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Mangosteen (*Garcinia mangostana*): Compositional profile and usage in cancer molecular docking studies

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SUMMARY

Background: Primitive medicinal plants and dietary variables have received increased attention in the hunt for novel compounds with possibly promising anti-cancer action. A wide range of natural compounds has been studied as chemopreventive or therapeutic agents. Indeed, paclitaxel, etoposide, camptothecin, and vincristine have all been utilized as anti-cancer medicines.

Aim: This literature review was collected from the web sources such as PubMed, Science Direct and Elsevier publications which summarizes the evidence of its properties and supports the case for future studies to assess the utility of Mangosteen pericarp as an adjunctive treatment option for cancer-related effects.

Review Results: Recent studies revealed that these xanthones which are isolated from the tree not only exhibited a variety of anti-inflammatory, anti-bacterial but also has anti-cancer effects. *Garcinia mangostana* is a tropical tree where the pericarp of Mangosteen fruit, for ages has been used as a medicinal ingredient in the treatment of various diseases due to its extraordinary anti-oxidant and anti-bacterial activities.

Conclusion: The results collected from numerous cancer cell lines, chemically-induced tumours and implanted tumours in animal models, as presented in the review, demonstrated that Mangosteen herb may effectively suppress the process of carcinogenesis with a pleiotropic mechanism of action.

Key words: mangosteen, anti-cancer, xanthones, mangostin

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INTRODUCTION

Garcinia mangostana is a tropical tree native to India, Myanmar, Malaysia, the Philippines, Sri Lanka, and Thailand [1]. This tree may reach a height of 6 m-25 m, has leathery, glabrous leaves, and grows slowly [2]. Mangosteen fruit is dark purple or reddish in colour, with a white, soft, and juicy edible pulp that has a slightly acidic and sweet flavour with a sweet redolence [2]. Mangosteen is referred to as "the queen of fruits" since it is one of the most delicious tropical fruits [3]. The Southeast Asian population has employed the pericarp of Mangosteen fruit for ages as a medicinal ingredient in the treatment of skin diseases and wounds [4]. The pericarp of Mangosteen fruit is widely used in Ayurvedic medicine [5]. The tree's fruit has been shown to contain a wide range of secondary metabolites, including prenylated and oxygenated xanthone [6].

The tree's pericarp, entire fruit, barks, and leaves have all yielded xanthones [7]. Several investigations have demonstrated that xanthones derived from Mangosteen fruit have amazing biological activity [8, 9]. The most investigated xanthones include α, β, γ mangostins, garcinone E, 8-deoxygartanin, and gartanin [10-12]. Furthermore, synthetic xanthones have been used in a number of studies. Some of the documented actions of xanthones extracted from GML include antioxidant, antitumoral, anti-inflammatory, antiallergic, antibacterial, antifungal, and antiviral properties [13, 14]. The pericarp has 10 times more phenolic chemicals and 20 times more antioxidant activity than the edible aril section of the fruit [15]. It should be noted that xanthones are tricyclic compounds, and their biological activity may be related to their chemical structure [15].

Extracts and individual xanthones have been shown *in vitro* and *in vivo* to cause apoptosis and decrease growth in cancer cells where these molecules interact with signalling pathways involved in cell cycle control and death thereby exhibiting their anti-cancer effects [16]. This literature summarizes the evidence of its properties and supports the case for future studies to assess the utility of Mangosteen pericarp as an adjunctive treatment option for cancer-related effects.

Mangosteen (*Garcinia mangostana*)-about the herb

Kingdom: Plantae

Family: Clusiaceae

Order: Malpighiales

Genus: Garcinia

Species: mangostana

Garcinia mangostana is a tropical tree endemic to Southeast Asia known as Mangosteen, the fruits of which have a unique and pleasant flavour, earning it the title "queen of the fruits [17]." The fruit's seeds and pericarps have a long history of usage in the region's traditional medical practices, and drinks containing Mangosteen pulp and pericarps are offered globally as nutritional supplements [18].

Compositional profile of the herb

The use of medicinal plants has been evidenced since ancient times for the treatment of a wide range of illnesses, and they have become increasingly important in healthcare [19]. Although the use of phytomedicines was based on empiric experience in the past, nowadays is increasingly based on scientific evidence regarding their chemical composition and associated medicinal properties [19]. Furthermore, herbal products available in the form of powder crushed material, essential oil and extracts capsules and tablets, make morphological identification of plant-based products difficult [20]. As a result, phytochemical studies may provide a useful tool for the identification and differentiation of similar plant species [20].

Mangosteen is rich in bioactive substances such as xanthones, terpenes, anthocyanin, tannins, phenols, and vitamins [21]. Mangosteen has 80.9 grams of water, 0.5 grams of protein, 18.4 grams of carbohydrates, 1.7 grams of fibre, 9 milligrams of calcium, 14 milligrams of phosphorus, 0.5 milligrams of iron, 2 milligrams of vitamin C, 0.09 milligrams of vitamin B1 (thiamin), 0.06 milligrams of vitamin B2 (riboflavin), and 0.1 milligrams of vitamin B5 (niacin) [22]. Fifty xanthones have been isolated from pericarp Mangosteen fruit of which the first isolated xanthone was mangostin (after it was named α-mangostin) in the year 1855 [23] (Figure 1). The other biologically significant xanthones include β-mangostin, γ-mangostin, mangostanol, isomangostin, euxanthone, mangostanin, gartanin, garcinone A,B,C,D and E, tovophyllin, garcinone which are isolated from pericarp, fruit and leaves of Mangostena bark [24].

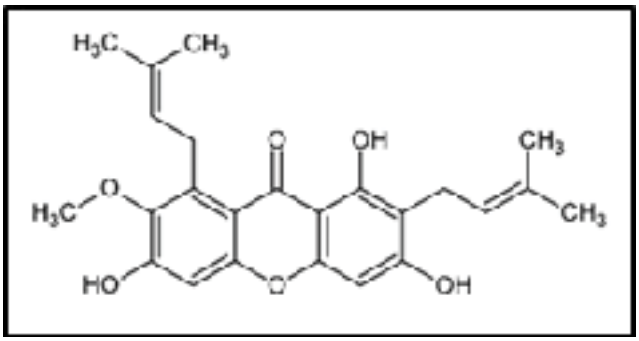

Fig. 1. Structure of α- mangosteen [23]

Three new xanthones were isolated from the whole Mangosteen-fruit: mangostenone C, D and E [25]. In total, 18 xanthones have been isolated from the whole Mangosteen-fruit. In addition, 21 xanthones have been isolated from trunk and branches of Mangostena. On the other hand, 1,6-dihydroxy-3-methoxy-2-isoprenyl-xanthone,1-hydroxy-6-acetoxy-3-methoxisoprenylxanthone and gartanin were isolated from Mangosteen leaves. Chin et al. isolated and identified two new compounds of Mangosteen powder fruit 1,2-dihydro-1,8,10-trihydroxy-2-(2-hydroxypropan-2-yl)-9-(3-methylbut-2-enyl)furo[3,2-a]xanthen-11-one and 6-deoxy-7-demethylmangostanin [26].

Biological and medicinal properties of mangosteen xanthones

Anti-oxidant properties: Excessive production of reactive oxygen species and reactive nitrogen species has been found to be related to various inflammatory diseases including cardiovascular disorders, diabetes mellitus, inflammation, and neurodegenerative diseases and cancer [27]. In 1855, several antioxidant xanthone compounds of mangosteen extracts were identified which included α-mangostin and γ-mangostin together with epicatechin, and procyanidins A2 and B2, using a ferric thiocyanate method [28]. Bioactivity-guided fractionation using a peroxynitrite-scavenging assay of the pericarp of mangosteen, led to unearthing of five active xanthones which included 8-hydroxyxanthone, gartanin, α-mangostin, γ-mangostin, and smeathxanthone that has extreme anti-oxidant properties [3]. Additionally, 16 xanthones obtained from this herb were tested in a hydroxyl radical-scavenging assay and it was found that γ-mangostin was the most active of the compounds tested and more potent than vitamin C (ascorbic acid) [29]. α-mangostin inhibited oxidative modification in a human low density lipoprotein Cu^{2+}-induced oxidation system. Furthermore, it was demonstrated that α-mangostin exhibited a protective effect on lipid peroxidation and an antioxidant tissue defence system against isoproterenol-induced myocardial infarction in rats [30]. There are compelling evidences from various studies that supports the usage of Mangosteen fruit juice for its antioxidant properties [31, 32] (Figure 2).

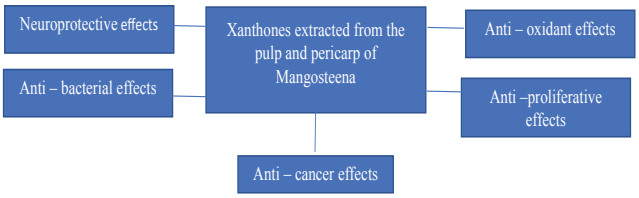

Fig. 2. Properties of Mangosteen pericarp

Anti-inflammatory and anti-allergic properties: Mangosteen has been shown to have antiallergic and anti-inflammatory activities in many in vitro models, including RBL-2H3 cells and C6 rat glioma cells, as well as multiple in vivo models in rats. The fruit shell of the mangosteen is effective in treating inflammatory-related disorders by inhibiting the production of NO and PGE2, however it has a minor impact via TNF- and IL-4 expression [33]. Furthermore, α-mangostin and γ-mangostin inhibited inducible NO synthase thereby exhibiting anti-inflammatory activity [34]. Fu et al. also showed that isogarcinol from mangosteen can maintain the immune

regulation and anti-inflammatory activity against the collagen-induced arthritis [35].

Antibacterial activity: There are various studies which have demonstrated that xanthone derivatives of Mangosteen such as γ-mangostin, garcinone D, mangostanin, α-mangostin, demethylcalabaxanthone have the strong inhibitory effect on Mycobacterium tuberculosis [7], Vancomycin-Resistant Enterococci (VRE) and Methicillin-Resistant *Staphylococcus aureus* (MRSA) [36]. The ethanol extract from mangosteen has an antimicrobial activity against methicillin resistant *Staphylococcus aureus* [36]. Furthermore, Chomnawang et al. found that the crude extract of mangosteen can inhibit the growth of Propionibacterium acnes and Staphylococcus epidermidis [37]. While, Hasegawa et al. reported that α-mangostin has also demonstrated an inhibitory effect against Helicobacter pylori [38]. Rassameemasmaung et al recently demonstrated that a herbal mouthwash containing the pericarp extract of GML has some effect against volatile sulphur compounds, plaque, and papillary bleeding in sixty subjects with mild or moderate chronic gingivitis, implying that the pericarp extract could be used as an adjunct in treating oral malodour [39].

Antiviral and antifungal activity: Puripattanavong et al discovered that Tinea species, such as *Trichophyton rudrum*, *Trichophyton mentagrophyte*, and *Microsporum gypseum*, had antifungal activity [40]. According to Gopalakrishnan et al., xanthones and α-mangostin have been found to have antifungal action against three fungus, *Fusarium oxysporum vasinfectum*, *Alternaria tenuis*, and *Dreschlera oryzae* [41].

Antihyperglycemic and antidiabetic activities: Several investigations have shown that mangosteen has antihyperglycemic and antidiabetic properties [42,43]. According to Husen et al. the extract of Mangosteen's pericarp has been shown to be efficient in lowering fasting blood cholesterol levels and lipid peroxidation in type 2 diabetic mice [44] Furthermore, Husen et al. investigated the antioxidant and anti-diabetic effects of mangosteen pericarp extract in streptozotocin-induced diabetic mice [44].

Renoprotective and hepatoprotective activities: Furthermore Ansori et al. revealed the renoprotective action of mangosteen pericarp extract in streptozotocin-induced diabetic mice [43]. In addition, Husen et al. reported an antioxidant activity assessment of alpha-mangostin for the improvement of kidney structure and function in diabetic mice [44]. Furthermore, Husen et al. noted that-mangostin has a hepatoprotective effect for improving the structure and function of the compromised liver in streptozotocin-induced diabetic mice [44].

Wound healing activity: One of the active components present in the peel of *Garcinia mangostana* is α- Mangostin which has been shown to have excellent wound healing properties. However due to its limited solubility in aqueous solutions, the herb has low availability for skin ulcers, thus limiting its use in wound healing [45].

Antidepressant activity: A bio-behavioural investigation in the flinders sensitive line rat revealed that mangosteen had antidepressant-like and pro-cognitive benefits in a hereditary animal model of depression [46].

Antihistamine activity: α-Mangostin and γ-mangostin are histaminergic and serotonergic receptor antagonists, respectively [47]. Furthermore, α-mangostin suppresses allergy mediators in bone marrow-derived mast cell [47]. Furthermore, Nakatani et al. demonstrated that an ethanol extract of the pericarp of the mangosteen suppresses both histamine release and prostaglandin E2 synthesis [48].

Analgesic activity: It has alos been seen that CEM and mangostins have powerful peripheral and central antinociceptive effects in mice and proposed that xanthones may be developed as new analgesics and anti-inflammatory medicines [49].

Antiviral activity: α-mangostin and γ-mangostin from mangosteen have been shown to suppress HIV-163. Furthermore, Vlietinck et al. found α-mangostin's activity as a non-competitive inhibitor of HIV-1 protease, disrupted the HIV viral replication cycle [50].

Antiparasitic and antithelmintic activities: α-Mangostin and γ-mangostin have been shown to limit the development of Plasmodium falciparum clone D6. Based on the skeleton of α-mangostin, several modified derivatives were created. In an in vitro experiment, xanthone derivatives containing alkylamine groups had the most powerful inhibitory action against P. Falciparum [51]. In vitro, α-mangostin, on the other hand, exhibits some promising activity against the trematodes Schistosoma, Echinostoma, and Fasciola hepatica [52]. α-Mangostin can be used as a substitute pesticide to control brown planthopper [53]. Finally, -Mangostin is a botanic mosquito sterol carrier protein-2 inhibitor with a larvicidal activity [54].

Anti-obesity activity: By inhibiting the activity of fatty acid synthase, α-Mangostin is shown to have cytotoxic activity to the preadipocytes (3T3-L1 cells) in vitro as compared to the adult adipocytes. This suggested that α-mangostin induced the apoptosis of by inhibiting Fatty Acid Synthase (FAS). The ability of α-Mangostin to suppress intracellular lipid accumulation in differentiating adipocytes and stimulation of lipolysis in the adult adipocytes was also accomplished by inhibiting FAS [55].

Effects of *Mangosteen xanthones* on cancer cells

Globally, cancer ranks third amongst the most commonly occurring diseases affecting the human population [56]. Despite enhanced options for cancer treatment, such as chemotherapy, radiation, and surgery, the death rate remains elevated [57]. These traditional cancer therapies are extremely toxic to normal cells, resulting in significant side effects. Treatment of cancer using naturally-derived molecules has gained acceptance as these are less destructive than the conventional methods [58].

Carcinogenesis is a multistep process that involves several signalling pathways and results in a quantitative change in cell physiology. Point mutations, rearrangements, amplifications, and deletions in genes are also involved in carcinogenesis [59]. Traditionally, a cell must experience six or more mutations before it may be converted into a malignant cell [60]. When

a cell turns malignant, it is no longer under the control of the body's regulatory processes.

At the level of the proto-oncogenes, genetic alterations can occur, leading in a gain of function. Alternatively, the recessive component might involve growth inhibitory or tumour suppressor genes, resulting in function loss [61]. Several researches have been conducted to investigate the anticancer properties of xanthones isolated from the pericarp of mangosteen fruit.

Xanthones and its role as an anti carcinogenic agent

Xanthones which are an important active compound present in the pericarp of the Mangosteen fruit is being known for its medical properties. In the recent times, commercial products obtained from Mangosteen with the addition of minerals such as green tea extracts, Aloe vera have been implicated in the treatment of cancer patients as a dietary supplement. Mangosteen possess significant biological properties such as anti-tumor, chemopreventive and chemotherapeutic properties that inhibits several molecular targets in the tumour cells including enzymes such as kinases, ribonucleotide reductases and DNA polymerases. The anti-cancer properties of these compounds are also associated with their tricyclic scaffold and structure that enhances their cytotoxic properties. These xanthones exhibit a wide range of anti-cancer properties such as cell cycle arrest, initiation of apoptosis, inhibition of adhesion, invasion and metastasis that provides a rationale for testing these xanthones in clinical trials for its anti-carcinogenic properties validated by below mentioned studies [32].

Molecular dock studies on cancer cells: Garcinone E, a xanthone isolated from the pericarp of mangosteen fruit has a strong cytotoxic impact on hepatocellular carcinoma cell lines, according to Ho et al. The author investigated the cytotoxicity of six xanthones extracted and discovered that garcinone E was the most hazardous. Garcinone E exhibited a very broad spectrum of dose- and time-dependent cytotoxic effects against various cancer cell lines [62]. Matsumoto et al investigated the impact of six xanthones derived from mangosteen fruit pericarp on the cell growth inhibition of a human leukaemia cell line. All xanthones inhibited growth significantly, but α, β, and γ-mangostins were most potent. The component with the inhibitoriest action was α-mangostin, which was the most abundant in the extract [63]. Nabandith et al explored whether ingesting -mangostin had short-term chemopreventive effects on putative preneoplastic lesions implicated in rat colon carcinogenesis, which were generated by a subcutaneous injection of for 2 weeks. They discovered that consuming α-mangostin dramatically reduced the incidence of indicators for short-term colon carcinogenesis [64]. Chiang et al evaluated the antileukemic activity of hot water and juice extracts of 17 commonly used fruits in Taiwan in K562, P3HR1, and U937 leukaemia cells where only the hot water extract of mangosteen-fruit pericarp exhibited a potent antileukemic activity [65]. Matsumoto et al investigated the mechanism of a-mangostin-induced cell death in the human leukaemia cell line HL60. They discovered that this xanthone causes apoptosis in HL60 cells, which is mediated in the early stages by mitochondrial dysfunctions. They discovered that α-mangostin activates caspases 9 and 3, causes mitochondrial membrane potential loss, and causes the release of ROS and cytochrome C. These results indicated that mitochondria play a pivotal role in induction of apoptosis by α-mangostin [66].

The antiproliferative effects of four prenylated xanthones (α, β, and γ-mangostins, as well as methoxy-β mangostin) in human colon cancer DLD-1 cells was investigated by Matsumoto et al With the exception of methoxy-β-mangostin, the other three xanthones substantially suppressed cell growth and their antitumor activity was associated with the quantity of hydroxyl groups. Apoptosis was linked to the antiproliferative effects ofα and γc-mangostins but not b-mangostin [67]. Jung et al. identified two novel xanthones (8-hydroxycudraxanthone G and mangostenone) as well as 12 recognized xanthones from mangosteen fruit pericarp. In a mouse mammary organ culture, they tested their antitumoral capabilities in preneoplastic where α-mangostin reduced DMBA-induced preneoplastic lesions [3]. Nakagawa et al. investigated α-mangostin's cytotoxicity against DLD-1 cells *in vitro*. They found that treatment with mangostin reduced the number of viable cells. They also demonstrated synergistic growth inhibition in cells by combining 2.5 mangostin with 2.5 5-fluorouracil (5-FU), a chemotherapeutic drug for colorectal cancer [68]. Mahendra et al. investigated the effect of mangosteen pericarp extract on oral cariogenic organisms thereby enumerating its anti-carcinogenic potential on oral cancer and cervical cancer cell lines grown *in-vitro*, oral cancer using molecular docking technique where the authors demonstrated that mangosteen is effective as an anticariogenic against Streptococcal species of microorganisms and anti-carcinogenic agent. The pericarp showed promising results as an anticancer agent by inducing apoptosis in both oral cancer and cervical cancer cell line [69].

In summary, the results suggest that α-mangostin and its analogs would be candidates for preventive and therapeutic application for cancer treatment. Because of the rising prevalence of cancer, there is a growing interest in disease management through dietary chemoprevention, which is the utilization of naturally occurring phytochemicals to halt the process of carcinogenesis [70]. Because of their health-promoting characteristics as well as their apparent safety, xanthones are a prospective option in the research of dietary chemoprevention due to their unique physical and chemical features [71]. Many xanthones from the mangosteen fruit, including α-Mangostin, have long been thought to have anti-cancer properties, including the induction of apoptosis through the regulation of cell death pathways, the suppression of cancer cell proliferation and metastasis through the inhibition of anti-apoptotic molecules, and cell cycle arrest [72]. They have also been shown in animal models to suppress the beginning, promotion, and progression of carcinogenesis. Xanthones have been demonstrated to control unregulated cell signaling pathways in cancer cells. In general, xanthone anti-cancer activity decreases with the addition of hydroxyl groups on the 5-carbon side chain, but xanthones having tetra oxygen groups with two 5-carbon isoprenyl groups in rings A and B have the best anti-cancer activity. Of all the xanthones, α-Mangostin has demonstrated the greatest anti-cancer activity

in prostate, breast, lung, and colorectal cancer [73] though these extracts obtained from Mangosteen have excellent medicinal properties, they have limitations on application. These include difficulty in obtaining the plant extract at a larger scale and their varying concentrations that would produce variable therapeutic effects which makes the standardization of the phytochemical more complex. Also, these extracts need to be procured in a larger amount to provide a beneficial effect at par with the conventional drugs.

In recent years, there has been growing interest in the ability of natural compounds such as α-Mangostin to serve as chemo preventive agents in the treatment of prostate and breast cancer. In most cases the progression of prostate and breast cancer occurs very slowly, spanning over a period of many years, with very distinct stages of initiation, promotion, and progression.

CONCLUSION

Cancer's morbidity and mortality rate could be attributed to present poor anticancer treatment modalities which have compelled researchers to investigate preventative measures as well as alternate therapies. Chemoprevention through the use of dietary phytochemicals has emerged as a cost-effective and feasible technique for cancer control and treatment. The results collected from numerous cancer cell lines, as well as chemically-induced tumours and implanted tumours in animal models, as presented in the review, demonstrated that Mangosteen herb may effectively suppress the process of carcinogenesis with a pleiotropic mechanism of action. In future, large number of prospective studies is needed to look at the precise processes and the efficacy of the herb in treating cancer patient's thereby reducing the risk of the various side effects caused by the usage of conventional chemotherapeutic drugs.

AUTHORS CONTRIBUTION

Jaideep Mahendra and Vivek Sharma have contributed to the analytical conceptualization of the topic, article design and proofreading of the article. Little Mahendra, Pavithra H Dave and Janani M have contributed by collecting the necessary data from various sources for the manuscript writing and by preparing the manuscript. Sajid. T. Hussain and Sunitha Janarthan have worked on redefining, editing and framing the manuscript. The final manuscript has been checked and approved by Jaideep Mahendra.

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