a doctor's supervision. In the case of ulcerative lesions, some of the ingredients described here may even cause clinical deterioration. Therefore, a patient with full-blown diabetic foot syndrome should use the care and treatment products indicated by medical personnel and, if in any doubt, consult a doctor or pharmacist.

4. Conclusions

Basic scientific research and clinical studies on forms of treatment for skin lesions in patients with diabetic foot syndrome are constantly being conducted. New active ingredients are being introduced, including plant extracts, biotechnology-derived, and zoonotic products, as well as new physicochemical forms of proposed foot skincare formulations. However, attention should be paid to the continuous education of patients regarding behaviors aimed at the prevention of changes affecting the skin and deeper tissues.

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