https://doi.org/10.48048/tis.2024.8254

Alpha(α)-mangostin (Xanthone of *Garcinia mangostana* L.): Augmenting Macrophages Activity for an Effective Diabetic Wound Healing

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Received: 31 March 2024, Revised: 29 April 2024, Accepted: 7 May 2024, Published: 30 September 2024

Abstract

Diabetic wounds are particularly difficult to treat medically because they heal at a slower pace than regular wounds. Macrophages are essential in all stages of normal wound healing, including inflammation, proliferation and rem odelling. When wound healing is affected, macrophages can reduce the level of growth factor and increase the level of interleukin-6 (IL-6), disrupt the balance between tissue inhibitors of metalloproteinase (TIMPs) and matrix metalloproteinase (MMPs), which can slow down healing. Alpha(α)-mangostin, a natural xanthone derived from the pericarp of the mangosteen, has gained considerable attention due to its anti-inflammatory properties, suggesting its potential to promote wound healing. However, its exact role in healing diabetic foot ulcers, common in diabetes, remains unclear. Hence, this study aims to explore how α-mangostin might affect diabetic wound healing by evaluating its impact on PDGF, CTGF, BFGF, VEGF, TGF-β, MMP-9, TIMP-2 and IL-6 secretion in macrophage cells. Human monocytic macrophages (THP-1) were incubated with a 35 mM glucose solution for 72 h to create a glucose-enriched medium. The cells were then incubated with α-mangostin (0.15, 2.5 and 5 µg/mL) together with 35 mM glucose. Carboxymethyl cellulose (CMC) served as positive controls; glucose-enriched media and media-alone served as negative controls. Protein expression was measured using ELISA. α-mangostin (2.5 µg/mL) increased the levels of PDGF and VEGF and decreased the level of MMP-9 compared to glucose controls. There was no significant difference in other growth factors, TIMP-2 and IL-6 protein levels across any of the treatment groups compared to glucose controls. In conclusion, α-mangostin particularly at 2.5 µg/mL demonstrated a significant increase in PDGF and VEGF levels while simultaneously reducing MMP-9 in macrophage cells under glucose-induced conditions. These findings suggest that α-mangostin holds the potential for enhancing the healing of chronic wounds in diabetic conditions.

Keywords: Alpha(α)-mangostin, Diabetic wound healing, Macrophage cells, Protein expression

Introduction

Diabetic foot ulcer (DFU) is one of the most common complications among diabetes mellitus patients. It occurs to due to prolonged hyperglycaemia leading to poor wound healing process [1]. Chronic diabetic foot ulcers (DFUs) precede 80 % of lower limb amputations and require extensive medical treatment. In clinical practice, DFUs are treated with debridement, infection control and moist dressings [2].

Poor wound healing in diabetes is a pressing problem with serious consequences, including ulceration, infection and ultimately amputation. Understanding the underlying causes of wound healing in diabetes is clearly an important public health issue that needs to be addressed [3].

Both pathological and normal healing depend heavily on the inflammatory response to tissue injury. The innate immune systems are activated immediately after injury, triggering a local inflammatory response that involves the mobilisation of inflammatory cells from the bloodstream. Inflammatory cell activity may play a role in the development of scar tissue and fibrosis [4].

Previous studies on how macrophages influence healing, particularly diabetic wound healing, are increasingly being investigated as they have the potential for development of new therapeutics to treat this costly and debilitating condition [5]. Macrophages play an important role in skin repair and their timely depletion at different stages of the wound healing process has a significant impact on the phase-specific repair mechanism. In the middle phase of the repair response, macrophages are important for the stabilisation of vascular structures and transformation of granulation tissue into scar tissue. Macrophages play different roles in the different phases of the repair response and coordinate the natural sequence of repair phases in the skin, required to restore homeostasis and integrity of the solid tissue after injury [6].

The gradient of different chemotactic agents, such as growth factors and proinflammatory cytokines are largely responsible for controlling the amount of macrophage infiltration into the wound site. By producing a number of growth factors, including TGF-β, basic fibroblast growth factor (BFGF), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), macrophages are thought to play a crucial role in the success of the healing response. These factors promote cell proliferation and the production of extracellular matrix molecules by the local skin cells [7]. Previous research has shown that macrophages are activated in different ways during physiological healing. This leads to the expression of VEGF and TGF-β, which promotes angiogenesis of the wound and differentiation of myofibroblast [6].

Studies on diabetics have shown that wounds that do not heal have a large number of macrophages. These findings and the fact that macrophages can produce a lot of reactive oxygen species and proteases that can damage normal tissue, suggest that macrophages are one of the reasons that wounds in diabetics do not heal as well. Diabetic chronic ulcers are characterised by an increase in MMP-9 levels and a decrease in TIMP-2 levels. These significantly increased MMPs levels are responsible for the degradation of extracellular matrix components such as fibronectin, growth factors and cytokines and significantly interfere with healing process [1]. There are also recent findings on the temporal regulation of macrophage presence in diabetic wounds: However, it is unclear whether the cytokines and growth factors produced are initially upregulated or downregulated after injury. A number of studies using a diabetic wound model have shown that inflammatory macrophages are present in diabetic wounds at an early stage [8].

Garcinia mangostana Linn, the pericarp of the mangosteen fruit, is known to contain a variety of oxygenated and xanthone compounds [9]. It is also known as the “Queen of Fruits” and is a plant whose biological functions and medicinal potential are being intensively researched. In the past, it has been used to treat infections, diarrhoea, inflammation, skin diseases and wounds. Research has shown that the mangosteen pericarp is rich in phenolic compounds that have the potential to be used as therapeutic agents, such as xanthones [10].

Xanthones are mangosteen metabolites extracted from the pericarp of the fruit. Xanthone derivatives are the major bioactive constituents of mangosteen; more than 50 xanthones have been isolated from the mangosteen pericarp [11]. The biological activity of xanthones derived from mangosteen pericarp has been reported in various reports. It has have been shown that xanthone have a potential for wound healing agent because they stimulate cell proliferation [12].

The most abundant xanthone in mangosteen pericarp is α-mangostin, which contributes to the wound healing properties. Xanthone is an organic polyphenolic molecule that has the formula $C_{13}H_8O_2$ at the molecular level. The tricyclic scaffold present in the structure of xanthones plays a crucial role in determining their biological properties. However, the exact nature of this role can change depending on the location of various functional groups and substitutions. Among the xanthones, $\alpha, \beta,$ and γ mangostins have been extensively studied due to their potential, with a particular focus on the α-mangostin, which is more notable and important when compared to others. In addition, α-mangostin is the xanthone that is found in the pericarp of the fruit in the highest concentration and the most abundant xanthones [13,14].

Extensive research has been conducted on these active chemicals in relation to wound healing, particularly α-mangostin, where various *in vitro* and *in vivo* investigations have revealed its potential in stimulating wound healing [14,15].

Due to its extensive biological and pharmacological activity, particularly in wound care, α-mangostin has caught the interest of research in medicinal plants [16]. High quantities of α-mangostin have been shown to possess high antioxidant properties which give the effect on wound healing [17,18].

However, the fundamental pathways by which α-mangostin impacts wound healing *in vitro,* notably its function on macrophage cells remain unknown. Therefore, this present study aims to investigate the effects of α-mangostin on macrophages in a glucose-enriched medium and its underlying mechanisms. In this study, macrophage cells were stimulated by high glucose before incubation with α-mangostin. Then, the protein expression of IL-6 (inflammatory markers), growth factors (PDGF, TGF-β, B-FGF, CTGF and VEGF) and proteinases (MMP-9 and TIMP), were determined.

Materials and methods

Preparation of culture medium and cell culture

Human monocytic cell line (THP-1) (American type culture collection (ATTC), USA) was cultured in Roswell Park Memorial Institute (RMPI) medium, 50 mL complete medium was prepared by mixing 44.5 mL of RPMI medium with 0.5 mL Penicillin/Streptomycin (1 %) solution (Thermo Fisher Scientific, USA) and 5 mL fetal bovine serum (Thermo Fisher Scientific, USA). Penicillin/streptomycin were used to prevent bacterial contamination and ensure the growth of the cells, this is an accepted method in cell culture protocol. The medium was aliquoted and kept at 4 °C until needed.

The THP-1 cells were quickly thawed by putting the lower half of the vial in a 37 °C water bath. The cells were then suspended gently and pipetted into the flasks containing medium and put inside the incubator with 5 % CO_2 and 90 % humidity at 37 °C. The cells were subculture at 1:3 ratio upon reaching 80 % confluency.

THP-1 monocytes were differentiated into macrophages through a 24-hour incubation with 100 μm phorbol 12-myristate 13-acetate (PMA) (Nacalai Tissue, Japan) in RPMI [19]. Following the differentiation into macrophages, PMA was removed and the cells were ready for further induction with α-mangostin and glucose.

Cell viability measurement

The Cell Titer 96® Aqueous 1 solution cell proliferation assay (MTS) reagent (Promega Corporation, Madison, USA) was used to determine the working concentrations of α-mangostin and glucose (negative) control. THP-1 cells at a seeding density of 20,000 cells were added into 96-well plates. Following this, PMA (100 µm) was introduced into wells containing 10 µL of RPMI medium. After a 24-hour period, cells were differentiated into macrophages. Subsequently, the cells were exposed to different concentrations of α-mangostin (ranging from 0 - 20 µg/mL) and glucose (ranging 0 - 100 mM) for an additional 24 h. After that, 10 uL of the MTS solution was added into each well and incubated for 2 h at 37 °C in a humidified incubator. The reagent colour change was then measured at 490 nm absorbance (Victor X5, Perkin Elmer, USA).

Based on the MTS result assay, the working concentrations determined for this experiment were: 0.15, 2.5 and 5 µg/mL α-mangostin and 35 mM glucose [20].

Sample collection for protein analyses

Cells were seeded and cultured in a 6-well culture plate. After 24 h, the cell monolayer was washed gently with phosphate-buffered saline (PBS). Then, the cells were incubated with a 35 mM glucose for 72 h at 37 °C. At the end of incubation, the high glucose medium was fully removed and replaced with 35 mM glucose medium and α-mangostin (at 0.15, 2.5 and 5 µg/mL). The positive controls were cells incubated with, carboxymethyl cellulose (CMC) together with 35 mM glucose (as a positive control); the negative controls are incubated with 35 mM glucose only (glucose control) and culture medium only (unstimulated controls). After 24 h of incubation, the cells were detached with accutase and collected in 15 mL centrifuge tubes. The cell harvest solution was then centrifuged to remove any debris. The supernatant was removed without disturbing the cell pellet and aliquoted into 1.5 mL microcentrifuge tubes and stored at –80 °C until analysis [21,22].

IL-6, growth factors, MMP-9 and TIMP protein analyses

Protein expression of IL-6, PDGF, TGF-β, B-FGF, CTGF, VEGF, MMP-9 and TIMP-2 were measured by enzyme-linked immunosorbent assay (ELISA) kits. Tests were performed according to the manufacturer's protocol. At the end of the experiment (after incubation with stop solution), the absorbance was measured with a microplate reader at 490 nm wavelength.

Statistical analysis

A total of 3 independent experiments were conducted in this study (n = 3). Graph pad was used to analyse all data. One-way ANOVA was performed to assess overall differences between different groups of treatment followed by post-hoc analysis (Bonferroni). Significant value was set at $p < 0.05$. Data are expressed as mean ± SEM.

Effect of α-mangostin on THP-1 cell viability

The effects of α-mangostin on cell viability in THP-1 cells are illustrated in **Figure 1**. α-mangostin greater than 5 µg/mL showed reduced cell viability as when compared to control untreated cell population. As a result, α-mangostin, no greater than 5 µg/mL were used to treat the cells for the experiments. Three concentrations of α-mangostin are selected (0.15, 2.5 and 5 µg/mL).

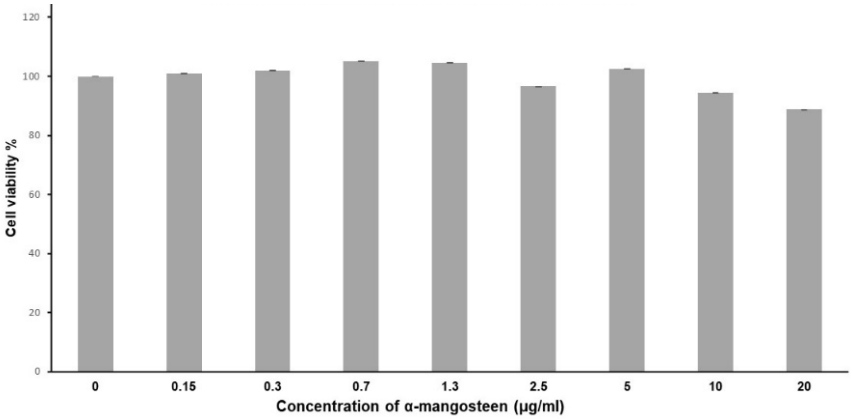


Figure 1 Effects of α-mangostin (0.15 to 20 µg/mL) on the cell viability in THP-1 macrophages. Data are expressed as percentage of cell viability. Data is presented as mean ± SEM (n = 3).

Effect of various concentrations of glucose on THP-1 macrophages viability

High amounts of glucose were added to the culture medium to mimic a diabetic environment [19]. Establishing the most suitable glucose level, ensuring both cell viability and experimental integrity, is pivotal. In this study, various glucose concentrations, ranging from 0 to 100 mM, were induced to the cells. The outcomes revealed that, among the tested concentrations, 35mM emerged as the optimal level for inducing hyperglycemia in the human monocytic cell line (THP-1) cells (**Figure 2**). It's noteworthy that this selection aligns with findings from prior studies [20,23].

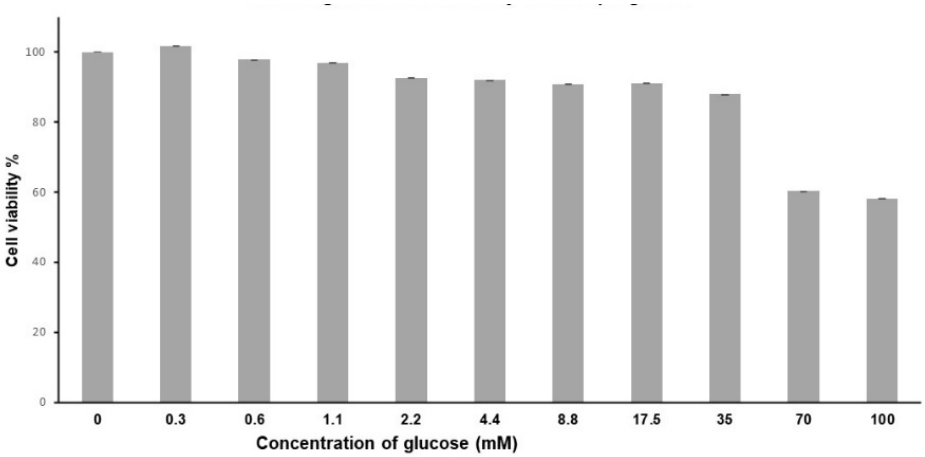


Figure 2 The effects of glucose (0 to 100 mM) on the cell viability (THP-1 macrophages). Data are expressed as mean ± SEM (n = 3).

Effects of α-mangostin on growth factors protein expression (PDGF, VEGF, BFGF, TGF-β and CTGF) in glucose stimulated THP-1 macrophages

The effects of α-mangostin on growth factors released by glucose stimulated THP-1 macrophages are illustrated in **Figure 3**. The study observed that treatment with α-mangostin at a concentration of 2.5 µg/mL resulted in an increase in the secretion of PDGF in THP-1 macrophages (**Figure 3 (a)**). Interestingly, the increment of PDGF was comparable with CMC ($p < 0.01$). Similarly, α-mangostin at 2.5 µg/mL had higher VEGF levels than glucose alone (**Figure 3 (b)**).

However, there was no significant differences in the released of BFGF, VEGF and TGF-β by α-mangostin treatment across all concentrations in glucose stimulated THP-1 macrophages compared to glucose alone controls (**Figures 3(c)** to **3(e)**).

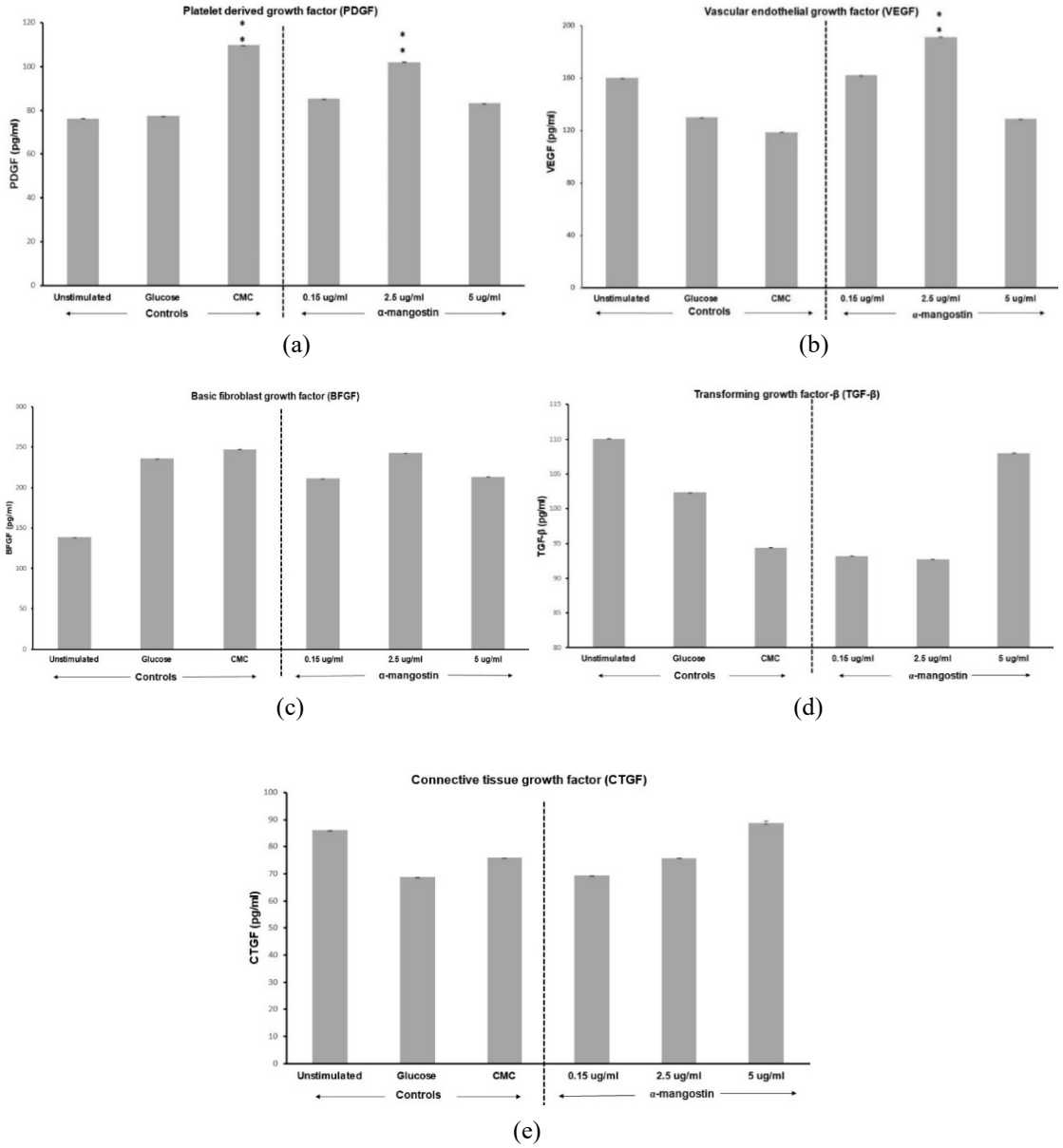
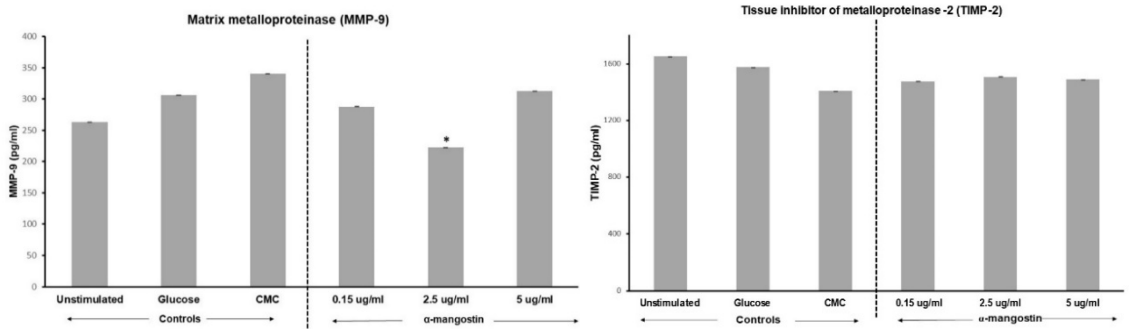


Figure 3 The effect of α-mangostin on the release of growth factors (a) PDGF, (b) VEGF, (c) BFGF, (d) TGF-β and (e) CTGF in THP-1 macrophages. Data are expressed as mean ± SEM (n = 3). $^{**}p < 0.01$ compared to glucose controls.

Effects of α-mangostin on MMP-9 and TIMP-2

Glucose treatment resulting in a significant increase of MMP-9 secretion by THP-1 macrophages when compared to glucose controls. However, there was no observed differences in TIMP-2 secretion compared to unstimulated control. Treatment with α-mangostin at a concentration of 2.5 µg/mL α-mangostin led to a significant decrement in MMP-9 secretion by THP-1 macrophages. Notably, there was no significant difference in TIMP-2 secretion among the treatment group (**Figure 4**).



(a) (b)

Figure 4 The effects of α-mangostin on (a) MMP-9 and (b) TIMP-2 in THP-1 macrophages. Data are expressed as mean ± SEM (n = 3). $^{*}p < 0.05$ compared to glucose controls.

Effects of α-mangostin on IL-6 secretion

There are neutral effects of α-mangostin treatment on IL-6 secretion in THP-1 macrophages stimulated with glucose (**Figure 5**).

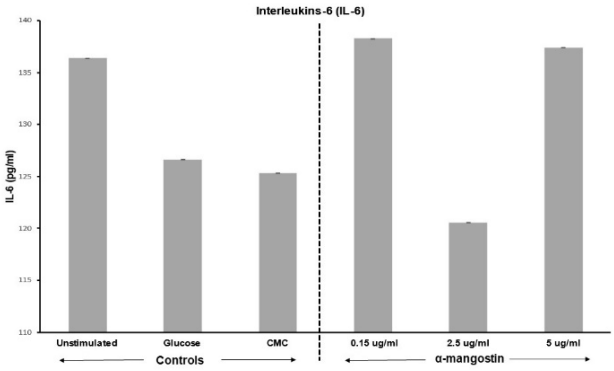


Figure 5 The effects of α-mangostin on the released of IL-6 from THP-1 macrophages stimulated with glucose. Data are expressed p as mean ± SEM (n = 3).

Results and discussion

The process of wound healing continues to pose a complex clinical challenge, prompting extensive research to devise an optimal approach. The goals to improve wound stability while reducing the formation of scar tissues and other significant complications, with the patient's optimal functioning as the end result. However, individuals with chronic wounds in the context of diabetes often encounter unconventional healing circumstances, adding complexity to the treatment process. These disorders are caused by disruptions in cellular and molecular signalling throughout the stages of wound healing. Diabetes disrupts the important of growth factors, cytokines and chemokines that normally control and maintain wound healing [24,25].

Natural products have demonstrated potential in enhancing diabetic wound healing. Several studies have found α-mangostin to be effective in improving diabetic wound healing *in vivo*. α-mangostin is the most abundance xanthones found in the mangosteen pericarp [26].

This study investigates the effects of α-mangostin treatment on THP-1 macrophages within a high-glucose environment. Selected for their pivotal roles in the inflammatory, proliferative and remodelling phases of wound healing, these cells serve as focal points in exploring the potential impact of α-mangostin

on cellular responses. The study aims to investigate the effect of α-mangostin in the context of wound healing, particularly under diabetic conditions.

Activated macrophages have critical functions in healing regulation and the healing process would not function normally without it. Macrophages patrol the wound region, ingesting and eliminating germs and removing devitalised tissue through the actions of secreted MMPs. Additionally, macrophages facilitate the progression of healing from the inflammatory to the proliferative phase by releasing variety of growth factor (PDGF, CTGF and VEGF) and cytokines (IL-6) [27]. In diabetic chronic wounds, it exhibits decreased levels of various growth factors, which play crucial roles in the wound healing process [28].

This study showed that in high glucose environment, THP-1 macrophages treated with α-mangostin produced higher levels of PDGF and VEGF compared to (glucose alone) control groups. While no difference observed in BFGF, CTGF and TGF-β. In another study (non-diabetic model experiment), previous study showed the effects of mangosteen peel extract on scratched human gingival fibroblast cell culture. The extract led to a significant increase in the expression of PDGF within 24 h [29]. The results of our study suggest that α-mangostin may have potential in the treatment of diabetic wounds, particularly through its ability to regulate growth factors. The positive effect on growth factors that was observed indicated that α-mangostin significantly affects cellular processes that are involved in the healing of wounds in diabetic patients. In a study conducted by Felicia on *Garcinia mangostana* using a non-diabetic *in vitro* model, it was suggested that xanthone exhibits the capability to accelerate angiogenesis. This is achieved by promoting the expression of VEGF and PDGF. The antioxidants within the extract effectively bind to superoxide radicals, leading to the release of nitric oxide (NO). Nitric oxide plays a pivotal role in enhancing VEGF and PDGF expression through the P13K-Akt pathway. This intricate cascade of signals influences the nuclease to activate both the growth factors gene, resulting in the production of VEGF and PDGF protein. This process simulates angiogenesis, potentially speeding up wound healing. Moreover, in that study, the effectiveness of natural product treatment was influenced by concentration and duration. In their experiment, the transient low FGF expression in the 48 h is linked to an 800 µg/mL concentration of mangosteen peel extract, contributing to limited effects on certain growth factors [29].

The control of MMP-9 is very important for wound healing, especially in diabetic foot ulcers. When MMP-9 is excessively active or overexpress, it serves as a red flag for potential complications for wound healing. It has been demonstrated that decreasing the expression of MMP-9 may improve better wound healing outcome [30]. This study demonstrated that THP-1 macrophages treated with α-mangostin displayed decreased MMP-9 levels when compared to the control group (glucose alone). Notably, there were no discernible differences observed in TIMP-2 levels between the groups.

A previous study (non-diabetic model experiment) utilised human keratinocyte cells to test the protective benefits of α-mangostin against radiation that causes inflammation of the skin. There was an increase in the expression of MMP-1 and MMP-9 after exposure to radiation; however, pretreatment with α-mangostin was able to reduce these changes, indicating the possibility of photoprotective effects, which are particularly significant to health of the skin and the healing of the wounds [31]. The results from this study that the manipulation of MMP-9, in conjunction with the potential effects of α-mangostin, holds considerable promise for enhancing the process of diabetic wound healing.

Recent research suggests that macrophages are responsible for the production of proinflammatory cytokines such as IL-6, which is a primary regulator of the acute inflammatory response [32]. A preceding study indicated that individuals with diabetic foot ulcers exhibited elevated levels of IL-6 [33]. However, in our study, treatment with α-mangostin did not lead to a decrease in the levels of IL-6. Further investigations are warranted and future studies should focus on varying the concentrations of α-mangostin to explore its potential effects. In a previous study, Jin *et al.* [34] demonstrated that α-mangostin protects

skin from UVB-induced aging by reducing inflammatory cytokines like IL-6 in human keratinocyte cells. Notably, by using a 2 μm concentration of α-mangostin instead of 10 μm, which showed no significant exposure to UVB, underscores its effectiveness by using low concentration. Returning to this study, the efficacy of α-mangostin in modulating IL-6 levels may hinge on the concentration used, which give an impact to influence the cytokine levels.

Conclusions

Treatment of THP-1 cells with α-mangostin at 2.5 μg/mL demonstrated a significant increase in PDGF and VEGF while simultaneously reducing MMP-9 in glucose-induced conditions. These findings suggest that α-mangostin holds the potential for enhancing the healing of chronic wounds in diabetic conditions. Further investigations are essential to ascertain the specific effects of α-mangostin in diabetic ulcers *in vivo.*

Acknowledgments

We would like to extend our gratitude and appreciation to the Ministry of Higher Education Malaysia for supporting this study. This research work has been supported by the Fundamental Research Grant Scheme from Ministry of Higher Education, Malaysia (FRGS/1/2017/SKK 08/ UITM/03/9) and Geran Insentif Penyeliaan (GIP), University Teknologi Mara (UiTM), Malaysia (600-RMC/GIP 5/3 (084/2022). We also thank the Faculty of Medicine UiTM for providing research facilities and equipment for laboratory work in this research project.

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