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Literature Study: The Effect of Giving Chitosan Water Gel (Hydrogel) on Healing Diabetic Ulcers Based on In Vivo Studies with Animal Models

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Abstract

Diabetic ulcers are one of the most common chronic complications and cause infection, gangrene to leg amputation if the treatment given is not appropriate. Chitosan has anti-microbial properties that make the wound area smaller and are anti-inflammatory to reduce pain. Water gel (hydrogel), which is water, is easily absorbed by the skin and penetrates perfectly into the wound so that it provides a moist effect and prevents bacteria from entering. This study aims to determine the effect of giving chitosan water gel (hydrogel) on the healing of diabetic ulcers. This study uses a literature study method by searching for related journals using keywords, then selected based on the last 5 years and indexed in SINTA, Google Scholar or Scopus, and the final results are 13 journals. This study took place in May - November 2021. The results of this study reported that the administration of chitosan water gel (hydrogel) combined with other ingredients for healing diabetic ulcers gave the same results. The results obtained are reducing inflammation, re-epithelializing wounds, accelerating angiogenesis, accelerating the formation of collagen and granulation tissue, and accelerating wound healing. Although all studies have the same results, the healing time produced by each study is different, this is because each ingredient used has a different content. The average wound changes were seen on the 3rd, 5th, 7th day and the wound healed completely on the 14th day. This study concludes that the administration of chitosan water gel (hydrogel) affects the healing of diabetic ulcer wounds in combination with other ingredients. because the time needed to close the wound is faster.

Keywords: Wound healing, diabetic ulcer, chitosan, water gel (hydrogel)

Review Article

Studi Literatur: Pengaruh Pemberian Kitosan Jel Air (Hydrogel) Terhadap Penyembuhan Luka Ulkus Diabetes pada Penelitian in vivo Hewan Coba

Abstrak

Ulkus diabetes adalah salah satu komplikasi kronik tersering dan menyebabkan terjadinya infeksi, gangren sampai amputasi kaki apabila tatalaksana yang diberikan tidak tepat. Kitosan memiliki sifat anti mikroba yang membuat luas luka mengecil dan anti inflamasi untuk mengurangi rasa nyeri. Jel air (hydrogel) yang dasarnya adalah air menjadi mudah diserap oleh kulit dan masuk secara sempurna ke luka sehingga memberikan efek lembab dan mencegah adanya bakteri yang masuk. Penelitian ini bertujuan untuk mengetahui pengaruh pemberian kitosan jel air (hydrogel) terhadap penyembuhan luka ulkus diabetes. Penelitian ini menggunakan metode studi literatur dengan mencari jurnal yang berkaitan menggunakan kata kunci, kemudian diseleksi berdasarkan 5 tahun terakhir dan terindeks di Scimagojr sehingga didapatkan hasil *akhir sebanyak 13 jurnal. Penelitian ini berlangsung pada bulan Mei - November 2021. Hasil dari penelitian ini melaporkan bahwa pemberian kitosan jel air (hydrogel) yang dikombinasikan dengan bahan lain terhadap penyembuhan luka ulkus diabetes memberikan hasil yang sama. Hasil yang didapatkan yaitu mengurangi inflamasi, re-epitelisasi luka, mempercepat angiogenesis, mempercepat pembentukkan kolagen dan jaringan granulasi serta mempercepat penyembuhan luka. Walaupun semua penelitian memiliki hasil yang sama tetapi waktu penyembuhan yang dihasilkan setiap penelitian berbeda, hal ini disebabkan karena setiap bahan yang digunakan memiliki kandungan yang berbeda. Rata – rata luka mengalami perubahan terlihat pada hari ke – 3, 5, 7 dan luka sembuh total pada hari ke – 14. Kesimpulan dari penelitian ini, bahwa pemberian kitosan jel air (hydrogel) berpengaruh terhadap penyembuhan luka ulkus diabetes yang dikombinasikan dengan bahan lain karena waktu yang dibutuhkan untuk menutup luka lebih cepat.*

Kata Kunci: *Penyembuhan luka, ulkus diabetes, kitosan, jel air (hydrogel)*

INTRODUCTION

Wounds are injuries that occur on the surface of the skin and cause damaged skin tissue (Handayani, 2016; Ramadhian & Widiastini, 2018). Wound healing can be carried out by injured epidermal tissue, with several processes that must be passed to achieve wound healing, namely the inflammatory, proliferative, and maturation phases (Childs & Murthy, 2017; Janis & Harrison, 2016). One example is wounded in people with diabetes, wound healing is influenced by several factors that cause thickening of the basement membrane of capillaries and arterioles. This thickening causes wound healing to be disrupted and not fully healed, resulting in the formation of diabetic ulcers (Putri & Sriwidodo, 2016; Shukla et al., 2016).

Diabetes is a chronic disease that kills or causes widespread disability throughout the world. One of the most common chronic complications of diabetes is diabetic ulcers, the more the number of diabetics in the world increases, the more cases of leg amputations occur (Bai et al., 2020; Detty et al., 2020). Around 326 million patients worldwide suffer from type 2 diabetes mellitus, and 15-25% develop diabetic ulcers, if not given proper treatment it will cause infection, gangrene, and even lower extremity amputation (Martínez et al., 2019). So treatment is needed that can reduce diabetic ulcers.

Diabetic ulcers can be caused by several things, including peripheral neuropathy, namely blockage in blood vessels (ischemia) and infection (Putri & Sriwidodo, 2016; Restuningtyas, 2016). Treatment is carried out in dealing with diabetic ulcer cases in several ways. First, surgery is performed to remove pus and reduce tissue necrosis. Second, use antibiotics to eliminate bacteria such as Staphylococcus or Streptococcus. Third, how to treat wounds properly and correctly to help speed up the wound healing process (Divandra, 2020; Hutagalung et al., 2019). Of the three treatments, the use of antibiotics has drawbacks, this is due to the possibility of bacterial resistance to antibiotics which will have an impact on morbidity and mortality as well as on socio-economic conditions (Ningsih et al., 2019; Sari et al., 2018). Several natural ingredients can be used in the treatment of diabetic ulcers, one of which comes from the exoskeleton of marine animals such as shrimp (Cifuentes et al., 2020; Prasathkumar & Sadhasivam, 2021).

Chitosan is a polysaccharide derived from shellfish exoskeletons such as shrimp, lobster, crab, or other parasites. Chitosan is made of β - (1-4) – linked D-glucosamine (deacetylation unit) and N-acetyl-D-glucosamine (acetylation unit). The sub-atomic weight of chitosan varies widely, but most of them have a lower weight, and if the degree of deacetylation is low it is associated with solubility (Aljebory et al., 2017; Prasathkumar & Sadhasivam, 2021). Many benefits are obtained from chitosan, one of which is for wound healing, because chitosan has properties that are acceptable to the body, nontoxic, and prevent infection from microbes so chitosan is good in the wound healing process (Cifuentes et al., 2020; Prastika et al., 2020).

Currently, water gel (*hydrogel*) is widely used in various fields, one of which is in medicine, namely for wound healing. The composition of the water gel (*hydrogel*) itself consists of water and a cross linked polymer network, because most of it is water it makes a physical similarity with the soft tissues in the body so that the water gel (*hydrogel*) can wrap hydrophilic drugs, then in the presence of polymer network also makes the water gel (*hydrogel*) denser so that a compound is formed that can help for wound healing. Following the above properties, causes water gel (*hydrogel*) to absorb exudate from the wound. There are three kinds of water gels (*hydrogels*) based on polymer composition, namely water gels (*hydrogels*) 3 homo-polymers, copolymers, and multi-polymer interpenetrating polymers (J. Li & Mooney, 2016; Singh, Shailesh Kumar, Dhyani & Juyal, 2017).

Incidents related to diabetic ulcer healing using antibiotics around the world, there are still many pros and cons to the effects (Sari et al., 2018) giving antibiotics still has drawbacks because it can cause bacterial resistance so has an impact on morbidity and mortality as well as socioeconomic status, so the researcher wants to know how to cure diabetic ulcers when using natural ingredients such as chitosan water gel (*hydrogel*). The purpose of this paper is to determine the effect of giving chitosan water gel (*hydrogel*) on the healing of diabetic ulcers. This writing is descriptive and qualitative research that uses a literature study method. The data used are taken from articles or journals related to what is discussed. The data that has been obtained based on the keywords "Wound healing", "Diabetic ulcers", "Chitosan", and "Water gel (*hydrogel*)" will be selected and sorted according to the topic and conducted research.

MATERIAL AND METHODS

This study used a literature study method. The study begins by searching and collecting data using keywords such as wound healing, diabetic ulcers, chitosan, and water gel (*hydrogel*) from recommended sources or references, and the publication has to indexed by SINTA, Google Scholar and or Scopus. This study uses a scientific literature search engine (*Pubmed* and *Google Scholar*), the method of sampling or data collection is using a scientific literature search engine that meets the inclusion criteria, then analyzing using descriptive and qualitative methods from the results and discussion in tabular form, so that conclusions can be drawn. The inclusion criteria for this study were articles or journals that directly conducted experimental research using experimental animals and related to the administration of chitosan water gel (*hydrogel*) for wound healing diabetic ulcers published from 2016 to 2021 that were indexed by SINTA, Google Scholar or Scopus, and *full text* accessible. While the exclusion criteria are that some indexed articles or journals and *the full text* cannot be accessed.

Data extraction is begun by reference searching use online application of Pubmed and Google Scholar, guidance by the keywords. It is continued by sorting the article based on the focus of each study, and analyzing the result, discussing according to a systematic tabulation. Data analyzing are descriptive and qualitative, begin from the results, then observed based on the topic, and make a conclusion.

RESULT

Following the result of a review several kinds of literature that have met the inclusion criteria and all literature indexed with SINTA, or Google Scholar, and or Scopus published in the period 2016 – 2021.

Table 1. Summary of chitosan properties and it's effect on diabetic ulcers healing

No.	Title and Author	Population	Instruments	Result
1.	*Fabrication of Apigenin loaded gellan gum–chitosan hydrogels (GGCH-HGs) for effective diabetic wound healing* (Shukla et al., 2016)	Male and female inbred wistar rats (200 - 250g)	Provision of water gel (*hydrogel*) containing apigenin made from gellan gum-chitosan (GGCH-HGs) for healing diabetic wound	• Water gel (*hydrogel*) made from gellan gum-chitosan using Polyethylene Glycol (PEG) as a cross-linker gave excellent results • Has good absorption properties thereby reducing the risk of wound dehydration Improved wound healing results due to antioxidant activity, polymer-based water gel (*hydrogel*), can be decomposed in the remodeling phase of the wound healing process so that

				there is an acceleration of wound closure • Water gel (*hydrogel*) containing apigenin made from gellan gum-chitosan (GGCHHGs) can stimulate wound contraction, increase collagen content and increase hydroxyl-proline content and protein content significantly • The increase in collagen was due to increased cross-linking and dry granuloma weight indicating a higher protein content. • 6 days for completely re-epithelialization
2.	*Fabrication of hydroxyapatite/chitosan composite hydrogels loaded with exosomes derived from miR-126-3p overexpressed synovium mesenchymal stem cells for diabetic chronic wound healing* (M. Li et al., 2016)	Adult male Sprague-Dawley (SD) rats 300-350 g	Using gene overexpression technology to generate high-expressing miR-126-3p (SMSCs-126) synovial mesenchymal stem cells (SMSCs). Exosomes derived from miR-126-3p were overexpressed (SMSCs-126-Exos) encapsulated in water gel (*hydrogel*) hydroxyapatite/chitosan composite (HAPCS)	• This study proves that the occurrence of re-epithelialization of the wound surface accelerates angiogenesis, and accelerates collagen maturation • 7 days for completely re-epithelialization
3.	*GMSC-Derived Exosomes Combined with a Chitosan/Silk Hydrogel Sponge Accelerates Wound Healing in a Diabetic Rat Skin Defect Model* (Shi et al., 2017)	24 male rats (280–320g)	The combined effect of 28 GMSC-derived exosomes and water gel (*hydrogel*) on improving wound healing in diabetic rats	• The isolation results from GMSCs and exosomes with an average diameter of 127 nm were shown to accelerate the healing of diabetic skin defects • Histological analysis revealed more re-epithelialization, deposition, collagen remodeling, and increased angiogenesis and neuronal growth in the exosomes-water gel (*hydrogel*) group • The findings also provide a novel noninvasive exosome application method with practical value for skin repair • 14 days for wounds almost completely closure
4.	*SIKVAV-Modified Chitosan Hydrogel as a Skin Substitutes for Wound Closure in Mice* (Chen et al., 2018)	72 female mice (8-12 weeks)	Effect of SIKVAV peptide-modified chitosan water gel (*hydrogel*) (Ser-Ile-Lys-Val-Ala-Val) for skin wound healing	• Water gel (*hydrogel*) can accelerate skin wound healing, re-epithelialization, collagen deposition, and angiogenesis Hematoxylin and eosin (H&E) staining showed accelerated wound re-epithelialization in negative and positive controls • Masson's trichrome staining showed more collagen fibers

				deposited in skin wounds in the negative and positive controls • Immuno-histochemical assays showed that more myo-fibroblasts were deposited and more angiogenesis in negative and positive controls • ELISA test showed an increase in skin growth factor secretion. water gel (*hydrogel*) promotes the secretion of growth factors in the skin in vivo • SIKVAV modified chitosan water gel (*hydrogel*) has the potential to be synthesized biomaterials for the treatment of skin wounds • *SIKVAV-Modified Chitosan Hydrogel as a Skin Substitutes for Wound Closure in Mice* • 7 days for more newly formed capillaries
5.	*Wound healing effects of a Curcuma zedoaria polysaccharide with platelet-rich plasma exosomes assembled on chitosan/silk hydrogel sponge in a diabetic rat model* (Xu et al., 2018)	40 female Sprague-Dawley (SD) mice (280-300g)	One homogeneous polysaccharide (ZWP)was isolated from Curcuma zedoaria to determine the potential of chitosan/silk water gel sponge (*hydrogel*) contains a lot of exosomes of platelet wood plasma (PRP-Exos), ZWP, or PRP-Exos/ZWP for diabetic wound healing in mice	• The use of PRP-Exos and ZWP alone or in combination was found to be successful for diabetic wound healing • More successful is PRP-Exos/ZWP combination therapy for wound healing • The results of this therapy are wound contraction which accelerates the process very significantly, re-epithelialization, collagen synthesis and deposition, and angiogenesis at the wound site • 15 days for wounds almost completely closure
6.	*Fluorinated Methacrylamide Chitosan Hydrogel Dressings Improve Regenerated Wound Tissue Quality in Diabetic Wound Healing* (Patil et al., 2019)	Adult male mice 8-12 weeks	Comparison of water gel (*hydrogel*) wound dressings developed based on fluorinated methacrylamide chitosan (MACF) with water gel dressings (*hydrogel*) commercial, AquaDerm, and no treatment control in a splint transgenic diabetic mouse wound model	• Topical treatment with $MACF^{+}O_2$ resulted in increased collagen synthesis, increased collagen fiber compatibility, and increased neovascularization • 14 days for wounds almost completely closure
7.	*A new waterborne chitosan-based polyurethane hydrogel as a vehicle to transplant bone marrow mesenchymal cells improved wound healing of ulcers in a diabetic rat model*	Adult female wistar rats aged 60 days (200-300g)	Using a novel chitosan-polyurethane (HPUC) water gel membrane HPUC) for transplantation bone marrow mesenchymal cells improve wound healing of diabetic ulcers in mice	• The results of the study of the synthesized chitosan tissue degrade continuously in an aqueous solution and the hydrolytic degradation of polyurethane blocks the water-soluble chitosan region

	(Viezzer et al., 2020)			• These biomaterials have low cytotoxicity and promote cell proliferation • Termination of the isocyanate group (NCO) of unmodified chitosan synthesis with a new crosslinker consisting of a low molecular weight polyurethane will crosslink with a chitosan-free amine • Using bone marrow mononuclear cells (BBMNC) can close the wound, reduce inflammation and increase neovascularization around the wound • Result of water gel (*hydrogel*) synthesized with bone marrow mononuclear cells (BBMNC) used as a diabetic wound dressing • 14 days for wounds almost completely closure
8.	*Chitosan hydrogels functionalized with either unfractionated heparin or bemiparin improve diabetic wound healing* (Cifuentes et al., 2020)	120 female wistar rats (183-260g)	Effect of chitosan water gel (*hydrogel*) using unfractionated heparin or bemiparin (low molecular weight heparin, LMWH) topically for diabetic wound healing in mice	• The results of the chitosan water gel (*hydrogel*) wound dressing filled with HEP or BEM improve diabetic wound healing with a reparative process and induce the formation of stable scar tissue and produce new, high-quality dermal tissue • 21 days for completely recovery
9.	*Rapid gelation of oxidized hyaluronic acid and succinyl chitosan for integration with insulin-loaded micelles and epidermal growth factor on diabetic wound healing* (Zhu et al., 2020)	Sprague Dawley (SD) male rat 60 days	The formation of a water gel (*hydrogel*) is responsive to pH from acid Oxidized hyaluronic acid (OHA) and succinyl chitosan (SCS) were then mixed with epidermal growth factor (EGF) and insulin-laden micelles (ILM)	• The results seen from the viscosity and rheology of the combination can form a gel quickly • Water gel (*hydrogel*) exhibits low cytotoxicity and good biocompatibility • Water gel (*hydrogel*) composite containing EGF and ILM showed excellent wound healing performance with fibroblast proliferation, the integrity of internal tissue structure, and deposition of collagen and myofibrils • 12 days the wound almost completely closure
10.	*Sulfated Chitosan Rescues Dysfunctional Macrophages and Accelerates Wound Healing in Diabetic Mice* (Shen et al., 2020)	Male rat C57BL/6J 7-8 weeks	Improved macrophage function with chitosan sulfate collagen type I (Col I/SCS) water gel (*hydrogel*) for diabetic wound healing	• The results of the water gel (*hydrogel*) Col I/SCS have been shown to improve macrophage function and accelerate diabetic wound healing by increasing re-epithelialization, collagen deposition, and neovascularization • Immunofluorescence test and flow cytometry analysis showed Col I/SCS water gel (*hydrogel*) reduced M1 macrophages and increased

				CD86+ CD206+ macrophages on day 7 • Other results show that there is a reduction in chronic inflammation • Water gel (*hydrogel*) also stimulates macrophages to secrete IL-4 and TGF-β1 and increases collagen and ECM synthesis and accelerates the formation of granulation tissue • 18 days for wounds almost completely closure
11.	*Synergistic Antibacterial Activity and Wound Healing Properties of Selenium-Chitosan Mupirocin Nanohybrid System: An in Vivo Study on Rat Diabetic Staphylococcus aureus Wound Infection Model* (Golmohammadi et al., 2020)	30 adult male wistar rats (15g)	Formulated Selenium-chitosan-Mupirocin (M-Senps-ccH) complex with a nanohybrid system using water gel (*hydrogel*) chitosan-cetyltrimethylammonium bromide (ctAB) based	• The results of the MSeNPs-ccH nanohybrid system that were formulated 3 times were much more capable of reducing than mupirocin • This formulation is also important in wound contraction, angiogenesis, fibroblastosis, collagen, and proliferation of hair follicles and epidermis • SeNPs-ccH can be developed into a mupirucin-based drug for the treatment of mild diabetic wound infections • 21 days for wounds almost completely closure
12.	*Regulation of inflammatory microenvironment using a self-healing hydrogel loaded with BM-MSCs for advanced wound healing in rat diabetic foot ulcers* (Bai et al., 2020)	Sprague-Dawley (SD) male rat 8 weeks (200-250g)	water gel (*hydrogel*) injection crosslinks N-chitosan and adipic acid dihydrazide (ADH) with hyaluronic acid-aldehyde (HA-ALD)	• The results obtained are the availability of a moist environment and can minimize inflammation to stimulate stem cell proliferation • Water gel (*hydrogel*) secretes growth factors from bone marrow mesenchymal stem cells (BM-MSCs) such as TGF-β1, VEGF, and bFGF • Water gel (*hydrogel*)as an inhibitor in the chronic inflammatory process, increases the formation of granulation tissue, collagen deposition, nucleated cell proliferation, and stimulates neovascularization resulting in increased wound healing of diabetic ulcers • 15 days for wounds almost completely closure

13.	*Novel Silver and Nanoparticle-Encapsulated Growth Factor Co-Loaded Chitosan Composite Hydrogel with Sustained Antimicrobility and Promoted Biological Properties for Diabetic Wound Healing* (Lee et al., 2021)	25 Sprague-Dawley (SD) mice 8-10 weeks (250-300g)	Synthetic chitosan-based composite water gel (hydrogel) ($SNP_E CGH$) combines silver ions (Ag^+) and nanoparticle encapsulated epidermal growth factor (EGF)	• Showed an increase in wound healing effect on day 3 and wound closed 97% on day 14 • In addition, wound treatment with (SNCGH) also showed reepithelialization, collagen deposition, and according to histological analysis accelerated collagen maturation • It is proven that SNCGH is very satisfactory in the treatment of diabetic wounds • 14 days for wounds almost completely closure

DISCUSSION

Research by Shukla et al., 2016 reported that this study was seen from the swelling after 5 hours of administration of GGCH-HGs showed much higher water absorption properties to reduce wound dehydration, and reach a balanced condition within 3 hours. Increased angiogenesis accelerated wound closure due to antioxidant activity, the wound area was measured every 2 days and on day 6 wound contraction of the GGCH-HGs treatment group containing APN was found to be significantly ($p<0.01$) increased with decreasing epithelialization period, and days 18th, almost complete healing. In this case, the collagen content, protein content, and granuloma weight measurements in the GGCH-HGs group were found to be significantly greater than in the control group, the increase in protein from the treated wounds indicated cell synthesis and proliferation. Protein synthesis plays a role in the formation of granuloma tissue.

Research by M. Li et al., 2016 reported that after culture for 12 hours the percentage of cell proliferation increased, on the 14th postoperative day the wounds treated with HAP-CS-SMSCs-126-Exos had closed completely significantly ($p< 0.05$) compared to the control group. SMSCs-126-Exos nanoparticles and HAP-CS composites contribute to increased re-epithelialization with thicker and mature layers, granulation tissue maturation, collagen enhancement, and angiogenesis formation and maturation. This happened because, on one hand, chitosan had excellent antibacterial and nontoxic properties so that no wound infection was detected in the animals during the postoperative period.

Research by Shi et al., 2017 reported after 14 days postoperatively that GMSC can accelerate diabetic ulcer wound healing by increasing re-epithelialization, collagen deposition, wound angiogenesis, inhibiting pro-inflammatory cytokine production, and increasing anti-inflammatory cytokines. This study uses a water gel sponge (hydrogel) not only as a wound dressing but to deliver exosomes directly to the wound, and the presence of chitosan is a hydrophilic polymer so that the results obtained are better. The water gel (hydrogel)-exosomes group showed the presence of a neo-epithelial with regular wavy collagen fibers (similar to normal skin), suggesting the positive influence of GMSC-derived exosomes on re-epithelialization and deposition and remodeling of the ECM. Immuno-fluorescent staining was applied to evaluate nerve regeneration at 14 postoperative days and GMSC-derived exosomes can facilitate nerve growth in the wound bed and significantly increase nerve density. I in animals during the postoperative period.

Research by Chen et al., 2018 reported that on the 3rd day after trauma, the remaining wound area was smaller in the SIKVAV group with chitosan, then on the 5th and 7th day the wound area was getting smaller, this proves that the water gel (hydrogel) modified SIKVAV peptide was able to improve wound healing. During wound healing, keratinocytes at the edges of the wound will cover the center gradually through proliferation and migration to form new epithelium on the surface of the granulation tissue which proliferates can be seen on the 3rd day after trauma. On the 5th day after the trauma, the wound surface was completely covered and on the 7th day after the trauma, the SIKVAV group with chitosan had completed re-epithelialization. New blood vessels in the wound provide nutrition to form granulation tissue and keratinocytes, on the 5th day after trauma the number of newly formed capillaries in SIVAV mice with chitosan was significantly higher than the control group, and on the 7th day after trauma formed more These new capillaries demonstrated that hydrogel SIKVAV's peptide-modified Collagen is important in the wound healing process because it plays a role in wound healing cells and regenerative blood vessels, on the 3rd day after trauma more collagen fibers are formed, on the 5th day after trauma the number of collagen fibers increases and on the 7th day more and more collagen fibers are formed. more collagen fibers were formed, this proves that the water gel (hydrogel) modified by SIKVAV peptide increases the deposition of collagen fibers. Wound healing involves several growth factors so that fibroblast secretion and synthesis occurs, keratinocyte proliferation and migration as well as endothelial cell proliferation and migration to form blood vessels, ELISA test is used to detect growth factor secretion in skin wounds, on days 3, 5, and 7 after trauma there are several factors such as EGF, b-FGF, TGF-β1, and VEGF significantly increased.

Research by Xu et al., 2018 reported that the 3rd to 15th day of wound contraction increased ($p<0.001$) significantly, and the wound area became smaller ($p<0.05$) statistically significant. The effect of wound closure treated with PRP-Exos/ZWP was 53.10% of the 49.50% value that was only given PRP-Exos. Wound healing is a complex process in which cells, ECM, cytokines, and growth factor the structural integrity of tissues is damaged. Collagen synthesis and deposition in PRP-Exos/ZWP were much higher than in the diabetic group ($p<0.001$) as shown by 7 mice. Dermal angiogenesis vascular intensity was also higher than in the control group.

The study Patil et al., 2019 reported that the open wound area used for measurement and MACF+O2 could close the wound significantly faster ($p<0.05$) and increase re-epithelialization (4.8-1.4 mm). Collagen synthesis as measured from collagen areas in wound tissue, using Trichrome Masson staining showed an increase in total collagen synthesis. Increased neovascularization by calculating the CD-105 positive vascular structure on the wound on day 14, this proves that local oxygen produced by MACF+O2 can increase neovascularization.

The study Viezzer et al., 2020 reported that there was a significant increase in tissue regeneration and wound closure >90% after day 14. To evaluate the role of BMMNC in remodeling and speed of tissue regeneration when transplanted with membrane HPUC taken from the wound area samples on days 7 and 14 and involving several cells of the BMMNC fraction from bone marrow aspiration had a positive effect on the anti-inflammatory process for differentiation. The important point of this study, the water absorption capacity of the HPUC membrane causes exudate retention so that there is a change in the levels of cytokines and wound surface growth factors.

Research by Cifuentes et al., 2020 reported that on the 3rd postoperative day, inflamed tissue appeared around the wound in the HEP and BEM groups, on the 7th day there was an inflammatory and proliferative phase, the granulation tissue process increased, and the tissue became thicker and thicker. regular. Day 14 showed good re-epithelialization, day 21 to more advanced stages of inflammation and vascular retraction, BEM group had the highest neo-epithelial thickness.

The study Zhu et al., 2020 reported that on the 6th day of the healing period, there was a rapid reduction in the wound area and good wound closure, on the 12th day the wound was almost completely closed. Usually in the first 3 days of treatment, there is an inflammatory phase, but chitosan, a component of water gel (hydrogel) has an antibacterial effect to reduce inflammation, and EGF in water gel (hydrogel) accelerates the proliferation of epidermal cells. The pH of the wound is acidic and the blood level is high, insulin is released from the ILM to suppress blood glucose. Evaluation of cell and tissue growth was carried out with H&E staining on the 6th day after treatment, granulation tissue and fibroblasts could be seen and the wound size decreased rapidly, after the 12th day blood vessels, glands, and hair follicles appeared in the wound, this study was shown to accelerate wound closure and promote the formation of skin appendages. Repair of the structure and function of the tissue formed by collagen was carried out with trichrome Masson staining, on the 6th day there was a small collagen deposition and on the 12th day, the accumulation of collagen continued to increase so that the healed wound tissue looked complete in the ILM-EGF-Gel-4 group.

The study Shen et al., 2020 reported that on the 14th post-traumatic day there was a reduction in wound area in the Col I/SCS group and almost completely healed with average healing of 97.3%, and on the 18th day, the wound was completely healed. This study observed the thickness of granulation tissue, the length of the wound edges, and the thickness of the epidermis on wound healing. On the 7th post-traumatic day, the thickness of the granulation tissue was significantly greater, the 18th post-traumatic day showed dense collagen deposition in the Col I/SCS group. On the 7th to 18th post-traumatic day, the length of the peripheral wound was reduced in the area of the Col I/SCS group. CD31 immunofluorescence staining (a typical marker of endothelial and neovascularization) was performed to determine angiogenesis occurred on the 7th and 18th post-traumatic days, the result was that CD31 was much higher in total wound granulation in the Col I/SCS group, this proves that Col I/SCS accelerates wound healing process and improve the quality of skin tissue. Immunofluorescence test and flow cytometry analysis showed that Col I/SCS was associated with macrophages in wound healing, there were pro-inflammatory CD86+ (M1) cells and pro-regenerative CD206+ (M2) cells, on the 3rd post-wound day mostly found in the wound bed and on the wound bed. The 7th post-traumatic day was reduced, however, due to the high number of CD86+ CD206+ macrophages, the reversed M1 polarization from the wound bed was directly induced to M2. The severe inflammatory phase occurred on day 7 of the Col I/SCS group. IL-6 was reduced in the Col I/SCS group on days 3 and 7, and TNF-α, IL-4, and TGF-β1 increased on days 7. Water gel (hydrogel) Col I/SCS decreased IL-6 and increased IL-4, IL-10, and TGF-β1 to produce anti-inflammatory and cytokine production to reduce pro-inflammatory.

The study Golmohammadi et al., 2020 reported that on the 10th day the M-Senps-ccH group had 80% healing and on the 21st day showed higher wound contractions than the other groups. Day 7 is the highest vascular formation, days 14 and 21 can be seen as the formation and presence of collagen, this result is based on three independent tests ($p<0.05$).

The study Bai et al., 2020 reported that during the first 3 weeks there was no change in glucose levels in the control group, but with treatment with water gel (hydrogel) + BM-MSC there was a decrease in blood glucose levels in the first 2 weeks ($p<0.05$). Wound healing was evaluated from the wound closure that occurred, where the water gel (hydrogel) group was significantly smaller than the control group ($p<0.05$), due to its moist nature to prevent cell death, increase epidermal migration, promote angiogenesis and collagen deposition, this proves the BM-MSCS group makes wound healing faster. On the 15th day, the wound was completely healed. Wound healing includes several processes, namely hemostasis, inflammation, proliferation, re-epithelialization, and remodeling, on day 6 the BM-MSC group had an appropriate inflammatory environment to accelerate healing, on day 12, few inflammatory cells remained which were affected by the gel dressing. water (hydrogel) to block external bacteria. The BM-MSC group also formed granulation tissue on days 6 and 12, during the maturation process of wound healing, collagen deposition also showed the process of wound contraction and scar formation with Trichrome Masson staining. Immuno-histochemical staining was used to visualize neovascularization.

Research by Lee et al., 2021 reported that the SNPECHG group healed faster and the wound size decreased on the 3rd day and the total healed on the 14th day, this is due to antimicrobial and cell growth. It was found that SNPECHG had lower adhesion thereby reducing the damage to the new tissue.

However, this study has disadvantages, it is because could not reviewing studies in which are experimental studies based on real clinical condition of patients with diabetic ulcer in hospitals.

CONCLUSION

Based on the results of this literature study, it can be concluded that the administration of chitosan water gel (*hydrogel*) combined with other ingredients affects the healing of diabetic ulcers. The chitosan water gel (*hydrogel*) action are reducing inflammation, re-epithelializing wounds, accelerating angiogenesis, accelerating the formation of collagen and granulation tissue, and accelerating wound healing. Therapy with chitosan water gel (*hydrogel*) can help reduce the cost of treating patients and reduce the occurrence of amputations in DM patients. This study suggests for the advance research in clinical case.

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