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Research article

Molecular and Immunological Mechanisms of Channa striata in Diabetic Wound Healing

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ABSTRACT

The prevalence of Diabetes Mellitus is increasing globally, approximately 463 million people in the year 2019, and is predicted to 700 million people by the year 2045, and it has high comorbidity and mortality based on International Diabetes Federation (IDF). The wound healing process can be divided into 4 phases, which are homeostasis, inflammatory, proliferation, and remodeling phase. Each phase plays a major important role and has an interconnecting signal network to complete the process. The hyperglycaemic condition has been known to have an impact on inhibiting vascular homeostasis, elevating oxidative stress, elevating procoagulant-proinflammatory cytokines, and inhibiting angiogenesis, therefore delaying the wound healing process. Diabetic wound healing is somehow made it very challenging. Various traditional medicine has been studied to have a pivotal role in enhancing immunological response at the molecular level. Channa striata (snakehead fish) has a potential role in regulating molecular and immunological mechanisms since it has been known to have an impact in accelerating the wound healing process, due to its antiinflammation, antioxidant, and promote cell proliferation and tissue remodeling. Several studies have revealed its molecular and immunological mechanisms, such as enhancing regulatory T-cell, inhibiting CD68+, inhibiting TNF-α, IFN-γ, IL-6, NF-κB, and increasing SDF-1α chemokines. The objective of this article is to review comprehensively the molecular and immunological mechanism of Channa striata in the diabetic wound healing process.

Keywords: Channa striata, diabetic wound healing, molecular, immunology

INTRODUCTION

The prevalence of Diabetes Mellitus is increasing globally, approximately 463 million people in 2019, and predicted to 700 million people in 2045. It has a mortality rate of around 4,2 million people (10,7%) in 2019. Indonesia, accounted for 7th worldwide diabetic countries, with an estimated diabetes population as 10,7 million people in 2019 and predicted to 16,7 million (9,9%) in 2045.[1]

The higher prevalence of diabetes has an impact on a higher complication rate in uncontrolled diabetes. Hyperglycaemia condition has been known to have an impact on inhibiting vascular homeostasis, elevating oxidative stress, elevating procoagulant-proinflammatory cytokines, and inhibiting angiogenesis, therefore delaying the wound healing process.[2]

Wound healing is a complex and dynamic process to restore cellular structures and tissue layers, which can be divided into 4 phases, which are: hemostasis (platelets activation which initiates coagulation cascade), inflammatory (neutrophils, macrophages, and lymphocytes activation), proliferation (new cellular matrix formation), and remodeling (new matrix maturation) phase. These mechanisms intercede between phases.[3]

Diabetic wound healing is a complex process, it has been known to inhibit the healing process through a multi-stage impaired molecular mechanism, therefore can lead to recurrent infection, ascending infection, depression, therefore prolong the hospital length of stay and increase health-care expenses. Diabetes-related wounds impose considerable clinical and economic burdens.[4]

Various traditional medicine included herbal medicine, has been studied to have a pivotal role in enhancing immunological response at a molecular level in several infectious diseases such as in typhoid fever[5-12], HIV[13-14], toxoplasmosis[15-17], Gardnerella vaginal infection[18], Vulvovaginal candidiasis[19-21], periodontitis and gingivitis[22-23] and non-infectious diseases such as bone degeneration[24-26], Alzheimer's disease[27], preeclampsia[28] and sedative in anesthesia[29-30]. Previously, the effect of snakehead fish (Channa striata) has been studied in albumin serum levels of post-operative neurosurgery patients[31].

Channa striata (C. striata) or snakehead fish is a freshwater fish that the majority can be found in tropical countries, including Indonesia. This snakehead fish has various names, based on its region, such as "Kutuk" (Java), "Kocolan" (Betawi), "Licingan" (Banjarmasin), "Bogo" (Sunda), "Kabos" (Minahasa), "Haruan" (Melayu). It has been used since a long time ago traditionally for wound healing and other essential nutrients, and since 1931 there has been in Malaysian literature discussion about wound treatment. It contains albumin, many amino acids (lysine, arginine, glutamic acid, aspartate), and arachidonate acid as antiinflammation, which play a role in the wound healing process.[32]

The acute diabetic wound is an inflammatory process which generates high reactive oxygen species (ROS), marked by superoxide dismutase (SOD) reduction and increase of malondialdehyde (MDA), which can be inhibited by C. striata due to its property of sulfuryl chain (-SH) in albumin which acts as an antioxidant by binding ROS, therefore decreasing MDA level.[33]

C. striata contain 25,5% of albumin which is higher than other fish and considered as main composition (64.61% of total protein), while it also contains omega-6, glycine, zinc, and striatin as its biologically active component.[34-35]

Albumin has a role in maintaining oncotic pressure, cell metabolism, drug transport, antiinflammation, acid-base balance, antioxidant, nutritional status, mild anticoagulant, and inhibits platelet aggregation, which is associated in the wound healing process.[36]

An animal study in C. striata reveals to reduce hyperglycemia by activation of regulatory T-cell, increasing macrophage cell, decreasing proinflammatory cytokines (TNF-α, IFN-γ, IL-6), inhibiting NF-kB in CD4 and CD8 cells, and accelerating wound healing process.[37]

A human study in C. striata has been extensively done in various conditions, including wound healing but only a few kinds of research in diabetic wound healing. This review will serve as the first extensive study on the molecular mechanism dan immune response of C. striata in the diabetic wound as a potential agent for accelerating the wound healing process.

Search Strategies

A comprehensive search of literature was conducted in PubMed (NIH), Scopus, EMBASE, and Google Scholar database using keyword combinations of the medical subject headings (MeSH) of 'Channa striata', 'snakehead fish', 'ikan gabus', 'luka diabetes', 'diabetic wound healing', 'molecular', 'immunology', and 'immunological'. Relevant reference lists were also manually searched.

Channa striata Extract

Channa striata (snakehead fish) is a freshwater fish, it also has been known as Ophiocephalus striatus, belongs to the Channidae family and is a carnivorous fish. This fish can be found in tropical and subtropical countries, such as in South America, Africa, and mostly in Asia, including Indonesia. In Indonesia, this snakehead fish widespread all over the region, a majority can be found in Sulawesi, Java, Sumatra, Bali, Lombok, Flores, Ambon, and Maluku with its region-based name.[32]

Since a long time ago, society has consumed this fish due to its nutritious content and for medicinal purposes, including accelerating the wound healing process. It contains many proteins, albumin, fatty acids, amino acids, vitamin, and beneficial minerals. Snakehead fish has higher protein and complete amino acids content compare to other fish. In the rural area, the post-circumcised boy was given snakehead fish to accelerate wound healing. It has also been used to accelerate the operative wound and section cesarean wound.[38]

C. striata contain 25,5% of albumin which is higher compared to milkfish (20%), goldfish (16.05%), snapper (20.0%), dan sardines (21.1%). Albumin is considered as the main composition (64.61% of total protein).[34] Protein is needed for all stages of the wound healing process, including fibroblast proliferation, collagen synthesis, angiogenesis, and immune function.[39]

The contents of snakehead fish extract were 17 amino acids including glutamic acid 1.87–43.13 mg/g, glycine 21.80–80.85 mg/g, leucine 7.85–

40.19 mg/g, aspartic acid 13.85–44.07 mg/g, proline 9.49–45.46 mg/g, alanine 11.38–35.25 mg/g, and arginine 5.99–21.79 mg/g. The fatty acid content includes palmitic acid 3.54–26.84%, stearic acid 3.25–15.90%, oleic acid 1.40–27.68%, linoleic acid 0.51–7.82% of total protein. This study concluded that snakehead fish contains bioactive components, especially amino acids, and fatty acids, which are important for the synthesis of collagen fibers during wound (particularly glycine), has high contents of arachidonic acid and polyunsaturated fatty acids that can promote prostaglandin synthesis, and antioxidants that can be used on wound healing and regulate immune system.[40]

Table 1: Composition of amino acids and fatty acid in Channa striata extract

	Fillet	Roe	Mucus	References
Amino acids	Glycine			
	Glutamic acid	(No study)	(No study)	Mustafa et al.
	Arginine			2012.[34]
	Aspartic acid			
Fatty acids	Eicosapentaenoic Acid (EPA)	Eicosapentaenoic Acid (EPA)	Oleic acid	
	Docosahexaenoic Acid (DHA)	Docosahexaenoic Acid (DHA)	Linoleic acid	Mustafa et al. 2012.[34]
	Palmitic acid	Hexadecanoic Acid		
	Oleic acid	Oleic acid		
	Stearic acid	Linoleic acid		
	Arachidonic acid			

Natural resources potency in both plants and animals is a very important resource in the development of new drugs. Indonesia's aquatic biological resources have huge potential, especially fish, but have not been utilized maximally. C. striata are one type of aquatic biological resources that had the potential as a drug. The use of C. striata as an animal protein source can be used as an alternative adjunctive therapy in the wound healing process. One of the benefits of C. striata extract is significant increases in fibroblast cells count in the wound healing process, in the remodeling phase.[41]

To gain the optimal effects of C. striata, it needs to be extracted. The simplest method for extracting is by using a water-based solvent, under several steps of fractionation, concentrating, and drying, so that it has more potent medicinal properties. These are the compound that can be obtained from the extraction of C. striata:

1. Albumin is one type of protein that can enhance the fibroblasts' proliferation, thus increase the synthesis, accumulation and collagen remodeling.[42]
2. Omega-3 has antiinflammation properties.[43]
3. Omega-6, mainly arachidonate acid, has antiinflammation property and accelerating wound healing process.[43]
4. Glycine is one of the primary amino acids required for of collagen synthesis.[44]
5. Glutamine plays a key role in inflammation and proliferation phase and also serves as energy source.[44]
6. Arginine modulates immune and endothelial function.[44]
7. Copper (Cu) plays a role in supporting connective tissue, linking the collagen and elastin, and promote angiogenesis.[45-46]
8. Iron (Fe) has specific function in collagen synthesis metabolism.[47]
9. Zinc plays a role in proliferation and maturation phase.[48]
10. Striatin, as a biochemical component for wound healing, enhancing cell proliferation and increasing serum albumin level.[35]

Molecular and Immunology Mechanism of Diabetic Wound Healing

Wound healing is a complex and dynamic process, which can be divided into 4 phases, which are: haemostasis, inflammatory, proliferation, and remodeling phase. These mechanisms intercede between phases.[3] Glucose is needed as energy for cell metabolism in wound healing process but the hyperglycemia state will alter its process. Systemic hyperglycemia is a state of heightened inflammatory state, high oxidative stress level known as radical oxygen species (ROS), reduced nitric oxide (NO), which causes major complications including impaired wound healing by damaging the microvasculature of small vessels that bring oxygen and nutrients to the wound. The excess amount of glucose makes the vessels' cell walls stiff, reducing the blood flow, permeability of erythrocytes, and inhibit cell migration, which is required for the development of new skin tissue.[49] Hyperglycaemic conditions inhibited cell migration due to an increase in oxidative stress that causes polarity loss, deficient adhesion, and profusion.[50]

ROS is known as the second messenger of tissue growth factor (TGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) production. Besides, nitric oxide (NO) is another key in wound healing for angiogenesis, inflammation, and tissue remodeling. NO inhibits vascular smooth muscle contraction and growth, prevents platelet aggregation, and maintains vessel homeostasis, thus it can stimulate endothelial cell proliferation and prevent cell apoptosis, thus promoting the formation of new blood vessels in angiogenesis.[51]

In the haemostasis phase, suddenly after the wound is developed, the blood clotting system will be activated to protect the vascular system. Endothelial cells through vascular cell adhesion molecule-1 (VCAM-1), platelet, and red blood cell form clots. Platelets will secrete platelet- derived growth factor (PDGF), platelet-derived angiogenic factor (PDAF), transforming growth factor-beta (TGF-ß), and epidermal growth factor (EGF) to initiate the migration of neutrophil, endothelial fibroblast and keratinocyte to wound site. The process is delayed in diabetic condition.[52]

In inflammatory phase, which is activated in days 1-3, a wave of neutrophils is recruited from the bloodstream. Responding to local cytokine gradients, the neutrophils adhere to the luminal wall of small postcapillary venules, traverse the endothelium, and migrate into the dermal tissue. Next, a second wave of leukocytes (monocyte/macrophages) arrives to remove the dead neutrophils that have released their granules and undergone apoptosis. In diabetic, the levels of cytokines and proteins associated with inflammation (interleukins IL-6 and IL-8, TNF-α, C-reactive protein, fibrinogen) were significantly elevated, and also has high expression of CD31 (proliferating vessels) and MMP-9 in the skin. These findings suggest a hyperinflammatory state.[53]

Macrophages have various functions in the inflammation and proliferation phase, including the cytokines activation, ECM synthesis, fibroblast proliferation, and secreting large amounts of transforming growth factor-beta (TGF-β), the major cytokine that stimulates fibroblasts to differentiate into myofibroblasts that produce most of the collagen (mediated by IL-4) and matrix molecules for developing new extracellular matrix (ECM) [52]. In diabetic condition, the total numbers of leukocytes and macrophages were decreased and the expression of TGF- β1 was lower in diabetes.[54-55] Recent studies found that there is macrophage dysfunction in chronic diabetic wounds. Classically activated or M1-like macrophages are known for killing microorganisms and producing proinflammatory cytokines. In contrast, the alternatively activated or M2-like macrophages produce anti-inflammatory factors. The transition of macrophages from a pro-inflammatory M1-like phenotype to an alternative M2-like phenotype has been suggested as a prerequisite for the switch from inflammatory to proliferative phase.[56]

In the proliferative phase, which is activated in days 3-10, neutrophil cells decreased while macrophage cells increased, due to several inflammatory mediators that had been released by neutrophils such as histamine lysozyme enzymes and platelet activation factors (PAF).[57] The study by Kruse et al. showed that high glucose inhibits both keratinocyte and fibroblast migration through inhibition of basic FGF (bFGF) signaling. The secretion of bFGF macrophages and fibroblasts increased on days 7 to 14 days after injury in line with the number of fibroblasts that increased in that period.[49,58]

Fibroblasts produce collagen, glycosaminoglycans, elastin fibres and glycoproteins that form the extracellular matrix that the wound cavity and provides a foundation for keratinocyte migration. Fibroblasts digest fibrin matrix and replace it with the glycosaminoglycan in conjunction with matrix metalloproteinase (MMP). Extracellular matrix will be replaced by type III collagen which is also produced by fibroblasts, and replaced by type I collagen in maturation phase.[46]

Growth factors and cytokines such as insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β), are diminished in diabetic wounds.[59] Reduction in levels of IGF-1 was observed in a study of cutaneous wounds in diabetic and non-diabetic mice, as well as in rats with streptozotocin-induced diabetes and in humans.[60] IGF-1 was shown to induce chemotactic activity in endothelial cell lines, as well as to stimulate keratinocyte and fibroblast proliferation and reepithelization and to increase wound strength.[61] Lerman et al. studied the fibroblasts and their ability to migrate and to release growth factors in 20-week-old db/db diabetic mice, and found that the migration of fibroblasts and the production of growth factors (VEGF) was significantly reduced.[62]

In remodeling/maturation phase, which is activated from day 10 to 3 months, albumin serves as the main ingredient through the body's catabolic remodeling to form collagen. Collagen is the main protein component to compile extracellular matrix components, then it will be degraded and removed by matrix metalloproteinases (MMPs), which is an essential part of the process of wound healing. An abnormal increase in MMP expression delays wound healing.[63-64]

Diabetic wound healing is characterized by a significant reduction in collagen deposition, decrease in the anti-inflammatory cytokine IL-10, reduction in the inflammatory phase, prolonged elevation in inflammatory cytokines (TNF-α, IL-1β and IL-6), activation of signal transducer and activator of transcription 3 (STAT3), reduction in the activation of protein kinase B and nuclear factor- κB (NF-κB), and decreased expression of β-defensin 2 and 3, vascular endothelial growth factor (VEGF), chemokines (macrophage inflammatory protein-1α, macrophage inflammatory protein-2, KC and CX3CL1) and transforming growth factors (TGF-β) in wounded tissue. The elevated level of IL-1β in conjunction with TNF-α decreases the expression of collagen mRNA via a pathway that increases matrix metalloproteinase (MMP) levels. Moreover, decreased expression of β-defensin 2 and 3 and increased incidence of bacterial infection are the main feature of delayed wound healing in animal`s model of diabetic wounds.[65] Moreover, there's also a marked reduction in the phosphorylation of Smad 2 and Smad 3 as well as a marked reduction in collagen production. Smads are intracellular proteins that transduce extracellular signals from transforming growth factor-beta ligands to the nucleus.[66]

Table 2: Immunology and Molecular Changes in Diabetic Wound

Main Changes in Diabetic Wound	Reference
Persistent of neutrophils	Al-Waili et al.[67]
Decrease macrophage activity	Al-Waili et al.[67]
Defective chemotaxis	Al-Waili et al.[67]
Inhibited proliferation	Al-Waili et al.[67]
Excessive inflammation	Al-Waili et al.[67]
Fibronectin deficiency	Al-Waili et al.[67]
AGEs accumulation	Al-Waili et al.[67]
Growth factors abnormality	Al-Waili et al.[67]
Peripheral vascular disease	Al-Waili et al.[67]
Neuropathy	Al-Waili et al.[67]
Increased TNF-α	Badr et al.[65]
Increased MMP 1 and 9	Badr et al.[65], Hozzein et al.[66]
Decreased β-defensin 2,3	Badr et al.[65]
Increased MMP-9, IL-1β, IL-6, IL-8	Hozzein et al.[66]
Decreased Smad2 and Smad3 phosphorylation	Hozzein et al.[66]
Decreased MIP-1α, MIP-2, KC, CX3CL1	Badr et al.[65]
Decreased VEGF expression	Hozzein et al.[66]
Decreased IL-10	Badr et al.[65]
Decreased Collagen	Badr et al.[65]

Molecular and Immunology Mechanism of Channa striata in Diabetic Wound Healing

C. striata have been used as a nutritious food and for medical purpose for almost a decade, yet its molecular mechanisms for wound healing properties are still under research. C. striata have been reported to induce cell proliferation and platelet aggregation, while amino acids promote wound healing process. Glycine is required for collagen synthesis, glutamine acts in inflammation and proliferation phase of wound healing, and arginine modulates immune function and promote endothelial function. C. striata contains protein that helps capillary formation, fibroblast proliferation, proteoglycan synthesis and wound remodelling.[44] The energy compound such as adenosine triphosphate in C. striata can decrease the healing time.[68]

It was reported that diabetic patients have lower SDF-1 and CXCR4. SDF-1 is a chemokine that stimulates the endothelial progenitor cells (EPC) mobilization derived from the bone marrow, which is important in the regulation of mobilization and recruitment of progenitor cells.[69] Supplementation of C. striata has shown a significant increase of chemokine SDF-1.[70]

Arginine is known for the ability to enhance growth factors, increased lymphocyte and monocyte proliferation and enhanced the formation of T-cell. It stimulates wound healing by modulating immune and endothelial function.[71] Glutamine has role in the inflammatory response, cell proliferation (white blood cell, fibroblast), collagen formation, enhancing immune function, and as energy source.[72]

Copper (Cu) has been known to play role in supporting myelin membrane integrity, bone formation, connective tissue, linking the collagen and elastin, and increase Vascular Endothelial Growth Factor (VEGF) that promote angiogenesis.[73] Iron (Fe) has specific function in collagen synthesis metabolism by procollagen-proline dioxygenase, and iron acts as a co-factor for protein and enzyme that involved in energy metabolism, apoptosis, and DNA synthesis and replication.[47] Zinc play a role in cell replication, cell regeneration, enhancing immune response, collagen synthesis as well as the proliferation of fibroblasts in proliferation and maturation phase.[48]

Fatty acids play role in cell membrane structure and function for new cells synthesis. Omega-3 has antiinflammation property, especially when consumed at a high level (> 10% of total fat), and at low level (< 10% of total fat) can increase immune system by increasing lymphocyte proliferation, NK cell activity, and macrophage activation. Omega-6, mainly arachidonate acid, has antiinflammation property and is related to accelerating the wound healing process. Arachidonate acid is a precursor of prostaglandin that can induce platelet aggregation and adhesion in endothelial tissue which activating coagulation cascade in wound healing process.[43]

Vitamin A increases the strength of scar tissue, and it is required for adequate inflammatory response, enhances immune response, promotes collagen synthesis and epithelialisation and has antioxidant properties. Vitamin B6 is involved in the inflammatory response and participated in the conversion of tryptophan into niacin which helps the wound healing process. Vitamin B is required for protein synthesis and formation of red blood cells which supply the wound with oxygen and nutrients and collagen linkage.[74]

C. striata increase the number of regulatory T cells, decreasing the number of macrophage cells and proinflammatory cytokines TNF-α, IFN-γ and IL-6 and inhibiting NF-κB in T lymphocytes CD4+, CD8+ and macrophages.[37] NF-kβ is a transcription factor to regulate proinflammatory process, therefore albumin is considered as an immunomodulator and immunostimulant.[75]

The latest, striatin, as a bioactive protein component for wound treatment is discovered. It contains amino acids (10 essential and 7 non-essential amino acids), fatty acids (palmitic acid, oleic acid, stearic acid, linoleic acid, arachidonic acid), vitamins (vitamin A, vitamin B6) and other nutrients (carbohydrate, dietary fiber, biotin, choline, inositol, L-carnitine, selenium) which are potential for wound healing by enhancing cell proliferation and increasing serum albumin level. It increases the growth of fibroblast cells, related to neo-angiogenesis and extracellular matrix secretion, needed for cell ingrowth and tissue development, and cytokines and growth factors production. Although does not contain albumin, this bioactive protein fraction accelerating albumin synthesis.[35]

Albumin is a protein that can enhance fibroblasts' proliferation and collagen remodeling, transport of oxygen and minerals (zinc, copper, iron), capable of stimulating TGF-β1 to increase fibronectin and collagen formation, synergizes with Zn for cell development and cell regeneration, as an antioxidant and as an inhibitor of apoptosis process for macrophages, neutrophil, lymphocyte, and endothelial cells.[76-77]

Albumin increases Prostaglandin E2 (PGE2) and prostaglandin D2 (PGD2) level. Prostaglandin plays a role in activating M1-like macrophages cell, which will produce IL-1 which subsequently stimulates IL-6 to increase lymphocyte differentiation and proliferation. IL-6 has important regulatory function in the immune system as a mediator of acute-phase response in wound healing process.[78] It is also recognized as an important cytokine for T and B lymphocyte differentiation.[79,80,81,82,83] Research conducted by Fauza also showed that the administration of C. striata extract capsules for 10 days as much as 3 g/day (3 × 2 per day) can increase albumin levels and protein intake and hemoglobin in patients with hypoalbuminemia.[80,84,85]

Table 3: Summary of Studies of Channa striata in Diabetic Wound Healing

Main effects of Channa striata	References
Collagen synthesis	Guo et al.[44], Mustafa et al.[34], Tempest M.[72]
Promote endothelial function	Guo et al.[44], Mustafa et al.[34], Fujiwara T et al.[71]
Fibroblast proliferation	Guo et al.[44], Tempest M.[72]
Proteoglycan synthesis	Guo et al.[44]

Wound remodelling	Guo et al.[44]
Accelerate wound healing process	Ali Khan et al.[68], Wheeler et al.[78]
Increase Chemokine SDF-1	Pradana et al.[70]
Enhance growth factors	Fujiwara T et al.[71]
Enhance T-cell formation	Fujiwara T et al.[71], Dwijayanti DR et al.[75]
Linking the collagen and elastin	Rahayu et al.[35], Hayes GL et al.[73]
Increase VEGF	Rahayu et al.[35]
Anti-inflammatory response Decrease TNF-α, IFN-γ and IL-6	Daud et al.[40], Tempest M.[72]
Immunostimulant – Immunomodulator	Daud et al.[40], Tempest M.[72] Wolf G et al.[79]
Source of energy	Tempest M.[72]
Cell replication and regeneration	Mustafa A et al.[34]
Induce platelet aggregation and adhesion Increase lymphocyte proliferation Increase NK cell activity Increase macrophage activation	Daud et al.[40], Wheeler et al.[78]
Increase the strength of scar tissue	Kemp S.[74]
NF-κB inhibitor	Dwijayanti DR.[75]
Stimulate TGF-β1	Bolitho et al.[76]
Antioxidant properties	Salazar J J et al.[77]
Increase Prostaglandin	Fujiwara T et al.[71] Wheeler et al.[78] Wolf G et al.[79]
Increase albumin, protein intake, hemoglobin	Fauza et al.[80]

Future Direction

There are several molecular mechanisms in the immune response that may be modulated by C. striata. The investigation of many possible effect of C. striata in molecular mechanism that involved in 4 phases of wound healing has not been discovered thoroughly in diabetic wound healing. The strategic modulation through other possible mechanisms in each phase need to be investigated in order to more understand its complex role in diabetic wound healing process so the treatment can be more effective as a primary or a supplementary treatment. There are a lot of more researches need to be done to explore its therapeutical mechanism.

CONCLUSION

Diabetes and its complication always become a global health problem and its prevalence is increasing. The comorbidities, especially peripheral artery disease like diabetic foot ulcer is a very devastating problem that can lead to delayed wound healing and may lead to amputation. Many treatment modalities are used to prevent it and the complication rate is still higher. There have been a vast discoveries of the C. striata for medical purpose, including wound healing, yet its role in diabetic wound healing is still limited. The understanding of diabetic wound molecular mechanisms has created opportunities to enhance a good healing process. C. striata has been used for more than a decade and emperically show many benefits. Its bioactive component has shown a potential role in modulating and accelerating diabetic wound healing process, as an antiinflammatory by reducing interleukines, antimicrobial, antioxidant, enhance cell proliferation and cell regeneration by increasing growth factors (IGF-1, TGF-β1) and fibroblast activation. Therefore, C. striata has a significant potential role in diabetic wound healing management as an adjuvant to standart treatment. However, there are plenty other molecular mechanisms that need to be explored.

CONFLICT OF INTEREST

There is no conflict of interest declared.

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