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Review article

Bioactive compounds in mangosteen and their potential uses for cancer treatment and prevention: A systematic review

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ABSTRACT

The aim of this review was to provide the existing information regarding their cytotoxic activity, antitumor activity, as well as the proposed underlying mechanisms of action on various types of cancer. Fifty-nine eligible research articles retrieved from PubMed and ScienceDirect databases up to December 2018 are included in the analysis. The xanthone α-mangostin was the most widely studies compound. Most studies demonstrated promising cytotoxic activity of mangosteen extract and its isolated compounds, but investigation of their antitumor potential in animal models as well as in humans was limited. Further studies should be focused on their antitumor activity in animals and humans to support the clinical application of mangosteen for cancer chemotherapy and chemoprevention.

Keywords: mangosteen, *Garcinia mangostana*, cancer, chemotherapy, chemoprevention

1. Introduction

Cancer is currently a major significant health problem causing morbidity and mortality worldwide, with most cases occurring in countries with low and middle income.[1] The death rates are projected to rise to 11 million in 2030 globally.[2] The major cause of deaths is due to late diagnosis, metastasis, and recurrence of cancer. Although some cancers are genetically inherited, gene mutations, smoking, unhealthy diet, and environmental factors constitute the critical contributing risk factors. The currently available therapies for cancer such as surgery, chemotherapy, and radiation have limited their success by serious adverse effects, high treatment failure rates, and high cost of treatment. There is an increasing demand for cost-effective chemotherapeutic and chemopreventive agents for various types of cancer.[1]

Recent evidence suggests that medicinal or herbal plants and their extracts are gaining popularity in curing several diseases and ailments, including cancer. In this context, herbal products have a vital role as drugs with regards to their safety, efficacy, and various biological activities particularly anti-inflammatory, anti-oxidant, antibacterial, antiviral, analgesic,

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anticancer, antifungal, and cardioprotective activities.[3] Mangosteen (*Garcinia mangostana*) is a herbal plant derived from the family Clusiaceae (Guttiferae) containing around 40 genera and 1,200 species. The plant is cultivated in Southeast Asian countries such as Thailand, China, Malaysia, India, and the Philippines. It has a pleasant aroma and sweet juicy fruit.[4] Purple in color consists of the pericarp (rind, hull, and peel). Mostly, the pericarp is the part that is used for anticancer activity. Few studies has been reported on stem bark, root bark,[5] whole fruit juice extract, and leaves.[6] In some studies, hexane,[7] chloroform,[7] methanolic,[8] and ethanolic extracts[9] were used as extracting solvents to prepare the crude extracts. The primary bioactive compound of mangosteen is xanthone group of compounds which possesses activity against various types of cancers, *e.g.*, breast, prostate, ovarian, liver, colon, brain, stomach, pancreatic, oral, gastric and skin cancers, leukemia, and melanoma. α-mangosteen is the most commonly used xanthone for cancer, but other xanthones, *i.e.*, γ–mangostin, β–mangostin, gartanin, garcinon E, garcinone D, magosenone F, and their extracts are also used.[2,5,6,10-24] The chemical structures of basic xanthone and bioactive xanthones were shown in Figure 1.

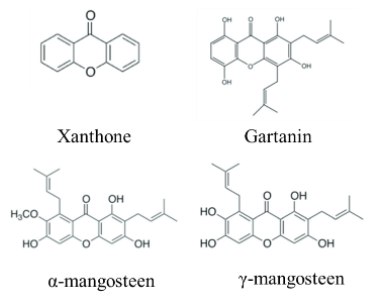

Fig 1. Chemical structures of basic xanthone and representative bioactive xanthones in mangosteen pericarp.

Recently, anticancer activities of the prenylated xanthones mangostenone C, D, and E have been reported.[11,24]

The potential use of mangosteen for cancer chemotherapy is supported by its ability to inhibit cancer cell proliferation and induction of apoptosis and necrosis. Cell apoptosis has been reported to be a consequence of activation of caspases,[8] loss of mitochondrial potential,[25] bid cleavage, and regulation of the expression of Bcl2, BAX, and PARP protein signaling pathways. The chemo-preventive potential of mangosteen has been demonstrated to be due to induction of autophagy (through regulation of protein expressions of LC3-I, LC3-II, and Beclin 1),[26] cytotoxicity, and cell cycle arrest. Besides, modulation of ER stress, anti-migration, inhibition of invasion, and reduction of tumor volume and growth have also been reported.[27] The current report aimed to systematically review the potential of mangosteen, either as active compounds or crude extracts, for treatment and prevention of various types of cancer.

2. Materials and Methods

2.1 Study selection and inclusion and exclusion criteria

This systematic review was conducted through the search from PubMed and Science Direct databases up to December 2018. The following keywords were applied: mangosteen, *Garcinia mangostana*, cancer, and cancer chemotherapy. The selection process was conducted according to PRISMA guidelines, which inclusion criteria for the selection of screened articles included: i) full-text articles published in English, ii) *in vivo*, *in vitro*, or clinical studies related to the investigation of anticancer activity of mangosteen. The review and duplicate articles and articles not having enough data for mangosteen anticancer activity are excluded. All duplicates, review articles, articles with unclear methodology, or articles related to animal cancer were excluded from the analysis.

2.2 Data extraction and collection

The following study information was extracted from each eligible article that fulfilled the inclusion and had none of the exclusion criteria: name of the compound

used, type of extract used, part of magosteen used, type of study, *in vitro* cytotoxic activity and cancer cell line used, and antitumor activity and animal model used. Final eligibility check of the full-text articles was performed. Only articles that were relevant to the review question and keywords were obtained and processed for final analysis.

3. Results

A total of 390 relevant research articles published up to December 2018 were retrieved from PubMed and ScienceDirect databases. All articles were imported and merged in EndNote reference management software. Two-hundred and seventy-eight duplicate articles and 12 review articles were excluded. Of the remaining 100 articles, 34 articles did not fulfill the eligibility criteria, 3 articles were not available as full-texts, and 3 articles did not provide adequate information for study analysis were further excluded. Finally, 59 articles fulfilling the inclusion criteria were included in the study (Figure 2). As some research article reported more than one type of study, the term 'study' rather than 'article' was used in this systematic analysis. Fourteen articles involved both *in vivo* and *in vitro* studies; 3 articles involved only *in vivo* study; and 42 articles involved only *in vitro* study. The mangosteen compounds and their activity, proposed mechanism of actions, and anticancer activities in various types of cancer are summarized in Table 1. Majority of the studies involved breast cancer (16 articles), followed by colon cancer (9 articles), hepatocellular carcinoma (8 articles), lung cancer (8 articles), prostate cancer (7 articles), leukemia (5 articles), pancreatic cancer (5 articles), skin cancer (5 articles), oral cancer (4 articles), brain cancer (3 articles), and cervical cancer (2 articles). One article each reported anticancer activity in cholangiocarcinoma, gastric adenocarcinoma, ovarian cancer, bladder cancer, and bone cancer.

4. Discussion

To the best of our knowledge, this is the first study that systematically reviewed the anticancer potential of mangosteen extracts and isolated compounds in various types of cancer. Mangosteen has been reported to exhibit a wide range of cytotoxic activity in various cancer cell lines. The underlying mechanisms of cell cytotoxicity included the induction of cell apoptosis, necrosis, autophagy, cell cycle arrest, cell mobility alterations, and modulation of ER stress. Mangosteen reduces cancer cell viability and proliferation through extrinsic (TNF-α and FASL) and intrinsic (cytochrome c/caspase 9) apoptosis pathways which coincide with its deleterious effects on mitochondrial membrane permeability and/or oxidative stress *via* exacerbated ROS production. It further leads to cell cycle arrest through cyclin and cyclin-dependent kinase down-regulation. In some studies, mangosteen was also shown to decrease transcription factor activity and alter transcriptional expression and/or protein levels of numerous cell signaling proteins important in cell proliferation and metabolism. Mangosteen, by altering cell migration, cell invasion, and adhesion, negatively affect the growth of cancer cells prominently.

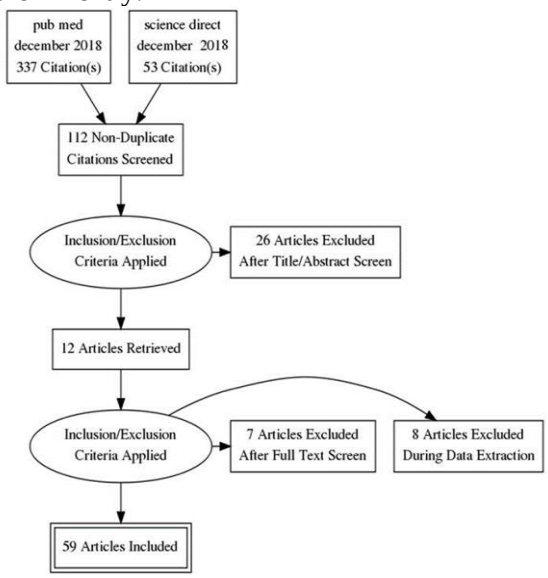

Fig 2. Flow chart of article selection process

Table 1. Cytotoxic and antitumor activity of mangosteen extracts and isolated compounds in various types of cancer

Compound	Part used	Model	Results	Ref.
Extracts				
Mangosteen (aceton:water; 80:20 extract) - major compound: α-mangostin	Pericarp	*In vitro:* hepatocellular carcinoma cell line (HepG2) *In vivo:* Zebra fish embryo	1. *In vitro*: - Cytotoxic activity [IC_{50}; 8.39 (α-mangostin) and 23 μg/mL (crude extract)] 2. *In vivo:* - α-mangostin: tail bend deformity in surviving zebra fish embryo at 12.5 μg/ml - Crude extract: No deformity	[28]
Mangosteen (ethanolic extract)	Pericarp	*In vitro:* squamous cell carcinoma (A-431), melanoma (SK-MEL-28), normal skin fibroblast (CCD-1064Sk), keratinocytes (HaCaT) cell lines	1. Antioxidant 2. Cytotoxic activity (EC_{50} for A-431 cancer cell = 5.07 μg/ml; SK-MEL-28 normal cell = 6.89 μg/ml; CCD-1064Sk = 12.62 μg/ml; and HaCaT = 8.32 μg/ml 3. Induction of apoptosis (intrinsic and extrinsic pathway); induction of cell cycle arrest at G1	[29]
Mangosteen (ethanolic extract)	Pericarp	*In vitro:* breast cancer cell line (MCF-7)	1. Absorption/release profiles based on total phenolic compounds, α-mangostin 2. Cytotoxic activity: α-mangostin > 17.4-18.4 μg/ml, < 5% survival of MCF-7 breast cancer cells	[30]
Mangosteen (ethanolic extract)	Whole fruit	*In vivo:* diethylnitrosamine (DEN)-induced hepatic carcinoma in Wistar rats (n=6), 200, 400, and 600 mg/kg bw, po.	1. Chemoprevention for hepatic cancer induced by DEN 2. Reduction of cancer biomarkers, tumor promoting growth factor; no pathological change in liver tissue	[31]
Mangosteen (ethanolic extract)	Pericarp	*In vitro*: breast cancer cell line (SKBR3)	1. Cytotoxic activity (IC_{50} 15.45 μg/ml)	[32]
Mangosteen (ethyl acetate extract) [α-mangostin (77.8%), γ-mangostin (15.9%)]	Pericarp	*In vivo:* colon cancer induced by 1,2-dimethylhydrazine in F344 rats (subcutaneous injection)	1. Inhibition of the induction and/or development of aberrant crypt foci (dose-dependent) 2. Inhibition of dysplastic foci, and β-catenin accumulate crypt induced by a carcinogen DMH (dose-dependent) 3. Lowering proliferating cell nuclear antigen (PCNA) labeling index in the colonic epithelial cells	[33]
Mangosteen (ethyl acetate extract) (α-and γ-mangostin main compounds)	Pericarp	*In vitro:* colorectal adenocarcinoma (COLO205, SW620, MIP-101), colonic carcinoma (CX1) cell lines *In vivo:* athymic nude mice bearing COLO 205	1. *In vitro:* - Cytotoxic activity (IC_{50} = 7.50, 17.7, 10.0 and 16.1 μg/ml for COLO, CX-1, MIP-101 and SW620, respectively) - Induction of apoptosis (extrinsic and intrinsic pathways) 2. *In vivo*: - Inhibition of tumor growth; formation of apoptotic bodies	[14]

Compound	Part used	Model	Results	Ref.
Mangosteen (fruit extract (MFE)) -major compound: α -mangostin	Pericarp	*In vitro*: prostate cancer (LNCaP, 22Rv1), primary epithelial (PrECs) cell lines	1. *In vitro:* - Cytotoxic activity - Induction of apoptosis (through enhancing ER stress markers, *i.e*., phosphorylated PERK, IRE1, CHOP, and spliced XBP-1 (no effect in PrECs) - Combination of CHOP siRNA + α-mangostin: increase of apoptosis activity	[34]
		In vivo: xenograft mice bearing 22Rv1 cells (35 mg/kg bw; 70 mg/kg bw; ip two times weekly)	2. *In vivo:* Inhibition of tumor growth	
Mangosteen (fruit extract (MFE)) - 35% α-mangostin and additional xanthones, such as β-mangostin and γ-mangostin	Pericarp, whole fruit extract	*In vitro:* prostate cancer (LNCaP, 22Rv1), primary prostatic epithelial (PrECs) cell lines	1. *In vitro:* - Cytotoxic activity - Induction of apoptosis - Induction of ER stress/UPR proteins [increased PERK, IRE1, CHOP protein expression; up-regulation of ER chaperones and induced spliced XBP-1]; selective promotion of ER stress/UPR in prostate cancer cells but not in non-cancerous prostate epithelial cells	[35]
		In vivo: xenograft nude mice bearing 22Rv1 (5 mg/kg bw, *i.p*.)	2. *In vivo:* Inhibition of tumor growth	
Mangosteen (methanolic extract)	Pericarp	*In vitro:* breast cancer cell line (SKBR3)	1. Cytotoxic activity (ED_{50} 0.64 μg/ml) 2. Induction of apoptosis 3. Antioxidant activity (inhibiting ROS production)	[8]
Mangosteen (methanolic extract) & isolated and purified 3 major phenols (P1, P2, P3) • P1 [1,3,6,7-tetrahydroxy-2,8-(3-methyl-2-butenyl) xanthone] • P2 [1,3,6-trihydroxy-7-methoxy-2,8-(3-methyl-2-butenyl) xanthone] • P3 (epicatechin)	Pericarp	*In vitro:* breast cancer (MCF-7), colon cancer (LOVO), normal embryonic lung fibroblast (HELF) cell lines	1. Cytotoxic activity (62.5 μg/ml); - P1: 73% MCF-7, 42% LOVO cytotoxicity - P2: 13% MCF-7, no activity - P3: 48% MCF-7, no data 2. Antioxidant activity (40 μg/ml)	[36]
Mangosteen (toluene extract) (81% α-mangostin and 16% γ-mangostin),	Pericarp	*In vitro:* colon cancer cell line (HCT 116)	1. *In vitro* - Cytotoxic activity (IC_{50} 6.5 μg/ml), anti-migration - Induction of apoptosis • 10 μg/ml exposure for 6 h: induction of apoptosis; reduction of transcription factor activities	[2]

Compound	Part used	Model	Results	Ref.
			• 7.5 μg/ml exposure for 6 h: no induction of apoptosis; induction of transcription factor activity of MAPK/ERK, Myc/Max and p53 signaling; inhibition of NF-κB	
		In vivo: athymic nude mice bearing HCT 116	2. *In vivo:* Inhibition of tumor size or growth; fewer blood vessels in tumor	
Mangosteen (water-extract) - partially purified α-mangostin	Pericarp	*In vitro:* breast cancer cell line (SKBR3)	1. α-Mangostin: - Antioxidant activity: DPPH radical (IC_{50}183.95 μg/ml), ROS (20 μg) - Cytotoxic activity (ED_{50} 8.21μg/ml) - Induction of apoptosis: membrane-blebbing, cell shrinkage, nuclear shrinkage and DNA fragmentation 2. Water soluble extract: - Antioxidant activity: DPPH radical (IC_{50} 54.57μg/ml), ROS (200 μg) - Weak inhibition of cell viability (ED_{50} 160.50 μg/ml)	[9]
Pure compounds				
1) 1,3,7-trihydroxy-2-(3-methyl-2-butenyl)-8-(3-hydroxy-3-methylbutyl)-xanthone, 2) 1,3,8-trihydroxy-2-(3-methyl-2-butenyl)-4-(3-hydroxy-3-methylbutanoyl)-xanthone, 3) garcinones C, 4) garcinones D , 5) gartanin, 6) xanthone I, 7) γ-mangostin	Pericarp	*In vitro:* nasopharyngeal carcinoma (CNE1, CNE2, SUNE1, HONE1), lung cancer (A549, GLC82), breast cancer (MCF-7), and hepatic cancer (Bel-7402) cell lines	1. Cytotoxic activity against all cell lines (IC_{50} 0.54-24.06 μM). 2. Potency of activity: Compound 1 & 2 similar to 3 & 7, > 4, 6 & hirsutanol A (positive control)	[37]
1) 7-O-demethyl mangostanin, 2) mangostanin, 3) 8-deoxygartanin, 4) gartanin, 5) garcinone E, 6) trapezifolixanthone , 7) padiaxanthone, 8) tovophyllin A, 9) 1,5,8-trihydroxy-3-methoxy-2 [3-methyl-2-butenyl]xanthone, 10) garcinone B, 11) 1,3,7-trihydroxy-2,8-di-(3-methylbut2-enyl)xanthone, 12) mangostenone D, 13) 2-geranyl-1,3,5-trihydroxyxanthone (mangostinone), 14)1,7-dihydroxy-2-(3-methylbut-2-enyl)-3-methoxyxanthone	Pericarp	*In vitro* : pheochromocytoma (PC12), nasopharengyl carcinoma (CNE-1, CNE-2), lung cancer (A549, H490), prostate cancer (PC-3), gastric carcinoma (SGC-7901), malignant glioma (U87) cell lines	1. Cytotoxic activity - Compounds 1, 2, 3, 4, 5, 11: inhibition of PC12 (pheochromocytoma cell) and U87 (human malignant glioma cell) - 7-O-demethyl mangostanin: CNE-1, CNE-2, A549, H490, PC-3, SGC-7901, U87 and PC12 with IC_{50}=3.35, 4.01, 4.84, 7.84, 6.21, 8.09, 6.39 and >50 μM, respectively 2. Induction of apoptosis in CNE-s cell (7-O-demethyl mangostanin)	[24]

Compound	Part used	Model	Results	Ref.
1) mangostanaxanthone V, 2) mangostanaxanthone VI, 3) mangostanaxanthone IV, 4) β-mangostin, 5) garci none E, 6) α-mangostin, 7) nor-mangostin, 8) garcimangosone D, 9) aromadendrin-8-C-β-D-Glucopyra noside, 10) 1,2,4,5-Tetrahy droxybenzene, 11) 2,4,3`-trihydroxybenzophenone-6-O-β-glucopyranoside, 12) maclurin-6-O-β-D-glucopyra noside (rhodanthe none), 13) epicate chin , 14) 2,4,6,3`,5`-pentahydroxybenzo phenone	Fruit hull	*In vitro*: hepatocellular (HepG2), breast (MCF-7), and colon cancer (HCT-116) cancer cell lines	1. Garcinone E: - Cytotoxic activity (IC_{50}15.8-16.7 μM) - Induction of cell cycle arrest at G0/G1 and induction of apoptosis/necrosis in HepG2 and HCT116 cells 2. Mangostanaxanthone IV, β-mangostin, α-Mangostin: moderate to weak cytotoxic activity (IC_{50} 45.7-116.4 μM) 3. α-Mangostin: induction of apoptosis/necrosis in HepG2 and moderate necrosis in HCT-116 cell	[38]
Garcinone E (screening of 24 xanthones and selected only garcinone e for investigation)	Pericarp	*In vitro:* ovarian cancer cell lines (HEY, A2780, A2780/Taxol)	2. Cytotoxic activity of γ-mangostin, β-mangostin, α-mangostin, garcinone C, 9-hydroxycalabaxanthone, 8-deoxygartanin, 8-hydroxycudraxanthone G, tovophyllin A, gacinone E, and 7-O-methylgarcinone E against HEY cells (IC_{50} < 10 μM) 3. Garcinone E: - Cytotoxic activity [IC_{50} = 3.55 μM (HEY), 2.91 μM (A2780), and 3.25 μM (A2780/Taxol)] - Induction of apoptosis (mitochondrial membrane, caspase-3 and PARP) - Induction of endoplasmic reticulum (ER) stress - Anti-metastasis (decrease of migration associated proteins: RhoA and Rac; decrease of invasion associated proteins: MMP-2,9; increase of TIMP1,2)	[39]
Gartanin	Pericarp	*In vitro:* hepatoma cell lines (Hep3B, HepG2, Huh7)	1. Cytotoxic activity (10-40 μmol/l) 2. Induction of apoptosis (caspase-8, -9, and -3, Bax) 3. Induction of autophagy (*via* JNK-Bcl-2 pathway): protection against cell death 4. Inhibition of JNK-Bcl-2 pathway: promotion of cell apoptosis (combination)	[20]
Gartanin (screening of 7 xanthones and selected only gartanin for investigation)	Pericarp	*In vitro:* human malignant glioma cell lines (U87, U251, T98G)	1. Cytotoxic activity against T98G cell (IC_{50} 10.8 μM) 2. Anti-metastasis (inhibition of migration, decrease of MMP 2, 9)-MAPK signaling pathway 3. Induction of cell cycle arrest at G1 4. Induction of autophagy by inhibition of PI3K/Akt/mTOR signaling pathway	[23]

Compound	Part used	Model	Results	Ref.
Maclurin	Heart-wood of fruit	*In vitro:* prostate cancer cell lines (PC3, DU145)	1. Moderate cytotoxic activity (IC_{50} 190.37 μmol/L) for both cells 2. Pro-oxidant activity in both cells 3. Induction of apoptosis in both cells 4. Anti-metastasis (anti-migration and decease of MMP 2,9) in both cells 5. Activation of p38 and inhibition of JNK, FAK, AKT and c-Myc signaling (PC3)	[40]
Mangosenone F (MSF)	Pericarp	*In vitro:* lung cancer cell lines (NCI-H460, NCI-H1299, NCI-A549) *In vivo:* xenografts in nude mice bearing NCI-H460 cells [1 or 3 mg/kg every 2 days (total 4 times) *ip*.]	1. *In vitro:* - Cytotoxic activity (no IC_{50} provided) - Induction of apoptosis (through enhancing ROS generation *via* activation of the MAPK pathway), decreasing Bcl-2 and Bcl-xL, and increasing Bax in NCI-H460 cells 2. *In vivo:* suppression of tumor growth	[21]
Prenylated xanthones: 1) mangostenones C, 2) D, 3) E, 4) thwaitesixanthone, 5) demethylcalabaxanthone, 6) garcinone B, 7) compound 7, 8) β-mangostin, 9) 8-desoxygartanin, 10) gartanin, 11) garcinone E, 12) α-mangostin, 13) mangostinone, 14) γ-mangostin, 15) mangostanol, 16) mangostanin, 17) garcinone D, 18) garcinone C, 19) metabolite 11-hydroxy-1-isomangostin	pericarp	*In vitro:* mouth carcinoma (KB), breast cancer (BC-1), small lung cancer (NC1-H187) cell lines	1. Mangostenone C: cytotoxic activities against KB, BC-1, and NCI-H187, with IC_{50} 2.8, 3.53, and 3.72 μg/ml, respectively 2. α-Mangostin: cytotoxic activity against BC-1 (IC_{50} 0.92 μg/ml) and KB (IC_{50} 2.08 μg/ml) 3. Gartanin: cytotoxic activity against NC1-H187 (IC_{50} 1.08 μg/ml)	[11]
Xanthones hexane and chloroform extract <u>Stem bark</u>: 1) 2,8-dihydroxy-6-methoxy-5-(3-methylbut-2-enyl)-xanthone <u>Root bark</u>: 2) α-mangostin, 3) β-mangostin, 4) γ-mangostin, 5) garcinone D, 6) mangostanol, 7) gartanin	Stem and root barks	*In vitro:* T-lymphoblastic leukemia cell line (CEM-SS)	1. Root bark/stem bark extract: cytotoxic activity (IC_{50} 0.3-17 μg/ml) 2. α–Mangostin, mangostanol, and garcinone D: cytotoxic activity (IC_{50} 5.5, 9.6, and 3.2 μg/ml, respectively) 3. 2,8-dihydroxy-6-methoxy-5-(3-methylbut-2-enyl)- xanthone: no cytotoxic activity (IC_{50} > 30 μg/ml)	[5]
Xanthones: 1) 11-hydroxy-3-O-methyl-1-isomangostin, 2) 11-hydroxy-1isomangostin, 3) 11α-mangostanin, 4) 3-isomangostin, 5) α-mangostin, 6) β-mangostin,	Stem bark	*In vitro:* colon cancer (HT-29) cell line	1. *In vitro*: - Cytotoxic activity against HT-29 [compounds 4-8; ED_{50} =4.9, 1.7, 1.7, 2.3, and 9.1 μM, respectively) - Inhibition of NF-κB signaling (α-mangostin):	[7]

Compound	Part used	Model	Results	Ref.
7) garcinone D, 8) 9-hydroxycalabaxanthone, 9) 8-deoxygartanin, 10) gartanin, 11) cratoxyxanthone			• Inhibition of p65 activation in (compounds 5–7, 9, and 10; IC_{50} = 15.9, 12.1, 3.2, 11.3, and 19.0 μM, respectively) • Inhibition of p50 activity (compound 6; IC_{50} 7.5 μM)	
		In vivo: xenograft models with HT-29 hollow fiber assay	2. *In vivo:* α-mangostin had no activity at highest tested dose (20 mg/kg bw)	
Xanthones: 1) crudaxanthone, 2) 8-deoxyartanin, 3) garcinone D, 4) garcinone E, 5) gartanin, 6) 8 hydroxycudraxanthon, 7) isomangostin, 8) α–mangostin, 9) γ–mangostin, 10) mangostenone, 11) smeathxanthone, 12) tovophylline A	Pericarp	*In vitro:* breast cancer cell line (SK-BR-3)	Activity against aromatase (percent control activity; PCA) 1. γ–Mangostin: strong inhibition of aromatase activity (PCA 4.7, IC_{50} 6.9 μM) 2. Garcinone D (PCA 10.0, IC_{50} 5.2 μM). 3. α-Mangostin (PCA 22.2, IC_{50} 20.7 μM) 4. Garcinone E (PCA 23.9, IC_{50} 25.1 μM) 5. Compounds 1, 2, 5, 7, 10, 12 (PCA > 50 μM)	[12]
Xanthones: 1) γ-mangostin, 2) α-mangostin, 3) β-mangostin, 4) 8-hydroxycudraxanthone G, 5) cudraxanthone G, 6) garcinone D, 7) mangostanin, 8) garcinone C, 9) 1-isomangostanin	Pericarp	*In vitro:* tongue cancer cell line (SP-C1)	1. Cytotoxicity: IC_{50} of compounds 1-9: 352.1, 14.4, 291.4, 64.0, 36.9, 72.4, 335.1, 76.0 and 146.7 μg/ml 2. Suppression of IL-8 production occurred only with 8-hydroxycudraxanthone G (35%) and garcinone C (30%) at 15.7 μg/ml in 24 h 3. Highest IL-8 suppression with 8-hydroxycudraxanthone G (45%) and lowest suppression with α-mangostin (15%) in 48 h	[18]
α -Mangostin	Pericarp	*In vitro*: intrahepatic cholangiocarcinoma cell line (KKU-M214)	1. *In vitro*: - Cytotoxic activity (IC_{50} 1.36 μM); anti-migration - Induction of apoptosis (caspase 3, Bax, p53 increased) and cell cycle arrest at G1 phase	[25]
		In vivo: hamster CCA allograft model	2. *In vivo:* - Suppression of tumor mass (weight and size) - Alteration of CCA pathology; reduction of positive staining for CK19 and PCNA	
α -Mangostin	Pericarp	*In vitro:* chronic myeloid leukemia (K562, KBM5, KBM5T315I) cell lines	1. Cytotoxic activity: - IC_{50} at 48 h: K562 = 13.8 μM, KBM5 = 8.2 μM, KBM5T315I = 7.08 μM 2. Induction of apoptosis 3. Induction of G1 phase cell cycle arrest 4. Induction of autophagy (promotion of cell survival) 5. Combination of α –mangostin + autophagy inhibitor: synergistic effect on cytotoxic activity	[26]

Compound	Part used	Model	Results	Ref.
α -Mangostin	Pericarp	*In vitro:* adenocarcinoma colon cell line (HT-29) *In vivo:* xenograft mice bearing HT-29 (n=48), 900 mg/kg bw	1. *In vitro:* - Cytotoxic activity (IC_{50} 26 μM) - Decrease of cellular Bcl2 and β-catenin 2. *In vivo:* Reduction of tumor volume and masses	[27]
α -Mangostin	Pericarp	*In vitro:* oral squamous cell carcinoma (HSC-2, HSC-3, HSC-4, Ca9-22, SAS) cell lines	1. c-Myc expression: high expression in SAS, low expression in HSC-4 2. Cytotoxic activity - α- mangostin: activity against SAS, but not HSC-4 - rhTRAIL: no activity against both cells - Combination: (20 μM) and rhTRAIL (100 ng/ml): synergistic activity on SAS, but not HSC-4 3. Combination: induction of apoptosis and S/G2/M-phase cell cycle arrest (SAS)	[41]
α -Mangostin	Pericarp	*In vitro:* pancreatic cancer (BxPC-3, MIAPaCa-2) cell lines.	1. Cytotoxic activity 2. Anti-metastasis: anti-migration/ anti-invasion (deceased MMP-2, MMP-9 and increased E-cadherin protein expression) 3. Inhibition of phosphorylation of extracellular-signal-regulated kinase (ERK) signaling pathway	[42]
α -Mangostin	Pericarp	*In vitro*: lung fibroblast (WI-38), non-small cell lung cancer (A549), peripheral blood mononuclear cells (hPBMC) cells	1. Cytotoxic activity (only on A549; IC_{50} ~10 μM) 2. Induction of apoptosis 3. Induction of ROS generation	[43]
α -Mangostin	Pericarp	*In vitro:* hepatocarcinoma (HepG2), anoikis-resistant HepG2 cell lines	1. Anoikis-resistant HepG2: more aggressive, rapid proliferation, doxorubicin resistance, up-regulation of anti-apoptotic protein levels, and epithelial-to-mesenchymal transition (EMT) phenotype 2. Cytotoxic activity: inhibition of anoikis-resistant HepG2 cell survival (through induction of caspase-9, caspase-8 and caspase-3 activity); increase of pro-apoptotic protein (Bax, Bim, t-Bid) levels; decrease of anti-apoptotic protein (c-FLIP, Mcl-1) levels 3. Anti-metastasis: reduction of cell re-adhesion and migration, MMP-2 and MMP-9 secretions, and EMT-involved protein (N-cadherin, αV, β1 integrin, and vimentin) expression 4. Suppression of AKT and ERK signaling pathways	[44]
α -Mangostin	Pericarp	*In vitro:* human colon cancer (DLD-1) cell line	1. *In vitro:* - Cytotoxic activity (IC_{50} 7.5 μM) - Induction of apoptosis (*via* endonuclease-G, not caspase) - Suppression of phospho-Akt pathway; increase of microRNA-143	[45]

Compound	Part used	Model	Results	Ref.
			- Combination of 2.5 μM α-mangostin + 2.5 μM 5-FU: synergistic activity on tumor growth inhibition	
α -Mangostin	Pericarp	*In vitro:* chondrosarcoma cell (bone cancer) cell line (SW1353)	1. Cytotoxic activity (IC_{50} 10 μg/ml) 2. Induction of apoptosis (mitochondrial pathway) 3. Suppression of ERK, JNK, and Akt signaling pathways	[4]
α -Mangostin	Pericarp	*In vitro:* breast cancer (MDA-MB-468, AU565, SKBR3, T47D) cell lines	1. Cytotoxic activity (IC_{50} 7.5 μM) 2. Induction of apoptosis (HER2/PI3K/Akt, and MAPK signaling pathways) 3. Suppression of phosphorylation of ERα, HER2, PI3K, Akt, and ERK1/2; increase of p-JNK1/2 and p-p38	[46]
α -Mangostin	Pericarp	*In vitro:* breast cancer (MDA-MB231) cell line	1. Cytotoxic activity (IC_{50} 20 μM) 2. Induction of apoptosis 3. Induction of G1-phase cell cycle arrest 4. Induction of $p21^{cip1}$ expression; decrease of cyclins, cdc(s), CDKs, and PCNA (proliferating nuclear antigen).	[47]
α -Mangostin	Pericarp	*In vitro:* gastric adenocarcinoma (BGC-823, SGC-7901) cell lines	1. Cytotoxic activity (< 3 μg/mL: no effect, optimal concentration =7 μg/ml) 2. Induction of apoptosis and mitochondrial dysfunctions 3. Suppression of Stat3/pSTAT3 activation	[48]
α -Mangostin	Pericarp	*In vitro*: human metastatic melanoma (SK-MEL-28) and human squamous cell carcinoma (A-431) cell lines	1. Cytotoxic activity 2. Anti-metastasis (anti-migration, anti-invasion, anti-adhesion; decrease of MMP-2, MMP-9, NF-κB and Akt1)	[49]
α -Mangostin	Pericarp	*In vitro:* mucoepidermoid carcinoma cell line (YD-15) *In vivo*: BALB/c nude mice bearing YD-15 (10, 20 mg/kg bw ip.)	1. *In vitro:* - Cytotoxic activity - Induction of apoptosis - Induction of cell arrest at sub-G1 phase - Suppression of phosphorylation of ERK1/2 and p38 MAPK and reduction of c-myc expression 2. *In vivo:* - Inhibition of tumor size - Induction of apoptosis in treated mice than control (through suppression of ERK1/2 and p38 MAPK signaling pathways)	[50]
α -Mangostin	Pericarp	*In vitro:* breast cancer (MCF-7, MDA-MBA-231) cell lines	1. Cytotoxic activity (IC_{50} MCF-7 = 3.6 μM 24 h / 2.7 μM 48 h; MDA-MB-231= 3.4 μM 24 h/ 2.3 μM 48 h) 2. Induction of apoptosis 3. Inhibition of fatty acid synthase (FAS) expression, FAS activity, FAS accumulation	[51]
α -Mangostin	Pericarp	*In vitro:* multicellular spheroids prepared from breast cancer	1. Cytotoxic activity (at 48 h---MDA-MB-231: IC_{50} 1.30 μg/ml; MCF-7: IC_{50} 1.60 μg/ml)	[52]

Compound	Part used	Model	Results	Ref.
		(MDA-MB-231, MCF-7) cell lines	2. Induction of apoptosis (through increasing caspase 3,6,7 activity) 3. Decrease in spheroid size, no cell migration	
α -Mangostin	Pericarp	*In vitro:* leukemia cell line (HL60)	1. Induction of apoptosis (mitochondrial pathway *via* caspase 3,9, but not 8) 2. No effect on the expression of bcl-2 family proteins and activation of MAP kinases	[53]
α -Mangostin	Pericarp	*In vitro:* prostate carcinoma cell line (PC-3)	1. Cytotoxic activity 2. Anti-metastasis (anti-adhesion, anti-migration, and anti-invasion) through reduction of MMP-2, MMP-9, and u-PA expression 3. Suppression of phosphorylation of c-Jun N-terminal kinase 1 and 2 (JNK1/2) and inhibition of activation of nuclear factor kappa B (NF-κB), c-Fos, and c-Jun	[54]
α -Mangostin	Pericarp	*In vivo:* skin cancer induced by DMBA/TPA in ICR mice (5, 20 mg/kg bw, ip.)	1. Inhibition of tumor formation and growth 2. Promotion of the production of anti-inflammatory factors 3. Induction of cell autophagy and apoptosis; inhibition of PI3K/AKT/mTOR signaling pathway (through decrease of the expression of phospho-PI3K (p-PI3K), p-Akt and p-mTOR). 4. No effect on the expressions of total proteins of PI3K, AKT and mTOR	[55]
α –Mangostin	Pericarp	*In vitro:* hepatocellular carcinoma (HepG2, Hep 3B,MHCC-97L,Huh 7), liver (L02) cell lines	1. Cytotoxic activity: - IC_{50} at 48 h: HepG2 = 10.69 μM, Hep 3B = 10.92 μM, MHCC-97L = 7.03 μM, Huh7 = 13.78 μM 2. Induction of cell cycle arrest at G0/G1 phase (HepG2, Hep 3B,MHCC-97L, and Huh 7) 3. Cytotoxic activity against doxorubicin-resistance (Hep 3B and Hep G2 exposed to IL6) and malignantly transformed cells (L02/H-Ras, and L02/K-Ras) 4. Down-regulation of cancer stem cell biomarkers on HepG2, Hep 3B, L02, L02/H-Ras, and L02/K-Ras (CD133 and CD44)	[56]
α –Mangostin	Pericarp	*In vitro:* pancreatic cancer (PL-45, PANC1, BxPC3, ASPC1) cell lines	1. *In vitro:* - Cytotoxic activity (IC_{50} 13-17 μM), no activity against non-tumorigenic human pancreatic duct epithelial (HPDE) cells (at 40 μM) - Anti-metastasis: decrease of invasion associated proteins: MMP9/ increase of TIMP1 - Induction of apoptosis - Inhibition of NF- κB and stat3 - Induction of cell cycle arrest at G1 phase	[57]

Compound	Part used	Model	Results	Ref.
		In vivo: ectopically and orthotopic xenograft mince bearing ASPC1/PL-45 cells (6 mg/kg bw, i.p. 5 days/week for 8 weeks)	2. *In vivo:* - Inhibition of tumor growth: primary (PL-45) and secondary (ASPC1) human PC cell-derived orthotopic and ectopic xenograft tumors - No sign of toxicity	
α –Mangostin	Pericarp	*In vitro:* pancreatic cancer (BxPc-3 and Panc-1), normal human pancreatic ductal epithelial cell(hTERT-HPNE) cell lines	1. *In vitro*: - Cytotoxic activity [32μ M; inhibited 80% on BXPc-3,Panc-1, and 50% in hTERT-HPNE] - Induction of apoptosis - Induction of cell cycle arrest (G1/G0 phase) - Anti-metastasis (anti-migration/anti-invasion; decrease of MMP-2, MMP-9, N-cadherin, vimentin, and increased E-cadherin) - Suppression of the PI3K/Akt Pathway	[19]
		In vivo: xenograft nude mice baring BxPc-3 cell. (50 or 100 mg/kg bw po).	2. *In vivo:* Inhibition of tumor growth	
α –Mangostin	Pericarp	*In vitro:* prostate cancer (LNCaP, PC3, DU145, 22Rv1) cell lines	1. *In vitro:* - Cytotoxic activity (IC_{50} 5.9, 6.9, 22.5 and 12.7 μM for LNCaP, 22Rv1, DU145 and PC3, respectively) - Induction of apoptosis (PC3, and 22Rv1) - Induction of cell cycle arrest at G1 phase (PC3, and 22Rv1) - Inhibition of several kinases: JNK and cyclin/cyclin-dependent kinase (CDK) proteins (cell-free based kinase assay) - Inhibition of proteins upstream of CDK4: INK proteins (p15 INK4B, p16 INK4A), p27 Kip1 and CDK4 in 22Rv1	[58]
		In vivo: xenograft mice bearing 22Rv1 cells (100 mg/kg bw, po.).	2. *In vivo:* Inhibition of tumor growth	
α -Mangostin and derivatives	Pericarp	*In vitro:* lung cancer (NCI-H460), colon cancer (SW-620), pancreas cancer (AS-PC1), breast cancer (MDA-MBA 231), skin cancer (B16-F10) *Structure Activity Relationship (SAR)*	1. Cytotoxic activity - IC_{50} of α-mangostin: 3.23, 2.97, 4.02, 3.04, 3.23 uM for NCI-H460, SW-620, AS-PC1, MDA-MBA 231, and B16-F10 - IC_{50} of γ-mangostin: 4.48, 5.69, 5.92, 5.87 uM for NCI-H460, SW-620, AS-PC1, and MDA-MBA 231 - Moderate cytotoxic activity in all cells: phenyl group at C3 (IC_{50}:4-6μM) and C6 (IC_{50}: 14–18 μM), C4 (IC_{50}: 10- 23 μM)	[59]

Compound	Part used	Model	Results	Ref.
			2. Modification of chemical structure: marked increase in solubility (3-19 fold of α-mangostin	
α-Mangostin, gartanin	Mangosteen fruit juice	*In vitro*: bladder cancer (T24, RT4, UMUC3, 5637, TCCSUP, HT1376 and J82) cell lines; mouse embryonic fibroblasts (MEFs): p53, TSC1 or TSC2 knockout mice	1. Cytotoxic activity - Gartanin (IC_{50} 4.1-18 μM) and α–mangosteen (IC_{50} 7.0-9.8 μM) - Gartanin against MEFs: less sensitive (IC_{50} p53 knockout; 18.5 μM; TSC1 knockout 31.2 μM,); TSC2 knockout = more sensitive 2. Gartanin: inhibition of the down-stream of the mTOR pathway *via* two different mechanisms in T24 and RT4 cells; activation of AMPKα and inactivation of AKT, respectively. 3. Induction of apoptosis 4. Induction of autophagy	[17]
α -Mangostin, γ-mangostin, and 8-deoxygartanin	Pericarp	*In vitro:* melanoma (SK-MEL-28) cell line	1. Cytotoxic activity [IC_{50} of α -mangosteen, γ-mangostin, and 8-deoxygartanin = 5.92, 3.55, and 3.83 μg/ml, respectively] 2. Induction of apoptosis (*via* caspase activation and disruption of mitochondrial membrane pathways) 3. Induction of cell cycle arrest at G1 phase (γ-mangostin and 8-deoxygartanine), α –mangostin; no induction of cell arrest but increase of sub G1 peak	[15]
α -Mangostin, γ -mangostin	Pericarp	*In vitro:* pancreatic cancer (MIA PaCa-2, PANC1) cell lines	1. Cytotoxic activity (IC_{50} 8-25 μM) 2. Induction of apoptosis 3. Induction of autophagy *(via* AMPK/mTOR and p38) 4. Downregulation of expression level of miR-18a 5. Combination with gemcitabine: synergistic activity against MIA PaCa-2, but antagonistic activity against PANC1	[22]
α-Mangostin, iso-mangostin, xanthone, 9,10 antraquinone, 9-antracincarboxilic acid, anthracene * α-Mangostin	Ethanolic extract	*In vitro:* lung cancer (A549), colon cancer (HCT116), cervix cancer (HeLa), liver cancer (HepG2), promyelocytic leukemia (HL-60), breast cancer (MCF-7), stomach cancer (NUGC-3), prostate cancer (PC3) cell lines	1. Cytotoxic activity - A549 (lung cancer): IC_{50} = 19.5 μM - HCT116 (colon cancer): IC_{50} = 18.5 μM - HeLa (cervix cancer): IC_{50} = 19.1 μM - HepG2 (liver cancer): IC_{50} =20.5 μM - HL-60 (promyelocytic leukemia): IC_{50} = 16.2 μM - MCF-7 (breast cancer): IC_{50} = 19.3 μM - NUGC-3 (stomach cancer): IC_{50} = 18.8 μM - PC3 (prostate cancer): IC_{50} = 20.0 μM 2. Inhibition of mammalian DNA polymerase (pol) α, β, γ, and κ activity 3. Inhibition of human on topo I & II (α-mangostin >2-fold more potent than that of mammalian pols activities)	[60]

Compound	Part used	Model	Results	Ref.
			4. Induction of cell cycle arrest at G2/M phase in HCT116	
α-Mangostin, β-mangostin, 3,6-di-O-Methyl-γ-mangostin, fuscax-anthone C, gartanin, 8-deoxygartanin, mangostanin, morusignin I	Fruit, pericarp, rind and leaves	*In vitro:* cervical cancer cell line (HeLa)	1. β-Mangostin: the strongest inhibitor; inhibition of mammalian DNA polymerase, human topoisomerase (IC_{50}: 6.4-39.6 and 8.5-10 μM, respectively); not act as a DNA intercalating agent, directly binds the enzyme to inhibit its activity 2. β-Mangostin: cytotoxic activity (LD_{50} 27 μM); induction of cell cycle arrest at S phase; induction of apoptosis *via* caspase	[6]
γ-Mangostin	Pericarp	*In vitro:* colon cancer cell line (HT29)	1. Cytotoxic activity (IC_{50} 68.48 μM at 48 h) 2. Induction of apoptosis 3. Induction of ROS generation	[61]
γ-Mangostin	Pericarp	*In vitro:* malignant glioblastoma cell lines, U87 MG (astrocytoma glioblastoma, grade III) and GBM 8401 (glastomaliob multiforme, grade IV)	1. *In vitro:* - Cytotoxic activity [IC_{50}:7 4.14 (U87 MG) and 64.67 (GBM 8401) μM at 48h]	[13]
		In vivo: Wistar rat brain mitochondria	2. *In vivo:* - Induction of apoptosis (*via* ROS generation) and mitochondrial dysfunction - Anti-oxidant: inhibition of $Fe^{2+}$and induction of lipid peroxidation in rat brain	
γ-Mangostin	Pericarp	*In vitro:* hepatocarcinonma cell line (HepG2); normal liver cell line (Chang liver)	1. *In vitro:* - Cytotoxic activity (IC_{50} HepG2 =51 μM, Chang liver = 149 μM)	[16]
		In vivo: Sprague-Dawley rat liver	2. *In vivo:* - Inhibition of LPO and scavenger of 2,2-diphenyl-1-picrylhydrazyl on liver mitochondria - Induction of apoptosis *(via* intracellular ROS production) and mitochondrial dysfunction - Induction of cell cycle arrest at sub-G1 peak (hypodiploid cells)	
α-Mangostin, β-mangostin, γ-mangostin, mangostinon, egarcinone E, 2-isoprenyl-1,4-dihydroxy-3-methoxyxanthone	Pericarp	*In vitro*: leukemia (HL60, K562, NB4, U937) cell lines	1. Cytotoxic activity - IC_{50} of α, β, γ–mangosteen against HL60 cell = 6.8, 7.6, and 6.1 μM, respectively - 10 μM of α-mangostin: marked inhibition of the growth of all cell lines (HL60, NB4, and U937) - K562: most resistant to α-mangostin 2. Induction of apoptosis (*via* caspase-3 activation)	[10]

4.1 Breast cancer

Breast cancer is the most common type of cancer diagnosed in women, and is the second highest cause of cancer deaths worldwide.[51] It also occurs in men, but with more than 100-fold less frequent than in women. Surgical resection, radiation therapy, chemotherapy, and hormonal therapy serve as the treatment options for early-stage breast cancer. However, the emergence of drug resistance and high toxicity of the chemotherapeutic drugs have undermined their clinical uses. The development of effective treatment strategies to cure and prevent breast cancer is therefore more demanding and inevitable.[8]

Various *in vitro* studies have demonstrated the cytotoxic potential of mangosteen and isolated compounds in various breast cancer cell lines, *i.e.*, SK-BR-3,[8,9,12,32,46] MDA-MBA 231,[47,59,51,52] MDA-MB-468, AU565, T47D,[46] BC-1,[7,11] and MCF-7,[21,30,36,38,51,52,60] α-Mangostin was reported to exhibit anticancer activity *via* various mechanisms including induction of cell cycle arrest (through increasing p21cip and decreasing of cyclins, CDK, and proliferating nuclear agent),[47] induction of apoptosis (through down-regulating ERα, HER2, PI3K, Akt, ERK1/2, and MAPK signaling pathways), up-regulation of p-JNK1/2 and p-p38,[46] inhibition of essential metabolism enzymes (aromatase[12] and fatty acid synthetase[51]), reduction of oxidative stress (through inhibition of DPPH radical activity and intracellular ROS (reactive oxygen species),[8,30,32] and inhibition of cell migration associated with cancer metastasis.[52] In response to ROS, a similar finding was observed with the crude methanolic and ethanolic extracts of mangosteen in SKBR3 and MCFC-7[8,30,32] cell lines. Ethanolic extract of mangosteen containing α-, isomangostin xanthone,[26,27] anthraquinone, 9-antracincarboxilic acid and anthracene, was shown to inhibit cell proliferation associated with the formation of apoptotic bodies and induce cell cycle arrest in G2/M phase.[60] Significant cytotoxicity against breast cell lines MCF-7 and BC-1 was demonstrated with the prenylated xanthones 1,3,7-trihydroxy-2-(3-methyl-2-butenyl)-8-(3-hydroxy-3-methylbutyl)-xanthone, 1,3,8-trihydroxy-2-(3-methyl-2-butenyl)-4-(3-hydroxy-3-methylbutanoyl)-xanthone, mangostenon C, 3-isomangostin, garcinon D and hydroxycalabaxanthone, together with the five known compounds garcinones C and D, gartanin, xanthone I, and γ-mangostin.[11,37] Moreover, modification of chemical structure of α-mangostin with phenyl group at C3, C4 and C6 provided compounds with moderate cytotoxic activity against MDA-MBA 231 cells.[59] The anticancer activity of γ–mangostin, garcinone D, and garcinone E was shown to be through inhibition of the aromatase activity, leading to reduction of estrogen production.[12] Mangosteen and its isolated compounds have been reported to effectively inhibit or suppress cancer growth through various pathways. Among all mangosteen compounds, α-mangostin appears to be the most promising candidate for further research and clinical application in breast cancer.

4.2 Colon cancer

Colorectal cancer is the third in incidence after lung and breast cancers and accounts for about 10% and 8% of total cases and deaths of cancer, respectively.[2] The antiproliferative and anticancer activity against colon cancer of mangosteen compounds have been supported by an impressive amount of data from human cell culture system as well as animal models.

α-Mangostin was shown to exert potent cytotoxic against the colon cancer cell lines HT-29,[7,27] HCT116,[60] and DLD-1.[45] The activity was demonstrated to be associated with inhibition of DNA polymerase, topoisomerase I and topoisomerase II,[60] induction of cell cycle arrest at G2/M phase,[60] and induction of apoptosis by endonuclease-G activation (caspase-independent)[45] (through suppression of cellular Bcl-2, β-catenin, AKT pathway, NF-κB pathway, and activation of miR-143).[7,27,45] Synergistic effect on tumor growth inhibition was demonstrated when given in combination with the conventional chemotherapeutic drug 5-fluorouracil (5-FU).[45] Potent antitumor activity of α-mangostin was shown in HT-29 C colorectal

carcinoma-bearing athymic nude mice.[27] However, it did not exhibit promising activity in the in *vivo* hollow fiber assay.[5] The cytotoxic activity against HT29 colon cancer cell of another xanthone compound, γ-mangostin, was shown to be linked with the induction of apoptosis through increasing ROS generation.[61]

Xanthone extract consisting of the two major compounds, *i.e.*, α- and γ-mangostin showed potent cytotoxic activity against colon cancer cell lines HCT116, COLO205, SW620, MIP-101, and CX-1.[2,14] The activity was associated with caspase-dependent apoptosis induction in both extrinsic and intrinsic pathways, inhibition of cell proliferation and tumor metastasis *via* up-regulation of the MAPK/ERK, c-Myc/ Max, p53, and JNK cell signaling pathways, as well as inhibition of NF-KB.[2,14] Potent antitumor activity was demonstrated in HT-29 and COLO 25-bearing athymic nude mice.[14,27] In addition, the extract was also shown to inhibit colon cancer development (oncogenesis) in 1,2 di-methyl hydrazine-induced colon cancer in rats.[33] Cytotoxic activity of other xanthones isolated from the stem bark of mangosteen was investigated in HCT-116,[38] and HT-29[7] human colon cancer cell lines. 3-Isomangostin, β-mangostin, garcinone D, and 9-hydroxycalabaxanthone showed potent activity against HT-29 colon cell line,[7] while garcinone E showed potent activity against HCT-116 cell line.[38]

4.3 Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver which is one of the most common cancers in the world. The primary risk factors for HCC include infection with hepatitis B or hepatitis C virus, alcoholic liver disease, and most probably non-alcoholic fatty liver disease.[16] α-Mangostin was shown to inhibit the proliferation of hepatocellular Hep-G2 cell,[28,38,44,56,60] HEP 3B, MHCC97L, Huh7,[56] and aggressive and drug-resistance hepatocellular[44,56] cell lines. The underlying cytotoxic activity of α-mangostin against hepatocellular cells was due to the induction of caspase activities, enhancement of pro-apoptotic protein, and reduction of anti-apoptotic protein levels.[44] This subsequently suppressed cell metastasis by inhibiting cell re-adhesion, cell migration, cell invasion, and epithelial-to-mesenchymal transition (EMT)-involved protein expressions. The modulatory effects of α-mangostin making the cells more susceptible to anoikis mechanisms, is probably due to the down-regulation of the ERK and AKT signaling pathways resulting in apoptosis induction.[44] Moreover, α-mangostin also reduced the cancer stem cell biomarkers in HepG2, Hep 3B, L02, L02/H-Ras, and L02/K-Ras cell lines.[56]

The anticancer activity of γ-mangostin was demonstrated both *in vitro* and *in vivo*.[16] It potently inhibited lipid peroxidation and scavenged 2,2-diphenyl-1-picrylhydrazyl on rat liver mitochondria. In addition, it also induced cell cycle arrest at sub G1 and induced apoptosis through enhancing intracellular ROS production. These findings suggest that γ-mangostin is a promising candidate compound for hepatocellular carcinoma.[16]

Gartanin is another xanthone which showed promising cytotoxic activity against Hep3D, HepG2, and Huh7 cancer cell lines. The underlying mechanism of action was through induction of apoptosis and autophagy.[20] The JNK-BCL2 pathway is a critical regulator of gartanin-induced autophagy. The combination of gartanin with JNK-BCL2 inhibitor promoted cell apoptosis.[20]

Xanthone crude extract was shown to exert cytotoxic activity against HepG2, with relatively lower toxicity on zebrafish embryo compared with α-mangostin (tail ben deformity).[28]

Mangosteen ethanolic extract showed *in vivo* chemoprevention in diethylnitrosamine (DEN)-induced hepatic cancer in rats.[31]

4.4 Lung cancer

Lung cancer is one of the most common malignant carcinomas, and its incidence has gradually increased worldwide over the last 10 years. Approximately 80-85% of lung cancers are classified as non-small cell lung cancer (NSCLC); the 5-year survival rate is only 15%.[21]

α-Mangostin was shown to exhibit cytotoxic activity against A549[43,60] and NCI-

H460[59] cell lines, possibly through induction of apoptosis *via* increased ROS generation.[43]

The cytotoxic activity of mangostenone C and gartanin was demonstrated in small cell lung cancer (NC1-H187) cell line[11] and the cytotoxic activity of 1,3,7-trihydroxy-2-(3-methyl-2-butenyl)-8-(3-hydroxy-3-methylbutyl)-xanthone, 1,3,8-trihydroxy-2-(3-methyl-2-butenyl)-4-(3-hydroxy-3-methylbutanoyl)-xanthone, garcinones C, and γ-mangostin was demonstrated in A549 and G1C82 human lung cancer cell lines.[37] On the other hand, 7-O-demethylmangostanin produced cytotoxic activity against A549 and H490 lung cancer cell lines.[24] The cytotoxic activity of manosenone F against lung cancer was shown to be through induction of apoptosis by enhancing ROS generation (*via* activation of the MAPK pathway), reducing Bcl-2, Bcl-xL, and increasing Bax in NCI-H460 cells. Moreover, significant suppression of tumor growth was demonstrated in NCI-H460 cells-bearing nude mice treated with 3 mg/kg manosenone F.[21]

4.5 Prostate cancer (PC)

Prostate cancer is commonly diagnosed in men at old age. Potent antiproliferative activity of α-mangostin was reported in various prostate cancer cell lines, *i.e.*, PC-3,[54,58,60] DU 145,[58] 22Rv1, and LNCaP.[34,35,58] The activity was associated with metastasis inhibition (through decreasing expression of MMP-2, MMP-9), and u-PA (through suppression of JNK1/2 and NF-κB signaling pathways),[54] induction of cell cycle arrest at G1 phase (through inhibition of upstream cyclin/cyclin-dependent kinase (CDK) proteins) *i.e.*, the INK proteins p15 INK4B, p16 INK4A, p27 Kip1, and CDK4),[58] and induction of apoptosis (through enhancing ER stress).[34,35] Significant suppression of tumor growth by α-mangostin was demonstrated in 22Rv1-bearing xenografted mice, [34,35,58]

Another mangosteen compound, maclurin showed moderate cytotoxic activity against prostate cancer cell lines (PC3 and DU145). It exhibited pro-oxidant and apoptotic activity, as well as inhibitory activity on cancer metastases (through activation of p38 and inhibition of JNK, FAK, AKT, and c-Myc signaling).[40] In addition, 7-odemethyl mangostanin was also shown to inhibit PC-3 cell growth.[24]

4.6 Leukemia

Promising cytotoxic activity of α-mangostin against leukemic cells was reported in KBM5, KBM5T3,[26] K562,[10,26] HL60,[10,53,59] NB4, and U937[10] cell lines. The activity was associated with the induction of cell cycle arrest at G1 phase,[26] induction of apoptosis (through activation of the caspase),[10,26,53] and induction of autophagy.[26] Combination of α-mangostin with the autophagy inhibitor (chloroquine) produced synergistic cytotoxic activity against chronic myeloid leukemia cell lines.[26] Moreover, the xanthone extracts from the stem and root bark (hexane and chloroform extracts) showed potent cytotoxic activity against T-lymphoblastic leukemic cell line (CEM-SS).[5]

4.7 Pancreatic cancer

Pancreatic cancer is one of fatal cancer found in both women and men.[55] The lethality of pancreatic cancer is due to aggressive local invasion, metastases, and resistance to chemotherapy.[17]

Cytotoxic activity of α-mangostin was demonstrated in various pancreatic cancer cell lines, *i.e.*, PL-45, PANC1, BxPC3, ASPCI, MIA PaCa-2, and Panc-1.[17,20,40,55] It inhibited metastasis by decreasing MMP-2, MMP-9, N-cadherin, vimentin, and increasing E-cadherin[17,40,55] through inhibition of extracellular-signal-regulated kinase (ERK) signaling pathway[40], inducing cell cycle arrest at G1/G0 phase, inducing apoptosis (through inhibition of NF-κB, STAT3 and PI3K/Akt pathways),[17,55] and down-regulating miR-18a.[22] It was also shown to induce autophagy through AMPK/mTOR and p38 pathways[22]. In addition, α-mangostin also significantly suppressed tumor growth in BxPc-3-xenografted nude mice.[19] Similar cytotoxic activity against pancreatic cancer cells was also observed with γ–mangostin.[22]

4.8 Skin cancer

Skin cancer, including melanoma and non-melanoma, is common in aging population and individuals exposing to intensive UV radiation as a result of ozone layer depletion.[29]

Failure of chemotherapy leads to cancer cell metastasis.[49]

Cytotoxic activity of α-mangostin was demonstrated in B16-F10,[59] SK-MEL-28, and A-431[29,49] skin cancer cell lines. The activity was associated with the induction of apoptosis through caspases activation and disruption of mitochondrial membrane.[49] It also inhibited cancer cell metastasis by suppressing NF-κB and Akt1pathways, resulting in the reduction of MMP-2 and MMP-9 levels.[49] Similarly to α-mangostin, γ mangosteen and 8 deoxy-gartanin also exhibited anti-proliferative activity through apoptosis induction. However, these two compounds induced cell cycle arrest at G1 phase, while α-mangostin did not induce cell arrest but increased the sub G1 peak.[49] In the *in vivo* model in DMBA/TPA-induced skin cancer in mice, α-mangostin inhibited tumor formation and tumor growth. It promoted the production of anti-inflammatory factors, and induced autophagy and apoptosis by suppressing PI3K/AKT/mTOR signaling pathway.[55] Besides, the cytotoxic activity of the crude ethanol extract of mangosteen pericarp was reported in human squamous cell carcinoma A-431 and melanoma SK-MEL-28 lines. The activity was related to its anti-oxidant property, as well as the induction of apoptosis *via* caspases activities, and the induction of cell cycle arrest at G1 phase.[29]

4.9 Oral cancer

Human oral squamous cell carcinoma (HOSCC) is the most common malignant neoplasm arising in the mucosa of the upper aerodigestive tract.[41]

Potent cytotoxic activity of mangostenone C and α-mangostin was demonstrated in mouth carcinoma (KB) cell line with IC_{50} (50% inhibitory concentration) of 2-3 μg/ml.[11] 8-Hydroxycudraxanthone, garcinone and α-mangostin showed promising cytotoxic activity against SP-C1 tongue cancer cell by suppression of interleukin-8.[18] In addition, α-mangostin also inhibited the growth of oral squamous cell carcinoma with high c-myc expression (SAS), but not cells with low c-myc expression (HSC-4).[41] Combination of α-mangostin with rhTRAIL produced synergistic effect on SAS through inducing apoptosis and cell cycle arrest at S/G2/M phase.[41] Moreover, α-mangostin exhibited potent cytotoxic activity against mucoepidermoid carcinoma cell line (YD-15). The underlying mechanisms of action included induction of apoptosis, induction of cell cycle arrest at sub-G1 phase, and suppression of phosphorylation of ERK1/2, p38 MAPK, and c-myc expression.[50]

4.10 Brain cancer

Glioma is an aggressive (rapid proliferation and extensive migration), and common primary tumor in the central nervous system (CNS).[23] 7-O-Demethyl mangostanin was reported to exhibit cytotoxic activity against malignant glioma cell (U87),[24] Another xanthone, gartanin, produced potent cytotoxic activity against T98G cell (IC_{50} 10.8 μM), as well as inhibited cancer cell metastasis (through induction of cell cycle arrest at G1 phase), and induction of autophagy (through inhibition of PI3K/Akt/mTOR signaling path-way).[23] Furthermore, γ-mangostin showed cytotoxic activity against U87 MG and GBM 8401 cell lines through induction of apoptosis *via* ROS generation, resulting in mitochondrial dysfunction. Moreover, it also exerted antioxidant activity through inhibition of Fe^{2+}-induced lipid peroxidation in rat brain.[13]

4.11 Cholangiocarcinoma

Cholangiocarcinoma (CCA) is a chronic infection by liver flukes. The cytotoxic and anti-migration activity of α-mangostin in KKU-M214 cell line was reported to be through induction of apoptosis and cell arrest at G1 phase. It also showed potent tumor-suppressing activity in CCA- allograft hamster model.[25]

4.12 Gastric adenocarcinoma

Gastric adenocarcinoma is very lethal disease. Cytotoxic activity of the xanthone compound 7-O-demethyl mangostanin was demonstrated in gastric carcinoma (SGC-7901) cell line.[24] α-Mangostin exhibited cytotoxic activity against gastric adenocarcinoma (BGC-823 and SGC-7901) cell lines through induction

of apoptosis and mitochondrial dysfunctions *via* suppressing Stat3/pSTAT3 pathway.[48]

4.13 Ovarian cancer

Ovarian cancer is the most lethal gynecological malignant tumor. Ninety percent of the patients were diagnosed as epithelial ovarian cancer and 60% as serious carcinoma with highly heterogeneous characteristics. Surgery and chemotherapy are available but their clinical treatment outcomes are unsatisfactory due to chemoresistance.

Potent cytotoxic activity of γ-mangostin, β-mangostin, α-mangostin, garcinone C, 9-hydroxy calabaxanthone, 8-deoxygartanin, 8-hydroxycudraxanthone G, tovophyllin A, gacinone E, and 7-O-methylgarcinone E was demonstrated in HEY cell (IC_{50}<10 μM). Garcinone E also exhibited cytotoxic activity against other ovarian cancer cell lines (A2780 and A2780/Taxol). This activity was associated with the induction of apoptosis and endoplasmic reticulum (ER) stress. It also showed anti-metastasis activity through inhibition of migration associated proteins (RhoA and Rac) and invasion associated proteins (MMP-2,9), as well as increase of TIMP1,2 proteins.[39]

4.14 Bladder cancer

Bladder cancer is the fourth most common cancer worldwide. New emerging cases and death cases from bladder cancer were reported during 2012.

4.15 Bone tumor

Chondrosarcoma is a malignant tumor which overproduces chondrocyte and cartilage matrix. α-Mangostin was reported to exhibit cytotoxic activity against the chondrosarcoma cell line (SW1353) through induction of apoptosis *via* the mitochondrial pathway by suppressing ERK, JNK, and AKT signaling pathways.[4]

4.16 Others

The cytotoxic activity of β-mangostin was demonstrated in human cervical (Hela) cell line. The mechanism involved was through induction of apoptosis and cell cycle arrest at S phase, as well as inhibition of DNA polymerase and topoisomerase enzymes.[6] Other xanthones, including 7-O-demethyl mangostanin also showed cytotoxic activity against nasopharyngeal carcinoma cell lines CNE1, CNE2, SUNE1, and HONE1.[24,37]

5. Conclusion

The present systematic review summarizes the potentials of mangosteen extracts and isolated compounds for cancer chemotherapy and chemoprevention based on previously published *in vitro* and *in vivo* studies. Xanthones, particularly α-mangostin, have been reported in various studies to be promising candidates for treatment of various types of cancer. Overall, mangosteen exerts its anticancer activity through inhibition of cell viability, induction of apoptosis, necrosis, autophagy, cell cycle arrest, and altering cell mobility alterations. Other proposed mechanisms include suppression of cancer by modulation of the signaling pathways, enhancement of ER stress, and inhibition of fatty acid synthetase.

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References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249.

[2] Aisha AF, Abu-Salah KM, Ismail Z, Majid AM. *In vitro* and *in vivo* anti-colon cancer effects of *Garcinia mangostana* xanthones extract. BMC Complement Altern Med. 2012;12:104.

[3] Sofowora A, Ogunbodede E, Onayade A. The role and place of medicinal plants in the strategies for disease prevention. Afr J Tradit Complement Altern Med. 2013;10(5): 210-229.

[4] Krajarng A, Nakamura Y, Suksamrarn S, Watanapokasin R. alpha-Mangostin induces apoptosis in human chondrosarcoma cells through downregulation of ERK/JNK and Akt signaling pathway. J Agric Food Chem. 2011;59(10):5746-5754.

[5] Ee GC, Daud S, Izzaddin SA, Rahmani M. Garcinia mangostana: a source of potential anti-cancer lead compounds against CEM-SS cell line. J Asian Nat Prod Res. 2008; 10(5-6):475-479.

[6] Onodera T, Takenaka Y, Kozaki S, Tanahashi T, Mizushina Y. Screening of mammalian DNA polymerase and topoisomerase inhibitors from Garcinia mangostana L. and analysis of human cancer cell proliferation and apoptosis. Int J Oncol. 2016;48(3):1145-1154.

[7] Han AR, Kim JA, Lantvit DD, Kardono LB, Riswan S, Chai H, et al. Cytotoxic xanthone constituents of the stem bark of *Garcinia mangostana* (mangosteen). J Nat Prod. 2009;72(11):2028-2031.

[8] Moongkarndi P, Kosem N, Kaslungka S, Luanratana O, Pongpan N, Neungton N. Antiproliferation, antioxidation and induction of apoptosis by *Garcinia mangostana* (mangosteen) on SKBR3 human breast cancer cell line. J Ethnopharmacol. 2004;90 (1):161-166.

[9] Moongkarndi P, Jaisupa N, Samer J, Kosem N, Konlata J, Rodpai E, et al. Comparison of the biological activity of two different isolates from mangosteen. J Pharm Pharmacol. 2014;66(8):1171-1179.

[10] Matsumoto K, Akao Y, Kobayashi E, Ohguchi K, Ito T, Tanaka T, et al. Induction of apoptosis by xanthones from mangosteen in human leukemia cell lines. J Nat Prod. 2003;66(8):1124-1127.

[11] Suksamrarn S, Komutiban O, Ratananukul P, Chimnoi N, Lartpornmatulee N, Suksamrarn A. Cytotoxic prenylated xanthones from the young fruit of *Garcinia mangostana*. Chem Pharm Bull (Tokyo). 2006;54(3): 301-305.

[12] Balunas MJ, Su B, Brueggemeier RW, Kinghorn AD. Xanthones from the botanical dietary supplement mangosteen (*Garcinia mangostana*) with aromatase inhibitory activity. J Nat Prod. 2008; 71(7):1161-1166.

[13] Chang HF, Huang WT, Chen HJ, Yang LL. Apoptotic effects of gamma-mangostin from the fruit hull of *Garcinia mangostana* on human malignant glioma cells. Molecules. 2010;15(12):8953-8966.

[14] Watanapokasin R, Jarinthanan F, Jerusalmi A, Suksamrarn S, Nakamura Y, Sukseree S, et al. Potential of xanthones from tropical fruit mangosteen as anticancer agents: caspase-dependent apoptosis induction *in vitro* and in mice. Appl Biochem Biotechnol. 2010;162 (4):1080-1094.

[15] Wang JJ, Sanderson BJ, Zhang W. Cytotoxic effect of xanthones from pericarp of the tropical fruit mangosteen (*Garcinia mangostana* Linn.) on human melanoma cells. Food Chem Toxicol. 2011;49(9):2385-2391.

[16] Chang HF, Wu CH, Yang LL. Antitumour and free radical scavenging effects of gamma-mangostin isolated from *Garcinia mangostana* pericarps against hepatocellular carcinoma cell. J Pharm Pharmacol. 2013; 65(9):1419-1428.

[17] Liu Z, Antalek M, Nguyen L, Li X, Tian X, Le A, et al. The effect of gartanin, a naturally occurring xanthone in mangosteen juice, on the mTOR pathway, autophagy, apoptosis, and the growth of human urinary bladder cancer cell lines. Nutr Cancer. 2013;65(Suppl 1):68-77.

[18] Setiawan AS, Oewen RR, Supriatno, Soewondo W, Sidik, Supratman U. 8-hydroxycudraxanthone G suppresses IL-8 production in SP-C1 tongue cancer cells. Nat Prod Commun. 2014;9(1):75-78.

[19] Xu Q, Ma J, Lei J, Duan W, Sheng L, Chen X, et al. Alpha-Mangostin suppresses the viability and epithelial-mesenchymal transition of pancreatic cancer cells by downregulating the PI3K/Akt pathway. Biomed Res Int. 2014;2014:546353.

[20] Kim MO, Lee HS, Chin YW, Moon DO, Ahn JS. Gartanin induces autophagy through JNK activation which extenuates caspase-dependent apoptosis. Oncol Rep. 2015;34(1):139-146.

[21] Seo KH, Ryu HW, Park MJ, Park KH, Kim JH, Lee MJ, et al. Mangosenone F, a furanoxanthone from *Garciana mangostana*, induces reactive oxygen species-mediated apoptosis in lung cancer cells and decreases xenograft tumor growth. Phytother Res. 2015;29(11):1753-1760.

[22] Kim M, Chin YW, Lee EJ. Alpha, gamma-mangostins induce autophagy and show synergistic effect with gemcitabine in pancreatic cancer cell lines. Biomol Ther. 2017;25(6):609-617.

[23] Luo M, Liu Q, He M, Yu Z, Pi R, Li M, et al. Gartanin induces cell cycle arrest and autophagy and suppresses migration involving PI3K/Akt/mTOR and MAPK signalling pathway in human glioma cells. J Cell Mol Med. 2017;21(1):46-57.

[24] Yang R, Li P, Li N, Zhang Q, Bai X, Wang L, et al. Xanthones from the pericarp of *Garcinia mangostana*. Molecules. 2017; 22(5):683.

[25] Aukkanimart R, Boonmars T, Sriraj P, Sripan P, Songsri J, Ratanasuwan P, et al. *In vitro* and *in vivo* inhibitory effects of alpha-mangostin on cholangiocarcinoma cells and allografts. APJCP. 2017;18(3): 707-713.

[26] Chen JJ, Long ZJ, Xu DF, Xiao RZ, Liu LL, Xu ZF, et al. Inhibition of autophagy augments the anticancer activity of alpha-mangostin in chronic myeloid leukemia cells. Leuk Lymphoma. 2014;55(3):628-638.

[27] Chitchumroonchokchai C, Thomas-Ahner JM, Li J, Riedl KM, Nontakham J, Suksumrarn S, et al. Anti-tumorigenicity of dietary alpha-mangostin in an HT-29 colon cell xenograft model and the tissue distribution of xanthones and their phase II metabolites. Mol Nutr Food Res. 2013;57 (2):203-211.

[28] Fazry S, Noordin MAM, Sanusi S, Noor MM, Aizat WM, Lazim AM, et al. Cytotoxicity and toxicity evaluation of xanthone crude extraction hypoxic human hepatocellular carcinoma and zebrafish (*Danio rerio*) embryos. Toxics. 2018;6(4):60.

[29] Wang JJ, Shi QH, Zhang W, Sanderson BJ. Anti-skin cancer properties of phenolic-rich extract from the pericarp of mangosteen (*Garcinia mangostana* Linn.). Food Chem Toxicol. 2012;50(9):3004-3013.

[30] Taokaew S, Nunkaew N, Siripong P, Phisalaphong M. Characteristics and anticancer properties of bacterial cellulose films containing ethanolic extract of mangosteen peel. J Biomater Sci Polym Ed. 2014;25(9):907-922.

[31] Priya VV, Jainu M, Mohan SK. Biochemical Evidence for the antitumor potential of *Garcinia mangostana* Linn. on diethylnitro-samine-induced hepatic carcinoma. Pharmacogn Mag. 2018;14(54):186-190.

[32] Moongkarndi P, Kosem N, Luanratana O, Jongsomboonkusol S, Pongpan N. Antipro-liferative activity of Thai medicinal plant extracts on human breast adenocarcinoma cell line. Fitoterapia. 2004;75(3-4):375-377.

[33] Nabandith V, Suzui M, Morioka T, Kaneshiro T, Kinjo T, Matsumoto K, et al. Inhibitory effects of crude alpha-mangostin, a xanthone derivative, on two different categories of colon preneoplastic lesions induced by 1, 2-dimethylhydrazine in the rat. Asian Pac J Cancer Prev. 2004;5(4): 433-438.

[34] Li G, Petiwala SM, Nonn L, Johnson JJ. Inhibition of CHOP accentuates the apoptotic effect of α-mangostin from the mangosteen fruit (*Garcinia mangostana*) in 22Rv1 prostate cancer cells. Biochem Biophys Res Commun. 2014;453(1):75-80.

[35] Li G, Petiwala SM, Pierce DR, Nonn L, Johnson JJ. Selective modulation of endoplasmic reticulum stress markers in prostate cancer cells by a standardized mangosteen fruit extract. PLoS One. 2013; 8(12):e81572.

[36] Yu L, Zhao M, Yang B, Bai W. Immunomodulatory and anticancer activities of phenolics from *Garcinia mangostana* fruit pericarp. Food Chem. 2009;116(4): 969-973

[37] Xu Z, Huang L, Chen XH, Zhu XF, Qian XJ, Feng GK, et al. Cytotoxic prenylated xanthones from the pericarps of *Garcinia mangostana*. Molecules. 2014;19(2):1820-1827.

[38] Mohamed GA, Al-Abd AM, El-Halawany AM, Abdallah HM, Ibrahim SRM. New xanthones and cytotoxic constituents from *Garcinia mangostana* fruit hulls against human hepatocellular, breast, and colorectal cancer cell lines. J Ethnopharmacol. 2017; 198:302-312.

[39] Xu XH, Liu QY, Li T, Liu JL, Chen X, Huang L, et al. Garcinone E induces apoptosis and inhibits migration and invasion in ovarian cancer cells. Sci Rep. 2017;7(1):10718.

[40] Lee YJ, Jung O, Lee J, Son J, Cho JY, Ryou C, et al. Maclurin exerts anti-cancer effects on PC3 human prostate cancer cells via activation of p38 and inhibitions of JNK, FAK, AKT, and c-Myc signaling pathways. Nutr Res. 2018;58:62-71.

[41] Fukuda M, Sakashita H, Hayashi H, Shiono J, Miyake G, Komine Y, et al. Synergism between α-mangostin and TRAIL induces apoptosis in squamous cell carcinoma of the oral cavity through the mitochondrial pathway. Oncol Rep. 2017;38(6):3439-3446.

[42] Yuan J, Wu Y, Lu G. α-Mangostin suppresses lipopolysaccharide-induced invasion by inhibiting matrix metalloproteinase-2/9 and increasing E-cadherin expression through extracellular signal-regulated kinase signaling in pancreatic cancer cells. Oncol Lett. 2013;5(6):1958-1964.

[43] Zhang C, Yu G, Shen Y. The naturally occurring xanthone α-mangostin induces ROS-mediated cytotoxicity in non-small scale lung cancer cells. Saudi J Biol Sci. 2018;25(6):1090-1095.

[44] Wudtiwai B, Pitchakarn P, Banjerdpongchai R. Alpha-mangostin, an active compound in *Garcinia mangostana*, abrogates anoikis-resistance in human hepatocellular carcinoma cells. Toxicol In Vitro. 2018;53:222-232.

[45] Nakagawa Y, Iinuma M, Naoe T, Nozawa Y, Akao Y. Characterized mechanism of alpha-mangostin-induced cell death: caspase-independent apoptosis with release of endonuclease-G from mitochondria and increased miR-143 expression in human colorectal cancer DLD-1 cells. Bioorg Med Chem. 2007;15(16):5620-5628.

[46] Kritsanawong S, Innajak S, Imoto M, Watanapokasin R. Antiproliferative and apoptosis induction of α-mangostin in T47D breast cancer cells. Int J Oncol. 2016;48(5):2155-2165.

[47] Kurose H, Shibata MA, Iinuma M, Otsuki Y. Alterations in cell cycle and induction of apoptotic cell death in breast cancer cells treated with α-mangostin extracted from mangosteen pericarp. J Biomed Biotechnol. 2012;2012:672428.

[48] Shan T, Cui XJ, Li W, Lin WR, Lu HW, Li YM, et al. α-Mangostin suppresses human gastric adenocarcinoma cells in vitro via blockade of Stat3 signaling pathway. Acta Pharmacol Sin. 2014;35(8): 1065-1073.

[49] Wang JJ, Sanderson BJ, Zhang W. Significant anti-invasive activities of α-mangostin from the mangosteen pericarp on two human skin cancer cell lines. Anticancer Res. 2012;32(9):3805-3816.

[50] Lee HN, Jang HY, Kim HJ, Shin SA, Choo GS, Park YS, et al. Antitumor and apoptosis-inducing effects of α-mangostin extracted from the pericarp of the mangosteen fruit (*Garcinia mangostana* L.)in YD-15 tongue mucoepidermoid carcinoma cells. Int J Mol Med. 2016;37(4):939-948.

[51] Li P, Tian W, Ma X. Alpha-mangostin inhibits intracellular fatty acid synthase and induces apoptosis in breast cancer cells. Mol Cancer. 2014;13:138.

[52] Scolamiero G, Pazzini C, Bonafè F, Guarnieri C, Muscari C. Effects of α-mangostin on viability, growth and cohesion of multicellular spheroids derived from human breast cancer cell lines. Int J Med Sci. 2018;15(1):23-30.

[53] Matsumoto K, Akao Y, Yi H, Ohguchi K, Ito T, Tanaka T, et al. Preferential target is mitochondria in α-mangostin-induced apoptosis in human leukemia HL60 cells. Bioorg Med Chem. 2004;12(22):5799-5806.

[54] Hung SH, Shen KH, Wu CH, Liu CL, Shih YW. Alpha-mangostin suppresses PC-3 human prostate carcinoma cell metastasis by inhibiting matrix metalloproteinase-2/9 and urokinase-plasminogen expression through the JNK signaling pathway. J Agric Food Chem. 2009;57(4):1291-1298.

[55] Wang F, Ma H, Liu Z, Huang W, Xu X, Zhang X. α-Mangostin inhibits DMBA/TPA-induced skin cancer through inhibiting inflammation and promoting autophagy and apoptosis by regulating PI3K/Akt/mTOR signaling pathway in mice. Biomed Pharmacother. 2017;92:672-680.

[56] Cai N, Xie SJ, Qiu DB, Jia CC, Du C, Liu W, et al. Potential effects of α-mangostin in the prevention and treatment of hepatocellular carcinoma. J Func Foods. 2016; 26:309-318.

[57] Hafeez BB, Mustafa A, Fischer JW, Singh A, Zhong W, Shekhani MO, et al. α-Mangostin: a dietary antioxidant derived from the pericarp of *Garcinia mangostana*

L. inhibits pancreatic tumor growth in xenograft mouse model. Antioxid Redox Signal. 2014;21(5):682-699.

[58] Johnson JJ, Petiwala SM, Syed DN, Rasmussen JT, Adhami VM, Siddiqui IA, et al. α-Mangostin, a xanthone from mangosteen fruit, promotes cell cycle arrest in prostate cancer and decreases xenograft tumor growth. Carcinogenesis. 2012;33(2):413-419.

[59] Fei X, Jo M, Lee B, Han SB, Lee K, Jung JK, et al. Synthesis of xanthone derivatives based on α-mangostin and their biological evaluation for anti-cancer agents. Bioorg Med Chem Lett. 2014;24(9):2062-2065.

[60] Mizushina Y, Kuriyama I, Nakahara T, Kawashima Y, Yoshida H. Inhibitory effects of α-mangostin on mammalian DNA polymerase, topoisomerase, and human cancer cell proliferation. Food Chem Toxicol. 2013;59:793-800.

[61] Chang HF, Yang LL. Gamma-mangostin, a micronutrient of mangosteen fruit, induces apoptosis in human colon cancer cells. Molecules. 2012;17(7):8010-8021.