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REVIEW ARTICLE

The Effects of Topical Applications of *Momordica charantia* Extract on Wound Healing: A Comprehensive Review

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SUMMARY

A wound is the event of deterioration of the integrity of soft tissue. The intricate tissue restoration process during wound healing involves cellular and molecular activities. Wound healing includes three phases: hemostasis and inflammatory phase, proliferation phase, and remodeling phase. Diabetes mellitus (DM), an endocrine system disease, occurs due to the absence of insulin or resistance to the effect of insulin. Problems with angiogenesis, immunity, and risk of infection make diabetic wound care difficult. Various studies have been carried out to increase wound healing in diabetes and skin wounds, and the use of herbal products in this direction is increasing. Momordica charantia (MC) is well-known for its ability to treat diabetes and repair wounds. MC is a plant widely grown in the world and in our country. It is a used both in the pharmaceutical industry and as a nutrient. MC, a member of the Cucurbitaceae family, is the scientific name for bitter gourd. Sterols, triterpenoids, polypeptides, saponins, flavonoids, and alkaloids are present in MC. Phytochemical studies have shown that bioactive components have antidiabetic, antioxidant, antiviral, antimicrobial, anti-inflammatory, antitumor, hypolipidemic, immunomodulatory, and wound-healing activities. Studies have shown that MC extract increases epithelialization, neovascularization and fibroblast proliferation in wounds and accelerates wound healing by suppressing inflammation. It is thought that the topical application of the extract of the MC plant can accelerate wound healing in skin and diabetic wounds and help treatment.

Key Words: *Momordica charantia, skin wound, diabetic wound, topical application.*

Momordica charantia Ekstraktının Topikal Uygulamalarının Yara İyileşmesi Üzerindeki Etkileri: Kapsamlı Bir Derleme

ÖZ

Yara, yumuşak dokunun bütünlüğünün bozulması olayıdır. Yara iyileşmesi, dokunun onarılması için hücresel ve biyokimyasal olayları içeren karmaşık bir süreçtir. Yara iyileşmesi, hemostaz ve inflamatuar faz, proliferasyon fazı ve yeniden olgunlaşma fazı olmak üzere üç evreden oluşmaktadır. Bir endokrin sistem hastalığı olan diabetes mellitus (DM) insülin yokluğuna veya insülinin etkisine olan dirence bağlı olarak ortaya çıkmaktadır. Anjiyogenez, bağışıklık ve enfeksiyon riski ile ilgili sorunlar diyabetik yara bakımını zorlaştırmaktadır. Diyabette ve deri yaralarında yara iyileşmesini arttırmak için çeşitli çalışmalar yapılmakta ve bu yönde bitkisel ürünlerin kullanımı giderek artmaktadır. Momordica charantia (MC), diyabeti tedavi etme ve yaraları onarma becerisiyle tanınır. MC dünyada ve ülkemizde yaygın olarak yetiştirilen bir bitkidir. Hem ilaç sektöründe hem de besin maddesi olarak kullanılmaktadır. Cucurbitaceae familyasının bir üyesi olan MC, acı kabakların bilimsel adıdır. MC'de steroller, triterpenoitler, polipeptitler, saponinler, flavonoitler ve alkaloitler bulunur. Yapılan fitokimyasal araştırmalar, bu bitkideki biyoaktif bileşenlerin; antidiyabetik, antioksidan, antiviral, antimikrobiyal, antiinflamatuar, antitümör, hipolipidemik, immunomodülatör ve yara iyileştirici aktivitelerinin olduğunu göstermiştir. Yapılan çalışmalar MC ekstresi uygulanan yaralarda epitelizasyonun, neovaskülerizasyonun ve fibroblast proliferasyonunun arttığını ve inflamasyonun baskılanarak yara iyileşmesinin hızlandığını göstermiştir. MC bitkisinin ekstresinin topikal uygulamasının deri yaralarında ve diyabetik yaralarda yara iyileşmesini hızlandırabileceği, tedaviye yardımcı olabileceği düşünülmektedir.

Anahtar Kelimeler: *Momordica charantia, deri yarası, diyabetik yara, topikal uygulama.*

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INTRODUCTION

A wound is an event in which the integrity of soft tissue is disrupted (Pekbilir, 1990). Accidental trauma is a frequent cause of skin wounds. The complex wound-healing process involves biochemical mechanisms (Sagástegui-Guarniz et al., 2021). Hemostasis, inflammatory response, proliferation, and remodeling are the stages of wound healing. The healing period for acute wounds is usually 5-10 days but can take up to a month. These types of wounds are generally skin, muscle, nerve, and tendon injuries caused by surgical incisions, aseptic wounds, and open or closed fractures (Durmuş & Başa, 2018). Infections lead to complications during the recovery period. The tissue's capacity to heal itself, the size and type of the wound, and the general condition of the tissue are important factors in wound healing (Sagástegui-Guarniz et al., 2021). If wound healing is disturbed during the inflammatory phase, healing is delayed. Oxygen plays an important role in wound healing as it is necessary for collagen synthesis and fibroblast migration. Hypoxia, diabetes, arterial disease, malnutrition, and steroid use cause chronic wound healing. Chronic wounds pose serious problems in veterinary medicine (Durmuş & Başa, 2018).

The most crucial complication of diabetes is the deterioration of wound healing processes (Hussan, Teoh, Muhamad, Mazlan, & Latiff, 2014). The cause of non-healing wounds in diabetes depends on many factors. The first metabolic event that occurs in diabetes is decreased oxygenation of the scar tissue and a delay in tissue mend and regeneration due to constriction of the arteries in the wound from hyperglycemia. In the later stages, perception of sensation is lost, and defense against infections is weakened as the peripheral nerves and immune system are damaged by chronic hyperglycemia (Singh, Garcia-Gomez, Gudehithlu, & Singh, 2017). Numerous studies are being done to enhance wound healing in diabetics, and more herbal medications are being used (Hussan et al, 2014).

Because of the limited efficacy, low availability, high cost, and some side effects of wound-healing agents, plants are widely used in the general population. According to numerous researchers, various plant extracts are effective in the wound healing (Sagástegui-Guarniz et al., 2021). Today, phytotherapy, which benefits from the healing effects of plants, has become widespread, and the use of natural remedies has come to the fore (Prisăcaru et al., 2013). Herbal medicines can be used for wound healing. Numerous herbal preparations such as MC, have been proven in studies to have wound-healing effects (Hussan et al., 2014). Additional names for MC include "bitter melon" or "bitter gourd" due to its bitter flavor, which becomes more apparent as the fruit ripens. MC grows widely in Asia, India, East Africa and South America, and in the west of the Marmara Region and the Aegean Region in Turkey. It is a climbing plant from the Cucurbitaceae family that can generally grow up to 5 meters tall. It is a tropical perennial plant (Joseph & Jini, 2013; Kısacık & Güneş, 2017).

It is thought that MC plant can be used in veterinary medicine to accelerate wound healing in skin and diabetic wounds.

Momordica charantia

MC is a plant grown both for consumption as food and for use in the pharmaceutical industry. Researches based on its pharmacological properties date back to the 16th century (Kısacık & Güneş, 2017).

Botanical Features of *Momordica charantia*

A member of the Cucurbitaceae family is the bitter gourd and is called MC (Kısacık & Güneş, 2017). It is known as 'Bitter Melon' in English (Ekizce, 2019). It is an annual, tropical plant whose thin leaves grow in the form of ivy. Momordica means 'bite' in Latin. It has various names like bitter melon, balsam pear, and bitter gourd. It is known that the plant, whose homeland is India, grows in the tropical regions of Asia, South America, and Africa, and in our country, in the west of the Marmara Region and the Aegean Region (Kısacık & Güneş, 2017). The leaves of the plant are

4-12 cm in size and have toothed edges. Its fruit is oval and rough. While immature fruits are green, this color becomes orange-yellow as they mature. The fruit is fleshy and has 3 parts, and as the fruit matures, it folds back and opens. When a fruit is opened, red seeds are seen within. It bears bitter fruit (Ekizce, 2019).

Chemical Composition and Biological Activities of *Momordica charantia*

Despite the bitter taste of the MC fruit, it is popular many locations around the globe. In many regions it is also used as herbal medicine. Fruits, leaves, roots of the plant; it is used by people for diseases such as toothache, diarrhea, boils, constipation, gout, jaundice and rheumatism. It is also known to be used as an anthelmintic. It is known that bitter gourd tea made from dried plant slices is quite common in some regions. Triterpenoids, alkaloids, polypeptides, flavonoids, saponins, and sterols are all present in MC. Phytochemical studies have shown that bioactive components have anti-inflammatory, antidiabetic, antioxidant, antiviral, antimicrobial, antitumor, hypolipidemic, immunomodulatory, and wound healing activities (Jia, Shen, Zhang, & Xie, 2017).

Bitter melon plant contains; momordicin, momorcharin, momordin, charantin, polypeptide-p, cucurbitacin B, linolenic acid (constitutes 60% of the seed oil of the plant), iron, calcium, magnesium, phosphorus, β-carotene, potassium, magnesium and vitamin A (Kısacık & Güneş, 2017). Except for methionine, lysine and cysteine, MC contains most of the essential amino acids (Yuwai, Rao, Kaluwin, Jones, & Rivett, 1991).

Phenolic compounds like gentisic acid, caffeic acid, benzoic acid, chlorogenic acid, tannic acid, and gallic acid are found in the fruits of MC. Tocopherol, catechin, and epicatechin in MC exhibit antioxidant properties. The seed membranes in ripe fruits are a source of lycopene (Ekizce, 2019). Phenolic compounds are metabolic aids that have a structure similar to benzene. They are tannins, coumarins, lignins, lignans, flavonoids, common phenols, and phenolic acids. They have antioxidant, antimicrobial, and anticancer effects (Faith Oyelere et al., 2022).

The predominant terpenoids in MC are momordicin, and charantin. Terpenoids, the largest group of secondary metabolites, are found mostly in lower invertebrates and plants. They have anti-cancer, anti-inflammatory, plant growth-promoting and cardiovascular disease-reducing effects (Faith Oyelere et al., 2022).

A combination of 5,25-stigmadiene-3β-ol-glycoside and β-sitosterol-β-D-glucoside makes up charantin (Sharma, Sharma, & Kohli, 2010). Chloroform and dichloromethane are less polar solvents in which charantin is readily soluble, due to its steroidal structure in the aglycone part. Due to charantin's glucoside structure, it can also dissolve in solvents such as ethanol and methanol (Türkoğlu, 2018). Active substances with hypoglycemic characteristics include charantin and polypeptide-p. Additionally, soluble pectins, 5-hydroxytryptamine, saponins, and steroidal glycosides are present in the MC plant (Hussan et al., 2014). MC's leaves, stems, fruits, and roots contain saponins. Cucurbitacins, alkyl-type saponins, are a group of mainly tetracyclic, triterpenic plant substances with a bitter taste and high oxygen content. Studies have shown that saponins have antidiabetic and hypoglycemic activities (Jia et al., 2017).

Several phytosterols have been identified in MC, such as β-sitosterol, campesterol, 25,26-dihydroesterol, stigmasterol, daucosterol, clerosterol, and diosgenin. Low amounts of a group of sterols called phytosterols can be found in plants. Phytosterols, which may contain up to 30 carbon atoms in their structure, have various effects such as anticholesterol, anticancer, immunomodulator, skin protector, antioxidant, hypocholesterolemic, and anti-inflammatory (Faith Oyelere et al., 2022).

Polysaccharides are classified as heteropolysaccharides and consist of glucose, galactose, arabinose, mannose, and rhamnose but their polysaccharide content can be affected by different conditions. By preventing the nuclear factor kappa B (NF-κB) signaling pathway, polysaccharides, one of the key bioactive components of MC fruit, are known to reduce oxidative stress, inflammation, apoptosis, and hyperlipidemia during myocardial infarction. They also have several other bioactivities, including antioxidant, immune-boosting, antidiabetic, neuroprotective, antitumor, and antimicrobial properties. Additionally, investigations have demonstrated that it boosts the synthesis of volatile fatty acids, modifies the rumen fermentation pathway, and impacts the population of cellulolytic bacteria (Jia et al., 2017).

Proteins and peptides the primarily functional compounds, are found in the fruits and seeds of MC. Many protein and peptide species such as lectin, anti-HIV protein, and α- β- γ- δ- ε-momorcharin have been extracted from different parts of MC and have a cancer-fighting, immune-suppressing, and antimicrobial effect. It is also reported to have properties such as RNA N-glycosidase activity, DNAase-like activity, polyalkylene glycol (PAG) activity, superoxide dismutase activity and phospholipase activity. Plant cells release a specific kind of hypoglycemic peptide that binds to carbohydrates called polypeptide-p, which is crucial for cell adhesion and recognition processes (Jia et al., 2017).

Wound Healing

The skin is the most elastic organ surrounding the body of all vertebrates and occupies the most significant space. Derived from the Latin word "cutis," the skin is referred to in the literature as "cutaneous." Histologically, three layers comprise the skin: the epidermis, dermis, and subcutis. The epidermis is the skin's topmost layer and consists of the stratum corneum, stratum basale, stratum spinosum, stratum granulosum, and stratum lucidum, in that order (Yumuşak, 2012). The epidermis acts as a waterproof barrier. Keratinocytes are the most abundant cells in the epidermis (about 90%). In addition, there are melanocytes, Langerhans cells, and Merkel cells (Nourian Dehkordi, Mirahmadi Babaheydari, Chehelgerdi, & Raeisi Dehkordi, 2019). The dermis layer is under the epidermis layer and provides elasticity to the skin. This layer, which contains blood and hair follicles, sweat glands, sebaceous glands, lymphatic vessels, and sensory nerves, is also responsible for supplying cells in the epidermal layer by diffusion through capillaries. Two layers, the stratum papillare and the stratum reticulare, comprise the dermis. The stratum papillare is a layer of connective tissue rich in fibrocytes and fibroblasts and contains sweat glands, sebaceous glands, and hair follicles. The stratum reticulare is the layer where the sweat glands and hair follicles are interwoven with the stratum papillare. The subcutis, which lies beneath the dermis, is the lowest layer. Subcutis is the subcutaneous connective tissue and contains fat cells, fibrocytes, fibroblasts, and dense collagen bundles. In this layer, which includes dense vascular and nervous structures, connective tissue cells are arranged parallel (Yumuşak, 2012).

The term "wound" refers to the deterioration of the skin's or mucosa's tissue integrity for various causes, such as illnesses or physical damage. Wounds in which the integrity of the skin tissue is not completely disrupted due to crush, sprain or dislocation are called 'closed wounds'. Wounds in which the integrity of the skin is completely disrupted due to cuts, stings, and punctures are called 'open wounds' (Baktır, 2019).

Normalization of cellular, biochemical, and systemic processes defines wound healing and the deterioration caused by trauma with the formation of new tissue. Fibroblast growth factor (FGF), transforming growth factor β (TGF-β), epidermal growth factor (EGF), granulocyte-macrophage colony-stimulating killing factor (GM-CSF), insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), tumor necrosis factor-alpha (TNF- α) and interleukins (IL-1 and IL-2), are a few examples of cytokines and growth factors that support the healing of wounds (Baktır, 2019).

Neutrophil granulocytes are the first cells to attack the area during the wound healing, and they play a role in both antimicrobial protection and the production of free oxygen radicals. The two main variables that slow the healing of wounds are inflammation and oxidative stress. Therefore, local antioxidant activity may be effective in the healing process (Chen, Liou, Tzeng, Lee, & Liu, 2013; Yadav, Singh, Yadav, & Verma, 2018).

During wound healing, excessive collagen or granulation tissue development may result in an atypical scar. TGF-β regulates scar development on its own. The three TGF-β isoforms are responsible for this. TGF-β3, which has been demonstrated to have anti-scar effects, balances out TGF-β2, which is implicated in producing scars. Thus, abnormal scar formation is prevented (Hussan et al., 2014).

Stages of Wound Healing

There are three stages of wound healing: Hemostasis and inflammation, proliferation, remodeling and maturation (Baktır, 2019).

Phase 1: Hemostasis and inflammation

As a result of the injury, bleeding occurs due to the destruction of vessels and tissues (Çiçek, 2015). Inflammation happens right after an injury and protects against bacterial contamination by cell growth. The coagulation system is initially activated to stop the bleeding (hemostasis) in the wound region (Yazıcıoğlu, 2009). The activation, adhesion, and aggregation process begins with platelets. Platelets bind to selectin and integrin receptors on extracellular matrix proteins. Later, with platelet degranulation, many factors (thromboxanes, prostaglandins, serotonin, fibrinogen, fibronectin, Von Willebrand factor, PDGF, EGF, and TGF-β1) in the granules are released into the environment (Çiçek, 2015). These factors provide both the formation of fibrin clots and the regulation of cellular response. Neutrophils are the first cells to arrive at the site of a wound (Yazıcıoğlu, 2009). Neutrophils stick to the endothelium once adhesive components close to the wounded tissue on the vascular endothelial surface are activated. Then, neutrophils reach the tissue space by passing through damaged capillaries or the spaces between endothelial cells. Neutrophils are crucial for tissue debridement and the prevention of infections. Since neutrophils produce various growth factors and proteases, they also show their effects by participating in the healing of wounds. Circulating monocytes quickly transform into adult macrophages as they enter the tissue area (Baltzis, Eleftheriadou, & Veves, 2014). After 2-3 days, the number of neutrophils decreases and macrophages become the most abundant cell population in the wound. Macrophages are responsible for clearing the impacted area of dead neutrophils, foreign objects, and injured tissue (Yazıcıoğlu, 2009). T-lymphocytes enter the location of the wound during at the late stages of inflammation and have a modulatory effect on tissue remodeling (Baltzis et al., 2014).

Phase 2: Proliferation

This stage starts the second day following the injury and lasts up to three weeks. Fibroblasts begin to produce new extracellular matrix and immature type III collagen when they are stimulated by cytokines and growth factors generated by inflammatory cells in the wound area. As collagen accumulates, the wound's resistance to stretching increases rapidly. Epithelial cells derived from the basal layer form a new surface at the edges of the wound. Wound contraction occurs due to the transformation of some of the fibroblasts into myofibroblasts (Baktır, 2019).

Phase 3: Remodeling and Maturation

This stage starts in the third week when the amount of fibroblasts in the wound region declines and collagen production approaches equilibrium. Epithelialization is complete. Remodeling stage is the remodeling of collagen fibers. Type III collagen, which is soft and gelatinous, transforms into tighter type I collagen. Some of the contractions also occur at this stage. Thus, the wound regains 80-95% of its initial strength at the end of 6 weeks. This phase, in which scar tissue is formed, lasts between 6 and 24 months (Baktır, 2019).

Studies have revealed that the typical wound healing phases are not entirely followed by diabetic wounds; diabetes causes ulcers and prolongs the healing process (Liu, Liu, Deng, Li, & Nie, 2021).

Diabetic Wound

DM, an endocrine system disease, occurs due to the absence of insulin or resistance to the effect of insulin. DM characterized by carbohydrate, protein, and fat metabolism disorders, is frequently observed in cats and dogs. DM can be asymptomatic, but usually clinical signs of DM, such as polyphagia, weight loss, polyuria, polydipsia, and weakness, are typically present. Due to metabolic abnormalities, the disease has a wide range of organ and systemic effects (Şimşek & İçen, 2008).

According to the latest classification system, there are four types of diabetes (Şahinduran & Vurkaç, 2018).

Hyperglycemia and the death of pancreatic beta cells are characteristics of type I diabetes (Wang, Bai, Wu, Li, Xie, Ji, & Gao, 2023). In this type of diabetes, the cells are destroyed by antibodies against ß-cells in the pancreatic islets of Langerhans. Type I diabetes is most common in dogs. In mild cases, the number and size of ß-cells are reduced. In severe cases, the damage is so severe that the cells are unrecognizable. It was observed that antibodies against ß-cells developed in half of the dogs with diabetes, and autoimmune damage occurred (Şahinduran & Vurkaç, 2018).

While the pancreas is macroscopically normal in type II diabetes, microscopic degenerative lesions are observed ß-cells in the pancreatic islets of Langerhans. II diabetes is most common in cats. Amyloid deposition in the islets of Langerhans with microscopic changes is observed in most cats with diabetes and is considered a characteristic finding for type II diabetes. Insulin resistance develops in target tissues with pancreatic secretion of abnormal insulin. Although insulin secretion is very high in the early stages of the disease, blood sugar is among the reference values. The failure to secrete insulin to maintain a healthy blood glucose level results in hyperglycemia in the later phases. As a result of hyperglycemia, loss of function in ß-cells occurs and an adequate amount of inability to secrete insulin. Thus, insulin deficiency and an increase in insulin release can be observed in this type of diabetes (Şahinduran & Vurkaç, 2018).

Type III gestational diabetes is typically seen in middle-aged dogs and during the second half of pregnancy. If diabetes continues to be observed after pregnancy or diestrus has ended, another disease other than gestational diabetes should be suspected and diagnosed. Gestational diabetes in dogs is rare, and a study has shown that diabetes cases are higher in pregnancies in winter (Şahinduran & Vurkaç, 2018).

Type IV secondary diabetes mellitus is a form of secondary diabetes that arises from other conditions. Endocrine abnormalities such as hyperadrenocorticism and progesterone-acting growth hormone problems are the most common causes of type IV diabetes in dogs. In addition, type IV diabetes is encountered in approximately 15% of acute pancreatitis cases (Şahinduran & Vurkaç, 2018).

The wound healing process is more extended in diabetic patients as many factors are negatively affected compared to routine wound healing. In routine wound healing, TNF-α level reaches its maximum level by macrophages 12-24 hours after wound formation. After the completion of the proliferative stage, TNF-α decreases to the basal level. Due to the increased TNF-α level in diabetic wounds, fibroblast proliferation, angiogenesis, cell proliferation, and cell migration are impaired. As the cytokines TNF-α and IL-6 increase, the amount of IL-10 decreases, which leads to a prolongation of the leukocyte infiltration time (Ekizce, 2019). There is a decrease in resistance to microorganisms in diabetic animals. Diseases such as pus cystitis, prostatitis, bronchopneumonia, and dermatitis can be observed chronically and recurrently due to dysfunctions in leukocytes. Hepatomegaly may develop due to fatty liver. Chronic kidney diseases, gangrene, and blindness may develop due to microangiopathy (Özmen & Topsakal, 2019).

In diabetic wounds, blood vessels are damaged, and their angiogenic capacity decreases, resulting in inadequate nutrition and low oxygenation in wounds. Intense use of oxygen by cells during inflammation causes hypoxia. Due to hypoxia, the concentrations of free oxygen radicals increase further, delaying the wound healing time. The first affected cells in DM are neurons (Dong, Wu, & Tian, 2023). Due to hyperglycemia, loss of function occurs in the schwann cells and myelin sheaths in the nervous system, resulting in neuropathy in the form of numbness, pain or atrophy. The loss of function observed in the sebaceous and sweat glands due to autonomic neuropathy causes the development of anhidrosis, drying, peeling, and hyperkeratosis on the plantar surface of the foot as a result of the deterioration of thermoregulation in the foot. Deformities in the foot and restricted joint movements result in excessive pressure on the plantar surface of the foot. If such long-term forces are applied continuously to a particular area, ulceration develops due to focal tissue ischemia, local inflammatory response, and tissue destruction. Foot ulcers, which are a severe diabetic complication, can grow at a rate of 15% throughout the life of diabetic patients and are essential because they may require amputation in 7-20% of cases (Ekim & Ekim, 2016).

Continuous hyperglycemia in diabetic patients affects wound-healing processes in various ways. Hypercoagulation and decreased skin functions are observed in the hemostasis phase. While some growth factors and irregularities in inflammatory factors in the inflammatory phase cause chronic inflammatory reactions, a predisposition to diabetic scar formation occurs due to the decrease in neutrophil concentration. Decreased migration and proliferation of keratinocytes due to prolonged hyperglycemia causes insufficient wound re-epithelialization. One of the reasons for poor wound healing in diabetic wounds is the different expression of the extracellular matrix formed by fibroblasts (Liu et al., 2021).

Problems in angiogenesis, immunity, and risk of infection make diabetic wound care difficult (Hussan et al., 2014). In addition, any wound in the lower extremities can become ulcers as they become susceptible to infections (Liu et al., 2021). Wounds usually require debridement, in some cases amputation may be performed. Various studies are being conducted to improve wound healing in diabetics, and the usage of herbal medications in this direction is growing. MC fruit extract is also known for its wound healing and antidiabetic properties (Hussan et al., 2014).

Topical Applications in Wound Healing

Vascular endothelial growth factor (VEGF), TGF-β, PDGF, IGF, and cytokines regulate the wound healing. In response to injury, platelets, fibroblasts, and macrophages produce TGF- β. This factor, which participates in every step of wound healing, speeds up the healing process by enhancing monosaccharide conversion to macrophages and promoting fibroblast contraction. TGF- β affects the chemotaxis of granulation tissue, activates fibroblasts and stimulates collagen, fibronectin synthesis, and extracellular matrix accumulation. A crucial component of the extracellular matrix is collagen. Collagen helps wound healing by binding to fibronectin (creates the environment for fibroblast proliferation and increases the elasticity of granulation tissue) and platelets. Excessive collagen or granulation tissue production, on the other hand, might result in aberrant scar formation. TGF- β regulates not normal scar formation by producing tissue inhibitors of metalloprotease and promoting matrix metalloproteinase production. Because of the three TGF- β isoforms' activity. TGF- β may also speed up collagen and total protein depositing, which could explain why MC-treated animals heal faster (Hussan et al., 2014).

Fibroblasts produce an extracellular matrix (ECM) at the time wound healing that meets the edges of the wounds. Wound contraction, re-epithelialization, and angiogenesis are required for complete wound closure. Angiogenesis ensures that nutrients reach the granulation tissue constituents (Pişkin et al., 2014). Protein content of injured tissue represents protein levels and cellular proliferation (Teoh et al., 2009). Any protein can affect the intracellular mechanism of tropocollagen synthesis or the extracellular deposition mechanism and organization of collagen fibers, thereby altering the repair process (Prashanthi, Mohan, & Siva, 2012).

Wound contraction happens due to a centripetal move of the wound margins to close a full-thickness wound. The increased pace of wound contraction due to the activation of IL-8, α-chemokine, and various growth factors, or the inhibition of proinflammatory indicators such as IL-1β and TNF-α, that influencing the activity and recruiting of different inflammatory cells. Increased quantities of hydroxyproline, the primary component of the collagen protein, are observed in the granulation tissue during the wound healing process. Proline and hydroxyproline are crucial for the integrity of collagen. The primary element of extracellular tissue, which provides strength and support, is collagen. Collagen deterioration results in the release of hydroxyproline and related peptides. It is possible to use the measurement of hydroxyproline as a collagen turnover index. Hexosamine is an essential substrate for collagen synthesis. At the beginning of wound healing, it is known to rise, then fall. Similar to previous results, a rise in uronic acid concentrations in animals suggests enhanced glycosaminoglycan production. The maximum force a material can withstand per unit of area is known as its 'tensile strength'. The higher collagen concentration and fiber stability could both be contribute factors to the rise in tensile strength. The collagen components that were produced at the site of the wound area cross-linked to create fibers. Tensile strength results from collagen remodeling and the formation of enduring intra- and intermolecular cross-links (Prashanthi et al., 2012).

Free radicals can be defined as unstable, reactive molecules. Free radicals occur as a result of biochemical reactions in the metabolism of cells, produced by endogenous and exogenous sources. When the production of free radicals increases, and antioxidants are insufficient or deactivated, 'oxidative stress' occurs. One of the important lipid peroxidation markers is malondialdehyde (MDA) and is an indicator of oxidative damage in tissues. MDA is formed by the breakdown of unsaturated fatty acids containing three or more double bonds. Superoxide dismutase (SOD) is the most effective antioxidant and is known to be found in all cells that use oxygen. Glutathione reductase (the antioxidant defense system enzyme) catalyzes the reduction of oxidized glutathione to decreased glutathione in its presence of Nicotinamide adenine dinucleotide phosphate (NADPH). With the decrease of glutathione reductase activity, the protection of cells from oxidative damage decreases (Ekizce, 2019).

The MC antioxidant activity has been linked to a faster rate of wound healing. Low reactive oxygen species and oxidative stress are necessary for wound healing physiology. Thus, excessive exposure to oxidative stress results in inadequate wound healing (Sagástegui-Guarniz et al., 2021).

Pişkin et al. (2014) conducted a study has shown that on 28 New Zealand rabbits (in the group in which MC was applied twice a day) compared to the other groups (dexpanthenol, nitrofurazone applied and control group), the rate of macroscopic wound healing and re-epithelialization rate was higher at the end of the 28th day. Under a microscope, the average ratio of epidermis to papillary dermis, the average number of fibroblasts, and the fraction of fibroblasts and collagen fibers in the reticular dermis were higher than the other groups. The MC group also had a thicker epidermis, more collagen bundles, capillaries, and macrophages than the other groups. They demonstrated that the MC oil extract increased epithelialization, neovascularization and fibroblast proliferation and accelerated wound healing by suppressing inflammation. In addition, the normal epithelium of the rabbit skin after treatment indicates that MC extract protects the skin against oxidative damage.

Teoh et al. (2009), observed that MC application shorter wound healing time in the group in which they induced DM, while MC application didn't make a significant difference in the group in which they didn't induce DM. On the 5th day, they observed a rise in the quantity of infiltrating cells and a well-formed epidermis layer in the MC-applied group compared to the other groups. They showed that the protein content was higher in the group with DM and MC extract was used compared to the different groups. High protein concentration, MC extract might encourage cellular migration and proliferation. Although there was no visible difference in wound healing, the presence of more granulation tissue in the non-DM MC extract group than in the control group raises the possibility that it may aid the healing process. The study showed that MC extract was beneficial in the diabetic wound healing process.

Prasad et al. (2006) showed that in the MC powder ointment group supported wound healing activity by inducing epithelialization, fibrosis, and angiogenesis. In addition, they found a higher level of hydroxyproline in the group using MC powder ointment than in the other groups.

Hussan et al. (2014) showed that in diabetic groups compared to the control group, incomplete epithelialization and epidermis and dermis layers did not intertwine. However, it was observed that these abnormalities were less in the MC ointment-applied group than in the other diabetic groups. In addition, the epidermis in the MC ointment applied group exhibited full-thickness epithelialization with regular collagen fibers, like the control group. On day 5, diabetic groups had a slower rate of wound closure than the control group. The group that received no treatment had the lowest closure rate. Compared to the other diabetes groups, the group receiving MC ointment on day 10 had the highest wound closure rate. They claimed increased TGF-β expression was related to a faster wound closure rate. The diabetic group who had not received treatment had low TGF-β expression and slow wound healing. Since excessive scar formation was not observed in the MC ointment group, all isoforms of TGF-β might play a role in maintaining its function. The fact that MC-treated animals had higher total protein levels shows that MC can increase the number of cells in scar tissues through migration or proliferation. Through increased TGF-β expression, topical administration of MC fruit extract sped up wound healing in animals with DM. The MC ointment-treated group has a higher wound closure rate, TGF-β expression, and better wound histological characteristics, compared to the MC powder-treated group.

Satar et al. (2013), in their research on New Zealand rabbits, showed that the oily extraction form of MC caused a decrease in the epithelialization time in the wound area. During their study, they performed complete blood counts in rabbits and did not detect any pathology. They argued that this data indicates that topical application of MC does not cause any systemic abnormalities. Animals treated with the oily extraction form of MC had a significant reduction in wound area and healing time compared to the other groups (MC powder, extra virgin olive oil, and control groups).

Prashanthi et al. (2012), in their study on albino rats, showed that wound contraction was faster in groups where MC extract was applied compared to the control group, thus inducing early healing. It was revealed in their study that the MC outer layer extract had higher hydroxyproline and protein content in the granulation tissue compared to other groups (seed extract and the control group). Hexosamine and uronic acid concentration was higher than the control group in the granulation tissue. Skin tissues healed in the MC-treated groups had considerably more tensile strength than those in the control group.

Ekizce (2019), according to his study in rats, found the most severe inflammation findings and changes characterized by fibroblastic activity and neovascularization related to delayed healing in the diabetic group without MC. Significant wound healing was observed compared to the group that did not receive MC. While there was no significantly differ from the wound group and the groups in which MC was applied to the wound in terms of MDA levels, a significant increase was detected in the diabetes group. It was determined that the MDA value, which increased in the group treated with MC by creating diabetes, decreased significantly at the end of the treatment compared to the diabetic group. Still, the MDA value was higher than in the non-diabetic groups. There was no discernible difference between the groups that had MC treatment and the wound group in terms of SOD, activities. There was a finding that SOD activity decreased considerably in the diabetic group and an increase was observed in the diabetic group in which potency pomegranate was applied, compared to the diabetic group. Still, the SOD value was discovered to be less than the non-diabetic groups. Regarding glutathione reductase value, when the group treated with MC and the group with diabetes were compared, it was determined that the glutathione reductase value increased considerably in the group treated with MC. It has been shown that there is no effect on blood glucose levels in external application on rats with diabetes and wounds on the skin.

Sagástegui-Guarniz et al. (2021), in their study, demonstrated that MC gel and cream shortened the time of skin wound healing in mice and 1% cream formulation was the most effective. Phytocomponents like steroids, flavonoids, and cucurbit triterpenes, which exhibit antimicrobial and antioxidant activities, have reportedly been linked to the healing process of MC. It has been suggested that the ingredients in MC acetonic extract are more effective than those in the cream formulation. Because of the formulation of these chemicals being lipid-soluble. Aglycone flavonoids are often extracted using less polar solvents like acetone. Acetone is thought to be the optimum solvent for extracting flavonoids from MC.

CONCLUSION

There are no standards in preparing MC fruit extraction, and studies on short-term diabetes are limiting. Although studies show that MC plant has a wound healing effect, more studies are needed on its wound healing mechanism. The MC plant can be used in veterinary medicine for wound healing in skin wounds and diabetic wounds due to its availability, ease of extraction, and lack of any side effects in topical application. Investigations should be conducted into how the active phytochemicals in MC affect the healing of wounds. More research is needed on the mechanism of action of growth factors and cytokines on wound healing. More studies should be on the effects on wound healing among powder, gel and cream formulations.

CONFLICTS OF INTEREST

The authors declare that there is no conflicts of interest.

AUTHOR CONTRIBUTION STATEMENT

The authors SA and MP contributed equally

REFERENCES

Baktır, G. (2020). Wound repair and experimental wound models. *Experimed, 9*(3), 130-137.

Baltzis, D., Eleftheriadou, I., & Veves, A. (2014). Pathogenesis and treatment of impaired wound healing in diabetes mellitus: new insights. *Advances in therapy, 31*, 817-836. doi: 10.1007/s12325-014-0140-x

Chen, W. C., Liou, S. S., Tzeng, T. F., Lee, S. L., Liu, I. M. (2013). Effect of topical application of chlorogenic acid on excision wound healing in rats. *Planta Medica, 79*(8), 616- 621. doi: 10.1055/s-0032-1328364

Çiçek, M. (2015). Deneysel olarak oluşturulan yara modelinde akupunkturun yara iyileşmesi üzerine etkisinin araştırılması (Master's thesis, Sağlık Bilimleri Enstitüsü).

Dong, J., Wu, B. V., & Tian, W. (2023). How to maximize the therapeutic effect of exosomes on skin wounds in diabetes mellitus: Review and discussion. *Frontiers in Endocrinology (Lausanne), 14*, 1146991. doi: 10.3389/fendo.2023.1146991

Durmuş, A. S., & Başa, A. (2018). Evcil hayvanların kronik yaralarında debridement yöntemleri. *FÜ Sag Bil Vet Derg, 32*, 63-67.

Ekim, M., & Ekim, H. (2016). Diyabetik ayak ülserlerinde etiyoloji ve tedavi. *Van Tıp Derg, 23* (2), 235- 241.

Ekizce, E. (2019). Deneysel olarak tip II diyabet oluşturulmuş ratlardaki yara modelinde kudret narı *(Momordica charantia)* meyvesi yağının yara iyileşmesi üzerine etkileri (Master's thesis, Sağlık Bilimleri Enstitüsü).

Faith Oyelere, S., Hezekiah Ajayi, O., Eunice Ayoade, T., Santana Pereira, G., Dayo Owoyemi, B. C., Olaoluwa Ilesanmi, A., & Amos Akinyemi, O. (2022). A detailed review on the phytochemical profiles and anti-diabetic mechanisms of Momordica charantia. *Heliyon, 8*(4), e09253. doi: 10.1016/j.heliyon.2022.e09253

Hussan, F., Teoh, S. L., Muhamad, N., Mazlan, M., & Latiff, A. A. (2014). *Momordica charantia* ointment accelerates diabetic wound healing and enhances transforming growth factor-β expression. *Journal of wound care, 23(8), 400–407.* doi: 10.12968/jowc.2014.23.8.400

Jia, S., Shen, M., Zhang, F., & Xie, J. (2017). Recent Advances in Momordica charantia: Functional Components and Biological Activities. *International journal of molecular sciences, 18(12), 2555.* doi: 10.3390/ijms18122555

Joseph, B., & Jini, D. (2013). Antidiabetic effects of *Momordica charantia* (bitter melon) and its medicinal potency. *Asian pacific journal of tropical disease, 3(2), 93-102.*

Kısacık, Ö. G., & Güneş, Ü. Y. (2017). Yara iyileşmesinde kudret narının etkisi. *Spatula DD, 7*(2), 53- 59.

Liu, Y., Liu, Y., Deng, J., Li, W., & Nie, X. (2021). Fibroblast Growth Factor in Diabetic Foot Ulcer: Progress and Therapeutic Prospects. *Frontiers in endocrinology, 12, 744868.* doi: 10.3389/fendo.2021.744868

Nourian Dehkordi, A., Mirahmadi Babaheydari, F., Chehelgerdi, M., & Raeisi Dehkordi, S. (2019). Skin tissue engineering: wound healing based on stem-cell-based therapeutic strategies. *Stem cell research & therapy, 10*(1), 111. doi: 10.1186/s13287-019-1212-2

Özmen, Ö., & Topsakal, S. (2019). İnsan ve Hayvanlarda Diabetes Mellitus. *Veterinary Journal of Mehmet Akif Ersoy University, 1*(1), 47-57.

Pekbilir, A. (1990). Yara iyileşmesi. *Uludağ Üniversitesi Veteriner Fakültesi Dergisi, 8-9*(1-2-3), 231-240.

Pişkin, A., Altunkaynak, B. Z., Tümentemur, G., Kaplan, S., Yazıcı, Ö. B., & Hökelek, M. (2014). The beneficial effects of *Momordica charantia* (bitter gourd) on wound healing of rabbit skin. *The Journal of dermatological treatment, 25(4), 350–357.* doi: 10.3109/09546634.2012.713459

Prasad, V., Jain, V., Girish, D., & Dorle, A.K. (2006). Wound-healing property of Momordica charantia L. fruit powder. *Journal of Herbal Pharmacotherapy, 6*(3-4), 105- 115. doi: 10.1080/j157v06n03_05

Prashanthi, R., Mohan, N., & Siva, G. V. (2012). Wound healing property of aqueous extract of seed and outer layer of *Momordica charantia* L. on albino rats. *Indian Journal of Science and Technology, 5*(1), 1936-1940.

Prisăcaru, A. I., Andrițoiu, C. V., Andriescu, C., Hăvârneanu, E. C., Popa, M., Motoc, A. G., & Sava, A. (2013). Evaluation of the wound-healing effect of a novel Hypericum perforatum ointment in skin injury. *Romanian journal of morphology and embryology, 54*(4), 1053-1059.

Sagástegui-Guarniz, W. A., Silva-Correa, C. R., Torre, V. E. V, González-Blas, M. V., Sagástegui- Guarniz, W. O., Calderón-Peña, A. A., Aspajo-Villalaz, C. L., Cruzado -Razco, J. L., & Hilario- Vargas, J. (2021). Wound healing by topical application of *Momordica charantia* L. formulations on mice. *Veterinary world, 14*(10), 2699–2704. doi: 10.14202/vetworld.2021.2699-2704

Satar, N. Y. G., Topal, A., & Yanık, K. (2013). Comparison of the effects of bitter melon (Momordica charantia) and gotu kola (Centella asiatica) extracts on healing of open wounds in rabbits. *Kafkas Univ. Vet. Fak. Derg, 19,* 161-166.

Sharma, S., Sharma, M. C., & Kohli, D. V. (2010). Wound healing activity of the ether- chloroform extract of *momordica charantia* fruits in rats. *Digest Journal of Nanomaterials and Biostructures. 5*(1), 123-26.

Singh, R., Garcia-Gomez, I., Gudehithlu, K. P., & Singh, A. K. (2017). Bitter Melon Extract Promotes Granulation Tissue Growth and Angiogenesis in the Diabetic Wound. *Advances in skin & wound care, 30*(1), 16–26. doi: 10.1097/01.ASW.0000504758.86737.76

Şahinduran, Ş., & Vurkaç, N. (2018). Köpeklerde diabetes mellitus. *Mehmet Akif Ersoy Üniversitesi Sağlık Bilimleri Enstitüsü Dergisi, 6*(1), 43-50.

Şimşek, A., & İçen, H. (2008). Kedi ve Köpeklerde Diabetes Mellitus. *Dicle Üniversitesi Veteriner Fakültesi Dergisi,* (1), 23-28.

Teoh, S. L., Latif, A. A., & Das, S. (2009). The effect of topical extract of *momordica charantia* (bitter gourd) on wound healing in nondiabetic rats and in rats with diabetes induced by streptozotocin. *Clinical and Experimental Dermatology. 34*(7), 815-22. doi: 10.1111/j.1365- 2230.2008.03117.x

Türkoğlu, S. (2018). Ticari Kudret Narı Ürünlerinin Antioksidan ve Antidiyabetik Bileşenlerinin Karşılaştırılması (Yüksek lisans tezi, Fen Bilimleri Enstitüsü).

Wang,W., Bai, D., Wu, C., Li, H., Xie, X., Ji, W., & Gao, J. (2023). A Protocol for Constructing a Rat Wound Model of Type 1 Diabetes. *Journal of visualized experiments : JoVE, (192), 10.3791/64914.* doi: 10.3791/64914

Yadav, E., Singh, D., Yadav, P., & Verma, A. (2018). Antioxidant and anti-inflammator properties of Prosopis cineraria based phenolic rich ointment in wound healing. *Biomedicine & pharmacotherapy*. doi: 10.1016/j.biopha.2018.09.180

Yazıcıoğlu, D. (2009). Antikoagüle edilmiş ve diabetik denek hayvanlarında diyot lazerin yara iyileşmesi ve kanama kontrolü üzerine etkilerinin incelenmesi.

Yumuşak, N. (2012). Köpek ve kedilerde deri ve eklenti tümörlerinin patomorfolojisi.

Yuwai, K. E., Rao K. S., Kaluwin C., Jones G. P., & Rivett D. E. (1991). Chemical Composition of *Momordica charantia* L. fruits. *J Agric Food Chem. 39*, 1762–1763.