Bioactive Xanthones from *Garcinia mangostana*

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Abstract

Garcinia mangostana Linn. (mangosteen) is a tropical plant, widely cultivated in Asia including Malaysia, Thailand, Indonesia and India. The pericarp of *G. mangostana* has been used traditionally to treat skin infections, wounds, dysentery, urinary disorders, cystitis and gonorrhoea. Claiming for its benefits in promoting health, mangosteen fruit juice is listed as one of the bestselling supplements worldwide. There are over 60 xanthones together with benzophenones and flavonoids that have been identified in the aerial parts of *G. mangostana*. Among the bioactives, xanthones are known to exhibit intriguing pharmacological activities including anti-cancer, anti-inflammation, anti-viral, anti-diabetic and anti-neurodegenerative properties. These medicinal effects are explored in greater detail to elucidate their potential uses as a therapeutic agent. This chapter presents an updated information on *G. mangostana* derivatives and their pharmacological effects and mechanisms of action against chronic diseases.

Keywords

G. mangostana · Bioactives · Xanthones · Pharmacological effects

13.1 Introduction

Garcinia mangostana is a tropical plant belonging to the family, *Clusiaceae*. It is believed that *G. mangostana* is an allotetraploid derived from *G. hombroniana* Pierre and *G. malaccensis* T. Anderson (Richards 1990; Lim 2012). The *G. mangostana* trees can grow up to 25 m in height. The leaves are dark green with glossy texture on the surface and yellowish beneath (Morton 1987) (Fig. 13.1). As tropical climate is required for the growth, *G. mangostana* is widely cultivated in the tropical countries of Southeast Asia (as shown in Fig. 13.2). Mangosteen, the fruit of *G. mangostana* is also known as the ‘queen of the fruits’. This edible fruit consists of

Fig. 13.1 *G. mangostana* leaf and unripe fruit (left), whole tree (middle) and fruit (right)

soft and juicy white internal pulp with a dark purple rind, and has a sweet taste and pleasant aroma.

Different parts of the *G. mangostana* tree have been used traditionally for various medicinal purposes. For example, the decoction of the *G. mangostana* pericarp was used as folk medicines to treat a wide array of diseases, such as diarrhoea, skin diseases, inflammation, cholera, wounds, urinary disorder and amoebic dysentery (Garnett and Sturton 1932; Chopra et al. 1956; Mahabusarakam and Wiriyachitra 1987; Pierce 2003). In countries, such as the Philippines and Malaysia, the leaves and bark decoction have been traditionally used as a febrifuge to treat fever, thrush, diarrhoea, dysentery and urinary disorder. The root decoction was consumed by women to regulate the menstrual cycle and ease menstrual pain (Lim 2012). Meanwhile, the bark and young leaves were employed to combat diarrhoea, dysentery and genital-urinary tract infections in India (Burkill 1966; Perry 1980; Lim 2012). In Indonesia, the mangosteen leaves were used for the wound recovery, especially after circumcision (Lim 2012).

To date, six clinical studies have been carried out to investigate the health potential of the mangosteen extract, including atrial fibrillation, chronic periodontitis and weight loss (http://www.clinicaltrials.gov). It is worth noting that no clinical study has been conducted on the mangosteen compounds. This chapter provides an update of the secondary metabolites of *G. mangostana* and the pharmacological effects of these bioactive compounds against emerging diseases including cancer, diabetes, influenza, neurodegenerative disorders, tuberculosis, as well as their anti-inflammatory potential.

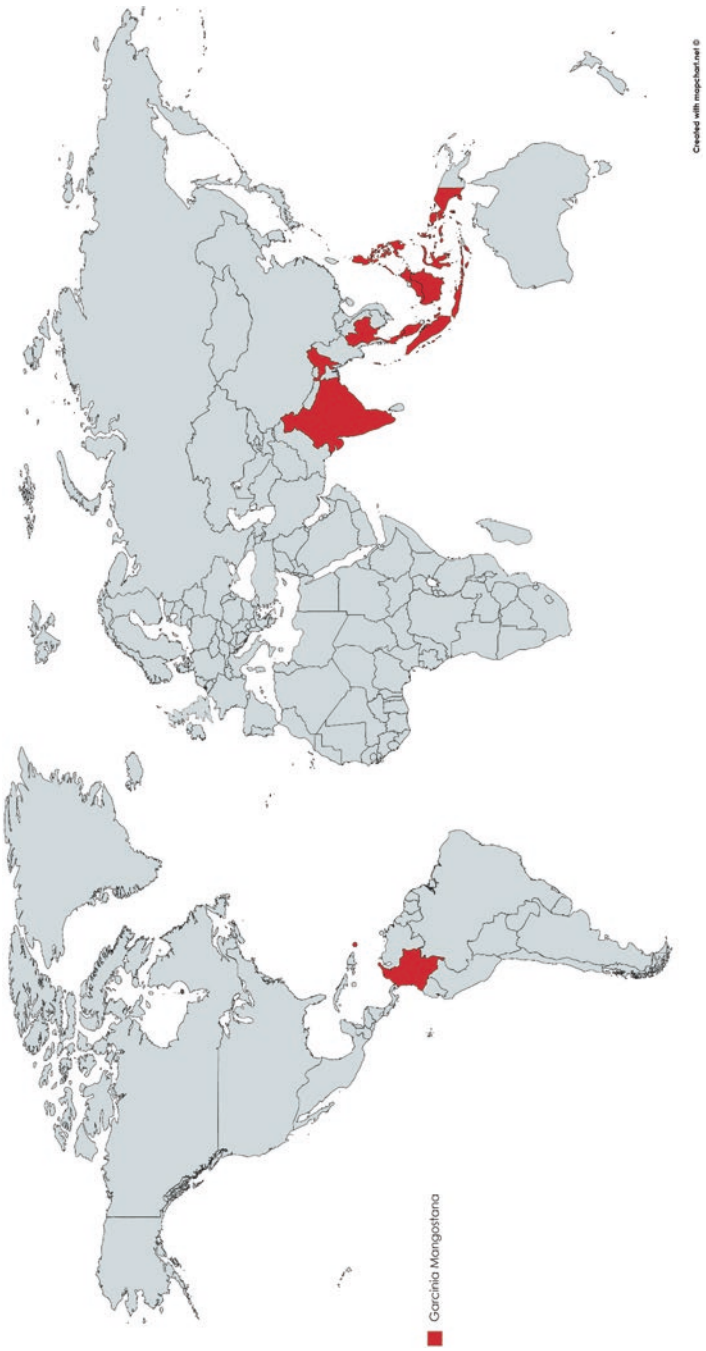

Fig. 13.2 The geographical distribution of *G. mangostana*

13.2 Extraction and Isolation of Xanthones from *G. mangostana*

Medicinal plants serve as a valuable reservoir of novel molecules with therapeutic potential as more than half of the clinically approved chemical entities in recent decades are derived from plants (Atanasov et al. 2015). Nevertheless, it is estimated that only a small portion of the molecules have been investigated phytochemically and pharmacologically for their therapeutic potential (Hostettmann and Wolfender 2000). The bioactive compounds derived from plants are classified into different classes based on their chemical structures, functions and biosynthesis origin. The major classes of phytocompounds include terpenes, flavonoids, saponins, alkaloids, coumarins and phenolic compounds.

G. mangostana is rich in phenolic compounds including xanthones, flavonoids and benzophenones. The majority of the compounds found in *G. mangostana* are prenylated and oxygenated xanthones. More than 60 naturally occurring xanthones have been purified from different parts of the plant including fruit hull, fruit, leaves and bark. Various conventional means have been used to retrieve secondary metabolites from a complex matrix of plant material, including maceration and soxhlet with some shortcomings, such as generation of hazardous organic wastes and degradation of heat labile compounds. Hence, cost-effective and efficient means are imperatively in need to replace the conventional extraction methods. Microwave-assisted extraction, enzyme-assisted extraction and supercritical fluid extraction are among the greener technologies with a shorter extraction time, and use of minimum or no organic solvent. Efficient and environment-friendly extraction methods have been applied in the extraction of compounds of *G. mangostana*, mainly α-mangostin. For example, Ghasemzadeh and colleagues demonstrated that the recovery of α-mangostin concentration in fruit hull by microwave-assisted extraction was 72.40% (v/v), with the extraction time of 3.16 min and microwave power of 189.2 W (Ghasemzadeh et al. 2018). The amount of α-mangostin in mangosteen pericarp was found to be 121.01 mg/g dry matter. Supercritical fluid extraction is another environmentally benign technology used for the extraction of α-mangostin from the fruit hull of mangosteen. The optimum conditions for the recovery of α-mangostin (yield 0.2% w/w) were 100 bar, 140 °C, extraction time of 1 h (Chhouk et al. 2016).

13.3 Biological Activities

Plants have been documented for their medical uses in treating illnesses in humankind. These medicinal plants have played significant and beneficial roles in drug discovery as they produce novel pharmacologically active compounds with unique and diverse structures (Khazir et al. 2014; de Oliveira Júnior et al. 2018). Several medicinal values of the extracts and compounds derived from *G. mangostana* have been determined, including anti-cancer, anti-inflammatory, anti-diabetic, anti-influenza and anti-neurodegenerative properties.

13.3.1 Anti-cancer Activity

Plant-derived secondary metabolites are the promising source of chemotherapeutic drugs (Khazir et al. 2014). These compounds are now being used as cancer therapeutics due to their ease of availability and cost-effectiveness (Kuppusamy et al. 2013). Almost half of the anti-cancer drugs are natural product-based compounds (Newman and Cragg 2015). The examples of plant-derived chemotherapeutic agents available for clinical use are vinca alkaloids (vinblastine and vincristine) from *Catharanthus roseus* (Blaskó and Cordell 1990), paclitaxel from the bark of *Taxus brevifolia* (Rowinsky and Donehower 1995) and camptothecin from *Camptotheca acuminata* (Wall et al. 1966). Many plants are still actively investigated for their potential for cancer treatment.

To date, more than seven xanthones including α-mangostin, β-mangostin, γ-mangostin, garcixanthone B, garcixanthone C, mangostinone, garcinone E and 2-isoprenyl-1,4-dihydroxy-3-methoxyxanthone have been isolated from different parts of *G. mangostana*, and studied extensively for their anti-cancer activities. Several research findings have revealed that these xanthones possess a broad spectrum of anti-cancer properties in a variety of cancers, such as breast cancer, colorectal cancer, leukaemia, gastric cancer, pancreatic cancer and liver cancer. Table 13.1 summarises some of the recent in vitro anti-cancer properties of the xanthones with their respective mechanisms of action.

Most of the anti-cancer effects of xanthones are contributed by their ability to inhibit cell proliferation, induce apoptosis and promote cell cycle arrest. Induction of apoptosis serves as one of the therapeutic strategies in cancer treatment (Igney and Krammer 2002). Apoptosis is described as programmed cell death, which maintains the physiological balance between cell death and survival in a multicellular organism. It involves complex molecular signalling mechanisms which lead to the changes in the nuclear morphology (including pyknosis and karyorrhexis), the formation of apoptotic bodies, blebbing of the plasma membrane and cell shrinkage (Kroemer et al. 2009). Apoptosis is the preferred mechanism in cancer treatment as compared to other types of cell death (necrosis and autophagy) as it possesses the advantage of the elimination of cells without causing inflammation (Festjens et al. 2006).

The molecular targets modulated by the xanthones on different signalling pathways for the anti-cancer effect are summarised in Fig. 13.3. Among the xanthones, α- and γ-mangostin are particularly highly cytotoxic by exerting apoptotic effect through intrinsic or mitochondrial pathway through up-regulation of the expression of pro-apoptotic Bcl-2-associated X protein (BAX) and activation of cysteine-dependent aspartate-directed proteases (caspase) such as caspase-3 and -9 (Krajarng et al. 2011; Chen et al. 2014; Kritsanawong et al. 2016). These xanthones also induced apoptosis via extrinsic or death receptor pathway with the activation of caspase-8, which further activated the cleavage of BH3 interacting domain death agonist (Bid) (Watanapokasin et al. 2011). Cancerous cell proliferation was inhibited through mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and human epidermal growth factor receptor 2 (HER2) signalling

Table 13.1 Pharmacological effect and mechanisms of action of compounds derived from *G. mangostana*

Compound	Type of cell	Pharmacological effect	Mechanisms of action	References
Bone cancer				
α-Mangostin	SW 1353	IC_{50} value of 10 μg/mL (24 h)	Induction of apoptosis through intrinsic pathway Inhibition of cell proliferation through MAPK and ERK pathway	Krajarng et al. (2011)
Breast cancer				
α-Mangostin	BT 474	IC_{50} values of 2.91 μM (24 h), 2.28 μM (48 h) and 3.15 μM (72 h)	Cell cycle arrest at G1 phase	Ittiudomrak et al. (2018)
	T47D	IC_{50} value of 7.5 μM (24 h)	Induction of apoptosis through intrinsic pathway with up-regulation of activated caspase-9 and Bax/Bcl-2 ratio	Kritsanawong et al. (2016)
	COLO205	IC_{50} value of 9.74 μM (24 h)	Induction of apoptosis through extrinsic pathway with activation of caspase-8 and t-Bid	Watanapokasin et al. (2011)
	MCF-7	IC_{50} values of 3.57 μM (24 h) and 2.74 μM (48 h)	Induction of apoptosis with up-regulation of cleaved PARP	Li et al. (2014)
	MDA-MB-231	IC_{50} values of 3.35 μM (24 h) and 2.26 μM (48 h)	–	Li et al. (2014)
γ-Mangostin	MCF-7	IC_{50} value of 5.27 μM (24 h)		
Garcixanthones B		IC_{50} value of 4.27 μM (48 h)		Xu et al. (2014)
Garcixanthones C		IC_{50} value of 3.081 μM (48 h)		Ibrahim et al. (2018a, b)

(continued)

Table 13.1 (continued)

Compound	Type of cell	Pharmacological effect	Mechanisms of action	References
Colorectal cancer				
α-Mangostin γ-Mangostin	HCT116 and SW480	IC_{50} value of 15 μM (72 h)	Down-regulation of the expression of beta-catenin protein	Yoo et al. (2011)
α-Mangostin	DLD-1	IC_{50} value of 7.5 μM (24 h)	Cell cycle arrest at G1 phase; induction of apoptosis through intrinsic pathway	Akao et al. (2008)
β-Mangostin	DLD-1	IC_{50} value of 8.1 μM (24 h)	Cell cycle arrest at G1 phase	
γ-Mangostin	DLD-1	IC_{50} value of 7.1 μM (24 h)	Cell cycle arrest at S phase	
γ-Mangostin	HT-29	IC_{50} values of 51.87 μM (24 h), 69.15 μM (48 h) and 85.38 μM (72 h)	Induction of apoptosis via induction of intracellular ROS	Chang and Yang (2012)
Leukaemia				
α-Mangostin	K562	IC_{50} values of 16.35 μM (24 h), 13.8 μM (48 h) and 7.71 μM (72 h)	Cell cycle arrest at G1 phase with significant up-regulation of p21; Induction of apoptosis by up-regulation of cleaved caspase-3 and PARP	Chen et al. (2014)
	KBM5	IC_{50} values of 10.26 μM (24 h), 8.2 μM (48 h) and 6.13 μM (72 h)		
	KBM5-T315I	IC_{50} values of 10.57 μM (24 h), 7.08 μM (48 h) and 5.87 μM (72 h)		
	K-562	IC_{50} value of 7.21 μg/mL (24 h)	–	Novilla et al. (2016)
	Lymphocyte (human donor)	IC_{50} value of 25 μg/mL (24 h)		
	HL-60	IC_{50} value of 1.12 μg/mL (24 h)		
	HL-60	IC_{50} value of 6.8 μM (72 h)	Induction of apoptosis via activation of caspase-3	Matsumoto et al. (2003)

(continued)

Table 13.1 (continued)

Compound	Type of cell	Pharmacological effect	Mechanisms of action	References
β-Mangostin	HL-60	IC_{50} value of 7.6 μM (72 h)	–	Matsumoto et al. (2003)
γ-Mangostin	HL-60	IC_{50} value of 6.1 μM (72 h)		
Mangostinone	HL-60	IC_{50} value of 19 μM (72 h)		
Garcinone E	HL-60	IC_{50} value of 15 μM (72 h)		
2-Isoprenyl-1,4-dihydroxy-3-methoxyxanthone	HL-60	IC_{50} value of 23.6 μM (72 h)		
Stomach cancer				
α-Mangostin	BGC-823 and SGC-7901	–	Induction of apoptosis via inactivation of STAT3 signalling pathway	Shan et al. (2014)
Pancreatic cancer				
α-Mangostin	MIA PaCa-2	IC_{50} values of 8.4 μM (48 h) and 8.5 μM (72 h)	–	Kim et al. (2017)
	PANC-1	IC_{50} values of 15 μM (48 h) and 11.7 μM (72 h)	Induction of apoptosis with up-regulation of caspase-3, cleaved PARP and Bax	
	MIA PaCa-2	IC_{50} values of 15 μM (48 h) and 11.7 μM (72 h)		
γ-Mangostin	PANC-1	IC_{50} values of 25 μM (48 h) and 10.2 μM (72 h)		
Brain tumour				
γ-Mangostin	U87 MG	IC_{50} value of 74.14 μM (24 h)	–	Chang et al. (2010)
	GBM 8401	IC_{50} value of 64.67 μM (24 h)	Induction of apoptosis via production of ROS	Chang et al. (2010)

(continued)

Table 13.1 (continued)

Compound	Type of cell	Pharmacological effect	Mechanisms of action	References
Nasopharyngeal cancer				
γ-Mangostin	CNE1	IC_{50} value of 1.85 μM (24 h)	–	Xu et al. (2014)
	CNE2	IC_{50} value of 1.81 μM (24 h)		
	SUNE1	IC_{50} value of 4.41 μM (24 h)		
	HONE1	IC_{50} value of 2.78 μM (24 h)		
Lung cancer				
γ –Mangostin	A549	IC_{50} value of 3.79 μM (24 h)	–	Xu et al. (2014)
	GLC82	IC_{50} value of 3.46 μM (24 h)		Xu et al. (2014)
Garcixanthones B	A549	IC_{50} value of 2.65 μM (48 h)	–	Ibrahim et al. (2018a, b)
Garcixanthones C	A549	IC_{50} value of 3.91 μM (48 h)		

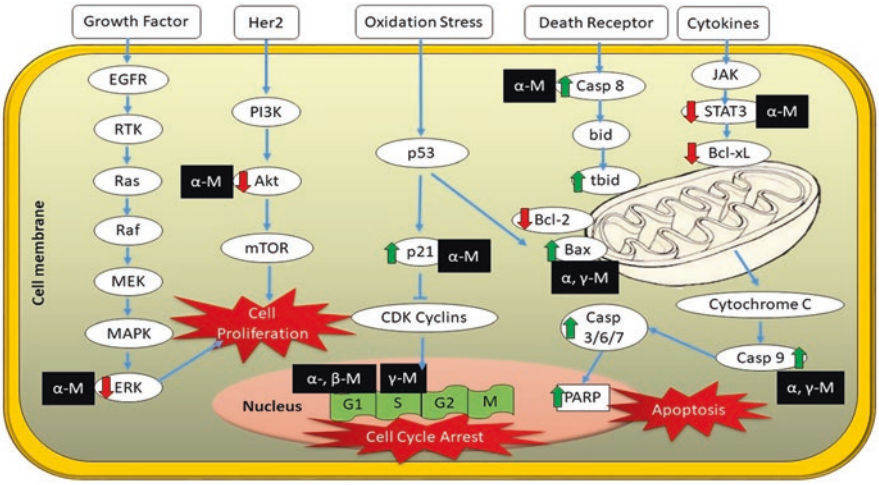

Fig. 13.3 Detailed mechanism of action and molecular targets modulated by the xanthones (α-, β- and γ-mangostin)

pathways by down-regulation of total and phosphorylated ERK1/2 and serine/threonine-protein kinase (Akt) after treatment with α-mangostin (Krajarng et al. 2011). Cell cycle arrest at the G_1 phase and S phase was induced by α- and γ-mangostin, respectively, by modulation of cyclin-dependent kinases (CDKs) and activation of p21 following reactive oxidative stress (ROS) (Akao et al. 2008; Ittiudomrak et al. 2018). From the literature, as most of the promising activities are mainly attributed

to α-mangostin, it is claimed that α-mangostin may act as a pleiotropic agent that targets multiple signalling pathways for its anti-cancer properties.

13.3.1.1 Against Lung Cancer

Lung cancer represents a serious health problem due to its high incidence with 2.094 million new cases diagnosed (about 11.6% of all cancers) and remains as the first cancer killer with 1.8 million deaths reported (approximately 18.4% of total cancer deaths) (Bray et al. 2018). Even with the advancement in the healthcare technology, the mortality and recurrence rate of this disease is still high, therefore urging the search for more efficient chemotherapeutic agents that would increase the survival and reduce the mortality rate of patients.

Zhang and colleagues isolated three xanthones (garcimangosxanthone A-C) to determine their cytotoxic effect against lung cancer cells. Garcimangosxanthone A and B exhibited promising in vitro cytotoxic assay against human alveolar basal epithelial cancerous cell A549 and human pulmonary adenocarcinoma cell LAC with half maximal inhibitory concentration (IC_{50}) values ranging from 5.7 to 25 μM after 72-h treatment (Zhang et al. 2010). Ibrahim and colleagues have demonstrated that garcixanthones B and C, the new xanthones extracted from the fruit pericarps, exhibited cytotoxic effects against human lung cancer cell A549 with IC_{50} values of 2.65 μM and 3.91 μM, respectively (Ibrahim et al. 2018a, b). Even though these xanthones have proven to exhibit high cytotoxicity against lung cancer cells, no study has been carried out to investigate the mechanism underlying the efficacy.

13.3.1.2 Against Breast Cancer

Breast cancer, the malignant tumour that forms in breast tissue, is the most common cancer diagnosed in women worldwide with an estimated 2.1 million new cases, representing 11.6% of total cancer diagnosed in 2018. It is the leading cause of death among women, with an estimated 0.7 million deaths, representing 6.6% of all cancer deaths (Bray et al. 2018). A number of studies proved that the xanthones, specifically α-mangostin, hold a great potential as the anti-breast cancer agent. It showed significant cytotoxicity against breast cancer cells with different molecular characteristics such as human breast ductal carcinoma BT474, oestrogen receptor (ER)-positive human breast carcinoma T47D, ER-positive human breast adenocarcinoma MCF-7 and ER-negative MDA-MB-231 cell lines with IC_{50} values less than 10 μM (Akao et al. 2008; Watanapokasin et al. 2011; Li et al. 2014; Ittiudomrak et al. 2018). Most of the studies have concluded that α-mangostin exerted its cytotoxicity by the induction of apoptosis through both intrinsic and extrinsic pathways and cell cycle arrest at the G_1 phase. Apart from α-mangostin, Xu et al. (2014) and Ibrahim et al. (2018a, b) demonstrated that γ-mangostin, garcixanthone B and C exhibited cytotoxicity against MCF-7 with IC_{50} values of 5.27, 4.27 and 3.08 μM, respectively.

Given the promising in vitro results, studies have been carried out to unveil the potential of xanthones in the in vivo breast cancer animal model. Shibata et al. (2011) demonstrated that oral administration of 20 mg/kg of α-mangostin has significantly increased the survival and suppressed the tumour growth of mouse

mammary BJMC3879luc2 model. This study showed that α-mangostin could be a potential anti-metastatic agent in which it significantly reduced the lymph node metastasis in the animal model. Another study carried out by Doi et al. (2009) revealed the potential of panaxanthone (consisting of 80% of α-mangostin and 20% of γ-mangostin) as an anti-metastatic agent against breast cancer with prominent suppression of the lung metastases in the BJMC3879 mouse model.

13.3.1.3 Against Colorectal Cancer

Colorectal cancer is the third most common cancer, with 1.8 million new cases being diagnosed worldwide (approximately 10.2% of the new cases reported). It is the second most common cause of cancer death after lung cancer with an estimated of 0.88 million of deaths reported (approximately 9.2% of all cancer deaths) (Bray et al. 2018). As the colorectal cancer is a slow progression disease (takes approximately 10–15 years to become invasive cancer), early diagnosis, screening and prevention are the keys to enhance the survival rate of the patients. With the limitations of screening tests and poor prognosis, research has been focused on chemoprevention properties to reduce the mortality rate (Yoo et al. 2011).

Yoo et al. (2011) revealed that the xanthones, specifically α- and γ-mangostin, could be potential chemoprotective agents for colorectal cancer by inhibiting the Wnt/β-catenin signalling pathway, a crucial part in the cancer development. The chemopreventive properties of α-mangostin are also proven by Akao et al. (2008), showing that dietary administration of α-mangostin (up to 0.05%) has significantly inhibited the development of aberrant crypt foci in the 1,2-dimethylhydrazine-induced rat model.

Apart from chemopreventive properties, some studies revealed the potency of xanthones as chemotherapeutic agents. Mangosteen-derived xanthones showed in vitro anti-cancer properties against human colorectal adenocarcinoma COLO 205 cell line by inhibition of cancerous cell proliferation and induction of cell death via apoptosis by activation of the caspase cascade. In vivo analysis using the COLO 205 tumour mouse model showed that the growth of tumours was repressed upon intra-tumoural administration of mangosteen xanthones at relatively low doses (0.25 mg per tumour).

13.3.1.4 Against Leukaemia

Leukaemia, a cancer of blood cells caused by abnormal proliferation of non-functional cells in the bone marrow, has been on the rise with 437,033 new cases reported with estimated 309,006 cancer deaths in 2018 (Bray et al. 2018). With the high mortality rate and relapsed upon treatment discontinuation, the search for an effective chemotherapeutic agent for leukaemia is required. Studies revealed that α-mangostin could be a potential anti-cancer agent for leukaemia as it selectively inhibited the proliferation and induction of apoptosis in human leukaemic cells including K562, KBM5, KBM5-T315I, HL60 and K-562 with minimal toxicity towards normal lymphocyte (Chen et al. 2014; Novilla et al. 2016). The α-mangostin induced apoptosis through up-regulation of cleaved caspase-3 and PARP and arrested cell cycle at G_1 phase with significant up-regulation of p21 (Chen et al.

2014). Other xanthones such as β-mangostin, γ-mangostin, mangostinone, garcinone E and 2-isoprenyl-1,4-dihydroxy-3-methoxyxanthone also exhibited cytotoxic effects towards HL-60 leukaemia cells with the IC_{50} values of 7.6, 6.1, 19, 15 and 23.6 μM, respectively, after 72-h treatment (Matsumoto et al. 2003).

13.3.1.5 Against Skin Cancer

Skin cancer, specifically malignant melanoma, is one of the major health problems with 287,723 cases reported and an estimated 60,712 deaths in 2018 (Bray et al. 2018). The cytotoxic effect of α-mangostin, γ-mangostin and 8-deoxygartanin was investigated on the human melanoma SK-MEL-28 cell line. The study revealed that γ-mangostin and 8-deoxygartanin at the concentration of 5 μg/mL increased cell cycle arrest at the G1 phase, while α-mangostin at a concentration of 7.5 μg/mL had the highest percentage of apoptotic cells (induced 59.6% early apoptosis). Also, α-mangostin induced apoptosis in SK-MEL-28 cell line via caspase activation (25-fold increase in caspase-3) and disruption of mitochondrial membrane potential (Wang et al. 2011).

13.3.2 Anti-inflammatory Activity

Pro-inflammatory cytokines play an essential role in inflammatory diseases. The overproduction of pro-inflammatory cytokines including tumour necrosis factor (TNF-α), interleukin-1-beta (IL-1β), interleukin-6 (IL-6) and interferon-gamma (IFN-γ) is associated with a spectrum of inflammatory-related diseases including cancer, neurodegenerative disease, atherosclerosis and diabetes (Kremer et al. 1996; Forstermann and Sessa 2012). Several studies have focused on the role of xanthones in *G. mangostana* in modulating inflammatory markers in rat glioma C6 cells, RAW264.5 macrophage and bone marrow mast cells (Nakatani et al. 2002; Tewtrakul et al. 2009; Cho et al. 2014).

The xanthones such as α-, β-, γ-mangostin significantly inhibited nitric oxide (NO) and prostaglandin E2 production in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophage cells. These xanthones were shown to exhibit anti-inflammatory activity by inhibition of carrageenan-induced paw oedema in a dose-dependent manner in mice (Chen et al. 2008; Syam et al., 2014) (Chen et al. 2014; Syam et al. 2014). Another study revealed that 1,3,6,7-tetrahydroxy-8-prenylxanthone attenuated inflammatory responses in RAW264.7 macrophage cells and TNF-α mediated inflammation in 3T3-L1 adipocytes by alleviating the activation of MAPKs and nuclear factor kappa B (NF-kB) pathway and promoting the expression of sirtuin 3 (Li et al. 2018). Cho and colleagues showed that mangostenone F inhibited the production of NO, inducible nitric oxide synthase (iNOS), pro-inflammatory cytokines and suppressed NF-kB and MAPK pathways in LPS-stimulated RAW264.7 macrophage cells (Cho et al. 2014). Liu and the team revealed that a dimeric xanthone, garcinoxanthones B, inhibited NO production and suppressed NO synthase expression in RAW264.7 macrophage cells (Liu et al. 2016).

Several studies have demonstrated the potential of mangosteen compounds against inflammatory arthritis. For instance, isogarcinol reduced the mRNA expression of cyclooxygenase-2 (COX-2), the level of nuclear factor of activated T cells (NFAT) and IL-2 expression through inhibition of NF-kB pathway in RAW264.7 macrophage cells and reduced ear oedema in collagen-induced arthritis mice (Fu et al. 2014). A study showed that α-mangostin might have a potential therapeutic value for osteoarthritis by inhibition of IL-1β-induced inflammatory cytokines in rat chondrocytes (Pan et al. 2017). Chan and colleagues revealed that α- mangostin and γ-mangostin alleviated mast cell-mediated allergic inflammatory responses by inhibition of IL-6, prostaglandin D2 (PGD2) and leukotriene C4 (LTC4) production and degranulation in phorbol myristate acetate (PMA) and A23187 induced bone marrow-derived mast cells (Hee-Sung et al. 2012). Taken together, the studies indicated that mangosteen derivatives possess the ability to modulate inflammatory markers in different experimental models.

13.3.3 Anti-influenza Activity

Influenza is an infectious respiratory disease caused by influenza viruses type A, B, C and D. The common symptoms associated with influenza include cough, fever, sore throat, runny nose, muscle pain, headache and fatigue (Krammer et al. 2018). Current treatment options for influenza are vaccines and anti-viral agents. Neuraminidase, a key enzyme involved in viral replication, spread, and pathogenesis, is considered as one of the promising targets for combating influenza (Grienke et al. 2012). Clinically used anti-viral agents, such as zanamivir, peramivir and oseltamivir, are neuraminidase inhibitors. Due to limitations, such as drug availability and drug resistance, there is an urgent need for the identification of next-generation neuraminidase inhibitor.

Twelve xanthones from the fruit hull of *G. mangostana* were screened for their in vitro inhibitory potential against bacteria neuraminidase inhibitory activity. Among the xanthones, smeathxanthone A was identified as the most potent nanomolar inhibitor with an IC_{50} value of 270 nM. Kinetic inhibition study revealed that smeathxanthone A was a competitive inhibitor with a *K*i value of 0.15 μM (Ryu et al. 2010).

13.3.4 Anti-tuberculosis Activity

Tuberculosis (TB) is a major health problem worldwide, particularly in low- and middle-income countries in Asia and Africa. It is one of the top 10 causes of death worldwide, with an estimated 1.3 million deaths in 2017 (https://www.who.int/tb/publications/global_report/en/). TB is an airborne disease caused by *Mycobacterium tuberculosis* that affects the lungs. The common symptoms of TB are severe coughing, fever, and chest pains (Fogel 2015). Rifampicin, pyrazinamide and isoniazid are the first-line drug regimen currently used for the treatment of TB. However,

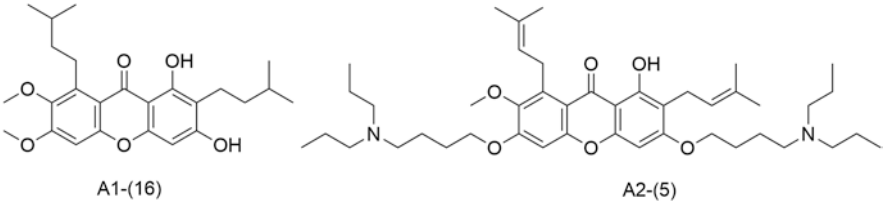

Fig. 13.4 Derivatives of α-mangostin

there is a need to discover and develop a more effective anti-TB drug in view of the *M. tuberculosis* resistance to these current anti-TB drugs. α-mangostin derivatives were evaluated for their antimicrobial potential against *Mycobacterium tuberculosis* H37Ra. Among the derivatives, A-1 (16) (Fig. 13.4) was potently active against *Mycobacterium tuberculosis* with the minimal inhibitory concentration (MIC) value of 0.78 μg/mL (Sudta et al. 2013). A recent study by Koh and colleagues demonstrated that amphiphilic xanthone (A2-(5)) (Fig. 13.4) was active against both *M. bovis* and *M. smegmatis* and able to disrupt the inner microbial membrane and led to ATP depletion. Also, A2-(5) possesses low cytotoxicity, superior metabolic stability and moderate activity against cytochrome p450 enzyme (Koh et al. 2016).

13.3.5 Antidiabetic Activity

Diabetes is a chronic disease associated with high levels of blood glucose in the blood system due to inability or absence of insulin (American Diabetes Association (ADA) 2014). It is implicated with long-term dysfunction and failure of different organs such as eyes, kidneys, nerves, heart, and blood vessels. Several studies have focused on anti-diabetic properties and the mechanisms of action of the extracts and compounds isolated from *G. mangostana*. Loo and Huang (2007) revealed that water fraction of *G. mangostana* containing polyphenols has inhibitory activity with an IC_{50} value of 5.4 μg/mL against alpha-amylase. A study by Hyung and colleagues demonstrated that γ-mangostin (IC_{50} value of 1.5 μM) was potently inhibited α-glucosidase which is an essential enzyme that reduces postprandial hyperglycaemia by suppressing the absorption of glucose (Hyung et al. 2011).

The α-mangostin has proven to enhance insulin production by activating insulin signalling pathway including insulin resistance (IR), pancreatic duodenal homeobox 1 (PDX-1), phosphoinositide 3-kinase (PI3K), Akt and extracellular signal-regulated kinase (ERK) and protected pancreatic beta cells against streptozotocin (STZ)-induced apoptotic damage (Lee et al. 2018). Another study showed that α-mangostin significantly attenuated the high-glucose-induced apoptosis, resulting in up-regulated cleaved caspase-3, Bax, ceramide and enhancement of acid sphingomyelinase activity (Luo and Lei 2017). Preclinical studies demonstrated that ethanol extract was able to reduce postprandial blood glucose levels in STZ-induced hypoglycaemia rats (Hyung et al. 2011). More clinical studies are needed to affirm the potential of α-mangostin as a potential nutraceutical.

13.3.6 Antineurodegenerative Activity

Neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis, Huntington's disease, amyotrophic lateral sclerosis, prion diseases and frontotemporal dementia, are the primary health problem worldwide. The pathophysiology of neurodegenerative diseases includes memory and cognitive impairments and difficulty to move, speak and breathe. However, despite extensive efforts to unravel mechanisms of disease and discovery of therapeutic agents, neurodegenerative diseases remain incurable and limited treatment options available. Up to date, AD patients rely on cholinesterase inhibitors as a symptomatic treatment since the discovery of disease-modifying drugs to treat Alzheimer's disease remains unmet. The α,γ-mangostin and garcinone C were reported active against acetyl and butyrylcholinesterase enzymes in vitro (Khaw et al. 2014). In vivo study using C57BL/6J mouse model postulated that xanthones rich extract of *G. mangostana* significantly attenuated cognitive impairment, increased brain-derived neurotrophic factor (BDNF) level and decreased p-tau in old B6 mice. On the other hand, the extract was proven to be neuroprotective, anti-oxidative, and anti-inflammatory with reduction of the Aβ deposition and p-tau (S202/S262) levels in the hippocampus of triple transgenic Alzheimer's (3 × Tg-AD) mice (Huang et al. 2014).

Mounting evidence suggested that generation of the neurotoxic Aβ peptide from sequential amyloid precursor protein (APP, a transmembrane protein for neuronal development, neurite outgrowth, and axonal transport) is related to the development of AD (O'Brien and Wong 2011). Aβ peptide, which consists of 38–43 amino acid peptide, was formed after sequential cleavages of APP by β-secretase (BACE 1) and γ-secretase (Chow et al. 2010). Recent findings suggested that both α- and β-mangostin inhibited β-secretase and γ-secretase activity in vitro (Zhao et al. 2017; Lee et al. 2019). Furthermore, α-mangostin was able to attenuate neurotoxicity induced by aβ oligomers. It is shown to inhibit and dissociate aβ aggregation in primary rat cortical neurons (Wang et al. 2012a, b). In a passive avoidance test, γ-mangostin at a dose up to 30 mg/kg significantly improved scopolamine-induced memory impairment in mice (Lee et al. 2019).

Microglia plays an essential role in the progression of neurodegenerative diseases by damaging, injuring and killing neurons (Hickman et al. 2018). A study by Hu and colleagues revealed that α-mangostin at nanomolar concentration attenuated the levels of pro-inflammatory cytokines and NO and reduced ROS production in α-synuclein-stimulated primary microglia cells (Hu et al. 2016). Nava Catorce and colleagues reported that α-mangostin attenuated the levels of IL-6, COX-2 and 18 kDa translocator protein (TSPO) in a peripheral LPS-induced neuroinflammation animal model. Collectively, α- and γ-mangostins are promising candidates to be explored as a therapeutic agent for AD.

13.4 Conclusions and Future Prospects

Over the last 20 years, there has been a significant increase in the research to unveil the potential of xanthones and their semi-synthetic derivatives as an armamentarium against chronic diseases. The α- and γ-mangostins were reported to be effective

against cancer, neurodegenerative diseases and diabetes. Meanwhile, smeathxanthone A and A2 might shed light to fight against influenza and tuberculosis. What makes these xanthones interesting is that it is readily available and possesses minimal toxicity. Although enormous effort has been made to understand the mechanisms of action underlying the pharmacological activities, the clinical translation of the mangosteen compounds is still not possible due to their high hydrophobicity. Low aqueous solubility of xanthones has hindered the absorption, and thus led to poor bioavailability and pharmacokinetic profile. Therefore, formulation and structure modification of xanthone(s) are required to improve the bioavailability of these compounds. Taken together, we believe that there is an enormous potential in the development of the xanthone(s) as a therapeutic agent to address the unmet needs of humankind.

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