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ALPHA-MANGOSTIN (*Garcinia mangostana* Linn.) AND ITS POTENTIAL APPLICATION IN MITIGATING CHRONIC WOUND HEALING

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ABSTRACT

Wound healing is a complex and dynamic cellular process to restore tissue function. Current treatments for chronic wounds especially diabetic ulcers are expensive, with adverse effects. Recently, numerous researchers have focused on the potential effect of natural products on wound healing. One of them is mangosteen (*Garcinia mangostana* Linn). It is a well-known tropical fruit that is native to Southeast Asia. The active ingredient of mangosteen pericarp contains xanthones that exhibit a wide range of pharmacological activities, including anti-inflammatory and anti-bacterial properties which are the core elements needed in wound healing. Firstly, this review discusses the concepts of abnormal and normal wound healing mechanisms. Then an in-depth observation of the pharmacological activities of mangosteen and its derivatives was presented to study their potentially beneficial applications in the treatment of chronic wound healing which is a contemporary medical issue.

Key words: Chronic wounds, *Garcinia mangostana*, natural product, wound healing

INTRODUCTION

Wound healing is a complicated and highly regulated process that is essential in the preservation of tissue function. The cascade of events involved in wound healing is protracted in chronic wounds causing significant discomfort and distress to the sufferer (Han & Ceilley, 2017). A chronic wound fails to heal in a timely and ordered manner, resulting in loss of anatomic and functional integrity (Yao *et al*., 2020). It does not heal within a few weeks of the commencement of treatment due to the variables such as infection and foreign objects leading to the formation of chronic ulcers. The main types of chronic ulcers are diabetic foot, pressure, arterial, venous ulcers, and fungal-infected wounds. (Liu *et al*., 2017). Although their aetiology differs from each other, they share some common characteristics of chronic wounds (Mustoe, 2004). The burden of treating chronic wounds is increasing at an alarming rate around the world, owing to rising healthcare expenses. For example, approximately 2% of the population in Denmark alone will suffer from chronic wounds during their lifetime. In the United States, chronic wounds are a silent pandemic that afflicts around 6.5 million people (Gottrup, 2004; Sen *et al*., 2009). In the Asian region, diabetic foot ulcer is the category with the highest incidence among all types of chronic wounds for decades, and the number is expected to rise dramatically (Gupta *et al*., 2021). The prevalence of diabetic wounds and the cost of care have recently increased significantly throughout Southeast Asia. In Malaysia, the prevalence of diabetic foot ulcers and lower-limb amputation increased by 30% between 2006 and 2011. Singaporean health statistics showed a rising trend in the clinical and financial burden of wound care where the gross healthcare costs for all inpatient wound management in 2017 were USD 216 million and USD 596000 in a primary care setting (Lo *et al*., 2020).

Although there are various treatments using technology or recombinant agents available for diabetic wounds they are not without side effects

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(Phillips & Dover, 1991). Therefore, the search for novel and potent natural plant medicines to treat chronic wounds has exploded in recent decades, particularly in patients with underlying metabolic problems. This is mostly owing to the significant complications of chronic wounds causing loss of function and mobility when amputation or death following sepsis occurs (Kapp & Santamaria, 2017).

Mangosteen is a tropical fruit that contains a substance with wound healing capabilities. In this review, we would like to discuss the use of an active compound derived from mangosteen pericarp. Our goal is to raise awareness of the benefits of mangosteen pericarp extracts in treating chronic wounds and subsequently to highlight the research area needed to optimize the fundamental knowledge about its mechanism of action.

Concepts of abnormal and normal wound healing mechanism

Abnormal wound healing occurs when wounds fail to heal promptly or when wounds progress through the healing process without restoring anatomical and physiological functions (Lazarus *et al*., 1994). Wound healing is a complex process that involves tissue restoration including skin following an injury, in which unwanted structures and tissue layers are replaced. Chronic wound healing may take many months to heal completely despite adequate wound care management (Abrigo *et al*., 2014). It is postulated that delayed healing is caused by persistent inflammation and an insufficient angiogenic response (Peppa *et al*., 2009). Angiogenesis, regeneration of functional connective tissue matrix, contraction, resurfacing, and remodeling are examples of biological events involved in chronic wound healing. Normal anatomical structure, as shown in Figure 1, and its biological events are disrupted by the wounds (Lazarus *et al*., 1994).

Hemostasis, inflammation, proliferation, and remodeling are the four stages of wound healing. The wound healing process is dependent on active participation and contributions to its cellular and metabolic components (Schultz *et al*., 2011). Each phase has its time length, cellular characteristics, extracellular agents, and growth factors that function as signals, suppressors, and promoters. The acute inflammatory response plays an important part in tissue repair, as it is essential for the equilibrium when blood begins to clot and helps to prevent excessive blood loss. The inflammatory response is an important aspect of the wound healing process after an injury. Its primary goal is to kill bacteria and remove foreign debris from the wound (Demidova-Rice *et al*., 2012; Slavich & Irwin, 2014).

Following the inflammatory phase, the wound enters the proliferative phase, in which the wound area is populated by proliferative fibroblasts, angiogenesis, and surface re-epithelialization. Next, the remodeling phase manifests itself by a decrease in angiogenesis and increases in the laying down of collagen and ground substances. This is near the conclusion of the healing process, as the new tissue gradually increases strength and flexibility (Nussbaum *et al*., 2015).

In chronic wound healing, the cells involved such as macrophages, endothelial cells, and fibroblasts, will release growth factors and cytokines such as interleukins (IL-6), tumor necrosis factor-α (TNF-α), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). The mediators form a signaling network between different cell types involved in wound healing. Endothelial cells are the lining of the vasculature, acting as a conduit for oxygen, nutrients, and blood-borne cells. Matrix remodeling influences endothelial integrin-matrix interactions during wound healing, increasing angiogenesis (Yussof *et al*., 2012; Lindley *et al*., 2016; Agyare *et al*., 2018).

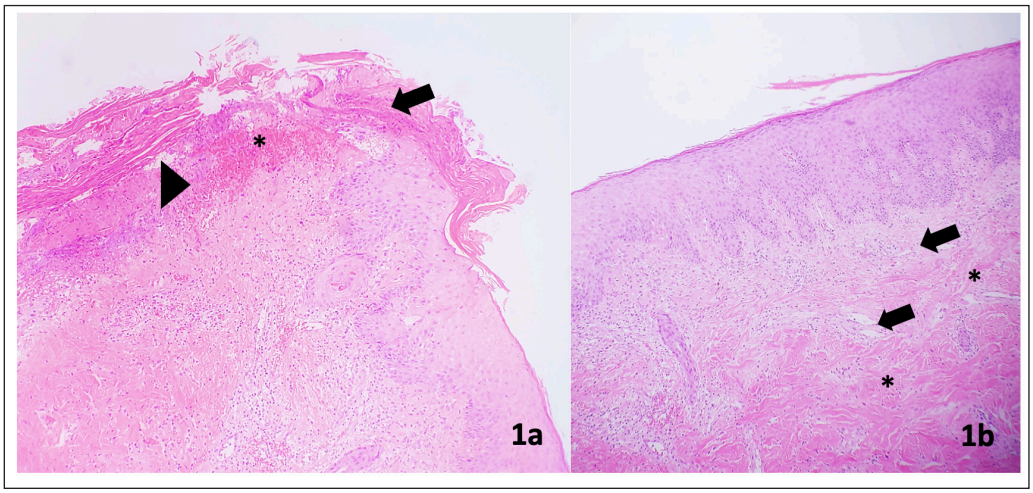

Fig. 1. Photomicrograph showing (1a) a skin wound (arrow) with blood clot (*) and the beginning of inflammatory cell infiltration (arrowhead), (1b) An area of healed wound with increase in collagen (*) and residual vascularization (arrows).

Small polypeptides called cytokines and growth factors affect cellular proliferation, migration, and metabolism. High levels of cytokines are associated with poor wound healing in chronic wounds. When fibroblasts become nonresponsive, cytokines secretions due to neutrophil and macrophages activity increase as a feedback mechanism to stimulate a response from the fibroblasts cells, resulting in higher levels of the pro-inflammatory cytokines in non-healing wounds compared to healing wounds. When healing commenced, these cytokines levels dropped considerably (Yussof *et al*., 2012b; Patel *et al*., 2016).

In the early stages of wound healing, macrophages promote neovascularization and surface epithelial proliferation by releasing growth factors and other mediators. Studies have shown that removing macrophages at the early stages of wound healing reduces neovascularization and re-epithelialization, whereas eliminating macrophages later in the healing process seems to promote tissue repair (Dulmovits *et al*., 2012). In a healthy healing wound, fibroblasts help to speed up the healing process where proliferation and epithelialization will happen (Darby & Hewitson, 2007).

Tissue enzymes such as matrix metalloproteinase (MMPs) and their inhibitors such as tissue inhibitors of metalloproteinase (TIMPs) are also involved in wound healing. In acute and chronic wounds, matrix metalloproteinases (MMPs) are present. Together with inhibitors, it serves a critical function in regulating extracellular matrix breakdown which is required for wound reepithelialization. Chronic wounds have high levels of MMPs. MMPs levels in wounds could be regulated to promote wound healing. MMPs are required for cell migration and tissue remodeling during all stages of wound healing (Caley *et al*., 2015). Figure 2 illustrates the difference in mechanisms involved in the normal and abnormal wound healing process.

The role of natural products in wound healing

Natural products have been studied to promote the wound healing process due to the anti-inflammatory, anti-antioxidant, and antibacterial activities of their active ingredients (Thakur *et al*., 2011). During wound healing, these phytochemicals can enhance the process by improving tissue remodeling and increasing angiogenesis by promoting the secretion of growth factors (Hsu, 2005; Berghe & Haegeman, 2010; Thangapazham *et al*., 2016). Therefore, studies on the underlying mechanism of the effects of these bioactive compounds are becoming an important focus in wound healing research (Jivad *et al*., 2016; Naji *et al*., 2017). One such compound is the mangosteen (Aukkanimart *et al*., 2017

Publications related to the use of mangosteen in promoting wound healing have surged in recent years. However, there are still no updated reviews on this flourishing research area. This article aims to review some available literature on the use of mangosteen pericarp extracts in wound healing.

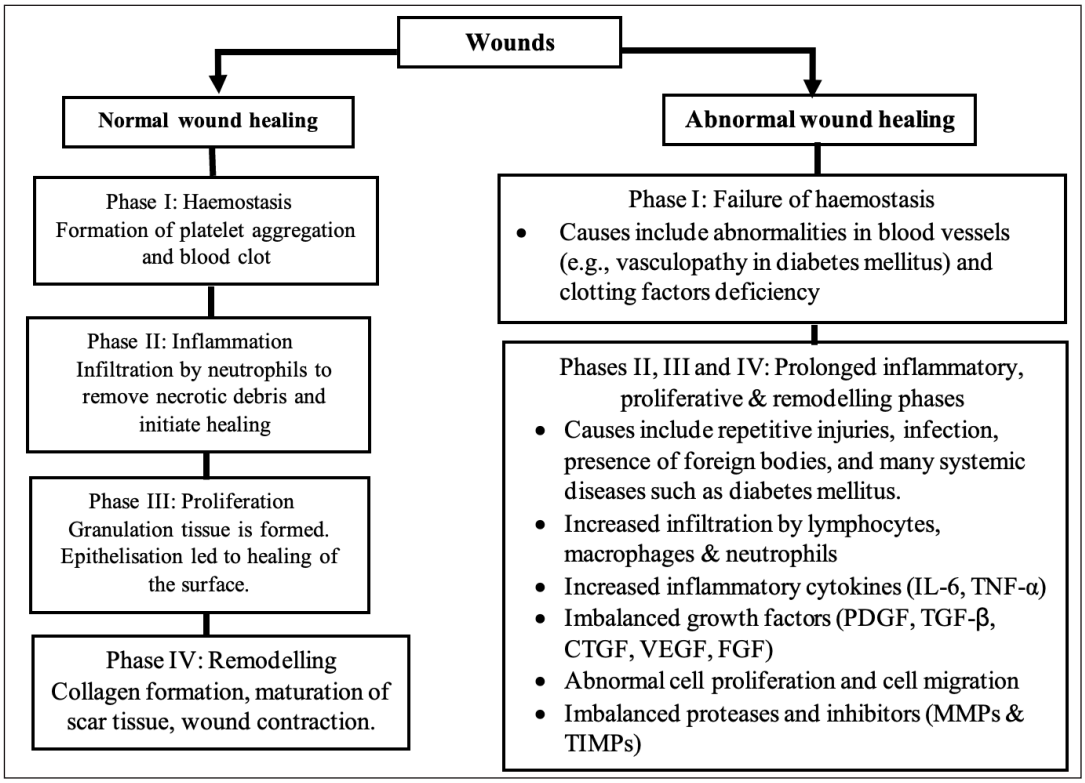

Fig. 2. The difference in mechanisms involved in the normal and abnormal wound healing process.

Mangosteen pericarp and wound healing

Mangosteen (*Garcinia mangostana* Linn) has a wide range of oxidative and xanthones derivatives sources (Yang *et al*., 2017). It has become a well-studied plant in the search for novel chemicals with interesting biological activities and therapeutic potential (Obolskiy *et al*., 2009).

The peels of mangosteen are rich in phenolic compounds such as xanthones (Suttirak *et al*., 2014). Xanthone derivatives are the main bioactive components in mangosteen fruits; more than 50 xanthones have been discovered from mangosteen pericarp (Pedraza-Chaverri *et al*., 2008). Antibacterial, anti-inflammatory, anticancer, antioxidant, and wound healing are some of the biological effects of xanthones found in mangosteen pericarp (Febrina *et al*., 2018). Xanthones are potentially effective as a wound-healing agent as they stimulate fibroblast cell proliferation. An increase in fibroblasts is a sign of good wound healing. Fibroblast begins when the number of neutrophils is reduced and the number of macrophages is increased (Hanafiah *et al*., 2019). Several studies reported that mangosteen exhibits wound healing properties by effectively inhibiting the growth of both gram-negative and positive bacteria and by having anti-fungal and anti-inflammatory properties and anti-fungal properties (Hafeez *et al*., 2014a; Panawes *et al*., 2017). Due to this, mangosteen pericarp has gained great attention in the field of wound healing (Shandiz *et al*., 2017; Ovalle-Magallanes *et al*., 2017).

Effect of mangosteen pericarp in *in-vitro* studies

Several studies suggested that mangosteen pericarp extract has good antioxidant activity and the ability to heal wounds. It could be effective in preparing pharmacologically beneficial drugs for wound healing (Shafy *et al*., 2019). A recent study found that mangosteen pericarp extract gave a positive effect on wound bed closure. It could also augment the healing of acute wounds (Sombolayuk *et al*., 2019a).

In a study by Gondokesumo *et al*. (2020), bioactive compounds in mangosteen pericarp that could help in curing skin burns were identified through a computational study. To identify the most active compounds, a targeted focused compound library technique was applied based on their database. The biochemical pathways of selected proteins were then studied to identify the pharmacological targets. They found out that mangosteen pericarp can act as a wound-healing agent through Interleukin-6, epidermal growth factor, and transforming growth factor pharmacological targets pathway. These pathways were strongly linked to wound healing and epithelial cell proliferation at the wound site (Gondokesumo *et al*., 2020).

In another study carried out by Rizqiawan *et al*. (2021), it has been suggested that mangosteen pericarp can increase transforming growth factor (TGF-1), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) gene expression in human gingival fibroblast cell cultures. They investigated the effects of these growth factors in human gingival fibroblast cell cultures after 24 and 48 h of culture with the pericarp extract. The extraction was based on the maceration method, which used distilled ethanol 70% as the solvent for collecting *Garcinia mangostana* L. peel extract. It showed that there was an increment of these growth factors' gene expression after 48 h. This indicates that mangosteen pericarp results in an improvement of fibroblast proliferation activity (Rizqiawan *et al*., 2021).

Boonmak *et al*. (2018) also created a poly (vinyl acetate) spray containing mangosteen as its bioactive ingredient for wound dressing. The experiment was performed on human keratinocytes and normal human fibroblasts cells. Cytotoxicity test revealed that it had no effect on the cells and was non-cytotoxic, with cell viability of 80%. Based on their findings, they conclude that poly (vinyl acetate) spray containing mangosteen can be used to facilitate wound healing by easily applied on top of wound sites (Boonmak *et al*., 2018).

Effect of mangosteen pericarp in *in-vivo* studies

Mangosteen pericarp cream applied at various concentrations on the acute wound in albino mice showed an increase in wound healing with enhanced granulation tissue formation and re-epithelialization (Sombolayuk *et al*., 2019b).

The wound healing effects of mangosteen pericarp had been investigated on a diabetic mice model. In one study, the duration of mangosteen pericarp treatment was 14 days and the mice were assessed on days 3,7, and 14. Histopathological examination was performed to assess the wound diameter, number of neutrophils, macrophages, fibroblast, and collagen densities. In diabetic open wounds, mangosteen extract was shown to accelerate wound closure. Compared to the other groups, diabetic mice treated with mangosteen pericarp had the fastest wound healing. In addition, there was an increase in the number of neutrophils, macrophages, fibroblasts, and fibrocytes within the wound area along with increased collagen density, contributing to the improved wound healing (Wulandari *et al*., 2021).

This finding was supported by another study where mangosteen extract was used in treating wounds in rats with diabetes mellitus type 1. In this study, mangosteen extract has been found to prevent free radical formation as well as reduce pro-inflammatory cytokines in diabetic wounds. Topically applied mangosteen extract reduced and controlled TNF-α levels during the inflammatory phase and accelerated diabetic type 1 wound healing. (Sunarjo *et al*., 2020) .

Another in-vivo study was performed using mangosteen pericarp extract on MRSA infected skin in mice. TNF-α, IL-6, IL-1, and TLR-2 gene expressions were high before the application of

the extract. Results showed that on the 10th day of treatment, the MRSA-infected wounds were cured. Skin regeneration had occurred in nearly all of the treated lesions. The gene expression of TNF-α, IL-6, IL-1, and TLR-2 was significantly lower compared to the controls (Tatiya-Aphiradee *et al*., 2019).

A study on burn skin lesions in rats showed that mangosteen increased the healing rate of second-degree burns at the interscapular area when applied topically. In this study, it was shown that on day 14 of treatment, the mangosteen treated group showed a greater reduction in wound area compared to the control group. The authors suggested that it may be due to the antimicrobial effects of the extract, which may prevent bacterial infections in the wound area and hence play a vital role in the healing process. In addition, after the application of mangosteen pericarp extracts topically, epidermal growth factors (EGF) protein expression are increased as indicated by western blot (Gondokesumo *et al*., 2019).

Alpha-mangostin and wound healing

The most abundant xanthones in mangosteen pericarp extract are alpha, beta, and gamma-mangostin, these compounds are believed to contribute to the wound healing property of many wounds. There are a few *in vitro* and *in vivo* studies on these active compounds related to wound healing potential, especially alpha-mangostin, reporting its potential in promoting wound healing (Mohan *et al*., 2018; Zhang *et al*., 2017). Alpha-mangostin was discovered as one of the major xanthones extracted from the mangosteen pericarp in 1855. The compound is a yellowish-colored compound that can also be obtained from other parts of the plant, such as dried sap and bark (Ibrahim *et al*., 2016). The chemical structure of alpha-mangostin is illustrated in Figure 3.

It has antibacterial properties and has been shown to have the same effect as the conventional antibiotics currently available in the market, such as ampicillin and minocycline. A study by Tantra *et al*. revealed that alpha-mangostin reduces inflammation and speeds up wound healing by renewing the damaged cells and tissues. Antioxidants in alpha-mangostin have been predicted to accelerate the wound healing process (Tantra *et al*., 2021). Because of its anti-oxidant and anti-inflammatory properties, alpha-mangostin has sparked a lot of interest in wound treatment (Hafeez *et al*., 2014b)

The pharmacological effect of alpha-mangostin has been identified in both *in-vitro* and *in-vivo* models where it targets several important cellular factors through a different mechanism of action. Even though alpha-mangostin has significant molecular versatility, its clinical application is still limited mainly due to the lack of scientific clinical study and controlled trials. Apart from wound healing potential, alpha-mangostin has been reported to demonstrate various other health benefits, however, the findings were inadequate to bring its emergence into clinical use. More follow-up studies on fundamental elements causing the benefits with subsequent clinical trials are needed for valid clinical application in the future.

Effect of alpha-mangostin in *in-vitro* and *in-vivo* studies

A scratch assay study has shown that alpha-mangostin accelerates wound closure by 24 hours compared to controls by promoting cell proliferation and migration (Siriwattanasatorn *et al*., 2020). Another study supports the anti-inflammatory property of alpha-mangostin**,** where it inhibits the expression of proinflammatory cytokines, IL-6, and IL-8 in human gingival fibroblasts (Yiemwattana & Kaomongkolgit, 2015).

An excision wound model on rats was used in a study by Chinnappan *et al*. (2020) to investigate the effects of alpha-mangostin on wound healing. According to their findings, alpha-mangostin topical ointment improved the wound healing process. The parameters used in that experiment were the duration for the wound closure and contraction of the wound. On the 20th day post-treatment with alpha-mangostin, 90% of wound healing is seen in the treated groups. Based on their study, the findings confirmed that alpha-mangostin has

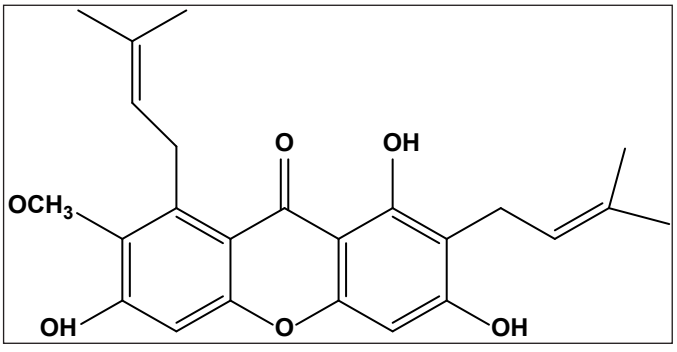

Fig. 3. Chemical structure of alpha-mangostin

wound healing properties (Chinnappan *et al*., 2020).

A recent study where sterile punch biopsy wounds were made on the mice's backs, and treated with a combination of alpha-mangostin and 2-hydroxypropyl-beta-cyclodextrin (α-mangostin/ HP-β-CD), showed that the combination of these compounds stimulated wound healing activity in the mice. The wound area was measured after 7 and 14 days of treatment. Based on their observation, α-mangostin/HP-β-CD CX had a faster wound closure rate compared to control groups (Wathoni *et al*., 2020).

CONCLUSION

In conclusion, these studies show that mangosteen pericarp extracts are potentially useful for wound care applications. Even though several *in vivo* and *in vitro* studies of mangosteen pericarp extracts have been conducted, the effects of its active ingredient on the healing of chronic wounds as well as their fundamental mechanism are still scarce and need further in-depth investigation. Further clinical research involving control trials is proposed before the extracts can be extensively used as a successful clinical alternative for wound management. Unavoidably, modern clinical modalities and drugs remain inaccessible and unaffordable to the majority of people due to high costs. It is hoped that treatment agents made from mangosteen fruit can become among the preferred options of treatment in the effort to optimize the potential of natural compound use. in a healthcare setting.

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