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RESEARCH ARTICLE

Therapeutic insights into *Garcinia mangostana*: Bioactivities, challenges, and future directions in drug discovery

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ABSTRACT

Garcinia mangostana is a tropical tree native to India, Sri Lanka, and Southeast Asia. In Traditional Medicinal Systems (TMS), decoctions and infusions prepared from mangosteen fruits have effectively treated skin lesions and various inflammatory conditions. Researchers have also reported its extensive biological activities, *viz.* antimicrobial, antioxidant, anticancer, antidiabetic, neuroprotective, and cardioprotective effects. This literature review comprehensively describes the biological potential of *G. mangostana* over the last twenty-five years. It includes a discussion of the bioactive compounds of *G. mangostana* and their extraction, purification, and characterization processes. Antimicrobial, anticancer, antitumorigenic, antidiabetic, anti-inflammatory, neuroprotective, and antiparasitic activities are discussed in detail. Furthermore, the paper addresses the main obstacles associated with using mangosteen extracts and suggests ways to overcome these challenges. The medicinal properties of *G. mangostana* are primarily attributed to α-mangostin and other bioactive xanthones. However, other bioactive compounds with potential therapeutic activities remain not fully characterized. Therefore, developing effective extraction methods for these bioactive compounds, along with their characterization, possible bioactivities (pharmacodynamics), and any synergistic effects, is essential. Additionally, pharmacokinetic studies, including absorption, distribution, metabolism, excretion, and toxicity (ADMET), are necessary. It is also worth considering plant parts other than the pericarp.

Keywords: *G. mangostana*; natural products; antimicrobial; biological products; biological activity; phytochemicals.

INTRODUCTION

The healthcare system places great emphasis on medicinal plants as the primary raw materials for traditional medicine preparation. These plants contain natural products with medicinal value that significantly contribute to drug discovery (Fabricant & Farnsworth, 2000). To properly evaluate these natural products, it is crucial to have a thorough understanding of the ethnopharmacological uses of various medicinal plants. Despite the rapid advancements in modern medicine, many people worldwide still prefer herbal remedies for several reasons. They believe in their effectiveness, have limited access to medical alternatives, find modern medicines expensive, and have cultural preferences (Hosseini *et al*., 2021). Furthermore, these natural medicinal plants offer medicinal benefits that are accessible, affordable, safe, and efficient. In addition to their medicinal applications, many plants are also used as food, healthcare

products, and in veterinary medicine, playing a vital role in our daily lives (Ahmed *et al*., 2023; Chaachouay & Zidane, 2024).

Garcinia mangostana L., commonly known as mangosteen, is a tropical evergreen tree belonging to the genus *Garcinia* in the family Clusiaceae. It is native to India, Sri Lanka, and Southeast Asia, including Thailand, the Philippines, Malaysia, and Indonesia (Nazri, 2014; Bohra, 2023). Among the various species of *Garcinia* – including *G. mangostana, G. schomburgkiana, G. dulcis, G. cowa, G. atroviridis, G. hanburyi, G. bancana, G. xanthochymus, G. thorelii, G. hombroniana,* and *G. speciose*– *G. mangostana* has gained significant attention for its wide range of applications, from traditional medicine to dietary supplements (Gutierrez-Orozco, F. & Failla, M.L.).

The mangosteen fruit is known for its delicious taste, fragrant white pulp, and deep purple rind (pericarp). This unique combination has earned it the title of "queen of fruits" (Morton, 1987; Mahattanatawee *et al*., 2006). The seeds and rind of the fruit hold a significant historical importance in traditional medicine, while beverages containing mangosteen pulp and rind are marketed globally as nutritional supplements. For over two hundred years, infusions and decoctions made from mangosteen peels and seeds have been used in traditional medicine to treat skin diseases, gastrointestinal and urinary tract infections, as well as to provide laxative, fever-reducing, and scurvy-preventing effects. Additionally, extracts from the fruit have demonstrated antioxidant, anticancer, antiallergic, antibacterial, antidepressant, antiparasitic, antiviral, anti-inflammatory, and neuroprotective properties (Ovalle-Magallanes *et al*., 2017). Research on mangosteen phytochemicals has identified various secondary metabolites, with prenylated and oxygenated Xanthones (approximately 70 types) and anthocyanins being the most promising and abundant compounds (Pedraza-Chaverri *et al*., 2008).

This literature review compiles evidence on the potential of *G. mangostana* as a source of bioactive compounds with therapeutic activities. It presents information related to *G. mangostana* as a bioactive-rich plant resource with versatile therapeutic applications, addressing significant health challenges such as cancer, diabetes, inflammation, neurodegenerative diseases, and infectious diseases. The review bridges traditional knowledge with modern scientific research, including possible mechanisms of its pharmacological activities. It guides further studies, advances drug discovery, and supports evidence-based, sustainable health solutions. Additionally, it contributes to the integration of natural products into mainstream medicine, benefiting both the scientific community and society by elaborating on *G. mangostana*'s therapeutic potential.

Bioactive compounds, extraction, purification and characterization

Garcinia mangostana is rich in various chemical compounds. Table 1 provides a comprehensive list of these chemical compounds, their origin in different parts of the plant, and their associated biological activities (USDA, n.d.). The presence of compounds with significant health benefits highlights the therapeutic potential of mangosteen.

Table 1. Chemical composition of *G.mangostana* according to Duke's database [13]

Sr No.	Chemical	Plant Part	Biological activity
1	1,3,6,7-tetrahydroxyanthone	Wood	Nil
2	1,3,6,7-tetrahydroxyanthone-o-glucoside	Wood	Nil
3	1,5-dihydroxy-2-(3-methylbut-2-enyl)-3-methoxyxanthone	Fruit	Nil
4	8-deoxygartanin	Fruit	Nil
5	Ascorbic acid	Fruit	Acidulant, Aldose-Reductase-Inhibitor, Analgesic, Angiotensin -Receptor-Blocker, Antiaggregant, Antiaging, Antiallergic, Anti-alzheimer's, Antiarthritic, Anti-asthmatic, Anti-atherosclerotic, Antibacterial, Anticataract, Anti-cervical dysplastic, Anti-climacteric, Anticold, Anti-Crohn's, Antidementia, Antidepressant, Antidiabetic, Antidote, Antieczemic, Antiedemic , Antiencephalitic, Antiendometriotic, Antifatigue, Antifibrotic, Antigallstone, Antigastritic, Antigingivitic, Antiglaucomic, Antihangover, Antihemorrhagic, Antihepatitic, Antihepatotoxic, Antiherpetic, Antihistaminic, Antihypertensive, Anti-infertility, Antiinflammatory, Anti-lepric, Antilithic, AntiLyme, Antimaculitic, Antimeasles, Antimenopausal, Antimigraine, Antimutagenic, Antineuramidase, Antinitrosic, Antiobesity, Antiorchitic, Antiosteoarthritic, Antiosteoporotic, Antioxidant, Antiparkinsonian, Antiparotitic, Antiperiodontitic, Antipneumonic, Antipodriac, Antipoliomyelitic, Antipyretic, Antiradicular, AntiRaynaud's, Antiretinotic, Antirheumatic, Antirhinitic, Antiscorbutic, Antiseptic, Antishingles, Antispasmodic, Antistress, Antisyndrome-X, Antitumor, Antiulcer, Antiviral, Apoptotic, Asthma-preventive, Beta-Adrenergic Receptor Blocker, Beta-Glucuronidase-Inhibitor, Calcium-Antagonist, Cancer-Preventive Cardioprotective, Cold-preventive, Collagenic, Detoxicant, Diuretic, Fistula-Preventive, Hypocholesterolemic, Hypoglycemic, Hypotensive, Immunomodulator, Immunostimulant, Lithogenic, Mucolytic, Pesticide, Uricosuric, Urinary-Acidulant, Vasodilator, Vulnerary
6	Beta-carotene	Fruit	Allergenic, Androgenic, Antiacne, Antiaging, Antiarthritic, Antiasthmatic, Anticancer, Anticarcinomic, Anti-cervical dysplastic, Anticoronary, Antihyperkeratotic, Antiichythyotic, Antileukoplakic, Antilipoperoxidant, Antilupus, Antimaculitic, Antimastitic, Antimutagenic, Antioxidant, Antiozenic, Antipapillomic, Antiphotophobic, Antipityriasic, AntiPMS, Antiporphyric, Antiproliferant, Antipsoriac, Antiradicular, Antirheumatic, Antistress, Anti10tumor, Antitumor, Antiulcer, Antixerophthalmic, Cancer-Preventive, Chemopreventive, Colorant, COX-1-Inhibitor, Gastroprotective, Immunostimulant, Interferon-Synergist, Mucogenic, Phagocytotic, Prooxidant, Thymoprotective

7	Beta-mangostin	Latex Exudate	Nil
8	Betulin	Leaf	Anti-carcinomic, Antifeedant, Antiflu, AntiHIV, Antiinflammatory, Antitumor, Antiviral, Cytotoxic, Hypolipemic, Prostaglandin-Synthesis-Inhibitor, Topoisomerase - II-Inhibitor
9	Catechins	Fruit	Tyrosine-Kinase-Inhibitor
10	Catechins	Petiole	Tyrosine-Kinase-Inhibitor
11	Cis-hex-3-enyl-acetate	Fruit	Nil
12	Cis-s-3-hexen-1-ol	Fruit	Nil
13	Citric acid	Fruit	Allergenic, Alpha-Amylase-Inhibitor, Antiatherosclerotic, Antibacterial, Anticalculic, Anticoagulant, Antileishmanic, Antimutagenic, Antioxidant Synergist, Antiseptic, Antitubercular, Antitumor, Disinfectant, Flavor, Hemostat, Irritant, Laxative, Litholytic, Mycobactericide, Odontolytic
14	Gamma-mangostin	Fruit	Nil
15	Garcinones	Petiole	Nil
16	Gartanin	Fruit	Nil
17	Hexyl-acetate	Fruit	FLavor FEMA 3-25
18	Maclurin	Wood	Dye
19	Mangostin	Latex Exudate	Antibacterial, Antiseptic, Fungicide, Pesticide
20	Mangostin	Fruit	Antibacterial, Antiseptic, Fungicide, Pesticide
21	N,7dihydroxy-2-(3-methylbut-2-enyl)-3-methoxyxanthone	Fruit	Nil
22	Niacin	Fruit	Antiacrodynic, Antiallergic, Antialzheimeran, Antiamblyopic, Antianginal, Anticataract, Antichilblain, Anticonvulsant, Antidementia, Antidermatitic, Antidiabetic, Antidysphagic, Antiepileptic, Antihangover, Antihistaminic, Antihyperactivity, Antiinsomnic, AntiLyme, AntiMeniere's, Antineuralgic, Antiparkinsonian, Antipellagric, AntiRaynaud's, Antiscotomic, Antispasmodic, Antivertigo, Cancer-Preventive, Cardioprotective, Circulotonic, Fibrinolytic, Hepatoprotective, Hepatotoxic, Hypocholesterolemic, Hypoglycemic, Hypolipidemic, Sedative, Serotoninergic, Vasodilator
23	Pectin	Fruit	Antiatheromic, Antibacterial, Antidiabetic, Antidiarrheic, Antienteritic, Antigallstone, Antigastritic, Antilithic, Antimetastatic, Antimutagenic, Antiobesity, Antitumor, Antitussive, Antiulcer, Cancer-Preventive, Chemopreventive, Demulcent, Fungicide, Hemostat, Hypocholesterolemic, Hypoglycemic, Peristaltic, Pesticide
24	Riboflavin	Fruit	Antiarabiflavinotic, Anticarpal-Tunnel, Anticataract, Anticephalagic, Anticervical dysplastic, Anticheilitic, Antidecubitic, Antiglossitic, Antikeratitic, AntiLyme, Antimigraine, Antioxidant, Antipellagric, Antiphotophobic, Cancer-Preventive
25	Thiamin	Fruit	Analgesic, Antialcoholic, Antialzheimeran, Antianorectic, Anti-bacteria, Antiberiberi, Anticanker, Anticardiospasmic, Anticataract, Anticolitic, Antidementia, Antidyspeptic, Antiencephalopathic, Antifatigue, Antigastritic, Antihangover, Antiheartburn, Antiherpetic, AntiLyme, Antimigraine, Antimyocarditic, Antineuralgic, Antineurasthenic, Antineuritic, Antineuropathic, Antipoliomyelitic, Insectifuge, Neuroprotective, Pesticide

The main bioactive compounds in *G. mangostana* are found in its pericarp, which consists of organic acids, tocopherols and fatty acids. Figure 1 presents the photograph of the mangosteen tree and its ripe fruit. Citric acid, β-tocopherol, and saturated fatty acids are the most abundant compounds in each group, respectively. However, the pericarp of mangosteen primarily contains compounds belonging to the Xanthone group (Figure 2), with α-mangostin being the most abundant, accounting for nearly 70% of its constituents. Following α-Mangostin is γ-Mangostin, which makes up approximately 20% (Espirito Santo *et al*., 2020; Albuquerque *et al*., 2023; Bi *et al*., 2023). Due to the prevalence of Xanthones, various extraction techniques have been developed to extract them. Seven different extraction solvents have proven to be the most effective in extracting Xanthone from mangosteen's pericarp, including acetone, ethyl acetate, methanol, ethanol, acetic acid, hexane, and water. Interestingly, infusions with drinking water, a traditional extraction technique, are still effective in obtaining almost 2% of the flavonoids present in the macerated pericarp. This method can be used in homemade remedies. However, their yield is relatively low compared to other extraction methods for applications other than homemade remedies. Therefore, stronger extraction solvents are required (Yuvanatemiya *et al*., 2022).

Ethanol is the most used solvent. When used in 5 grams of dried mangosteen pericarp, it can recover 31.55 mg/g of Xanthones (Yuvanatemiya *et al*., 2022; Li *et al*., 2023). However, a low yield of 1.19 mg/g of Xanthone was obtained from 1 kg of mangosteen pericarp that macerated with 4L of 95% ethanol for seven days. It is important to note that although this solvent provide good yields, it requires longer extraction periods, which can be a disadvantage. Additionally, they require larger amounts of solvent, which can be costly and toxic to handle (Yuvanatemiya *et al*., 2022).

To address the limitations of current extraction methods, new techniques have been developed. One such method that is gaining popularity is microwave extraction, especially suitable for large-scale Xanthone extraction. This method utilizes an electromagnetic field to immobilize polar molecules, generating heat that damages plant cells and releases the desired compounds. To isolate Xanthones, this technique is combined with the use of an organic solvent such as methanol, water or dimethyl sulfoxide (Lopez-Avila & de Castro, 2014). However, a study by Ghasemzadeh *et al*. (2018) discovered that using ethyl acetate as a solvent could significantly enhance the yield of extracted Xanthones. In fact, with less than 3 minutes of irradiation, they were able to achieve an increase of 120.68 mg/g. Extraction with an appropriate solvent allows for

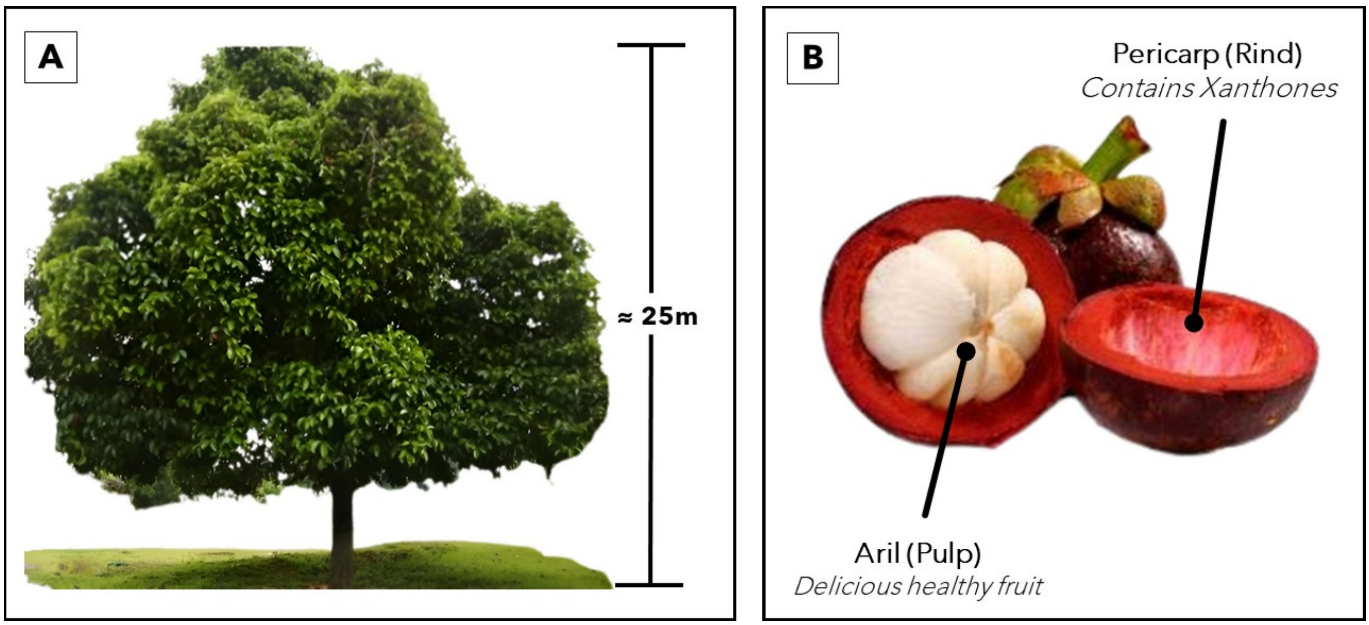

Figure 1. (A) Mangosteen tree (B) Ripe fruit and its internal structure.

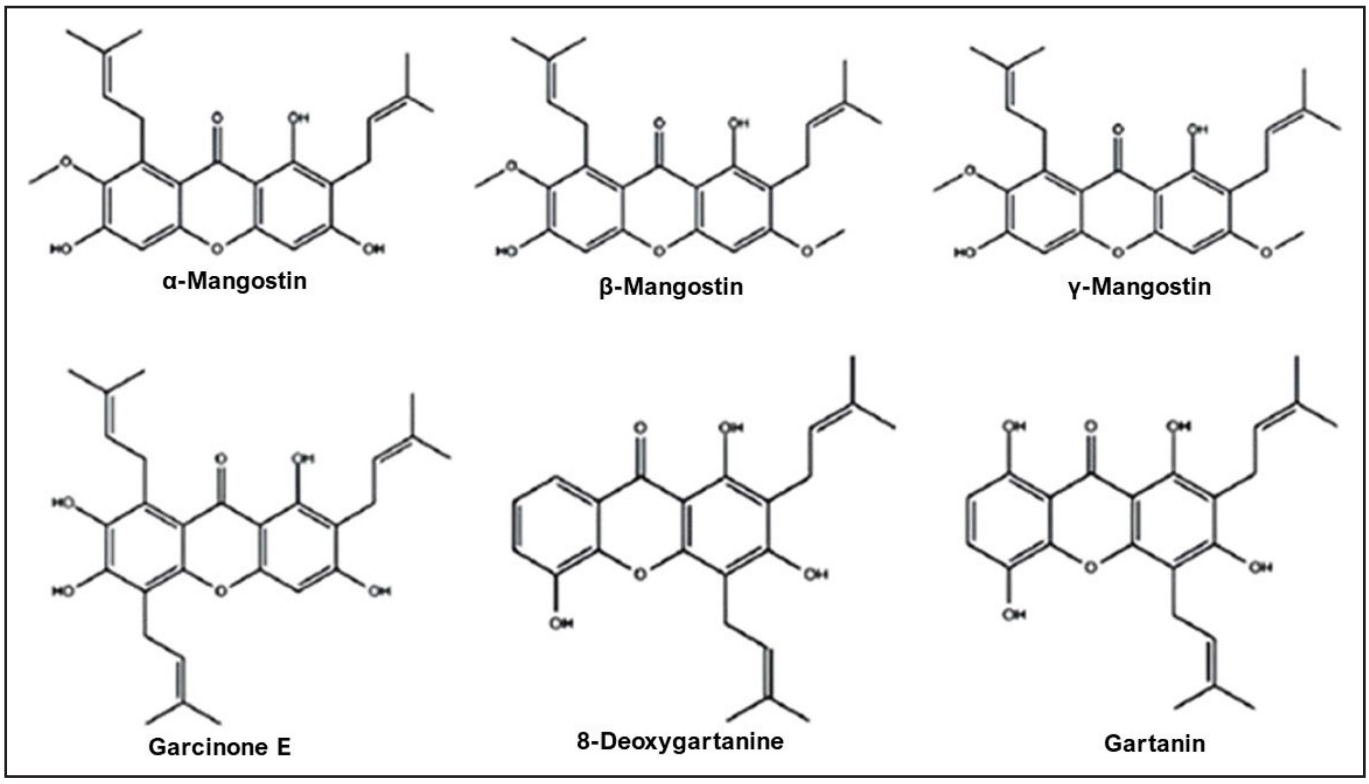

Figure 2. Chemical structures of some Xanthone compounds found in *G. mangostana.* Among these compounds, α-Mangostin is the most abundant, followed by γ-Mangostin.

the separation of compounds. As mentioned earlier, the choice of solvent will determine the amount of the target compound that can be recovered based on its chemical interaction. However, to obtain more information about the bioactive compounds present in mangosteen, further characterization is required using analytical methods.

To evaluate the variety and quantity of Xanthones in mangosteen, the most used method is liquid chromatography. This method separates compounds based on their affinity with an analytical column and allows for their identification. Liquid chromatography has long been employed as an analytical tool because it can accurately identify and quantify the compounds in a sample. The isolation of Xanthones relies on the choice of columns for chromatographic separation, as well as the mobile phases used (Rajendran, 2023). Walker (2007) developed a protocol for High Performance Liquid Chromatography to analyze Xanthones in mangosteen. In this study, extraction was conducted using an acetone/water (80:20) solvent mixture applied to the rind of the fruit. The mobile phases consisted of 0.1% formic acid in water and methanol, with a C-18 column utilized. These parameters, resulted in an average recovery rate of 97% to 103% for the identified Xanthones, demonstrating high resolution and selectivity in the separation and identification of these compounds. Therefore, liquid chromatography is a widely used method that can be easily

performed using equipment commonly found in most laboratories. This method allows for the identification of compounds based on their retention time. Additionally, liquid chromatography is often combined with mass spectrometry analysis, which involves ionizing and characterizing the separated compounds based on their mass-to-charge ratio. LC-MS is an essential tool for discovering new Xanthones found in mangosteen that possess medical properties. It enables the determination of a compound's chemical structure, even when it has been modified by the position of one functional group. This is crucial for advancing the research in the field. In such cases, the analysis is facilitated by two consecutive analyses in the spectrometer, involving fragmentation of the formed ions. This not only provides greater resolution but also allows for easier identification of new compounds (Zarena & Sankar, 2009; Schmitz & Meckelmann, 2023).

Antimicrobial activity

Antimicrobial resistance (AMR) pathogens pose a significant risk to public health and veterinary medicine, primarily due to the overuse and misuse of antimicrobial agents for treatment, metaphylaxis, and growth promotion. Livestock and companion animals can serve as potential sources of resistant bacteria and AMR genes, which can be transmitted to humans through close contact, the food chain, or the environment. Consequently, the transfer of resistant bacteria and AMR genes can occur between companion animals and humans (Vaou *et al*., 2021; Irfan *et al*., 2022). A comprehensive review of the antibacterial activity of mangosteen was conducted by Andani *et al*. (2021). The review focused on the main components of *Garcinia*, including the bark, leaves, fruit peel, fruit and seed, that have been studied for their antibacterial properties against a wide range of gram-positive and gram-negative pathogens. The active ingredients, such as flavonoids, saponins, alkaloids, terpenoids, steroids, and tannins, are present in all solvent and water extracts. The bioactive compounds found in mangosteen rind include mangostin, mangostenol, mangostinon A, mangostenon B, trapezifolixanthone, tovofillin B, α mangostin, β mangostin, garsinon B, mangostanol, flavonoids, epicatechin, gartanin, gamma mangostin, garsinon E, and epicatechin (Andani *et al*., 2021; Cahya *et al*., 2023).

In vitro studies have examined the bactericidal activity of α-Mangostin for treating skin diseases caused by *Staphylococcus* spp. in companion animals. Clinical isolates of *S. aureus, S. epidermidis, S. felis, S. pseudintermedius,* and *S. schleiferi* showed strong inhibition at MIC_{50} 4-8 µg/mL. This inhibitory activity is attributed due to interactions with the major histocompatibility complex II analogous protein (MAP) domain-containing protein in the cytoplasmic membrane of *S. pseudintermedius* through hydroxyl groups at C-3 and C-6. Furthermore, studies have revealed the interaction of α-Mangostin with the cytoplasmic membrane of *S. aureus,* resulting in the disruption of cell membrane integrity (Park *et al*., 2023).

The failure of antimicrobial therapy is also associated with the formation of bacterial persister cells, which are responsible for recalcitrant infections. α-Mangostin has shown inhibitory and antibiofilm activity against methicillin-resistant *Staphylococcus aureus* (MRSA) at a MIC of 2 µg/mL. This activity is mediated by membrane permeabilization and disruption of biofilm formation, as demonstrated *in vitro*. Moreover, it down-regulated genes associated with the formation of persister cells and biofilms, such as norA, norB, dnaK, groE, and mepR, ranging from 2- to 4-fold. *In vivo* studies have revealed that α-Mangostin was effectively achieved 75% survival of *Galleria mellonella* larvae infected with MRSA persister at 8 mg/kg (Felix *et al*., 2022).

The antibiofilm activity of α-Mangostin against planktonic cells of *Streptococcus mutans*, was observed to be mediated through the inhibition of key enzymatic systems associated with exopolysaccharide synthesis (30-45%) and acidogenicity. These enzymatic systems include glucosyltransferases B and C, phosphotransferase-PTS system, and F1F0-ATPase. The α-Mangostin exhibited its activity at a concentration of 150 µM (Nguyen *et al*., 2014). In another study, α-Mangostin was found to be active against planktonic cultures of *Lactobacillus rhamnosus* (99%) and *C. albicans* (78%) biofilms at concentrations of 8 mg/L and 1000 mg/L, respectively. These results were comparable to those of chlorhexidine and therefore α-Mangostin was proposed as an agent for endodontic therapy (Leelapornpisid, 2022).

Garcinia mangostana has been reported to have antibacterial activity against *Propionibacterium acnes* and *S. epidermidis*. This activity is mediated through α-Mangostin, with a minimum inhibitory concentration (MIC) of 3.91 µg/mL. The minimum bactericidal concentration (MBC) values against *P. acnes* and *S. epidermidis* are 3.91 and 15.63 µg/mL, respectively. In another study, a GM (*G. mangostana*) hydrogel patch was found to be effective against *Cutibacterium acnes, S. epidermidis,* and *S. aureus,* indicating its potential as an acne-protective agent. Additionally, γ-mangostin was shown to inhibit *P. acnes* at a MIC 4 µM. The probable mechanism of action involves inhibiting the growth of pathogens and suppressing the expression of pro-inflammatory cytokines (such as TNF-α, IL-1β, and IL-6) in keratinocytes. This is achieved by inhibiting the activation of NF-κB and MAPK signaling pathways and attenuating the skin's inflammatory reaction (Pithitirat *et al*., 2010; Xu *et al*., 2018; Phumlek *et al*., 2022).

The ethanol extract of mangosteen leaves inhibited *Pseudomonas aeruginosa*, a common pathogen for skin infections, with a MIC of 10%. The inhibitor zone was measured to be 13.20 mm in diameter (Suhartati *et al*., 2019). Meanwhile, the peel extract of mangosteen demonstrated inhibitory effects on *E. coli* with a MIC of 0.62% and a zone of inhibition measuring 15 mm (Sulistyo *et al*., 2016). Additionally, the ethanolic extracts of the pericarp, seed, and pulp of mangosteen showed inhibitory effects on *S. aureus* ATCC11632 with the level of inhibition increasing with concentration (Lim *et al*., 2013). Furthermore, both the ethanolic and water extracts of mangosteen pericarp exhibited inhibitory activity against *S. aureus* (31.25 µg/mL; 7.8 µg/mL), *E. coli* (125 µg/mL; 15.6 µg/mL) and *C. albicans* (125 µg/mL; 7.8 µg/mL) when compared to α-Mangostin respectively (Taokaew *et al*., 2018).

Palakawong *et al*. (2013) reported strong pH-dependent bacteriostatic and bactericidal effects of mangosteen bark and fruit extracts against *Listeria monocytogenes* and *S. aureus.* The study found that the inhibitory activity of the water extract from the bark and pericarp increased as the pH decreased from 7 to 4, with MIC values ranging from 8 mg/mL to 2 mg/ml for *S. aureus* and from 10 mg/mL to 0.84 mg/mL for *L. monocytogenes*. The methanolic extract showed even lower MIC values, ranging from 0.42 mg/mL to 0.02 mg/mL for *S. aureus* and from 5mg/mL to 16 mg/mL for *L. monocytogenes*. Similarly, methanolic extract from the pericarp exhibited MIC values ranging from 0.11 mg/mL to 0.05 mg/mL for *S. aureus* and from 0.52 mg/mL to 0.05 mg/mL for *L. monocytogenes* (Palakawong *et al*., 2013). *S. mutans* and *Porphyromonas gingivalis* induce caries and periodontal disease. The ethanolic fruit peel extracts of mangosteen contain flavonoids, tannins, saponins, and Xanthones, which have antibacterial properties and antibiofilm activity of up to 100% in 6-24 hours (Widyarman *et al*., 2019).

The antibacterial and antifungal activity of Xanthones was studied by Sundaram *et al.* in 1983. The bacterial species susceptible to Xanthones included *S. aureus, P. aeruginosa, Salmonella typhimurium, Bacillus subtilis, Klebsiella* sp., *Proteus* sp., and *E. coli.* Among the fungi, *Epidermophyton floccosum, Alternaria solani, Mucor* sp., *Rhizopus* sp. and *Cunninghamella echinulata* were found to be more susceptible to Xanthones, followed by *Trichophyton mentagrophytes*, *Microsporum canis, Aspergillus niger, Aspergillus flavus, Penicillium* sp., *Fusarium roseum* and *Curvularia lunata.* The MIC value for α-mangostin ranged between 12.5 and 50 µg/mL for bacteria and 1 and 5 µg/mL for fungi, respectively. The efficacy of the bioactive compounds was found to be in the following order:

α-mangostin > isomangostin > 3-O-methyl mangostin > 3, 6-di-O-methyl mangostin (Sundaram *et al*., 1983).

The antifungal activity of different derivatives, such as Xanthone, xanthione, and euxanthone showed promising results against three phytopathogenic fungi: *Fusarium oxysporum vasinfectum, Alternaria tenuis,* and *Drechslera oryzae*. The inhibition ranged from 23-79% at concentrations of up to up to 1000 ppm (Gopalakrishnan *et al*., 1997). α-Mangostin exhibited antibacterial activity against MRSA, with MIC values ranging from 1.57 to 12.5 µg/mL (Iinuma *et al*., 1996).

Another study observed inhibitory activity of α-mangostin against vancomycin-resistant *Enterococci* (VRE) and MRSA at MIC values of 6.25 and 12.5 µg/mL, respectively (Sakagami *et al*., 2005). Sivaranjani *et al*. (2019) conducted a systematic study on the antibacterial potential of α-Mangostin in *S. epidermidis* RP62A, using an integrated transcriptomic and proteomic approach. The study revealed the importance of gene expression related to cytoplasmic membrane integrity (yidC2, secA, and mscL), as well as downregulation of genes involved in various cell survival metabolic pathways (FASII pathway, cell division, DNA replication and repair machinery, resistance development, teichoic acid biosynthesis, fatty-acid biosynthesis, biofilm formation, and cellular stress response), leading to rapid bactericidal activity (Figure 3) (Sivaranjani *et al*., 2019).

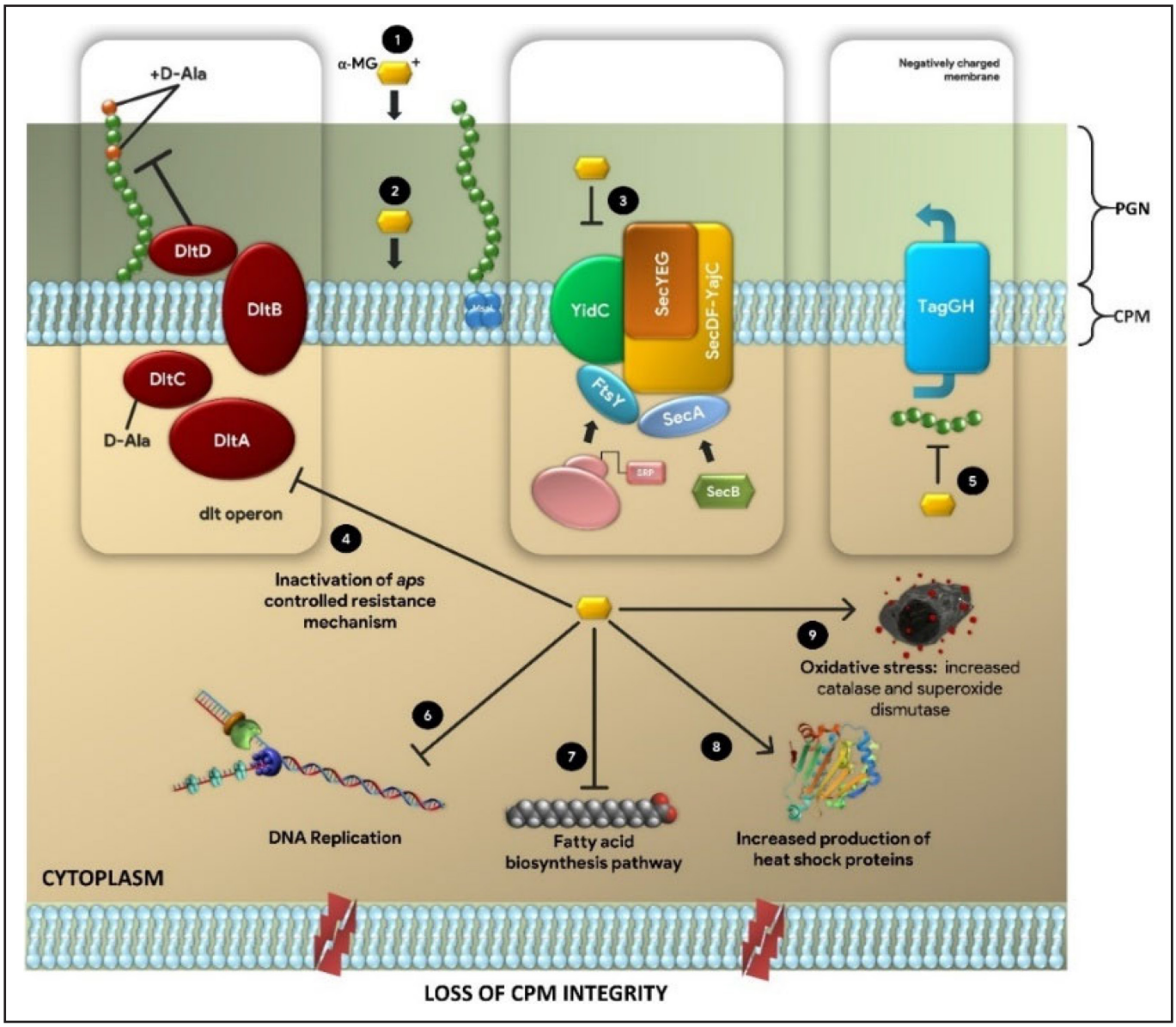

Figure 3. Representation of Sivaranjani's *et al*. (2019) [46] schematic representation of multifarious antibacterial mode of action for α-MG. (1) Electrostatic interaction of α-MG with the negatively charged bacterial membrane, binding to the bacterial inner membrane. (2) Strong hydrophobic interaction with the lipid alkyl chain of the cytoplasmic membrane is believed to be the main driving force behind its rapid bactericidal properties. Additionally, α-MG forms hydrogen bonds with transmembrane precursor proteins. (3) Downregulation of YidC2, SecA, FtsY, and MscL provides evidence that α-MG compromises the integrity of the cytoplasmic membrane. (4) Downregulation of dltA inhibits the d-alanylation of anomeric teichoic acids, preventing the development of resistance against α-MG. (5) TagG, a component of the two-component ABC transporter responsible for exporting anomeric polyglycerophosphate chains (TAs) from the cytoplasm, is affected when its activity is inhibited. This inhibition disrupts the teichoic acid biosynthetic pathway, as TagG is localized in the cytoplasmic membrane. This could be due to the loss of cytoplasmic membrane integrity, resulting in decreased export of teichoic acids from the cytoplasm. (6) α-MG treatment downregulates DNA replication and mismatch repair mechanisms. (7) α-MG also inhibits the fatty acid biosynthesis pathway. (8) Furthermore, α-MG enhances the expression of heat shock proteins. (9) α-MG has also been shown to increase the expression of genes involved in oxidative stress response. CPM refers to the cytoplasmic membrane, while PGN stands for peptidoglycan.

α-Mangostin also displayed *in vitro* antibiofilm activity against *S. epidermidis* RP62A (ATCC 35984) biofilms at MIC and MBS values of 1.25 and 5 µg/mL, respectively (Sivaranjani *et al*., 2017). The *G. mangostana* pericarp ethanolic extract (GME) demonstrated *in vivo* wound healing activity against MRSA-induced skin infection in a tape stripping mouse model. It was effective for up to nine days, restoring the expressions of pro-inflammatory cytokines TNF-α, IL-6, and IL-1β via the TLR-2 pathway, compared to α-mangostin (Tatiya-Aphiradee *et al*., 2016; Tatiya-Aphiradee *et al*., 2019). γ-Mangostin also exhibited effective inhibitory activity against HIV-1 protease, with an IC50 value of 4.81±0.32 µM, followed by α-Mangostin with an IC50 value of 5.12±0.41 µM. The positive control, pepstatin A, had an IC50 value of 76±5.5 µM (Chen *et al*., 1996).

In another study, *Neosartorya spathulata* (EYR042) mediated biotransformation of α-mangostin forming a potent anti-mycobacterial compound called mangostin 3-sulfate (Arunrattiyakorn *et al*., 2011). The antituberculosis potential of prenylated Xanthones, derived from the fruit hulls, edible arils, and seeds of *G. mangostana*, has been tested. α- and β-Mangostins, as well as garcinone B, have shown strong inhibitory effects against *Mycobacterium tuberculosis* with a minimum inhibitory concentration (MIC) value of 6.25 µg/mL. It has been observed that tri- and tetra-oxygenated Xanthones with di-C5 units or with a C5 and a modified C5 group are crucial for high activities. Furthermore, substitutions in the A and C rings have been found to alter the bioactivity of the compounds (Suksamrarn *et al*., 2003).

α-Mangostin was examined for its effectiveness in treating oral candidiasis caused by the pathogen *C. albicans,* with MIC values of 1,000 µg/mL and MFC values of 2,000 µg/mL (Kaomongkolgit *et al*., 2009). The extract of mangosteen has also shown promise as a treatment for animal pathogens. The study revealed that α-Mangostin exhibited inhibitory activity against *Eimeria tenella* pathogen in broiler chickens within 14 days of intake, against *Zoothamnium* sp. infection in white leg shrimp (*Litopenaeus vannamei*) with 100% removal in 21 hours, and against *Vibrio harveyi,* a causal agent of skin ulcer disease in *Epinephelus fuscoguttatus* (Daenroj & SanoThong, 2017; Akmal *et al*., 2021; Sriboonyong *et al*., 2022).

The antibacterial activity of mangosteen water peel extract was studied against the *Aeromonas hydrophila* pathogen in dumbo catfish (*Clarias gariepinus*) and seabass fingerling (*Lates calcarifer*). The ethanol extract was found to kill *A. hydrophila* bacteria *in vitro* with an MIC value of 25 ppm, without any observed toxicity (Cahya *et al*., 2023; Thiankham *et al*., 2024). In many studies, mangosteen extracts have been immobilized with various polymers such as Polyvinylpyrrolidone (PVP), chitosan, sodium alginate, sodium silicate, polyethylene glycol, propolis, maltodextrin and chitosan-kappa carrageenan, to access their ability to protect food and improve therapeutic efficacy (Charernsriwilaiwat *et al*., 2013; Sriyanti *et al*., 2018; Wathoni *et al*., 2019; Suhandi *et al*., 2023).

Though α-mangostin derived from mangosteen xanthones have shown remarkable antimicrobial efficacy, the pharmacokinetic characteristics of these agents are relatively underexplored. The absorption and bioavailability of α-mangostin in systemic circulation would determine its ability to treat systemic infections such as MRSA. Its hydrophobic nature could, for example, limit solubility and absorption, thus requiring advanced formulations, such as nanoemulsions or liposomal delivery systems, to improve its distribution (Felix *et al*., 2022). Furthermore, extensive studies on the metabolism and potential toxicity of α-mangostin in combination with traditional antibiotics might open doors to synergistic therapies with minimal harmful effects.

Antiviral activity

Garcinia mangostana has also been reported to exhibit antiviral activity due to its active compounds, which include Xanthones, flavonoids, tannins, and phenolic acids (Obolskiy *et al*., 2009). Among these compounds, Xanthones such as α-Mangostin and γ-Mangostin are particularly notable for their antiviral properties. Xanthones can inhibit the replication of various viruses by targeting essential viral enzymes and interfering with viral entry into host cells. α-mangostin, for instance, has been shown to inhibit the replication of the herpes simplex virus (HSV) by suppressing viral DNA polymerase activity (Ansori *et al*., 2023). On the other hand, γ-mangostin can inhibit the activity of the human immunodeficiency virus by disrupting reverse transcriptase activity (Chen *et al*., 2008; Ansori *et al*., 2023).

Another study on *G. mangostana* found that its extracts inhibit the influenza virus by preventing neuraminidase, an essential enzyme that facilitates the release of newly formed viral particles from infected host cells (Ryu *et al*., 2010). Additionally, it was discovered that these extracts have the potential to inhibit SARS-CoV-2, the causative agent of COVID-19 (Suroengrit *et al*., 2024). In an *in-silico* study, it reports that the bioactive compounds of *G. mangostana,* such as xanthones, may interact with the main protease (Mpro) of SARS-CoV-2, an essential enzyme in viral replication, thereby inhibiting its activity (Ansori *et al*., 2022). Beyond direct antiviral effects, the immunomodulatory properties of mangosteen compounds, such as their ability to enhance innate immune responses and reduce pro-inflammatory cytokines, further bolster their antiviral potential (Gutierrez-Orozco & Failla, 2013).

In addition, the high antioxidant content of *G. mangostana* helps mitigate oxidative stress, which is often exacerbated during viral infections and contributes to disease severity. The fruit may have the potential to protect against oxidative damage in host tissues, thus improving its therapeutic profile (Pedraza-Chaverri *et al*., 2008). The antiviral effects of *G. mangostana* are complex, including direct viral inhibition, immunomodulation, and antioxidant action, making it a very interesting candidate for further research in antiviral drug development. Although these findings underscore the promising antiviral properties of *G. mangostana*, most studies are preclinical, necessitating rigorous clinical trials to validate efficacy and safety in humans.

Anticancer and antitumorigenic activity

The use of phytochemicals as anticancer and antitumorigenic agents has increased. Around 50% of the newly approved compounds against cancer are unmodified derivatives of natural products (Pérez-Soto *et al*., 2019). α-Mangostin is currently the most potent known phytochemical with anticarcinogenic properties, capable of inhibiting the initiation of tumor formation. Tumorigenic agents, such as environmental pollutants, are usually eliminated from the body through biotransformation mediated by phase I and II enzymes. These enzymes are responsible for detoxifying reactive metabolites formed from tumorigenic agents, preventing them from becoming active carcinogens and targeting DNA, which can cause mutations (Shan *et al*., 2011). In a study by Chin *et al*. (2008), α-Mangostin isolated from the pericarp of *G. mangostana* showed the ability to induce the activity of quinone reductase, a phase II enzyme. The concentration of α-Mangostin required to double quinone reductase induction activity in this study was only 0.95 µg/mL. Therefore, α-Mangostin demonstrates a potent effect against the initiation of tumor formation (Chin *et al*., 2008).

Furthermore, extracts from *G. mangostana* have been found to induce cell apoptosis by targeting mitochondria. Matsumoto *et al*. (2004) demonstrated that α-Mangostin activates the caspase-9/caspase-3 apoptotic pathway in human leukemia HL60 cell lines. The activity of these caspases showed an almost twofold increase. The pathway is known to be involved in mitochondrial-mediated apoptosis. Additionally, within the first two hours of treatment with α-Mangostin, the mitochondria also exhibited swelling, a decrease in intracellular ATP, loss of membrane potential and accumulation of ROS (Matsumoto *et al*., 2004).

As described, mangosteen can inhibit the initial formation of tumors by inducing the activity of phase II enzymes, and it can

also help destroy tumors that have already formed by inducing apoptosis. To enhance the anticancer properties of mangosteen, it is important to highlight its capacity to prevent metastasis. A study conducted with renal carcinoma demonstrated that α-Mangostin reduced the expression of MMP-9. Metalloproteinases (MMPs) are proteolytic enzymes that allow cancer cells to access blood vessels, enter the bloodstream, and spread to other parts of the body, leading to metastasis. By inhibiting the expression of these proteins, α-Mangostin helps reduce the incidence of metastasis formation (Chen *et al*., 2017a).

The use of phytochemicals in the treatment and prevention of cancer can also be extended to modern medical techniques, such as nanotechnology. In a study conducted by Scolamiero *et al*. (2018), it was found that α-Mangostin decreased cellular viability in multicellular tumor spheroids (MCTSs), which are commonly used in breast cancer research. The authors noted a reduction in spheroid volume when a concentration of 30 µg/mL of α-Mangostin was administered. Even small amounts of compounds (0.1-0.5 µg/mL) resulted in a significant decrease in cell viability (20-30%) (Scolamiero *et al*., 2018). More recently, the same group of authors explored the effects of α-Mangostin on MCTSs encapsulated in lipidic nanoparticles. When encapsulated, a concentration of 0.1 µg/mL was sufficient to completely disaggregate the MCTSs. This suggests that encapsulation of the compound may potentially prolong its effectiveness after administration, allowing for the use of lower concentrations (Bonafè *et al*., 2019). Moreover, nanoparticles enable targeted therapeutic agent delivery, thereby reducing potential cytotoxic effects (Herdiana *et al*., 2021).

Other compounds found in mangosteen have been examined for their effectiveness against various types of cancer. Ovalle-Magallanes *et al*. (2017) offer a comprehensive review of these substances and their anticancer properties. The research on anticancer and antitumorigenic effects *G. mangostana* primarily involves human cell lines, which have shown minimal cytotoxicity. This suggests that cancer treatments based on phytochemicals derived from this species could be safe. However, additional studies are required to assess the safety of this therapy in humans using other experimental models.

Antidiabetic properties

Diabetes is a chronic metabolic disease that occurs when the pancreas does not produce enough insulin to regulate blood sugar levels, or when the body cannot effectively use insulin. This leads to an increase in blood sugar levels, also known as glycemia, which can cause significant damage to the nervous and cardiovascular systems (Schuster & Duvuuri, 2002; Banday *et al*., 2020). According to the World Health Organization, the prevalence of diabetes has increased in the past three decades, with a 3% increase in the mortality rate between 2000 and 2019. In comparison, the other three main noncommunicable diseases (cardiovascular diseases, cancer, and respiratory diseases) have seen a 20% decrease in mortality. However, diabetes has shown an increase. In low-income countries, diabetes rates have surpassed the 3% and reached a rate of 13% (WHO, 2023).

In a study conducted by Taher *et al*. (2016), it was found that the ethanolic extract of *G. mangostana* can reduce glycemia in diabetic rats. The authors used an ethanolic extract from the pericarp of mangosteen without separating the compounds. They found that even a single dose treatment with 50 mg/kg could effectively lower glucose levels in diabetic rats within the first two of treatment. The reduction in glucose levels believed to be attributed to the presence of xanthones, such as α-Mangostin, and tannins in pancreatic β-cells. These compounds help increase the population of insulin-producing cells (Taher *et al*., 2016).

Just as for the anticancer properties of nanotechnology have been described, the use of nanotechnology has also been explored for its antidiabetic effects with α-Mangostin. In a study conducted by Usman *et al*. (2021), it was found that nanosponges, a type of polymeric nanoparticles with high porosity, can enclose bioactive compounds (Usman *et al*., 2021). These particles can encapsulate both hydrophilic and hydrophobic compounds, and their high porosity results in better drug absorption (Garg *et al*., 2024). This study builds upon the findings of Taher *et al*. (2016), who discovered that α-Mangostin can increase the number of pancreatic β-cells, leading to an increase in insulin production and a reduction in glycemia. By encapsulating α-Mangostin, a prolonged and gradual antidiabetic response can be achieved over a 12-hour treatment period. This slow exposure of insulin-producing β-cells to α-Mangostin reduces the chances of over-sensitization and lowers the likelihood of adverse effects associated with this treatment. Additionally, molecular docking analysis showed that α-Mangostin forms a complex with α-glucosidase (Usman *et al*., 2021). α-glucosidase is an enzyme responsible for the final stages of polysaccharide metabolism. Common antidiabetic medications typically inhibit the activity of this enzyme, resulting in a delay in glucose production (Kashtoh & Baek, 2022). The fact that α-Mangostin can form a complex with this enzyme suggests that it may be able to block its activity. Therefore, α-Mangostin could serve as a natural alternative to common antidiabetics that target α-glucosidase.

In addition to its action against α-glucosidase, mangosteen also showed a similar effect against α-amylase. This metalloenzyme plays a similar role to α-glucosidase, as it is responsible for breaking down polysaccharides into smaller molecules, including glucose. It is closely associated with postprandial hyperglycemia. Like α-glucosidase, α-amylase is commonly targeted by antidiabetic medications. However, the usual inhibitors for α-amylase are drugs that often have side effects (Kaur *et al*., 2021). Therefore, there has been a significant search in recent decades for α-amylase inhibitors that can be used as dietary supplements or even incorporated into our food. Loo & Huang (2007) demonstrated that extracts from the pericarp of this fruit were 56 times more effective in inhibiting α-amylase than tannic acid, a well-known inhibitor. Hence, *G. mangostana* could potentially serve as a valuable source of dietary supplements with antidiabetic properties, especially in reducing postprandial hyperglycemia. However, its pharmacokinetic studies demonstrate poor absorption along with rapid hepatic metabolism, which are problems. Its therapeutic efficacy can be improved by developing nanosponges or polymeric carriers, which can help in enhancing solubility along with a controlled release mechanism (Kashtoh & Baek, 2022).

Anti-inflammatory activity

In this review, our focus has been on the xanthones found in mangosteen. These compounds are the most abundant in this species, with α-Mangostin being the first isolated xanthone and the bioactive compound best described for its medicinal properties. However, several other phytochemicals from mangosteen exhibit potent properties. Zhang *et al*. (2020) conducted a study focused on the polysaccharides present on the rind of mangosteen. They isolated and characterized an arabinofuranan (GMP90-1) in this study. This compound showed the ability to increase phagocytosis by 40% compared to a control group when applied at a concentration of 100 µg/mL (Zhang *et al*., 2020). This indicates that GMP90-1 can induce the activity of macrophages, one of the main components of the immune system and one of the first to be recruited in the immune response (Rosales & Uribe-Querol, 2017), ultimately leading to an increase in the phagocytosis rate. The authors also concluded that the induction of macrophage activity was due to an increase in the production of chemokines and cytokines, including TNF-α, IL-6, and IL-1β. When a concentration of 200 µg/mL of GMP90-1 was applied, the production of these molecules was found to be 10 times higher than that of the control group (Zhang *et al*., 2020). Chemokines are immune mediators that stimulate

the secretion of cytokines, which are signaling molecules that activate immune response pathways (Palomino & Marti, 2015). Thus, GMP90-1 present in *G. mangostana* proves to be a powerful immunomodulator by altering the levels of production and secretion of these molecules, capable of regulating immune response. Although the initial increase in cytokines suggests pro-inflammatory activity, GMP90-1 could possibly downregulate these pathways or induce regulatory cytokines that temper inflammation. It is possible when the compound triggers an initial immune activation phase followed by the release of anti-inflammatory mediators, such as IL-10. Alternatively, GMP90-1 might increase macrophage function in a manner that clears inflammatory stimuli and thus reduces chronic inflammation. To address this gap in knowledge, detailed kinetic studies and mechanistic analyses are needed. Additionally, comparing known immunomodulatory and anti-inflammatory agents can shed light on these questions.

Another compound extracted from mangosteen that is not well-known is isogarcinol. It has been studied for its anti-inflammatory properties in disease models for lupus, psoriasis, and rheumatoid arthritis. These diseases are autoimmune diseases that manifest in different ways, but they all occur when the immune system attacks the cells of the host's body (Pisetsky, 2023). In the case of lupus, a concentration of 60 mg/kg isogarcinol inhibited the activation of CD4 T cells, which play a role in cytokine secretion. Isogarcinol also downregulated Th1 and Th2 cells, responsible for macrophage activation and lymphocyte proliferation, respectively. At the same concentration, it also reduced the inflammatory cytokines TNF-α, IL-6 and IL-1β. These results demonstrate that isogarcinol can act as an immunosuppressor to alleviate lupus symptoms (Li *et al*., 2023). In the case of psoriasis, isogarcinol exhibited the same effects as in lupus disease models: it inhibited CD4 T cells and reduced pro-inflammatory cytokines (Chen *et al*., 2017b). Additionally, it decreased the proliferation of keratinocytes, which trigger further immune responses, by interacting with immune cells through cytokine mediation. This interaction leads to skin inflammation and, as a result, skin lesions (Abate *et al*., 2022). In arthritis disease models, isogarcinol decreased NO production by downregulating mRNA expression providing protection to cartilaginous tissue since NO is associated with the initiation of apoptosis in chondrocytes (Fu *et al*., 2014). These studies have demonstrated that isogarcinol isolated from mangosteen possesses powerful anti-inflammatory properties, mainly associated with the regulation of pro-inflammatory cytokines and can be used to alleviate symptoms of some of the most prevalent autoimmune diseases. Nevertheless, isogarcinol requires detailed pharmacokinetic studies to evaluate its absorption and potential immunotoxicity in chronic use (Li *et al*., 2023).

Going back to xanthones, Jang *et al*. (2012) have demonstrated their ability to reduce airway inflammation in cases of allergic asthma. Allergic asthma is a common inflammatory disease, and one of the most prevalent noncommunicable diseases that affects both children and adults (WHO, 2024). This condition is caused by the infiltration of inflammatory cells in the airways, resulting in hyperresponsiveness (Hammad & Lambrecht, 2021). In the study, mice treated with 30 mg/kg of mangosteens' xanthones, both α and γ, showed a significant reduction in pathological changes such as thickening of the airway epithelium and the presence of debris in the airway lumen. This reduction can be attributed to a decrease in inflammatory cell infiltration in the airways. The effects of xanthones demonstrated in the study are comparable to those of commonly used anti-asthmatic drugs, such as montelukast and dexamethasone (Jang *et al*., 2012). Thus, they are presented as new alternatives for the development of anti-asthmatic therapies based on natural compounds.

The anti-inflammatory properties of *G. mangostana* have been extensively studied. Common compounds found in this plant, such as xanthones, as well as recently isolated ones like isogarcinol and arabinofuranan, have been evaluated in human cell lines and animal models. In addition to their anticancer properties, these compounds have shown promise as novel therapies.

Neuroprotective activity

Xanthones found in *G. mangostana* have demonstrated several neuroprotective properties. They can reduce the decline of cholinergic, adrenergic and serotonergic neurons, as well as prevent the death of hippocampal cells (Huang *et al*., 2014). Furthermore, they increase the levels of brain-derived neurotrophic factor, which is a neurotransmitter modulator that plays a role in neuronal plasticity and is associated with both Parkinson's and Alzheimer's disease when levels are inadequate (Bathina & Das, 2015). Xanthones also decrease the occurrence of apoptosis in brain tissue (Tangpong *et al*., 2011) and can act as scavengers for reactive oxygen species that may cause tissue damage (Phyu & Tangpong, 2014). Additionally, Yang *et al*. (2016) demonstrated that garcinone D, another type of xanthone found in mangosteen, can stimulate the proliferation of neural cells by promoting the transition from G1 to S phase of the cell cycle. However, the blood-brain barrier permeability of these compounds is limited, and this limits their potentials in the efficacies of central nervous system disorders (Do & Cho, 2020). The encapsulation of these compounds in lipid-based nanoparticles may improve blood-brain barrier permeability and escape first-pass metabolism.

Do & Cho (2020) conducted a comprehensive review of the therapeutic effects of xanthones found in the pericarp of mangosteen on Alzheimer's, Parkinson's, and depression. They also discussed the safety of using these natural compounds. The overall findings of the review indicate that both extracts and isolated compounds have favorable safety profiles in animal disease models and human cell lines. However, it is important to note that these compounds have low bioavailability in the human body, which requires the administration of higher doses. This could potentially increase cytotoxic effects. Additionally, while both extracts and isolated compounds have good distribution to organs such as the liver, kidneys and intestine, only a few xanthones, including γ-mangosteen, garcinone C, and gartanin, have been found capable of crossing the blood-brain barrier (Gutierrez-Orozco & Failla, 2013). This poses an obstacle for the use of mangosteen-derived treatments for neurodegenerative disorders. Interestingly, treatment with extracts from mangosteen leads to higher bioavailability compared to isolated compounds. This finding indicates a potential synergistic effect of the phytochemicals present in the plant. These results highlight the next areas for future studies (Do & Cho, 2020).

To overcome the issues of low bioavailability and cytotoxicity resulting from higher doses, Chen *et al*. (2020) tested several α-Mangostin derivatives and their effects on Alzheimer's disease, using computational systems for pharmacological analysis (Chen *et al*., 2020). The authors synthesized 16 α-Mangostin derivatives and found that the derivative number 1 showed potent effects against Alzheimer's in a one-molecule, multiple-target manner. It could prevent neuronal loss and injury in the disease model, while maintaining healthy neuron morphology. This study demonstrates that altering the chemical structure, such as creating derivatives, can help create compounds with greater neuroprotective properties, while increasing their bioavailability and decreasing toxicity.

In addition to synthesizing optimized derivatives, incorporating them into nanoparticles is also an interesting solution. Nanotechnology enables controlled release rates of therapeutic agents, addressing both bioavailability and cytotoxicity issues. Furthermore, it facilitates targeted drug delivery, helping to overcome the challenge of certain xanthones being unable to cross the blood-brain barrier.

Antiparasitic activity

Antiparasitic properties of *G. mangostana* have been tested against various parasites, including protozoans, nematodes, and helminths.

To evaluate these properties, both isolated compounds and total extracts from different parts of the plant, such as ethanolic, methanolic, ethyl acetate or dichloromethane can be used. In Table 1, a summary of the minimum concentrations required to inhibit or reduce the growth of several pathogenic parasites using either mangosteen extracts or its isolated compounds presented. Additionally, the solvent fractions also influence the effectiveness of the compound against the parasite. Tjahjani (2017) demonstrated that different fractions of the same ethanolic extract resulted in different inhibitory concentrations, with the hexane fraction exhibiting the lowest IC_{50} against *Plasmodium falciparum*, the causative agent of malaria.

Additionally, Al-Massarani *et al*. (2013) compared the inhibitory concentration of two different extracts: dichloromethane and ethyl acetate. They also isolated α-Mangostin and tested its efficacy against four species of protozoans. The study concluded that the dichloromethane extract had lower values of IC_{50}, indicating greater antiparasitic activity. This highlights the extraction procedure as one of the most suitable methods for obtaining compounds with antiparasitic properties from *G. mangostana*. Furthermore, the antiparasitic properties of *G. mangostana* against different species of nematodes and trematodes have been studied. These studies have revealed that trematodes are more susceptible to treatment with this plant species, while nematodes are highly resistant and require a higher treatment concentration (Keiser *et al*., 2012; Markowicz *et al*., 2019). Table 1 also presents the parasitic protozoan *Acanthamoeba*, the causative agent of amoebic keratitis. Sangkanu *et al*. (2021) showed that both the ethanolic extract and α-Mangostin had significantly higher minimum inhibitory concentrations (MICs) for cysts. Cysts are the dormant stage of *Acanthamoeba* and are therefore more resistant to treatment. Furthermore, this study combined α-Mangostin with chlorhexidine, a commonly used treatment for these infections. The combination of both substances demonstrated a synergistic effect reducing MIC values by up to 25%.

Interestingly, combining chlorhexidine is not the only way to enhance the effect of α-Mangostin against *Acanthamoeba*. Some delivery systems, such as nanoparticles or nanovesicles, have been shown to increase the antiparasitic activity of natural products (Mahboob *et al*., 2020). Niosomal delivery systems consist of nanovesicles generated by non-ionic surfactants that assemble in aqueous solutions and are commonly used in ocular therapy delivery. These vesicles have been tested for their potential use in anti-*Acanthamoeba* therapy by encapsulating *G. mangostana* extracts. This delivery system enhanced the anti-*Acanthamoeba* effects of *G. mangostana*, producing MIC values of 0.25-4 mg/mL (Sangkana *et al*., 2024).

Methanolic extracts of *G. mangostana* have also been tested against *Opisthorchis viverrine*, a liver fluke that is usually acquired through the ingestion of contaminated fish. *G. mangostana* exhibited an inhibitory effect on the development of the parasite's reproductive organs by altering fat metabolism. This resulted in a decrease in the number of parasite eggs found in fecal samples. Additionally, the extract interfered with the parasite's tegument, causing it to detach from the infected area (Aukkanimart *et al*., 2015).

Garcinia mangostana, commonly known as mangosteen, contains various phytochemical constituents with several active principles including antiparasitic properties. Table 2 highlights the extensive research conducted on the effects of this plant against various parasite species. However, the focus of these studies has primarily been on xanthones, particularly α-Mangostin due to their abundance and well-characterized nature. Consequently, it becomes essential to explore other bioactive compounds present in mangosteen, apart from xanthones, and investigate their presence

Table 2. Extracts and/or isolated compounds with antiparasitic activity and their respective minimum required concentrations to inhibit/reduce de growth of parasites

Extract/compound	Parasitic pathogen	Minimum concentration to inhibit/reduce growth	Reference
Ethanolic extract + hexane, ethylacetate, buthanol and water fractions	*Plasmodium falciparum*	*Ethanolic extract - IC_{50} = 0.42 µg/mL*	(*Tjahjani, 2017)*
		Hexane fraction - IC_{50} = 0.12 µg/mL	
		Ethylacetate fraction - IC_{50} = 1–10 µg/mL	
		Buthanol fraction - IC_{50} = 1152 µg/mL	
		water fraction - IC_{50} > 100 µg/mL	
Dichloromethane extract	*P. falciparum*	*IC_{50} = 2.7 µg*	*(Al-Massarani et al., 2013)*
	Trypanosoma cruzi	*IC_{50} = 7.6 µg*	
	Leishmania infantum	*IC_{50} = 7.5 µg*	
	Trypanosoma brucei	*IC_{50} = 0.5 µg*	
Ethyl acetate extract	*P. falciparum*	*IC_{50} = 40.3 µg*	
	T. cruzi	*IC_{50} = 34.6 µg*	
	L. infantum	*IC_{50} > 64 µg*	
	T. brucei	*IC_{50} = 56.4 µg*	
α-Mangostin	*P. falciparum*	*IC_{50} = 2.2 µM*	
	T. cruzi	*IC_{50} = 8.9 µM*	
	L. infantum	*IC_{50} = 8 µM*	
	T. brucei	*IC_{50} = 7.9 µM*	
Mangostin	*Trichuris muris* (*adults*)	*IC_{50} >100 µg/mL*	*(Keiser et al., 2012; Markowicz et al., 2019)*
	Heligmosomoides polygyrus (*L3*)	*IC_{50} >100 µg/mL*	
	Ancylostoma ceylanicum (*L3*)	*IC_{50} >100 µg/mL*	
	A. ceylanicum (*adults*)	*IC_{50} = 9.0 µg/mL*	
	Fasciola hepatica	*IC_{50} = 15.6 µg/mL*	
	Schistosoma mansoni	*IC_{50} = 2.9 µg/mL*	
	Echinostoma caproni	*IC_{50} =7.1 µg/mL*	
α-Mangostin	*Caenorhabditis elegans*	*LC_{50} = 3.8 ± 0.5 µM*	*(Keiser et al., 2012; Markowicz et al., 2019)*
Ethanolic extract	*Acanthamoeba triangularis cyst*	*MIC = 4 mg/mL*	*(Mahboob et al., 2020; Sangkanu et al., 2021; Sangkana et al., 2024)*
	A. triangularis trophozoite	*MIC = 0.25 mg/mL*	
α-Mangostin	*A. triangularis cyst*	*MIC = 1 mg/mL*	
	A. triangularis trophozoite	*MIC = 0.5 mg/mL*	

Table 3. Summary of biological properties of *Garcinia mangostana*, its active compounds, mechanisms of action, and its targets

Biological Property	Active Compound(s)	Mechanisms of Action	Target/System	Reference
Antimicrobial Activity	Alpha-mangostin, Gamma-mangostin, Xanthones	Disrupts bacterial cell membranes, inhibits biofilm formation, downregulates genes related to persister cells and biofilms (norA, norB, dnaK, groE, mepR), and suppresses NF-κB/MAPK signaling pathways.	MRSA *S. aureus* *S. epidermidis* *C. albicans* *E. coli* *Lactobacillus rhamnosus* *Propionibacterium acnes*	(Palakawong *et al*., 2013; Nguyen *et al*., 2014; Felix *et al*., 2022; Park *et al*., 2023)
Antiviral Activity	Alpha-mangostin, Gamma-mangostin, Xanthones	Inhibits viral replication by suppressing viral DNA polymerase (HSV), reverse transcriptase (HIV), and neuraminidase (influenza). Blocks SARS-CoV-2 main protease (Mpro), preventing viral replication.	HSV HIV Influenza virus SARS-CoV-2.	(Chen *et al*., 2008; Ryu *et al*., 2010; Ansori *et al*., 2023; Suroengrit *et al*., 2024)
Anticancer and Antitumorigenic Activity	Alpha-mangostin, Garcinone D, Xanthones	Induces apoptosis via caspase-9/caspase-3 pathways, reduces mitochondrial membrane potential, increases ROS, inhibits metastasis via MMP-9 suppression, and activates phase II enzymes (quinone reductase).	Human leukemia cells, renal carcinoma, breast cancer spheroids, various cancer cell lines.	(Matsumoto *et al*., 2004; Chin *et al*., 2008; Chen *et al*., 2017; Scolamiero *et al*., 2018)
Antidiabetic Properties	Alpha-mangostin, Tannins, Xanthones	Enhances pancreatic β-cell population, inhibits α-glucosidase and α-amylase enzymes, delays glucose metabolism, and increases insulin production.	Diabetes mellitus, glycemia control, postprandial hyperglycemia.	(Loo & Huang, 2007; Taher *et al*., 2016; Usman *et al*., 2021; Kashtoh & Baek, 2022)
Anti-inflammatory Activity	GMP90-1 (arabinofuranan), Isogarcinol	Enhances macrophage activity and phagocytosis, modulates cytokine production (e.g., TNF-α, IL-6, IL-1β), inhibits CD4 T-cell activation, downregulates NO production, and decreases inflammatory cell infiltration in airway models.	Autoimmune diseases (lupus, psoriasis, rheumatoid arthritis), asthma, macrophages.	(Jang *et al*., 2012; Fu *et al*., 2014; Zhang *et al*., 2020; Li *et al*., 2023)
Neuroprotective Activity	Alpha-mangostin, Garcinone D, Xanthones	Scavenges ROS, prevents hippocampal cell death, enhances brain-derived neurotrophic factor, modulates neurotransmitter pathways (cholinergic, adrenergic, serotonergic), and stimulates neural cell proliferation (G1 to S-phase transition).	Neurodegenerative diseases (Alzheimer's, Parkinson's), cognitive decline, neuronal plasticity.	(Huang *et al*., 2014; Bathina & Das, 2015; Yang *et al*., 2016; Do & Cho, 2020)
Antiparasitic Activity	Alpha-mangostin, Ethanolic/Methanolic Extracts	Inhibits parasite tegument development, reduces reproductive organ functionality, disrupts cyst walls, and interferes with lipid metabolism in parasites. Enhances antiparasitic effects when combined with delivery systems like nanoparticles.	*Plasmodium falciparum* *Acanthamoeba* cysts *Opisthorchis viverrine* (liver flukes) *Zoothamnium* sp. *Vibrio harveyi*	(Al-Massarani *et al*., 2013; Aukkanimart *et al*., 2015; Daengroj & SanoThong, 2017); Tjahjani, 2017; Sangkana *et al*., 2024;

in different parts of the plant, excluding the pericarp, which is the primary source of xanthone extraction.

The summary of the biological properties of *G. mangostana* is presented in Table 3. This table also includes the active compounds identified for each biological property, their targets, and the mechanisms of action.

CONCLUSION AND FUTURE DIRECTIONS

The medicinal properties of *G. mangostana* have been extensively documented. The pulp, seeds, and pericarp of the fruit have been used in traditional medicine for centuries, and research has confirmed the presence of multiple bioactive compounds. The most abundant of these bioactive compounds are xanthones, which have been well-studied. The most prevalent xanthone in mangosteen is α-mangostin. Many studies focused on the bioactivity of this compound, as discussed in this review. However, it is important to note that mangosteen contains other classes of compounds that have not been fully characterized and may have powerful biological properties.

Mangosteen is known for its antibacterial, anticancer, antidiabetic, anti-inflammatory, neuroprotective and antiparasitic activities, as described in this review. However, the extraction procedure used to isolate these phytochemicals plays a significant role in their effectiveness. The extraction process can result in the loss of bioactive compounds, so it is important for future studies to develop and standardize extraction protocols that allow for efficient and selective separation of compounds of medical interest.

In future studies, pharmacokinetic studies, focusing on absorption, distribution, metabolism, excretion, and toxicity (ADMET), are important to ensure that mangosteen-derived compounds are clinically relevant and nontoxic. These studies help in providing valuable information regarding bioavailability, therapeutic windows, and potential side effects that are essential for developing effective and safe therapeutic intervention. Moreover, understanding the metabolic pathways and the possible interactions

of mangosteen-derived compounds with other drugs is important to reduce side effects and enhance therapeutic benefits. The inclusion of ADMET studies in future research will bridge the gap between preclinical findings and clinical applications, thus facilitating the transition of mangosteen phytochemicals into mainstream medicine.

Additionally, it is important to understand the synergistic effects of the diverse compounds in mangosteen, as the antiparasitic activity can vary between isolated compounds and extracts. Finally, while most studies utilize pericarp extracts, it is important to explore the potential biological benefits of other parts of the plant.

Conflict of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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