Chemical Compounds and Pharmacological Activities of Mangosteen (Garcinia mangostana L.) - Updated Review

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Abstract: Mangosteen (Garcinia mangostana L.) is a tropical fruit belonging to Guttiferae (syn. Clusiaceae) family. Research on mangosteen has been widely conducted. Also, numerous in vitro and in vivo studies related to mangosteen have been published, indicating its significance and potential usefulness in the research field. This review was constructed by collecting and analyzing more than 50 research articles to explore the phytochemical contents and the medicinal benefits of mangosteen. A significant level of xanthones greatly contributes to the extensive pharmacological activities of mangosteen. Apart from xanthones, mangosteen also contained benzophenones, flavonoids, and anthocyanins. Mangosteen had a wide range of pharmacological effects, including antioxidant, anti-acne, anti-aging, anti-hyperpigmentation, antibacterial, antidiabetic, anti-obesity, anti-inflammatory, antimalarial, antiparasitic, and antitumor. Additionally, mangosteen has shown an advantageous activity toward pathological conditions such as Alzheimer's, bipolar disorder, schizophrenia, neuropathic pain, and pulmonary fibrosis. This literature review indicated that xanthone in mangosteen had potential and promising to be developed as a drug candidate. More extensive explorations, especially in pharmacokinetic, pharmacodynamic, and xanthone targeting effects, are widely open to be carried out for future research.

Keywords: mangosteen; chemical compounds; pharmacological activities.

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1. Introduction

Mangosteen (Garcinia mangostana L.) is one of the most common tropical fruits found in Southeast Asia. It is mainly cultivated in Thailand, Indonesia, Malaysia, Sri Lanka, the Philippines, Myanmar, and India. The Garcinia genus contains about 35 genera and up to 800 species worldwide [1]. Mangosteen hulls have been used in folk medicines to treat gastrointestinal disorders such as abdominal pain, diarrhea and dysentery; cystitis; skin disorders such as psoriasis and eczema; healing of a wound, suppuration and chronic ulcers [2]. Dietary supplements of mangosteen extract have been marketed in the United States lately. Extensive in vivo and in vitro studies on mangosteen pericarp were reported in recent years demonstrated broad pharmacological activities including antioxidant, anticancer, antinociceptive, anti-inflammatory, neuroprotective, anti-obesity, anti-hyperglycemic [3]. Xanthones are the most abundant and the main bioactive component from mangosteen. Publications related to mangosteen have been raised annually, and novel xanthones have been discovered each year. This review article aims to define an update in the chemical compounds and pharmacological activities corresponding to the latest research articles.
2. Materials and Methods

This literature review was performed by collecting and analyzing research articles related to the phytochemical content and the pharmacological effects of mangosteen. All articles were published in PubMed and compiled based on multiple keywords such as ‘Mangosteen, G. mangostana, phytochemicals of mangosteen, xanthones, antioxidants, antidiabetic, antimalarial, anti-acne, anticancer, Alzheimer, anti-aging, anti-obesity, antibacterial of mangosteen’. The analysis in this review was elaborated by a minimum of 50 articles published in the last 10 years, including 20 articles in the last 2 years, and the articles must have Digital Object Identifier (DOI).

3. Chemical Compounds

Numerous phytochemical screenings on mangosteen pericarps revealed the existence of polyphenolic compounds such as xanthones, benzophenones, flavonoids, and anthocyanins. Xanthones were the main compound present in the mangosteen. Furthermore, mangosteen also contained many nutrients [4]. The nutritional composition of the mangosteen fruit is shown in Table 1. The chemical structure of several phytochemical molecules isolated from G. mangostana is described in Figure 1.

<table>
<thead>
<tr>
<th>Nutrient (units)</th>
<th>Value per 100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Proximates}</td>
<td></td>
</tr>
<tr>
<td>Water (g)</td>
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<tr>
<td>Protein (g)</td>
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<tr>
<td>Total lipid (g)</td>
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<tr>
<td>Carbohydrate (g)</td>
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<td>Magnesium, Mg (mg)</td>
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<tr>
<td>Potassium, K (mg)</td>
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<tr>
<td>\textit{Vitamins}</td>
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<tr>
<td>Vitamin A (IU)</td>
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</tr>
<tr>
<td>Thiamin, Niacin, Pantothenic acid, Vit. B-6</td>
<td>A few</td>
</tr>
</tbody>
</table>

3.1. Polyphenolic compound.

Mangosteen peels contained 10 times more phenolic compounds and 20 times more antioxidant activity compared to mangosteen pulp. Extraction of the mangosteen pericarp by organic solvent led to the isolations of nonpolar compounds such as xanthones and prenylated benzophenone derivatives. The polar fraction harbor some polar compounds of polyphenols and condensed tannins such as catechins, procyanidins, and anthocyanidins [5].

3.1.1. Xanthones.

Xanthones are the major bioactive component found in mangosteen. At least over 68 xanthones derivatives isolated from mangosteen fruit were reported [1,3]. Some xanthones of mangosteen included α-mangostin, β-mangostin, γ-mangostin, gartane, 8-deoxygartane, mangostinone, 11α-mangostin, mangostanol, 1-isomangostin, 3-isomangostin, and garcinone E. The most abundant xanthones in mangosteen pericarp and bark are α- and γ-mangostin [6]. α-mangostin is the major xanthones derivatives isolated from mangosteen and have been drawn
attention in the medicinal plant research area due to its extensive biological and pharmacological activities.
Figure 1. The molecular structure of some phytochemical compounds isolated from G. mangostana, especially xanthones and its derivatives (1-35), new xanthones (33-35) found between 2019-2020, benzophenones (1A-3A), and flavonoid (1B).

In another study, ethanolic extract of mangosteen peels resulted in isolation of 14 xanthon derivatives included 7-O-demethyl mangostatin (1), mangostatin (2), 8-deoxygartanin (3), gartanin (4), garcinone E (5), trapezifolixanthone (6), padiaxanthone (7), tovophyllin A (8), 1,5,8-trihydroxy-3-methoxy-2 [3-methyl-2-butenyl]xanthone (9), garcinone B (10), 1,3,7-trihydroxy-2,8-di-(3-methylbut-2-enyl)xanthone (11), mangostenone D (12), mangostinone (13), and 1,7-dihydroxy-2-(3-methylbut-2-enyl)-3-methoxyxanthone (14) [7].

3.1.2. Benzophenones.

The major benzophenones in mangosteen fruits have been identified as garcimangosone D, kolanon, and maclurin [8]. In another study, four benzophenones (rhodanthenone B;
garcimangosone D; 3,4,5,3′-tetrahydroxybenzophenone; 4,6,3′,4′-tetrahydroxy-2-methoxybenzophenone) have been extracted from mangosteen peels using hot water as the minor constituent in isolate [5].

3.1.3. Anthocyanins.

Anthocyanins components in mangosteen fruits have been elucidated as cyanidin-3-O-glucoside, cyanidin-3-O-sophoroside, and chrysanthemum [8].

3.1.4. Other phenolic compounds.

NMR proton of hot water extract from mangosteen peels revealed epicatechin (flavonoid) along with procyanidin B2 (epicatechin dimer) as the main polyphenolic components in the isolate [5].

4. Pharmacological Activities

4.1. Anti-acne.

Multiherb extracts (G. mangostana, Lithospermum officinale, Tribulus terrestris L., Houttuynia cordata Thunb) in cleanser formulation were tested on 60 patients with mild to moderate acne for 8 weeks. Acne lesion counts were performed and resulted in a significant reduction in inflammatory and non-inflammatory acne. The average reduction in inflammatory acne was 56% compared to day 0 and non-inflammatory acne was reduced by 36% [9].

Another study was conducted on 77 patients with mild to moderate acne. Patients were randomly distributed into groups then given a topical herbal extract formula (tea tree oil, mangosteen pericarp, niacinamide 4%) or 2.5% Benzoyl Peroxide for 12 weeks. The analysis of the lesion showed a significant reduction in acne. These antimicrobial and anti-inflammatory activities against C. acnes are due to terpinen-4-o and xanthone components in tea tree oil and mangosteen peels [10].

Another clinical study on 28 patients with mild to moderate acne revealed the 0.5 % mangosteen peel extracts (containing 94% α-mangostin based on high-performance liquid chromatography- HPLC) in nanoparticle-loaded gel significantly reduced about 67% of comedones and inflammatory lesions after 12-week treatment. Alpha-mangostin possessed a strong antimicrobial against C. acnes [11].

4.2. Anti-aging and anti-hyperpigmentation.

An increase of reactive oxygen species (ROS) was the main cause of oxidative stress lead to skin aging, and the application of antioxidants such as mangosteen pericarp extract (MPE) can delay the occurrence of aging. Skin aging was also associated with decreased skin elasticity and the degradation of hyaluronic acid, which generates hyperpigmentation. MPE showed a strong anti-elastase effect. Elastase of human skin was a process of elastin degradation that led to the loss of skin elasticity. Based on its IC50 value, elastase inhibition activity increased as follow: γ-mangostin < garcinone D < α-mangostin < garcinone C < MPE. Gamma-mangostin had the potential as an anti-hyaluronidase that maintained skin moisture and anti-tyrosinase to prevent hyperpigmentation [12]. Other studies have shown that alpha-mangostin had the potential to reduce skin wrinkles due to ultraviolet B (UV-B) exposure in hairless mouse models with UV-B damage-induced HaCaT cells [13].
4.3. Alzheimer.

Alpha-mangostin could be a potential candidate for therapy of Alzheimer’s disease (AD), considering the beneficial activities of mangosteen such as anti-inflammatory, antioxidant, and neuroprotective [14]. In vitro studies on the rat model suggested that α-mangostin with EC₅₀ values of 3.89 Nm inhibits amyloid aggregation via limitation of Aβ fibril formation [15].

4.4. Bipolar disorder, schizophrenia and cholinesterase inhibitor.

Bipolar disorder and schizophrenia have been comprehended to be related to a substantial increase in oxidative stress levels such as reactive oxygen species (ROS), reactive nitrogen species (RNS), thiobarbituric acid reactive substances (TBARS) and malondialdehyde (MDA). Mangosteen hulls were found to reduce those four types of oxidative stress levels significantly in a rat model. Thus, the mangosteen hulls appear as possible supplemental therapy for bipolar disorder and schizophrenia [16].

Another study revealed that the methanol extract of mangosteen peels and calyx possessed strong inhibitory activities against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) with IC₅₀ values of 0.90 and 0.37 µg/ml due to α- and γ-compounds [17].

In vitro studies demonstrated six xanthones compounds isolated from mangosteen peels extract had cholinesterase inhibitory effects with IC₅₀ value of 1.28-8.0 µg/ml through Ellman’s microplate assay. The results showed that one of the xanthonic derivatives, Garcinone C possessed strong inhibitory effects in AChE with an IC₅₀ value of 1.24 µM, while γ-mangostin inhibits BChE with IC₅₀ value of 1.78 µM. Molecular docking study exposed mangostanol, 3-isomangostin, garcinone C and α-mangostin contributed to the AChE inhibitory activities, 8-deoxygarctanin in BChE inhibitor, while γ-mangostin inhibited both AChE and BChE [18].

Another study suggested that α-mangostin could be a potential adjuvant therapy for schizophrenia and haloperidol due to its antidepressant-like properties, further assisting the anti-immobility responses to these drugs through maternal immune activation (MIA) models [19].

A clinical trial using adjunctive 1000 mg/day of the mangosteen pericarp on 150 schizophrenia patients for 24 weeks was shown in the positive and negative symptom scale and successfully gained ethical and regulatory approval [20].

4.5 Neuropathic pain.

The effects of α-mangostin on the peripheral neuropathic pain caused by chronic constriction injury (CCI) were evaluated in rats for 14 days. This study suggested that α-mangostin ameliorates the progression and the existence of CCI-induced neuropathic pain due to its antioxidant, anti-inflammatory, and anti-apoptotic properties. Antioxidant properties were measured as malondialdehyde (MDA) and glutathione (GSH) level. Anti-inflammatory properties were evaluated by analysis of inflammatory markers (cyclooxygenase-2 (COX2), interleukin 1 beta (IL-1β), inducible nitric oxide synthase (iNOS), nitric oxide (NO), toll-like receptor 4 (TLR-4), metalloproteinases-2 (MMP2), and tumor necrosis factor-alpha (TNF-α) level. Anti-apoptotic properties were evaluated by Bcl-2, Bax, and caspase-3 levels. The results showed that α-mangostin increased MDA level and decreased GSH level. Both MDA level and
GSH level were conversely observed in CCI group. Alpha-mangostin (50 mg/kg) enhanced the levels of all inflammatory markers, Bax, and caspase-3 on the day 7 and 14 [21].

4.6. Antibiotic growth promotoripolar disorder.

Mangosteen peel extract (MPE) 2% was fed to a group of 30 1-day-old broiler chicks for 30 days and showed no increase in the rate of antibiotic resistance, while the colistin-treated group had increases in antibiotic resistance rate. Thus, MPE poses a potential as natural antibiotic growth promoters, which develop the performance of boilers production without elevating the antibiotic resistance rate [22].

4.7. Antibacterial.

An in vitro research reported the antibacterial activity of mangosteen pericarp extract against methicillin-resistant *Staphylococcus aureus* (MRSA) with the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) 0.02 to 1.25 mg/ml and 0.03 to 5 mg/ml, while for α-mangostin were 1.56 to 12.50 μg/ml and 3.91 to 100 μg/ml [23].

In another study, alpha-mangostin showed antibacterial activity against *S. pseudintermedius* (both methicillin-resistant *S. pseudintermedius* (MRSP) dan meticillin-susceptible *S. pseudintermedius* (MSSP) ) with the MIC of α-mangostin related to MSSP was 0.53 ± μg/ml and the MIC on MRSP was 0.47 ± 0.27 μg/ml through in vitro time-kill method [24].

In vitro experiment was carried out to demonstrate inhibitory effects of mangosteen peel extracts (MPE) on *S. mutants* and *P. gingivalis* in biofilm formation (tooth) through crystal violet biofilm assay. The results indicated that MPE significantly inhibited both bacterial during incubation of 6 h, but the effective concentration of MPE was 100% over an incubation period of 24 h [25].

Mangosteen peel extracts (MPE) with 5 mg/ml concentration in natural products biosynthesized silver nanoparticle (Ag-NPs) formula was evaluated against oral infection caused by *Listeria monocytogenes* in BALB/c female mice. The in vivo experiment reported that MPE enhanced the immunogenicity against *L. monocytogenes* as demonstrated by the elevated survival time, decreased pathological changes in intestinal tissue, and enhancement of immune response [26].

4.8. Antidiabetic.

Garcimangostin A, a new xanthone from the mangosteen pericarp extract, had an α-amylase inhibitory effect with 94.1 % inhibition compared to acarbose (96.7%). This result showed that mangosteen can decrease the postprandial glucose absorption, thus advantageous for the treatment and/or prevention of diabetes [27]. The in vitro antidiabetic activity of the aqueous extract of mangosteen vinegar rind (MVP) was analyzed in streptozotocin-induced type II diabetes nephropathy mice. The result indicated that MVP induced α-amylase inhibitory activities with the IC50 values 422.82±7.83 μg/ml [28]. Another in vitro study on High Fat Diet/-Streptozotocin or HFD/-STZ-induced DM mice suggested that xanthones (α-mangostin and γ-mangostin) in the mangosteen pericarp inhibited pancreatic-α-amylase with IC50 values 409.59 ± 6.81 μg/ml [29].
4.9. Anti-inflammatory and wound healing.

A topical formulation containing *G. mangostana* pericarp ethanolic extract (GME) was tested on MRSA-infected tape stripping model mice. The wounds were completely healed on the last day of the experiment (day 10) and the number of MSRA-colonies decreased from the first day of the study. Significant reduction of pro-inflammatory cytokines expression (TNF-α, IL-6, and IL-1β) was exhibited by GME through modulation of TLR-2 pathway by α- β- and γ-mangostin also garcinone B components [23]. Another study revealed that the combination of 1 µg/ml mangosteen and 34 µg/ml propolis extracts were highly effective as anti-inflammatory and in vitro bone formation agents [30]. In another study, 1 µg/ml of the mangosteen extract reduced IL-6 and IL-8 (inflammatory cytokines) expression in 5 µg/ml *P. gingivalis* KCOM 2804 LPS-treated hTERT-hNOF cells [31].

4.10. Antioxidant.

The fresh and frozen peel (pericarp) and the flesh (pulp) of *G. mangostana* were extracted by ultrasound-assisted extraction method for 15, 30 and 60 min. Ethanol within 20%, 40%, 70% and 96% (v/v) concentrations were used as solvent. The antioxidant activity was measured using 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2′-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid (ABTS), cupric reducing antioxidant capacity (CUPRAC), ferric reducing antioxidant power (FRAP) and ferrous ion chelating (FIC) methods, whereas the total phenolic content was measured using the Folin-Ciocalteu (F-C) method. The result indicated that a higher antioxidant activity in fresh peel extracts corresponds to several antioxidant compounds. The F-C technique measured the highest polyphenol content from the fresh plant material extract [8]. Pectin was isolated from the mangosteen peel extract and the antioxidant potential was observed by the DPPH method. The result showed a moderate antioxidant activity with the IC$_{50}$ of about 161.93 ± 31.57 µg/ml [32].

4.11. Antitumor.

*In vitro* studies on the phytochemicals from mangosteen had been demonstrated to inhibit the cancer cells proliferation and metastasis and exhibited an anti-apoptosis effect in certain human malignancies such as breast [33–35], lung [36], liver [37–40], colon [37], oral [41–43], skin [44], leukemia [45], prostate [46,47] and cervical cancers [43,48].

In breast cancer, mangostanaxanthone VII from the chloroform fraction of mangosteen pericarps extract was able to decrease the breast cancer cells viability towards the A549 and Michigan Cancer Foundation-7 (MCF-7) cancer cell lines through Sulforhodamine B (SRB) assay with the IC$_{50}$ values 26.1 to 34.8 µM [33]. Another xanthone, alpha-mangostin from the mangosteen extract, was tested on the MDA-MB-231 spheroid breast tumor cell lines to demonstrate the anti-proliferative activities. The experiment reported that α-mangostin significantly decreased the cell viability in MDA-MB-231 for 48 h incubating period with doses higher than IC$_{50}$ = 0.70-1.25 µg/ml) [34]. Additionally, four phytochemicals compounds (α-mangostin, β-mangostin, mangaxanthone B, and mangaphenone) were isolated from the stem barks of *G. mangostana* and *G. benthamiana* (Planch. & Triana) Pipoly were also reported to promote apoptosis towards MCF-7 and MDA-MB-231 breast cells line through 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay with the IC$_{50}$ values in the range of 4.4 - 12.0 µM via estrogen receptor (ER) and fatty acid synthase (FAS) signaling pathways [35].
In the lung cancer, alpha-mangostin showed a considerable anti-proliferative effect on small cell lung cancer [36]. In liver and colon cancer, anticancer activities of garcinone E, 7-O-methylgarcinone E and α-mangostin components from mangosteen have been demonstrated in the human hepatocellular, breast, and colorectal cancer cell lines [37]. Alpha-mangostin was shown to possess an anti-proliferative effect on the liver cell line [38].

In oral and cervical cancer, alpha-mangostin was effective against the YD-15 tongue mucoepidermoid carcinoma cells and the squamous cell carcinoma of the oral cavity [41,42]. Mangosteen pericarp ethanolic extract (MPE) was tested in the human tongue squamous cell carcinoma (H357) cells and the cervical cancer cells (HeLa) for anticancer activities through the MTT assay, Terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End Labeling (TUNEL) assay, western blotting, and flow cytometry techniques. The results revealed that MPE significantly repressed the growth of H357 and HeLa cells in a dose-dependent manner and early apoptosis was induced by MPE after incubation for 48 h. The results indicated that MPE also increased the expression of pro-apoptotic proteins such as caspases and Bax, and decreased the expression of anti-apoptotic protein Bcl-2. These results proved the cytotoxic and apoptotic effect of MPE on oral and cervical cancer due to its rich constituents, including tannins, flavonoids, proteins, steroids, and cardiac glycosides [43]. The anticancer effect of α-mangostin on the human cervical cancer cell was investigated using in vitro and in vivo studies [48].

In the skin cancer, α-mangostin had the ability to inhibit 9, 10-dimethylbenz[a]anthracene (DMBA)/TPA-induced skin cancer by reducing the inflammation and inducing autophagy and apoptosis via three key proteins phospho-PI3K (p-PI3K), p-AKT and p-mTOR (PI3K/Akt/mTOR) signaling pathway in mice [44]. In leukemia, α-mangostin induced autophagy augments in the chronic myeloid leukemia cell [45].

In prostate cancer, α-mangostin also showed an apoptotic activity against 22Rv1 prostate cancer cells [46]. Mangosteen pericarp powder (MPP) effect was evaluated on prostatic hyperplasia in 24 male F344 rats. This study suggested that MPP application can alleviate the development of prostatic hyperplasia because of its anti-proliferative effect by lowering the serum testosterone level and dihydrotestosterone concentrations, promoting lipid peroxidation, also improving of inflammation and mitochondrial function in the prostate tissues [47].


Mangosteen extract and α-mangostin reduced the degree of ulcerative colitis (UC) induced by dextran sulfate sodium (DSS) in mice. Furthermore, a recent study revealed that this mechanism occurred by suppressing nuclear factor-kappa B (NF-kB) activation due to mangosteen's anti-inflammatory and antioxidant effect [49,50].


Administration of α-mangostin (50 mg/kg) for 5 weeks in HFD-induced obesity mice have been proved to decrease the hepatic steatosis, accumulation of fat and body weight through the regulation of lipid metabolism via modulation of SIRT1-adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor γ (PPARγ) pathways [51].

Antimalarial activity of α-mangostin was demonstrated by virus titer assay through plaque assay method. Alpha-mangostin was tested against the dengue virus infection (DENV-2) in human peripheral blood mononuclear cells (PBMC). Alpha-mangostin could potentially inhibit virus replication due to its higher concentration. The results showed 50% viral reduction after treatment using 10 and 20 μM of α-mangostin at 24- and 48-h post-infection, in which the 48 h treated group had a more percentage reduction effect. The IC_{50} values were 5.47 and 5.77 μM for 24- and 48-h treatments, respectively [52].

Another in vitro study was conducted on the antimalarial activity of α-mangostin in DENV infection in hepatocellular carcinoma HepG2 and Huh-7 cell lines. The results demonstrated that α-mangostin inhibited both DENV production and cytokine/chemokine expression in HepG2 cells [53].

4.15. Antiparasitic.

Alpha-Mangostin was tested on nematode Caenorhabditis elegans. The results revealed that α-mangostin caused growth inhibition in C. elegans population with the LC_{50} value of 3.8 ± 0.5 μM [54].

4.16. Pulmonary fibrosis.

In vivo study indicated that α-mangostin treatment (10 mg/kg/day) significantly reduced the oxidative stress in bleomycin (BLM)-induced pulmonary fibrosis in mice by initiating AMPK mediated signaling pathway and stimulated primary lung fibroblasts (PLFs) and downregulated the accumulation of extracellular matrix (ECM) [55].

4.17. Chronic kidney disease (CKD).

In silico study predicted the protective role of α-, β-, γ-mangostin in PbAc-induced CKD by activating the Nrf-2 and regulating NF-kB and MAPK pathways. The plausible mechanisms correlated to the antioxidant activity of these xanthones [56].

5. Conclusions

The mangosteen (G. mangostana L.) contained several chemical compounds, especially xanthones, benzophenones, flavonoids, and anthocyanins. These components were proven to generate beneficial human health conditions through various pharmacological activities such as antioxidant, anti-acne, anti-aging, anti-hyperpigmentation, antibacterial, antidiabetic, anti-obesity, anti-inflammatory, antimalarial, antiparasitic, and antitumor. Furthermore, chemical compounds isolated from mangosteen have shown advantageous outcomes for multiple pathological conditions includes Alzheimer’s, various cancers, bipolar disorder, schizophrenia, neuropathic pain, CKD, and pulmonary fibrosis. This review indicated that xanthonate in mangosteen has the potential to be developed as a promising drug candidate. Further exploration of mangosteen as drug candidates may include pharmacokinetic, pharmacodynamic, and xanthonate targeting effects that possible to be carried out in the future study.
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Conflicts of Interest

The authors declare no conflict of interest.

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