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Potentials of Immunonutrition in Wound Healing: A Review
(Potensi Imunonutrisi dalam Penyembuhan Luka: Tinjauan)

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ABSTRACT

A delayed wound healing process can lead to detrimental complications in chronic wound patients such as tissue necrosis and systemic infections. Application of immunonutrition (IN) in experimental animal models and chronic wound patients has shown promising and improved wound healing processes. IN restores the supply of essential nutrients that are critical for cell growth and tissue repair in the wounded subjects. Several commonly found nutrients in IN formulations include polyunsaturated fatty acids (PUFAs), essential amino acids, trace elements such as zinc and vitamins. Recently, some studies suggested the use of traditionally used herbs like curcumin in IN recipes due to its efficient wound healing properties. The roles and functions of IN in wound healing encompass recruitment of white blood cells, platelets and fibroblasts into the wounded area during the coagulation and inflammation phases, enhancement of fibroblast proliferation, collagen synthesis and neovascularization in the proliferation phase; and lastly, regulation of tissue re-epithelization for wound closure and recovery. In this review, the roles and functions of individual nutrients were deliberately discussed alongside their mechanisms of action in wound healing. This aims to provide a more holistic insight into the potentials of those nutrients when used as part of IN for major wound patients. Despite its remarkable effects in wound healing, several criteria should be considered in an IN formulation: the type and severity of wounds, administration timing and mode of administration, and concoction of immune-boosting nutrients in order to ensure the optimal wound healing effects.

Keywords: Wound healing; immunonutrition; PUFAs; amino acids; vitamins

ABSTRAK

Proses penyembuhan luka yang tergendala dapat membawa komplikasi yang memudaratkan kepada pesakit luka kronik, contohnya nekrosis tisu dan jangkitan sistemik. Aplikasi imunonutrisi (IN) dalam model haiwan kajian dan pesakit luka kronik menunjukkan proses penyembuhan luka yang memberangsangkan serta baik. IN memulihkan bekalan nutrien penting untuk pertumbuhan sel dan pembaikan tisu dalam luka. Beberapa nutrien yang biasanya digunakan dalam formulasi IN ialah asid lemak tak tepu (PUFAs), asid amino penting, unsur sirih seperti zink dan vitamin. Kebelakangan ini, terdapat kajian mencadangkan penggunaan herba tradisional seperti curcumin dalam resipe IN atas sebab kesan penyembuhan luka yang efisien. Kegunaan dan kefungsian IN dalam penyembuhan luka termasuk mengaruh kemasukan sel darah putih, platelet dan fibroblast ke kawasan tercedera sewaktu fasa koagulasi dan inflamasi, peningkatan kadar proliferasi fibroblast, sintesis kolagen serta neovaskularisasi dalam fasa proliferasi; akhirnya kawal atur proses pembentukan lapisan epitilia tisu bagi penyembuhan luka. Dalam tinjauan ini, kegunaan dan kefungsian setiap nutrien telah dibincangkan secara teliti di samping mekanisme tindakannya dalam penyembuhan luka. Hal ini bertujuan untuk membekalkan idea yang holistik tentang potensi nutrien tersebut apabila digunakan sebagai sebahagian daripada IN untuk pesakit luka major. Biarpun terbukti mempunyai kesan penyembuhan luka yang baik, beberapa kriteria perlu dipertimbangkan bagi suatu formulasi IN: jenis dan keterukan luka, waktu dan cara pemberian, dan kombinasi nutrient bagi mengoptimumkan kesan penyembuhan luka.

Kata kunci: Penyembuhan luka; imunonutrisi; PUFAs; asid amino; vitamin

INTRODUCTION

Wound healing is often described as an essential physiological process consisting of a combination of numerous cell types and their products in the human body. Different immune cells are involved in wound healing processes such as platelets, macrophages, fibroblasts, epithelial and endothelial cells involved in the stages of wound (Barchitta et al. 2019; Zainalabidin et al. 2020). The hemostasis phase including vasoconstriction and platelets activation, adhesion and aggregation at the site of injury take place to prevent excessive bleeding. The clot and the surrounding tissue release pro-inflammatory cytokines and growth factors such as transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF) to initiate the inflammatory phase (Guo et al. 2010). The inflammatory phase usually occurs within the first 24 hours after injury and the process may last up to two weeks or longer depending on the injury scale (Barchitta et al. 2019). A longer healing duration is often needed in chronic non-healing wounds. The granulocyte that actively mediates the pro-inflammatory phase is mast cell. It releases granules filled with enzymes, histamine and other active amines to promote the inflammatory response, which usually manifests as redness, warmth, swelling and pain sensation around the wound (Barchitta et al. 2019). In addition, the other phagocytes such as neutrophils, monocytes, and macrophages are also activated and armed during the inflammatory phase. They help cleanse the damaged tissue debris, fight potential infections, and release soluble mediators such as proinflammatory cytokines and growth factors to recruit and activate fibroblasts and epithelia for wound healing (Zainalabidin et al. 2020).

Next, the proliferative phase succeeds. This process aims to restore or repair the wounded area. Deposition of collagen fibers, proteoglycans, and fibronectin occurs along the wounded tissue. This stage is also coupled with cell proliferation and posterior differentiation in order to expedite the healing. Lastly, the tissue remodeling implies the final stage of the healing process. In this stage, newly formed tissue layers mature into scar and the tissue tightness is increased. Simultaneously, regression of many newly formed capillaries also occurs so that vascular density of the wound returns to its normal condition (Zainalabidin et al. 2020).

Table 1: Functions of IN in wound healing

IN components	Examples	Functions	Outcomes
Amino acids	•Arginine •Glutamine	• Glutamine is a precursor for glutathione that modulates inflammatory responses in wounds. • L-arginine is a precursor for nitric oxide that aids in vasodilation, and a precursor for proline that is involved in collagen production. • Metabolic fuel sources for proliferating cells. • Restoration of hydroxyproline. • Enhance tissue re-epithelization, vascularization, wound contraction and closure. • Improve tensile strength and collagen content. • Recruitment of leucocytes. • Regulate apoptosis of leukocytes and production of superoxide. • Arginine promotes the release of growth hormone and insulin-like growth factor 1 (IGF-1) for proper wound healing.	• Prevent microbial infections and inflammation in wounds. • Shorter hospital stay. • Improved wound healing rate.

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Polyunsaturated fatty acids (PUFAs)	• Eicosapentaenoic acid (EPA) • Docosahexaenoic acid (DHA) • Linoleic acid	• Reduce inflammation. • Regulate regulated neutrophil and macrophage counts. • Alter the expression of eicosanoids. • Regulate the expression of nuclear transcription factor kappa beta (NF-κB) that is responsible for the expression of proinflammatory cytokines	• Enhanced synthesis of new vessels. • Higher fibroblast and collagen fiber organization.
Vitamins	• Vitamin A (E.g. retinol, retinoic acid and beta-carotene)	• Promotes B and T cell functions and antibody production. • Promotes epithelialization, collagen synthesis, and tissue granulation.	• Improved immune responses, wound recovery and shorter hospital stay. • Less susceptibility to pathogen infections.
	• Vitamin C (E.g. ascorbic acid)	• Aids in cell migration and transformation, collagen synthesis, antioxidation, and blood vessel formation.	
Zinc		• Aids in membrane repair, tissue re-epithelialization and scar formation. • Promotes aggregation of platelets and blood clotting. • Acts as a co-factor in DNA replication of inflammatory and epithelial cells.	• Damaged tissue clearance and rapid wound healing.
Curcumin		• Stimulation of cell growth. • Anti-inflammation and antioxidant. • Promotes early tissue re-epithelialization, neovascularization, and cell migration.	• The balance between inflammation and antioxidative stress is restored. • Speedy wound closure. • Prevention of microbial invasion.

Wound healing is often affected by a few factors such as age, infections, diseases, obesity, alcoholism, smoking, medications and nutrition (Guo et al. 2010). Besides, interruptions or prolonged cellular activities may result in a delayed wound healing or non-healing chronic wound. It is believed that changes in nutrient intake might play a role in the wound healing process particularly in modifying the inflammatory or immune responses, this phenomenon is therefore termed immunonutrition (IN). IN has been shown to influence various aspects of immune functions and the production of inflammatory mediators (Calder 2003).

Numerous studies including meta-analyses, clinical trials, and systematic reviews have been carried out to assess the benefits of IN in a variety of populations and diseases, for instance cancers, trauma, surgery as well as critically ill patients (Paranjothi Yanok et al. 2020). In these studies, IN helps control inflammatory responses, reduce infection complications, preserve liver functions and regeneration. It eventually results in significant reduction in infection and mortality rates, and length of hospital stay (Paranjothi Yanok et al. 2020; Zhang et al. 2017). This review aims to provide insightful information on the benefits of individual components such as amino acids, fatty acids, vitamins, zinc and curcumin in wound healing (Table 1). Their benefits in various clinical and laboratory researches are deliberately discussed in this review.

ROLES AND FUNCTIONS OF ESSENTIAL AMINO ACIDS IN WOUND HEALING

Biologically, essential amino acids such as glutamine and arginine act as the primary metabolic fuel sources for actively proliferating cells (Chow & Barbul 2014). Under chronic circumstances such as stress and catabolic conditions like during injury, surgery, wounds, burns and trauma, glutamine is highly demanded in order to help

restore the body's homeostasis (Goswami et al. 2016). In the abovementioned situations, the glutamine level in the plasma is often low, which eventually interrupts the collagen synthesis (Kesici et al. 2015). It therefore becomes a risk factor for mortality among the chronically wounded patients. Jabłońska & Mrowiec (2020) showed that concurrent administration of glutamine and arginine managed to restore hydroxyproline concentration by 19% chronic wound patients. Goswami et al. (2016) also proved that oral administration of glutamine (1g/kg/day) in Wistar rats with incised wound enhanced tissue re-epithelization along with the formation of new blood vessels, increased wound contraction and closure, improved tensile strength and collagen content. Meanwhile, the activities of macrophages, lymphocytes and fibroblasts in the wounded parts also increased following the glutamine administration, thus prevented possible microbial infections (Karimipour et al. 2018). To prevent further inflammation-induced tissue damage in wounds, glutamine administration induces heat shock protein synthesis to avoid uncontrollable inflammation (Chow & Barbul 2014), serves as a precursor for glutathione (an important cell membrane stabilizer), regulates apoptosis of leukocytes and production of superoxide (Chow & Barbul 2014).

According to the American Society for Parenteral and Enteral Nutrition, supplying parenteral glutamine as early as possible, between 0.2 and 0.5 g/kg/day is able to improve chronic conditions among patients. This was supported by McRae (2018) in which administration of glutamine at 0.3 to 0.5 g/kg/d helped restore the gut function particularly in terms of the height of villi in the small intestine. It then further heightened the gut immunity and prevented bacterial translocation; hence reduction in the secondary infection rate. Moreover, Zhou et al. (2003) also showed that the length of hospital stay was shortened following the supplementation of glutamine. Similarly, Sun et al. (2013) demonstrated that the administration of 0.3g/kg glutamine dipeptide in burn patients for 10 days successfully shortened the total hospital stay, improved wound healing rate, and lowered inflammatory cytokines (IL-6, TNF-α) and molecules [bacterial lipopolysaccharides (LPS)] than the control group. In burn patients, the plasma and muscular levels of glutamine is purportedly reduced which in turn increases the risk for secondary infections (Jalilimanesh et al. 2011; Jabłońska & Mrowiec 2020). This is because glutamine deficiency might lead to intestinal mucosal injury and increased intestinal wall permeability; it ultimately causes bacterial translocation and infections (McRae 2018). The glutamine-containing nutritional formulations are believed to promote the wound healing process in the patients via the expression of vascular endothelial growth factor (VEGF) and neovascularization around the wounded region. This is particularly evident in individuals recovering from reconstructive and plastic surgery (Goswami et al. 2016). Ischemic episodes could occur in the distal area of skin flap surgery due to insufficient blood flow and tissue damages by free radicals and inflammatory mediators. The adverse outcomes of ischemic episodes include cell necrosis and death. As a result, an early administration of glutamine is highly recommended for chronic wound patients in order to prevent severe complications and infections.

Despite many studies have proved that glutamine aids in immune-boosting and wound healing, whether the presence of excessive amount of glutamine in the time of chronic wounds is truly beneficial remains debatable (Paranjothi Yanok et al. 2020). Many studies support that adults with balanced diet intake and without compromised immunity do not require additional supplementation of glutamine and the other amino acids. Kesici et al. (2015) argued that supplementation of glutamine did not benefit deltoid implant patients aged 70 years and above due to poor protein absorption. Of note, glutamine requirement for wound healing should be investigated and monitored case-by-case among chronic wound patients in order to maximize the wound healing process.

Besides glutamine, L-arginine, an end product of glutamine metabolism, is another heavily studied nutrient for its effects in wound healing (Karimipour et al. 2018). In terms of wound healing, it is a precursor for nitric oxide that aids in vasodilation. Administration of arginine has been associated with improved circulation (Alexander & Supp 2014). Arginine also promotes the release of growth hormone and insulin-like growth factor 1 (IGF-1) that aid in proper wound healing (Alexander and Supp 2014).

On top of that, arginine is also a precursor for proline which is involved in the process of collagen synthesis. Chow and Barbul (2014) showed that oral and parenteral supplementation of arginine increased collagen deposition in wound hence speedy wound healing. Furthermore, oral administration of arginine has also shown promising effects in patients with epidermal burns, and premature infants suffering from necrotizing enterocolitis (Amstrong et al. 2014). Interestingly, the healing effects of arginine is not only observed among chronic wound cases but also proven to restore collagen composition in the corneal of those suffering from keratoconus (KC) (McKay et al. 2021). KC is commonly characterized by the thinning of the central corneal apex which is probable to cause remarkable reduction in visual acuity. In the study, provision of arginine was shown to improve collagen type I secretion. This is believed to be attributable to the expression of arginase that converts arginine to ornithine and subsequently to proline and hydroxyproline (Alexander & Supp 2014; MacKay et al. 2021) for collagen and

polyamine synthesis in order to support protein synthesis, cell growth and proliferation. Such observations further substantiate the ability of arginine in improving wound recovery through collagen synthesis and deposition; hence the recommendation of including arginine in IN formulations (Chow & Barbul 2014).

In addition to the aforementioned cases, the wound healing effects of arginine have also been well documented in several other clinical studies. Brewer et al. (2010) found that spinal patients administered with an arginine-supplemented drink showed a two-fold greater healing rate of pressure ulcer (PU). Similar observations were also reported by Cereda et al. (2015) in which an oral nutritional formulation fortified with arginine, zinc, and antioxidants was found to significantly improve pressure ulcer healing in malnourished patients after 8 weeks of oral administration. Durmus et al. (2017) explored the role of arginine as ointment (arginine silicate inositol, also known as ASI) for topical wounds. Tissue granulation was reportedly quicker in ASI-treated mice, with a substantially smaller wound size and greater percentage of total wound healing. In spite of its remarkable benefits in wound healing, provision of arginine in IN recipes requires more rigorous empirical and clinical investigations in order to better understand the mechanisms of action involved, so that chronic wound patients readily benefit from arginine supplementation (McKay et al. 2021).

ROLES AND FUNCTIONS OF POLYUNSATURATED FATTY ACIDS (PUFAS)

The quality and composition of fatty acids may impact on the wound healing process, as high-fat diets have been associated with various chronic diseases, inflammation and impairment of wound healing (Shield 2021). Polyunsaturated fatty acids (PUFA) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that are commonly found in deep sea fish are considered high-quality (Djuricic & Calder 2021). Intake of EPA and DHA are reported to lower the incidence of chronic diseases caused by elevated inflammation (Djuricic & Calder 2021).

The roles and functions of PUFAs have been tested in animal models and clinically in order to substantiate their impacts on wound healing. Meng et al. (2021) demonstrated that mice fed with omega-3 (a form of PUFA) diet showed less severe tissue damage post UV-exposure. Their wounds also healed more readily than the control mice fed with standard diet. Similar observations were also reported by Rodrigues (2016) in which diabetic rats fed with linoleic acid (LA) had better regulated leucocyte counts such as neutrophils and macrophages in the early and late phase of wound healing, respectively. In the injured tissues, release of cytokines and growth factors (VEGF) by leucocytes that enhance the synthesis of new vessels showed positive changes hence speedy recovery process. In another study by Babaei et al. (2017), the effects of Omegaven (a type of fish oil) on diabetic wound were examined in diabetic male rats. The wound was introduced via excision. The results showed that the wound size reduced drastically in seven days with a significant increase in the number of mast cells that were responsible for tissue re-epithelialization, angiogenesis and tissue scarring. Similarly, Skuladottir et al. (2007) also found that Omegaven could prevent the overexpression of inflammatory cytokines such as IL-1, IL- 6, and TNF-α, which in turn increased the ability of wound contraction.

The wound healing effect of PUFAs, for instance omega-3, is also attributable to the higher fibroblast and collagen fiber organization upon PUFAs supplementation. Peng et al. (2017) found out that rats fed with PUFAs emulsion led to a spike in tissue cellularity around the wounds after 14 days. Formation of new blood vessels and tissue granulation were, too, detected in the damaged area (Hankenson et al. 2000). Upon PUFAs intake, the production of eicosanoids especially prostaglandins (PGE2), leukotrienes and lipoxins is expected to be altered due to a shift in the membrane lipid composition (Futagami et al. 2002). Altogether, the aforementioned biological events might speed up wound closure and recovery (Lania et al. 2019).

Clinically, in gastric cancer patients undergoing gastrectomy, an early postoperative enteral diet supplemented with arginine, omega-3 fatty acids, and RNA was shown to enhance hydroxyproline synthesis and thus improved the healing of surgical wounds (Farreras et al. 2005; Paranjothi Yanok et al. 2020). McDaniel et al. (2011) supplemented two types of omega-3 PUFAs, i.e. docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) derived from fish oils to healthy human subjects, followed by an induction of blisters on their arms. The subjects had significantly higher plasma levels of EPA and DHA than the placebo group. The wound fluid was also remarkably reduced after 28 days. It is believed that the combination of EPA and DHA is able to limit the synthesis of inflammatory eicosanoids, such as cyclooxygenase (COX) and lipoxygenase (LOX) from the cell membrane lipids (Sun et al. 2007). Owing to their prominent anti-inflammatory functions, the increased EPA and DHA bioavailability can limit the overly reactive inflammation in chronic wounds, hence speedy healing.

In addition, Theilla et al. (2012) studied the efficacy of fish oil on patients with pressure ulcers grade II or higher. A pressure ulcer is defined as a localized damage to the skin and underlying tissues due to tremendous pressure,

friction, shear or any of those combinations. The plasma level of inflammatory C-reactive protein (CRP) was found to be significantly lower on day-14 in comparison to those receiving isocaloric control formulation. The study implies the critical role of essential fatty acids in diminishing the inflammatory response which in turn minimizes tissue injury and benefits wound healing.

Based on the aforementioned clinical trials, several underlying PUFAs-associated anti-inflammatory mechanisms that promote wound healing in patients have been deduced. Firstly, via the production of inducible nitric oxide synthase (iNOS) and nitric oxide (NO) by immune cells after PUFAs supplementation (Djuricic & Calder 2021). Immune cells such as macrophages express iNOS that oxidizes L-arginine into NO and the other free radicals. NO and free radicals help promote the activation of macrophages and fibroblasts, collagen synthesis and proliferation of keratinocytes. These tissue repairing events accelerate reepithelization in wounds. Secondly, PUFAs are believed to reduce the activation of nuclear transcription factor kappa beta (NF-κB) that is responsible for the expression of proinflammatory cytokines (Djuricic & Calder 2021). A prolonged, chronic inflammation caused by proinflammatory cytokines such as IL-1ß and IL-6 can lead to tissue damage, metabolic changes and loss of function which delay wound healing (Djuricic & Calder 2021). Mcdaniel et al. (2008) also reported that supplementation of omega-3 fatty acids in the form of fish oil capsules decreased the proliferation of lymphocyte systemically and the synthesis of proinflammatory cytokines. Thirdly, while the activation of NF-κB is reduced, the production of activator protein (AP)-1 is elevated (Rodrigue et al. 2011). The elevated AP-1 level enhances the expression of genes that are related to the proliferation of keratinocytes and fibroblasts and therefore enables the proliferative phase of wound healing to start early.

Although proven beneficial when consumed adequately, administration of PUFA in a larger scale of trials is warranted in order to determine the optimal dose and composition of fatty acid supplementation that may improve wound healing (Paranjothi Yanok et al. 2020). Furthermore, investigating the impact of omega-3 PUFA in combination with the other macronutrients such as amino acids and the other essential fatty acids on wound healing is also recommended (Paranjothi Yanok et al. 2020).

IMPORTANCE OF VITAMINS A AND C IN WOUND HEALING

There are many forms of vitamin A, such as retinol, retinoic acid and beta-carotene. Polcz and Barbul (2019) showed that vitamin A deficiency might cause a delay in wound healing as a consequent of poor wound closure and lower rate of collagen synthesis. In wound healing, vitamin A accelerates the inflammatory phase and collagen synthesis. Vitamin A deficiency can undermine B and T cell functions and antibody production in the inflammatory phase, and decrease epithelialization, collagen synthesis, and tissue granulation in the proliferative and remodeling phases (Barchitta et al. 2019). Zinder et al. (2019) reported that vitamin A supplementation could prevent delay in wound healing caused by corticosteroid treatment by downregulating the synthesis of tumor growth factor (TGF)-β and insulin-like growth factor-1 (IGF-1). Nonetheless, vitamin A intake requires strict compliance to the prescription in order to avoid toxicity. A short-term supplementation of 10,000–25,000 IU/day is recommended for patients suffering from chronic wounds. Vitamin A toxicity can result in the following symptoms: acute toxicity causes nausea and vomiting, headache and increased intracranial pressure whereas chronic toxicity causes an abnormal rise in liver markers, changes in skin, hair and nails besides headache and increased intracranial pressure. Apart from oral administration, vitamin A is often applied topically (Polcz & Barbul 2019). Retinoids added into the topical medications bind to specific cellular receptors; the binding then initiates RNA transcription and protein synthesis that are essential for the regeneration of new cells (Polcz & Barbul 2019).

Vitamin C, also known as ascorbic acid is involved in various processes of wound healing (Moores 2013). Vitamin C is essential for cell migration and transformation, collagen synthesis, antioxidation, and blood vessel formation (Barchitta et al. 2019). Guo and DiPietro (2010) showed that vitamin C deficiency might delay recovery and healing processes as a result of decreased collagen synthesis and fibroblast proliferation, lack of angiogenesis and increased capillary fragility. Altogether, it leads to impaired immune responses, delayed recovery and longer hospital stay and higher susceptibility to pathogen infections.

During the inflammatory phase, vitamin C helps in neutrophil clearance meanwhile in the proliferative phase, it is required for collagen synthesis and maturation via hydroxylation of proline and lysine residues (Shield et al. 2021). Deficiency in vitamin C might lead to fragility of new blood vessels. Ascorbic acid is also found to prevent exacerbation of tissue damage in wounds by counteracting the damaging effects of free radicals (Barchitta et al. 2019). Currently, vitamin C supplementation range is recommended from 500 mg/day in mild, less severe wounds to 2 g/day in severe wounds. Vitamin C functions most effectively in improving wound healing in combination with zinc and arginine (Barchitta et al. 2019).

The impacts of vitamin C on wound healing have been tested in both experimental animals and human subjects. In wounded diabetic rats, a dietary ascorbic acid formulation seemed to improve the collagen deposition in diabetes-perturbed connective tissues (Christie-David et al. 2015). Lee et al. (2012), on the other hand, proved that incorporation of vitamin C in the animal feed provided excellent antioxidant and anti-apoptotic activities. Such effects subsequently enhanced the maturation of dermal and epidermal layers in the wounded areas.

Clinically, Bikker et al. (2016) reported in a case study involving a 59-year-old male patient who underwent an exploratory laparotomy for abdominal pain, that after 2.5 weeks of 1000 mg ascorbic acid intake, his wound size showed progressive reduction, and 2.5 months later, the surgical wound had fully closed. In another case study that involved a 79-year-old female with medical history who was first admitted due to severe ulcer on her leg, the patient complained of a new wound two months after discharge (Bikker et al. 2016). The new wound was found near to the area where a necrotic tissue surgery and pinch grafting were performed. Her plasma ascorbic acid level was found lower (8 umol/L) than the normal range (25-28 umol/L). Immediately, the patient was put on ascorbic acid supplementation (1000 mg/day). Interestingly, her health status started to improve including the surgical wound and she completely recovered after 8 months.

Besides being prescribed orally, Haddadi et al. (2021) also explored the use of vitamin C as a topical ointment for wounds. In the study, vitamin C was added into an ointment formulation in combination with silver sulfadiazine and applied on burn wounds. The intervention successfully raised the level of ascorbic acid in the patients and therefore led to rapid wound recovery.

Based on the reported observations, vitamin C supplementation could be beneficial to the healing of chronic wounds even if given post-surgery and injury. In order to ensure a vitamin C supplementation exerts its best benefits in target patients it is always advisable to monitor their vitamin C levels pre- and post-surgery.

ZINC

Collagen synthesis, protein synthesis and cell replication require the presence of zinc (Lin et al. 2008). Zinc is essential to the wound healing process due to its roles in membrane repair, tissue re-epithelialization and scar formation (Lin et al. 2018). Zinc causes aggregation of platelets and blood clotting through phosphorylation of platelet proteins by protein kinase C (PKC). In addition, zinc also induces alpha-granule release by platelets that subsequently recruits immune cells to the injured area for healing purposes (Blair & Flaumenhaft 2009).

The presence of zinc is essential for DNA replication in inflammatory and epithelial cells. During the inflammatory stage in wound healing, activation and proliferation of lymphocytes, and antibody production are enhanced by zinc (Barchitta et al. 2019). Zinc deficiency is often associated with low populations of both precursor and mature B cells hence lower humoral immunity for protection and wound clearance and healing (Barchitta et al. 2019). Supplementation of zinc in Acquired Immune Deficiency Syndrome (AIDS) patients was capable of restoring the phagocytosis of foreign particles by neutrophils (Lin et al. 2018). Moreover, during the proliferation phase, zinc ensures the stability and integrity of cell membrane, efficient protein synthesis, and DNA replication and RNA transcription in fibroblasts. The importance of zinc in accelerating wound closure is also implied by its impact on the proliferation and activities of regulatory T (Treg) lymphocytes. Treg is responsible for limiting pro-inflammatory responses, promoting re-epithelization and tissue contraction (Lin et al. 2018). Although zinc has shown positive effects on neovascularization, consumption of zinc in excess is likely to lead to failure in blood vessel formation in wounds (Lin et al. 2018). The lack of newly formed blood vessels in wounds limits the oxygen and nutrient supply that are essential for cell growth and recovery, thus delays wound closure and healing. In order to ensure zinc supplementation promoting cell growth, tissue repair and re-epithelization, and wound closure without compromising angiogenesis, it is suggested that supplementation of zinc to be used only in individuals with zinc deficiency (Lin et al. 2018).

CURCUMIN (DIFERULOYLMETHANE)

Some traditionally used herbs such as curcumin (an active compound derived from turmeric) have been recommended to be applied as part of IN especially in wound healing. Demirovic and Rattan (2011) tested the effects of curcumin treatment on human skin fibroblasts undergoing aging *in vitro*. They found that curcumin could affect the wound healing process in biphasic dose-response dependent fashion, i.e. it facilitates cell growth and proliferation at small doses, however, exerts its inhibitory effects at larger doses. In order to better apply curcumin as an IN component, Cheng et al. (2001) initiated curcumin administration on patients who were at high risk of pre-malignant lesion. The results indicated that curcumin was not toxic to the subjects at concentrations up to 8000 mg/day when administered orally for three months.

Given the well-defined toxicity profile and its ability to stimulate cell growth, curcumin was used to treat wounds without dexamethasone (a type of glucocorticoid medication for skin conditions) in mice (Mani et al. 2002). The wound size and gap of the treated mice were remarkably smaller than that of the normal control mice. Surprisingly, the curcumin treatment was equally effective when administered orally and topically. Several anti-inflammatory and antioxidant properties of curcumin are believed to contribute to the wound healing processes. For instance, reduction of TNF-α and IL-1 expression, and restoration of the balance between reactive oxygen species (ROS) production and antioxidant activity (Barchitta et al. 2019). In wounded areas, cytokines such as TNF-α and IL-1 and ROS are produced to initiate the inflammation phase. This allows infiltration of fibroblasts and white blood cells into wounds in order to fix the injured and damaged tissues while prohibit the intrusion of pathogenic microorganisms (Paranjothi Yanok et al. 2020). Nonetheless, a prolonged inflammation is dangerous for cell structures due to excessive oxidative stress (Barchitta et al. 2019). Upon curcumin treatment, the balance between inflammation and antioxidation is restored to status quo. Furthermore, the number of M2-like macrophages that are responsible for anti-inflammatory response also increases following curcumin administration. Altogether, the wound healing is able to progress into the proliferation and regeneration phases more smoothly and readily (Barchitta et al. 2019).

The wound healing effect of curcumin was also proven in wounded diabetic rats (Sidhu et al. 1999). The curcumin treatment promoted early tissue re-epithelialization, neovascularization, and migration of various cells into the wounded area. The migration of dermal myofibroblasts, fibroblasts, and macrophages into the wound sped up wound closure meanwhile prevented microbial invasion into the wound. This eventually encouraged greater collagen deposition and higher expression of transforming growth factor-1 (TGF-1) in the curcumin-treated wounds than the control group. Similarly, Gopinath et al. (2003) also observed better biochemical and histological readings in mice treated with curcumin-infused collagen matrix (CICM) than the control group. The CICM-treated rats showed improved wound reduction, higher cell proliferation, and more efficient free radical scavenging following the treatment.

As curcumin is relatively safe and less toxic for use in cells, a high-dose curcumin treatment was attempted in rats induced with nasal mucosal trauma for fifteen days (Emiroglu et al. 2017). Comparing the treated and control rats, the former showed less ciliary degeneration and loss, as well as reduced cellular hyperplasia. The growth of nasal epithelia was not adversely affected by the treatment. As a result, curcumin was believed to speed up the wound epithelialization hence quicker recovery.

CONSIDERATIONS FOR THE IMPLEMENTATION OF IN IN WOUND HEALING

Several lines of evidence provided above imply the potentials and importance of IN in wound healing. However, a few noteworthy considerations should be made prior to deciding on the IN formulations for chronic wound patients, i.e. the nature of wounds (surgical incision site, lacerations and abrasions), administration timing (pre- or post-injury or surgery), mode of delivery (enteral, parenteral, oral or topical administration), concoction of immune-boosting nutrients, toxicity profile and mechanisms of action (pro- or anti-inflammatory) of the nutrients of choice for wound healing (Barchitta et al. 2019). Although insignificantly impacts on wound closure, some nutrient combinations are possible to reduce the quality of healing. Burger et al. (2019) stated that orally ingested EPA-rich oil slightly delayed the rate of wound healing. The delay was speculated to be driven by the overexpression of anti-inflammatory IL-10 throughout the wound healing processes. This notion was supported by Yamane et al. (2020) in which a poor-quality protein meal was shown to exert deleterious effects on wound healing in mice as a consequence of failure in properly modulating the matrix metalloproteinase-2 (MMP-2) activities in the experimental animals. In terms of mode of delivery, oral administration seems to be more effective than topical application. For example, some curcumin gel preparations were proven to be ineffective in improving skin excision healing in alloxan-induced diabetic mice (Berbudi et al. 2018).

CONCLUSION

IN generally has been proven to be beneficial for wound healing. It complications due to post-surgery wound infections and shortens the length of hospital stay, hence lower treatment costs. In a nutshell, IN is able to deliver specific nutrients that are required and essential for wound healing directly to chronic wound patients and thereby accelerates the wound healing.

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