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Antioxidant, Wound Healing Potential and In Silico Assessment of Naringin, Eicosane and Octacosane

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Abstract: 1. Diabetic chronic wounds, mainly foot ulcers, constitute one of the most common complications of poorly managed diabetes mellitus. The most typical reasons are insufficient glycemic management, latent neuropathy, peripheral vascular disease, and neglected foot care. In addition, it is a common cause of foot osteomyelitis and amputation of the lower extremities. Patients are admitted in larger numbers attributable to chronic wounds compared to any other diabetic disease. In the United States, diabetes is currently the most common cause of non-traumatic amputations. Approximately five percent of diabetics develop foot ulcers, and one percent require amputation. Therefore, it is necessary to identify sources of lead with wound-healing properties. Redox imbalance due to excessive oxidative stress is one of the causes for the development of diabetic wounds. Antioxidants have been shown to decrease the progression of diabetic neuropathy by scavenging ROS, regenerating endogenous and exogenous antioxidants, and reversing redox imbalance. Matrix metalloproteinases (MMPs) play vital roles in numerous phases of the wound healing process. Antioxidant and fibroblast cell migration activity of *Marantodes pumilum* (MP) crude extract has previously been reported. Through their antioxidant, epithelialization, collagen synthesis, and fibroblast migration activities, the authors hypothesise that naringin, eicosane and octacosane identified in the MP extract may have wound-healing properties. 2. The present study aims to identify the bioactive components present in the dichloromethane (DCM) extract of *M. pumilum* and evaluate their antioxidant and wound healing activity. Bioactive components were identified using LCMS, HPTLC and GCMS. Excision wound on STZ-induced diabetic rat model, human dermal fibroblast (HDF) cell line and colorimetric antioxidant assays were used to evaluate wound healing and antioxidant activities, respectively. Molecular docking and pkCMS software would be utilised to predict binding energy and affinity, as well as ADME parameters. 3. Naringin (NAR), eicosane (EIC), and octacosane (OCT) present in MP displayed antioxidant action and wound excision closure. Histological examination HDF cell line demonstrates epithelialization, collagen production, fibroblast migration, polymorphonuclear leukocyte migration (PNML), and fibroblast movement. The results of molecular docking indicate a substantial attraction and contact between MMPs. pkCMS prediction indicates inadequate blood-brain barrier permeability, low toxicity, and absence of hepatotoxicity. 4. Wound healing properties of (NEO) naringin, eicosane and octacosane may be the result of their antioxidant properties and possible interactions with MMP.

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1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder that is becoming increasingly prevalent in many developed countries including Malaysia. Diabetic patients with badly controlled glucose levels are highly likely to develop diabetic foot ulcer (DFU) with an incidence rate of 19–34% and DFUs have a tendency to get infected due to the ulcers' position under the foot [1]. It has been estimated that the global DFU treatment market alone would increase from 7.03 billion USD to 11.05 billion USD by 2027. The most typical reasons are insufficient glycemic management, latent neuropathy, peripheral vascular disease and neglected foot care. In addition, it is a common cause of foot osteomyelitis and amputation of the lower extremities. Patients are admitted in larger numbers attributable to chronic wounds compared to any other diabetic disease. In the United States, diabetes is currently the most common cause of non-traumatic amputations. Approximately five percent of diabetics develop foot ulcers, and one percent require amputation [2]. Hyperglycaemia-induced wounds persist in the inflammatory phase and impair wound closure through the disruption of protein synthesis, migration and proliferation of keratinocytes and fibroblasts [3], thereby impeding the formation of granulation tissue and reducing wound tensile strength.

Oxidative stress greatly contributes to the development of chronic wounds as excessive reactive oxygen species (ROS) generated from the activation of several biochemical pathways including the AGE/RAGE, polyol and hexosamine pathways which induce high oxidative stress that increases advanced glycation end products (AGEs). AGEs have been reported to impair wound contraction and prolong inflammation that hampers ECM proliferation [4]. High level of MMPs, especially MMP-9 leads to the development of non-healing chronic diabetic wounds. Therefore, antioxidants have been widely studied and applied as an effective treatment strategy in diabetic wound treatment and management.

Wound healing is a complex yet organized biological process that restores the anatomic integrity of the skin upon any form of injury. The healing process involves the interaction of various intracellular and extracellular processes which are mostly regulated by a group of enzymes known as the matrix metalloproteinases (MMPs). MMPs are a family of endopeptidases that are involved in releasing growth factors from the ECM, cleavage of growth factor receptors from the cell surface, and ectodomain shedding of adhesion molecules from membranal proteins of the cell surface [5].

The hallmark of the proliferative stage in the wound healing process is the rebuilding of new granulation tissue and ECM synthesis. The organization and maintenance of the ECM are highly dependent on various intracellular and extracellular processes which are mostly regulated by a group of enzymes known as the matrix metalloproteinases (MMPs). Four distinct classes of enzymes are associated with wound healing: collagenases, gelatinases, stromelysins and membrane-type metalloproteinases. Although these enzymes play a pivotal role in cell migration and tissue remodelling, an imbalance of these MMPs leads to excessive degradation which has been linked with the nonhealing nature of diabetic ulcers [6]. As such, MMP inhibitors (MMPIs) are essential in ensuring that the MMP activity is balanced throughout the wound healing process. Many naturally occurring and synthetic MMPIs have been explored for wound healing. Some examples of natural MMP inhibitors include curcumin, resveratrol, theaflavin and catechin derivatives [7].

However, with the evolution of technology such as artificial intelligence, molecular docking and in silico studies, the search for effective natural compounds has become more productive and efficient. *Marantodes pumilum* var. alata, popularly known as Kacip Fatimah, is a Malaysian herb that has been widely used in traditional medicine by women to facilitate post-partum recovery, relieve menstrual problems and treat dysentery. Previous studies