

A Computational Study to Predict Wound Healing Agents from the Peel of the Mangosteen (*Garcinia mangostana* L.) Extract

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Abstract: This study aimed to identify potentially active compounds from mangosteen peel extracts that heal skin burns and to evaluate their molecular mechanisms. There are about 120 compounds that have been identified in mangosteen peel by datamining, including 60 types of xanthones. The SMILE format of each compound was downloaded from the PubChem database. The compound data was then analyzed for potential anti-inflammatory, antioxidant, and antibacterial activities with PASS SERVER. To prediction mechanisms, firstly, target protein predictions were made with Swiss target prediction and HitPick. Target Protein data was then analyzed by interaction with STRING to determine its molecular mechanism. Further analysis of the shortest pathway was done with Cytoscape. The screening process of fifty compounds, which are predicted to have anti-inflammatory, antioxidant, and antibacterial activities by PASS SERVER. The four highest potency compounds were Smeaxanthone A, Garcinone E, γ -mangosteen, and Gartanin, which were types of xanthone. Based on the result of computational study these four compounds have

potential targets prediction related to interleukin 6, epidermal growth factor, and transforming growth factor beta 1, that are involved in the regulation of epithelial cell proliferation which plays a role in the healing process of skin burns.

Keywords: *Mangosteen peel, Skin burns, Wound healing, Xanthones, Molecular docking.*

Introduction

Burn injuries contributed to 180,000 deaths in 2004, while nearly 11 million people worldwide were severely burned and required medical treatment [32]. Wound healing involves 3 overlapping phases: inflammation, cell proliferation, and remodeling [8]. Antioxidants, anti-inflammatory agents, and antimicrobials all have roles in the wound healing process and prevent further aggravation of the wound condition [5].

Many factors slow the wound repair process, such as the presence of oxygen free radicals [33]. Reactive Oxygen Species (ROS), along with their derivatives, are abundant at the wound site [6]. Open wounds are prone to bacterial infection and provide an entry point for systemic infections [5]. When a cell is injured, inflammatory mediators such as cytokines, tumor necrosis factor (TNF), interleukin-1 (IL-1) from leukocytes, monocytes and macrophages are released as a response to pain. When this happens the production of cyclooxygenase (COX) 5-lipoxygenase (5-LO), prostaglandins (PGE) and Nitric Oxide (NO) are increased [3, 19, 44].

Generally, wound treatment of skin burns with early antioxidant therapy reinforces cellular antioxidant defense mechanisms, decreases free oxygen radicals, and promotes the healing process [4]. Free radical scavenging agents involve in the de-activation, reduction, and ROS removal, as well as promoting the wound-healing process. Consequently, topical applications of compounds with free radical scavenging properties can protect tissues from oxidative damage and also significantly improve wound healing [8, 38]. Topical antibacterial agents are also commonly used to facilitate wound healing in patients [38].

Over many years, herbal medicines have been widely utilized for natural medication of skin burn injuries [2, 16, 17, 37]. *Garcinia mangostana* L. (Clusiaceae), known as mangosteen, has been used as a traditional medicine in southeastern Asia for diarrhea, dysentery, inflammation, and ulcers, as well as for wound healing [1, 27, 30].

Mangosteen rind extract and purified constituents have been subjected to a vast array of biological tests relating to infectious diseases, cancer chemoprevention and chemotherapy, diabetes, and neurological conditions [4, 21, 27, 43]. Mangosteen extract and its constituent xanthones have been shown to have antioxidant [7, 39], anti-inflammatory [44], and antibacterial activities [20].

In our previous research, we have analyzed the main components peel of mangosteen extract containing Smeaxanthone A, Garcinone E, γ -mangosteen, and Gartanin using LC-MS/MS [13]. We used peel of mangosteen extract in the administration of topical gels to treat burns on the skin of mice that show good recovery results with the mechanism of increasing Epidermal Growth Factor (EGF) expression through immunohistochemistry and confirmed by western blot protein results [14].

The purpose of computational studies is to prove that there are major components contained in mangosteen peel extract, which has strong potential for skin repair in burning conditions.

Materials and methods

Collection of compounds in mangosteen rind extract

Active compounds were identified from datamining the Knapsack herbal database. The structure of each compound was further analyzed through the simplified molecular-input line-entry system (SMILES) in PubChem (<http://pubchem.ncbi.nlm.nih.gov>).

Prediction of biology activity

Biological activities of compounds were analyzed with the Prediction of Activity Spectra for Substances (PASS) server (<http://www.pharmaexpert.ru/passonline/>). Predictions were made using the structure-activity relationship (SAR) approach. Compounds with a similar structure and active cluster were considered to possess similar activities. For the PASS Server, the probability that a compound was active (Pa) was set at a threshold 0.7, such that $Pa > 0.7$ indicated a compound with a high probability for activity on experimentation [10]. The biological properties measured included anti-inflammatory, antioxidant, and antibacterial activities. The prediction was based on cluster analysis of potential compounds. A combination of compounds with anti-inflammatory, antioxidant, and antibacterial activities was expected to enhance wound healing.

Prediction of targeted protein

The potentially most active compounds were further analyzed with the servers HitPick (<http://mips.helmholtz-muenchen.de/hitpick/>) and Swiss Target Prediction (<http://www.swisstargetprediction.ch/>), using a targeted-focused compound library approach to make identifications. The principle was to predict structural aspects and functional activities of new compounds based on similarities to compounds in the database [25]. The biochemical pathways of targeted proteins were then analyzed to study the processes that could be targeted by drugs.

Pathway of compound-protein interaction

Potential interactions between targeted and others proteins were analyzed with STRING (<http://string-db.org>). The primary interaction unit in STRING was one of functional association [36]. This database was usually used to propose new pathways regarding drug interactions. Pathways were further analyzed with Cytoscape (<http://www.cytoscape.org>) to determine the most essential pathway as well as the type of interaction in the protein network.

Results and discussion

Several docking tools were combined to provide more reliable results for the understanding of compound-target relationships and the construction of herb-target networks. In the present study, all compounds from mangosteen peel extract were predicted to be involved in wound healing by interacting with single or multiple target proteins. This constraint gave a clear molecular mechanism for novel formula designs where active herbs were linked with different disease-related proteins. Disease intervention could be effectively achieved by simultaneously attacking multiple targets [31, 45].

Compound collecting with the Knapsack database identified about 120 compounds in mangosteen rind extract. Furthermore, SMILE analysis from PubChem identified 50 compounds. Active compounds that have combined activities including antioxidant, antiinflammatory and antibacterial, could be promising candidates in wound healing (Fig. 1).

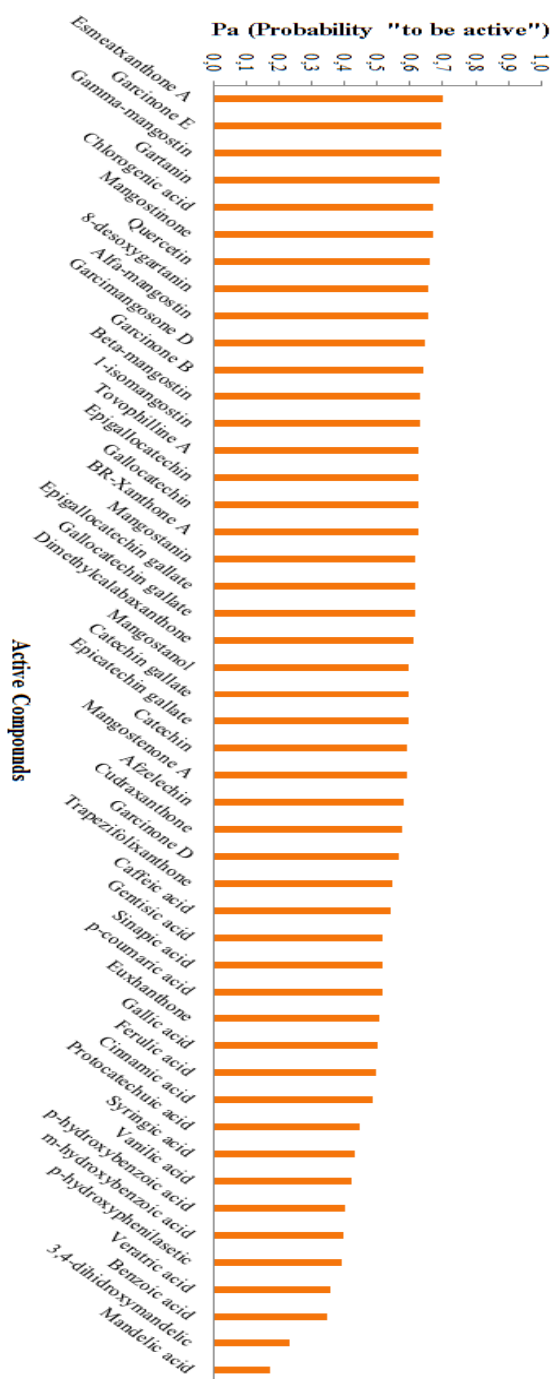


Fig. 1 Prediction of antioxidant, antiinflammatory, and antibacterial activity of compounds in mangosteen rind extract by PASS SERVER

Fig. 2 shows Smeatxanthone A possessed the highest probability with regard to active antioxidant, antiinflammatory, and antibacterial activities ($P_a = 0.700$), followed by Garcinone E ($P_a = 0.694$), γ -mangosteen ($P_a = 0.693$) and Gartanin ($P_a = 0.692$). The four compounds are major components in mangosteen peel extract, which have been identified by their contents using LC-MS/MS [13], and mangosteen peel extract in gel preparations has activity to repair burns on mice skin in our previous research [14].

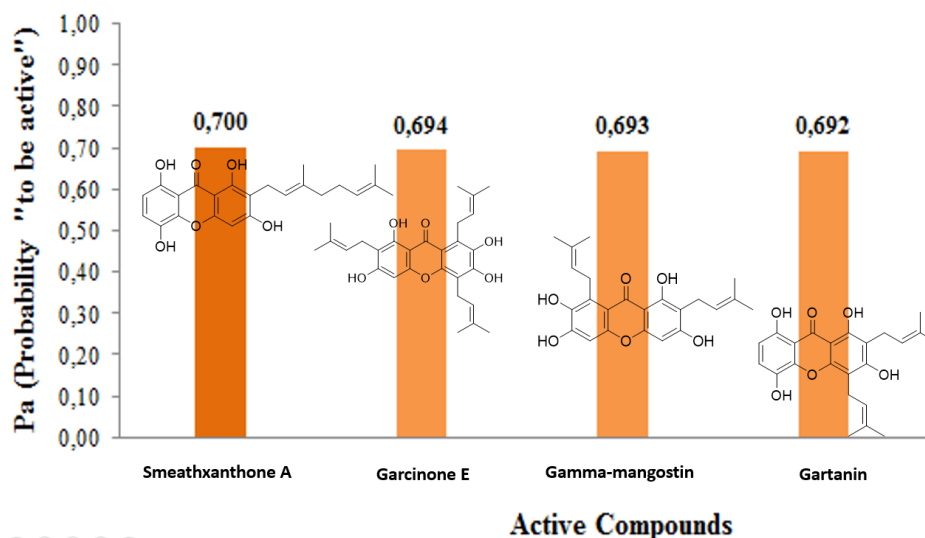


Fig. 2 Four compounds (xanthenes group) with most active prediction as antioxidant, antiinflammatory, and antibacterial by PASS SERVER

The potential mechanism of these compounds was identified based on prediction analysis. Results showed potential targets of these compounds were related to the expression of interleukin 6 (IL6), EGF, and transforming growth factor beta 1 (TGFB1) (Fig. 3, Table 1).

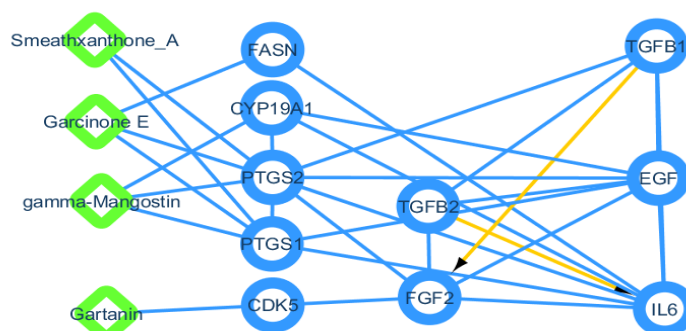


Fig. 3 Herbs-protein interaction

Table 1. Expression score based on interaction prediction (scale 0-1)

Protein	Expression score
TGFB1->FGF2	0.450
TGFB2->IL6	0.517

Results showed that the expression of IL6 might be affected by mangosteen extracts through TGFB2. Expression of IL6 was higher than fibroblast growth factor 2 (FGF2). The primary mechanisms affected in the body comprised 2 areas of regulation, epithelial cell proliferation (FGF2, TGFB1, IL6, TGFB2), and leukocyte homeostasis (TGFB1, IL6). These pathways were strongly associated with wound healing, epithelium cell proliferation and leukocytic elimination of antigens at the wound site. The regulation of these pathways was further analyzed to identify the potential modes of action of the compounds in mangosteen rind (Fig. 4).

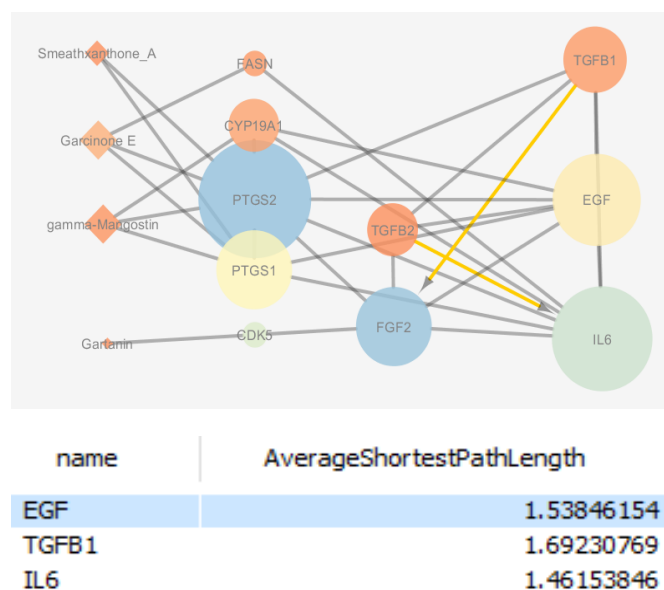


Fig. 4 Most activated pathways by mangosteen rind extract

Results showed prostaglandin-endoperoxide synthase 2 (PTGS2) had a significant role in these pathways. This enzyme would cause IL6 to be activated, mostly, followed by EGF and TGFB1. TGFB1, EGF, and IL6 have crucial roles in wound healing. The TGFB family of proteins consists of multifunctional regulators that have been linked to wound repair, affecting all cell types involved in the process. TGFB1 has the broadest spectrum of action. It can induce chemotaxis of the inflammatory cells into the wound [12], as well as both angiogenesis and extracellular matrix formation; and it also initiates granulation tissue formation during and after inflammation [12, 26]. The primary structural component of granulation tissue is collagen, which can be induced directly by TGFB1 [11, 23, 42]. TGFB1 can stimulate wound contraction by inducing fibroblasts to differentiate to myofibroblasts [41, 42]. These contractile cells express proteins such as α -smooth muscle actin (SMA), stress fibers, vinculin-containing adhesion complexes and fibronectin fibrils for wound contraction [41].

IL6 was previously reported to precisely modulate the expression of TGFB in the skin and IL6KO fibroblasts [24]. IL6 is a pleiotropic cytokine involved in the growth and differentiation of numerous cell types, including those of dermal and epidermal origin [35]. Epidermal keratinocytes are a primary producer of IL6 within the skin, while macrophages, Langerhans cells and fibroblasts in the dermis represent other sources of the cytokine [28]. Increased levels of IL6 have been associated with some skin pathologies, such as psoriasis [15], scleroderma [22] and systemic lupus erythematosus [9]. Overexpression of IL6 in the skin of normal rats induces epidermal proliferation and inflammation [34], while overexpression in transgenic mice results in little more than a thickened stratum corneum [40].

The EGF family comprises multiple mediators of tissue-specific homeostasis of proliferation and differentiation. Human epidermal keratinocytes maintain high steady-state levels of extracellular-signal-regulated kinase (ERK) activity, mostly via their autocrine production of EGF receptor (EGFR) ligands [18]. The EGFR can be activated by transactivation from a variety of G-protein-coupled receptors, integrins, and cytokine receptors, so that it can act as a significant transducer in disparate cell functions, including changes in proliferation rate, cellular shape, attachment and motility, and regulation of proinflammatory activation [29].

Bioinformatics study results are also in line with the results of burn repair in mice by inducing EGF expression by western blot analysis and EGF immunohistochemistry in previous studies [14].

Conclusion

There are four main compounds contained in mangosteen peel extract, which in comparative studies show anti-inflammatory, antibacterial, and antioxidant activities that play a role in the healing process of burns through signaling the interleukin 6 pathway, epidermal growth factor, and transforming growth factors beta 1, which is involved in the regulation of epithelial cell proliferation.

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