Food and Chemical Toxicology 46 (2008) 3227–3239

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

Medicinal properties of mangosteen (*Garcinia mangostana*)

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ARTICLE INFO

Article history:
Received 14 May 2008
Accepted 25 July 2008

Keywords:
Garcinia mangostana
Mangosteen
Xanthones
Medicinal properties

ABSTRACT

Many tropical plants have interesting biological activities with potential therapeutic applications. *Garcinia mangostana* Linn. (GML) belongs to the family of Guttiferae and is named "the queen of fruits". It is cultivated in the tropical rainforest of some Southeast Asian nations like Indonesia, Malaysia, Sri Lanka, Philippines, and Thailand. People in these countries have used the pericarp (peel, rind, hull or ripe) of GML as a traditional medicine for the treatment of abdominal pain, diarrhea, dysentery, infected wound, suppuration, and chronic ulcer.

Experimental studies have demonstrated that extracts of GML have antioxidant, antitumoral, antiallergic, anti-inflammatory, antibacterial, and antiviral activities. The pericarp of GML is a source of xanthones and other bioactive substances. Prenylated xanthones isolated from GML have been extensively studied; some members of these compounds possess antioxidant, antitumoral, antiallergic, anti-inflammatory, antibacterial, antifungal and antiviral properties. Xanthones have been isolated from pericarp, whole fruit, heartwood, and leaves. The most studied xanthones are α-, β-, and γ-mangostins, garcinone E, 8-deoxygartanin, and gartanin. The aim of this review is to summarize findings of beneficial properties of GML's extracts and xanthones isolated from this plant so far.

Contents

Abbreviations: ABTS, 2,20-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid); BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; CAT, catalase; CD, concentration required to double QR induction activity; CNS, central nervous system; COX, cyclooxygenase; CPK, creatine phosphokinase; DHR-123, dihydrorhodamine 123; LD_{50}, lethal dose 50%; DMH, 1,2-dimethylhydrazine; DMBA, 7,12-dimethylbenz[*a*]anthracene; DPPH, 2,2-diphenyl-1-picrylhydrazyl; ED_{50}, effective dose in 50% of the test organisms; 5-FMT, 5-fluoro-α-methyltryptamine; 5-FU, 5-fluorouracil; GOT, glutamate oxoloacetate transaminase; GSH, reduced glutathione; GML, *Garcinia mangostana Linn.*; H_2O_2, hydrogen peroxide; GPx, glutathione peroxidase; GPT, glutamate pyruvate transaminase; GST, glutathione-*S*-transferase; 5-HT, 5-hydroxytryptamine; HIV-1, human immunodeficience virus; $HO^{\cdot}$, hydroxyl radical; IC_{50}, inhibitory concentration at 50%; LDH, lactate dehydrogenase; LDL, low density lipoprotein; LOX, lipoxygenase; LPS, lypopolisaccharide; M, α-mangostin; 1M, 1-isomangostin; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MT, mangostin triacetate; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide; $NO^{\cdot}$, nitric oxide; iNOS, inducible nitric oxide sintase; $ONOO^{-}$, peroxynitrite; $O_2^{\cdot-}$, superoxide anion; PGE_2, prostaglandin-E_2, PML, polymorphonuclear leucocyte; QR, quinone reductase; ROS, reactive oxygen species; SOD, superoxide dismutase; TBARS, thiobarbituric reactive substances; VRE, vancomycin resistant *Enterococci*.

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doi:10.1016/j.fct.2008.07.024

1. Introduction

Mangosteen (*Garcinia mangostana* Linn.) (GML) is a tropical tree from India, Myanmar, Malaysia, Philippines, Sri Lanka, and Thailand. This tree can reach 6–25 m and it has leathery, glabrous leaves and is slow to grow (Morton, 1987).

The mangosteen-fruit is dark purple or reddish, with white, soft and juicy edible pulp with a slightly acid and sweet flavor and a pleasant aroma (Jung et al., 2006). Mangosteen is known as "the queen of fruits" because it is one of the best tasting tropical fruits. The pericarp of mangosteen-fruit has been used as a medicinal agent by Southeast Asians for centuries in the treatment of skin infections and wounds (Mahabusarakam et al., 1987; Pierce, 2003), amoebic dysentery (Garnett and Sturton, 1932; Chopra et al., 1956), etc. (see Table 1). In Ayurvedic medicine the pericarp of mangosteen-fruit has wide use against inflammation and diarrhea (Balasubramanian and Rajagopalan, 1988), and cholera and dysentery (Sen et al., 1980b).

GML has been shown to contain a variety of secondary metabolites such as prenylated and oxygenated xanthones (Govindachari and Muthukumaraswamy, 1971; Sultanbawa, 1980; Peres et al., 2000).

Xanthones or xanthen-9H-ones are secondary metabolites found in some higher plant families, fungi and lichens (Peres et al., 2000; Vieira and Kijjoa, 2005), and they comprise an important class of oxygenated heterocycles. The xanthone nucleus is known as 9-xanthenone or dibenzo-γ-pyrone and it is symmetric (Fig. 1) (Vieira and Kijjoa, 2005; Pinto et al., 2005; Souza and Pinto, 2005; Gales and Damas, 2005). Xanthones have been classified in five groups: (a) simple oxygenated xanthones, (b) xanthone glycosides, (c) prenylated xanthones, (d) xanthonolignoids and (e) miscellaneous xanthones (Sultanbawa, 1980; Jiang et al., 2004).

From 20 higher plant families (122 species in 44 genus), 19 fungi species and 3 lichens species, 278 new xanthones were identified between 2000 and 2004 (Vieira and Kijjoa, 2005). Currently, approximately 1000 different xanthones have been described (Souza and Pinto, 2005). The biological activities of this class of compounds are associated with their tricyclic scaffold but vary depending on the nature and/or position of the different substituents (Souza and Pinto, 2005; Jiang et al., 2004; Bennett and Lee, 1989; Mandal et al., 1992; Peres and Nagem, 1996).

Xanthones have been isolated from pericarp, whole fruit, bark, and leaves of GML. Several studies have shown that xanthones obtained from mangosteen-fruit have remarkable biological activities (Suksamrarn et al., 2006). α-, β- and γ-mangostins, garcinone E, 8-deoxygartanin and gartanin are the most studied xanthones. In addition, synthetic xanthones have been used in several studies. Antioxidant, antitumoral, anti-inflammatory, antiallergy, antibacterial, antifungal and antiviral are some of the reported activities of xanthones isolated from GML which are discussed in the present review.

2. Xanthones isolated from the pericarp of mangosteen-fruit

Fifty xanthones have been isolated from pericarp mangosteen-fruit (Table 2). The first of them was named mangostin (after it was named α-mangostin) when it was isolated in 1855 (Fig. 1) (Schmid, 1855). It is a yellow coloring matter that can also be obtained from bark and dried sap of GML (Dragendorff, 1930).

Later, Dragendorff (1930) and Murakami (1932) elucidated the mangostin structure. Yates and Stout (1958) established the molecular formula, and type and position of substituents of α-mangostin. Furthermore, Dragendorff (1930) isolated β-mangostin, the structure of which was not elucidated until 1968 (Yates and Bhat, 1968). Jefferson (1970) and Govindachari and Muthukumaraswamy (1971) also isolated α- and β-mangostins.

Recently, mangosharin was isolated from the bark of GML (Ee et al., 2006) and α- and β-mangostins were isolated from the root of *Cratoxylum cochinchinense*, which is a shrub tree belonging to the Guttiferae family (Laphookhieo et al., 2006).

Other xanthones that have been isolated from the pericarp of mangosteen-fruit are γ-mangostin (Jefferson et al., 1970), gartanin and 8-deoxygartanin (Govindachari and Muthukumaraswamy, 1971), 5,9-dihydroxy-8-methoxy-2,2-dimethyl-7-isopre-

Table 1
Traditional medicinal properties of *Garcinia mangostana*

Illness	References
Dysentery	Garnett and Sturton (1932), Chopra et al. (1956), Morton (1987) and Yates and Stout (1958)
Diarrhea and chronic diarrhea in adults and children	Garnett and Sturton (1932), Chopra et al. (1956), Morton (1987) and Wan et al. (1973)
Haemorrhoids	Pierce (2003)
Food allergies	Pierce (2003)
Arthritis[a]	Pierce (2003)
Wounds[a]	Mahabusarakam et al. (1986, 1987), Wan (1973) and Pierce (2003)
Skin infections	Mahabusarakam et al. (1987), Pierce (2003) and Jinsart et al. (1992)
Tuberculosis	Harbone et al. (1999) and Suksamrarn et al. (2006)
Inflammation	Saralamp et al. (1996), Chairungsrilerd et al. (1996a,b) and Harbone et al. (1999)
Ulcers	Harbone et al. (1999) and Hasegawa et al. (1996)
Micosis	Saralamp et al. (1996) and Harbone et al. (1999)
Affections of the genito-urinary tracts	Caius (2003)
Gonorrhea, cystitis and urethra suppuration	Garnett and Sturton (1932), Morton (1987) and Moongkarndi et al. (2004a)
Mouth aphthae	Caius (2003)
Fever	Caius (2003), Morton (1987) and Yates and Stout (1958)
Amoebic dysentery	Caius (2003) and Morton (1987)
Eczema[b]	Morton (1987)
Acne[c]	Saralamp et al. (1996) and Chomnawang et al. (2005)
Thrush	Morton (1987)
Abdominal pain	Moongkarndi et al. (2004a)
Suppuration	Moongkarndi et al. (2004a)
Leucorrhoea	Moongkarndi et al. (2004a)
Cholera	Sen et al. (1980a)
Convulsants	Malawska (2005)

[a] Pericarp poultice.
[b] Local use as ointment.
[c] Cosmetic cream.

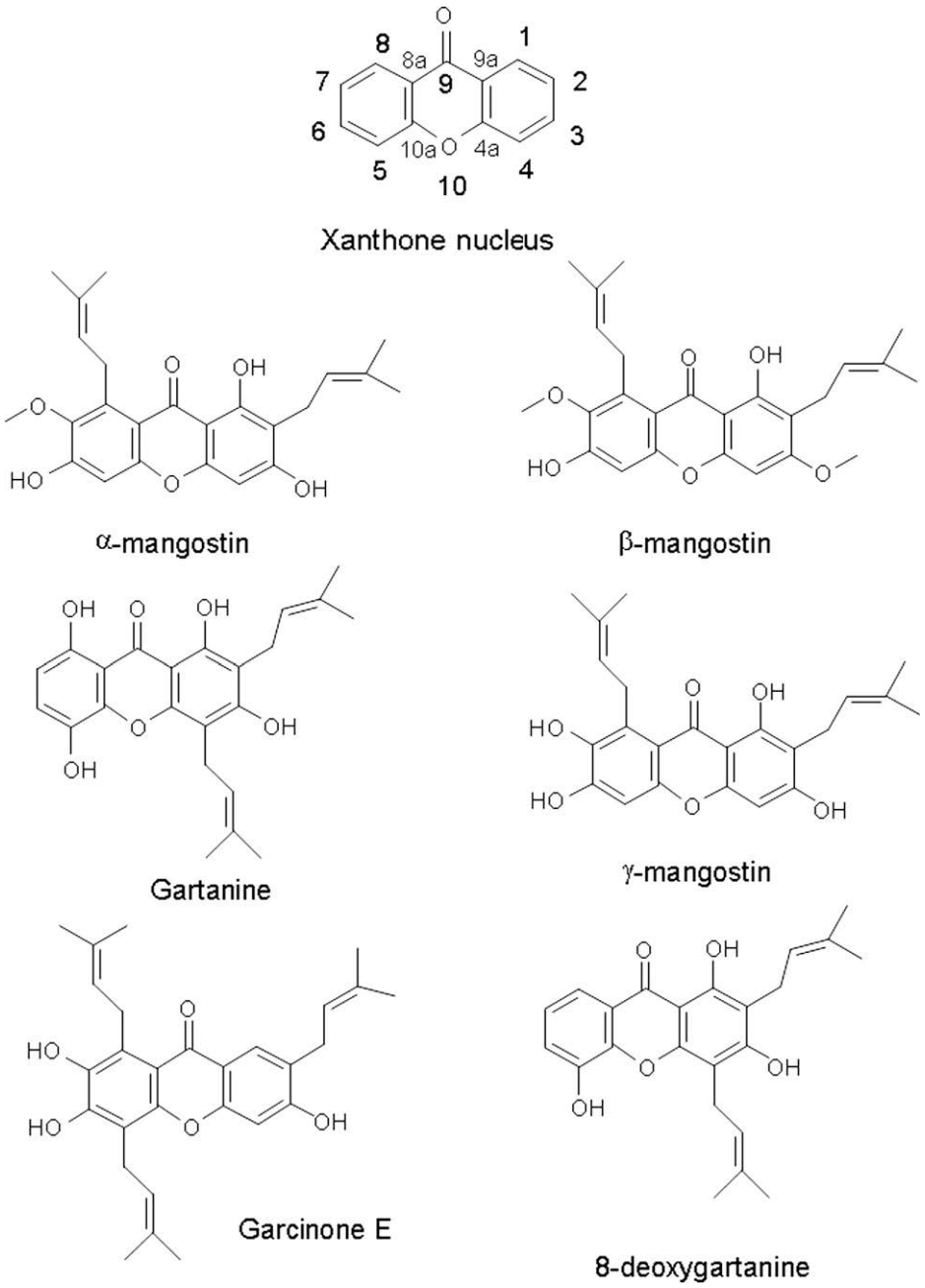

Fig. 1. Xanthone nucleus with IUPAC numbers of carbons and chemical structure of the most studied xanthones.

nyl-2H,6H-pyrano [3,2-*b*] xanthen-6-one (Sen et al., 1980a), garcinone A, B and C (Sen et al., 1980a, 1982), garcinone D (Sen et al., 1986), garcinone E (Dutta et al., 1987), BR-xanthone A and BR-xanthone B (Balasubramanian and Rajagopalan, 1988), 1,5-dihydroxy-2-isoprenyl-3-methoxyxanthone, 1,7-dihydroxy-2-isoprenyl-3-methoxy xanthone and mangostinone (Asai et al., 1995), 2,7-di-isoprenyl-1,3,8-trihydroxy-4-methyl xanthone and 2,8-di-isoprenyl-7-carboxy-1,3,-trihydroxy-4-methyl xanthone (Gopalakrishnan and Balaganesan, 2000), mangostanol (Chairungsrilerd, 1996a), euxanthone (Gopalakrishnan et al., 1997), garcimangosones A, B, C and D, tovophyllin A and B and 1,3,6,7-tetrahydroxy-8-isoprenyl-9H-xanthen-9-one (Huang et al., 2001), mangostenol, mangostenone A and B (Suksamrarn et al., 2002), 2-isoprenyl-1,7-dihydroxy-3-methoxyxanthone (Matsumoto et al., 2003), compound 7 and mangostanine (Suksamrarn et al., 2003), 8-hydroxycudraxanthone G, mangostinone and esmeatxanthone A (Jung et al., 2006), caloxanthone A, macluraxanthone and 1,7-dihydroxyxanthone (Iinuma et al., 1996). Smeathxanthone A has also been isolated from *Garcinia smeathmannii* (Komguem et al., 2005).

Calabaxanthone was isolated from the bark of *Calophyllum calaba* and *Calophyllum bracteautum* in 1972 (Somanathan and Sultanbawa, 1972), it was studied by ^{13}C MNR (Westerman et al., 1977) and later was also isolated from the pericarp of mangosteen-fruit (Mahabusarakam et al., 1987; Sen et al., 1980a).

Seven new xanthones were isolated from the pericarp of mangosteen-fruit in 1987: 1-isomangostin, 1-isomangostin hydrate, 3-isomangostin and 3-isomangostin hydrate (Mahabusarakam

Table 2
Xanthones isolated from *G. mangostana* pericarp

Xanthone	References
α-Mangostin	Schmid (1855), Yates and Stout (1958) and Stout and Krahn (1968)
β-Mangostin	Dragendorff (1930), Yates and Bhat (1968) and Mahabusarakam et al. (1987)
γ-Mangostin	Jefferson et al. (1970), Mahabusarakam et al. (1987) and Jinsart et al. (1992)
Mangostanol	Chairungsrilerd (1996a), Suksamrarn et al. (2002, 2003) and Huang et al. (2001)
Mangostenol	Suksamrarn et al. (2002, 2003)
1-Isomangostin	Mahabusarakam et al. (1987) and Jung et al. (2006)
1-Isomangostin hydrate	Mahabusarakam et al. (1987)
3-Isomangostin	Huang et al. (2001) and Mahabusarakam et al. (1987)
3-Isomangostin hydrate	Mahabusarakam et al. (1987)
1,6-Dihydroxy-7-methoxy-8-isoprenyl-6′,6′-dimethylpyrano(2′,3′:3,2)xanthone (compound 7)	Suksamrarn et al. (2003)
Toxyloxanthone A (trapezifolixanthone)	Suksamrarn et al. (2002, 2003)
Calabaxanthone[a]	Mahabusarakam et al. (1987) and Sen et al. (1980a)
Demethylcalabaxanthone	Mahabusarakam et al. (1987) and Suksamrarn et al. (2003)
Caloxanthone A	Iinuma et al. (1996)
Macluraxanthone	Iinuma et al. (1996)
1,7-dihydroxyxanthone	Iinuma et al. (1996)
Euxanthone	Gopalakrishnan et al. (1997)
Cudraxanthone	Jung et al. (2006)
8-hydroxycudraxanthone G	Jung et al. (2006)
Esmeatxanthone A	Jung et al. (2006)
BR-xanthone A	Balasubramanian and Rajagopalan (1988)
BR-xanthone B	Balasubramanian and Rajagopalan (1988)
Mangostanin	Suksamrarn et al. (2003)
Mangostenone A	Suksamrarn et al. (2002, 2003)
Mangostenone B	Suksamrarn et al. (2002)
Mangostinone	Asai et al. (1995), Suksamrarn et al. (2002, 2003) and Matsumoto et al. (2003)
Gartanin	Govindachari et al. (1971), Mahabusarakam et al. (1987) and Asai et al. (1995)
8-Deoxygartanin	Gopalakrishnan et al. (1997), Govindachari et al. (1971) and Huang et al. (2001)
Garcinone A	Sen et al. (1980b, 1982).
Garcinone B	Sen et al. (1980b, 1982), Huang et al. (2001) and Suksamrarn et al. (2002, 2003)
Garcinone C	Sen et al. (1980b, 1982)
Garcinone D	Sen et al. (1986), Gopalakrishnan et al. (1997) and Huang et al. (2001)
Garcinone E	Dutta et al. (1987), Sakai et al. (1993) and Asai et al. (1995)
Garcimangosone A	Huang et al. (2001)
Garcimangosone B	Jung et al. (2006) and Huang et al. (2001)
Garcimangosone C	Huang et al. (2001)
Garcimangosone D	Huang et al. (2001)
Tovophyllin A	Huang et al. (2001), Ho et al. (2002) and Jung et al. (2006)
Tovophyllin B	Huang et al. (2001) and Suksamrarn et al. (2002, 2003)
1,5-dihydroxy-2-isoprenyl-3-methoxyxanthone	Asai et al. (1995), Iinuma et al. (1996) and Huang et al. (2001)
Mangostingone [7-methoxy-2-(3- isoprenyl)-8-(3-methyl-2-oxo-3-buthenyl)-1,3,6-trihydroxyxanthone	Jung et al. (2006)
5,9-Dihydroxy-2,2-dimethyl-8-methoxy-7-isoprenyl-2H,6H-pyrano [3,2-*b*] xanthen-6-one	Sen et al. (1980b), Huang et al. (2001) and Chairungsrilerd (1996a)
2-(γ,γ-Dimethylallyl)-1,7-dihydroxy-3-methoxyxanthone	Mahabusarakam et al. (1987)
2,8-Bis(γ, γ-dimethylallyl)-1,3,7-trihydroxyxanthone	Mahabusarakam et al. (1987)
1,3,7-Trihydroxy-2,8-di-(3-methylbut-2-enyl) xanthone	Mahabusarakam et al. (1987)
1,7-Dihydroxy-2-isoprenyl-3-methoxyxanthone	Asai et al. (1995), Iinuma et al. (1996) and Huang et al. (2001)
2,7-Diisoprenyl-1,3,8-trihydroxy 4-methylxanthone	Gopalakrishnan and Balaganesan (2000)
2,8-Diisoprenyl-7-carboxy-1,3 dihydroxyxanthone	Gopalakrishnan and Balaganesan (2000)
2-Isoprenyl-1,7-dihydroxy-3 methoxyxanthone	Matsumoto et al. (2003)
1,3,6,7-Tetrahydroxy-8-(3 methyl-2-buthenyl)-9H-xanthon-9-one	Huang et al. (2001)

[a] This xanthone was originally isolated from bark of *Calophyllum calaba* and *Calophyllum bracteautum* (Somanathan and Sultanbawa, 1972).

Table 3
Xanthones isolated from *Garcinia mangostana* fruit

Xanthone	References
Thwaitesixanthone[a], mangostinone[b], mangostenone E, mangostenone D, mangostenone C, mangostanol[b], mangostanin[b], gartanin[b], garcinone E[b], garcinone D[b], garcinone C[b], garcinone B[b], demethylcalabaxanthone[b], compound 7[b], 11-hydroxy-1-isomangostin,	Suksamrarn et al. (2006)
1-Isomangostin[b]	Sundaram et al. (1983)
1,2-Dihydro-1,8,10-trihydroxy-2-(2-hydroxypropan-2-yl) -9-(3-Methylbut-2-enyl)furo[3,2-*a*]xanthen-11-one; 6-deoxy-7-demethylmangostanin	Chin et al. (2008)

[a] It was previously isolated from *Calophylum macrocarpum* and *Calophylum walkeri* by Ampofo and Waterman (1986).
[b] It was was also isolated from mangosteen-fruit pericarp (see Table 2). It was previously isolated from *Cratoxylum cochinchinense* by Sia et al. (1995).

Table 4
Xanthones isolated from bark of *G. mangostana*

Xanthone	References
1,3,6,7-Tetrahydroxyxanthone (Norathyriol)	Holloway and Scheinmann (1975)
1,3,6,7-Tetrahydroxy-*O*-glucosylxanthone	
Mangoxanthone, dulxanthone D, 1,3,7-trihydroxy-2-methoxyxanthone	Nilar et al. (2005)
1,3,5-Trihydroxy-13,13-dimethyl-2H-piran[7,6-*b*]xanthen-9-one	
2,6-Dihydroxy-8-methoxy-5-(3-methylbut-2-enyl)-xanthone (mangosharin)	Ee et al. (2006)
Garciniafuran, 6-*O*-Methylmangostanin, mangostanin[a],	Nilar and Harrison (2002)
1,6-Dihydroxy-3,7-dimethoxy-2-isoprenylxanthone	
1,6-Dihydroxy-2-(2-hydroxy-3-methylbut-3-enyl)-3,7-dimethoxy-8-isoprenyl xanthone	
1,6-Dihydroxy-8-(2-hydroxy-3-methylbut-3-enyl)-3,7-dimethoxy-2-isoprenyl-xanthone	
1,6-Dihydroxy-3,7-dimethoxy-2-isoprenyl-8-(2-oxo-3-methylbut-3-enyl)-xanthone	
(16*E*)-1,6-dihydroxy-8-(3-hydroxy-3-methylbut-1-enyl)-3,7-dimethoxy-2-isoprenyl-xanthone	
1-Hydroxy-2-(2-hydroxy-3-methylbut-3-enyl)-3,6,7-trimethoxy-8-isoprenyl-xanthone	
1-Hydroxy-8-(2-hydroxy-3-methylbut-3-enyl)-3,6,7-trimethoxy-2-isoprenyl-xanthone	
(16*E*)-1-hydroxy-8-(3-hydroxy-3-methylbut-1-enyl)-3,6,7-trimethoxy-2-isoprenyl-xanthone	
1,3-Dihydroxy-2-(2-hydroxy-3-methylbut-3-enyl)-6,7-dimethoxy-8-isoprenyl-xanthone	
1-Hydroxy-3,6,7-trimethoxy-2-(2-hydroxy-3-methylbut-3-enyl)-8-isoprenyl-xanthone	
1-Hydroxy-3,6,7-trimethoxy-2-isoprenyl-8-(2-oxo-3-methylbut-3-enyl)-xanthone	
1-Hydroxy-3,6,7-trimethoxy-2-isoprenyl-xanthone	

[a] It was also isolated from mangostan-fruit and pericarp (see Tables 2 and 3).

Table 5
Xanthones isolated from mangosteen leaves (Parveen and Khan, 1988)

1,6-Dihydroxy-3-methoxy-2-isoprenyl xanthone
Gartanin[a]
1,5,8-Trihydroxy-3-methoxy-2-isoprenyl-xanthone

[a] It was also isolated from mangosteen-fruit and pericarp (see Tables 2 and 3).

et al., 1987). 2-(γ,γ-dimethylallyl)-1,7-dihydroxy-3-methoxy-xanthone, demethylcalabaxanthone, 1,3,7-trihydroxy-2,8-di-(3-methylbut-2-enyl)xanthone and 2,8 bis (γ,γ-dimethylallyl)-1, 3,7-trihydroxyxanthone were isolated of the arils (seed coats). They also obtained several xanthones already isolated (mangostin, gartanin, β-mangostin, γ-mangostin, and calabaxanthone).

Recently, α- and β-mangostin, 9-hydroxycalabaxanthone, 3-isomangostin, gartanin, and 8-desoxygartanin have been extracted of the fruit rind of mangosteen, identified and quantitatively determined used high performance liquid chromatograpy (HPLC) (Walker, 2007). The xanthones 3-isomangostin, 8-desoxygartanin, gartanin, α- and β-mangostins and 9-hydroxycalabaxanthone also have been identified by UV spectra and quantified by HPLC with photodiode array detector and HPLC with time-of-flight mass spectrometry system coupled with electrosplay ionization interface (Ji et al., 2007).

Table 6
Synthetic derivatives of α-mangostin

Derivative	References
3-*O*-methylmangostin	Sundaram et al. (1983)
3,6-di-*O*-methylmangostin	
Mangostin triacetate	
Mangostin 3,6-d-*O*-tetraacetylglucoside	Shankaranarayan et al. (1979)
Mangostin 3,6 di-*O*-glucoside	
1-Hydroxy-3,6,7-trimethoxy-2,8-bis-(isoprenyl)-9H-xanthen-9-one	Mahabusarakam et al. (2000)
1,3-Dihydroxy-6-acetoxy-7-ethoxy-2,8-bis(isoprenyl)-9H-xanthen-9-one	
1,6-Dihydroxy-3-(2,3-dihydroxypropoxy)-7-methoxy-2,8-bis(isoprenyl)-9H-xanthen-9-one	
1-Hydroxy-3,6-di(2,3-dihydroxypropoxy)-7-methoxy-2,8-bis(isoprenyl)-9H-xanthen-9-one	
1-Hydroxy-3,6-di(4-cianopropoxy)-7-methoxy-2,8-bis(isoprenyl)-9H-xanthen-9-one	
1,3-Dihydroxy-6-(4-cianopropoxi)-7-methoxy-2,8-bis(isoprenyl)-9H-xanthen-9-one	
1,3-Dihydroxy-6-(*N*,*N*-diethylaminoethoxy)-7-methoxy-2,8-bis(isoprenyl)-9H-xanthen-9-one	
1-Hydroxy-3,6-di(*N*,*N*-diethylaminoetoxi)-7-methoxy-2,8-bis(isoprenyl)- 9H-xanton-9-one	
1,3-Dihydroxy-6-(*N*,*N*-dimethylaminoethoxy)-7-methoxy-2,8-bis(isoprenyl)-9H-xanthen-9-one	
1,3-Dihydroxy-6-(*N*,*N*-dimethylaminopropoxy)-7-methoxy-2,8-bis(isoprenyl)-9H-xanthen-9-one	
1,3-Dihydroxy-6-(2-hydroxy-3-*N*,*N*-dimethylaminopropoxy)- 7-methoxy-2,8-bis(isoprenyl)-9H-xanthen-9-one	
1,3-Dihydroxy-6(2-hydroxy-3-*N*-isopropylaminopropoxy)-7-methoxy-2,8-bis(isoprenyl)-9H-xanthen-9-one	
1-Hydroxy-3,6-di(2-hydroxy-3-*N*-isopropylaminopropoxy)-7-methoxy-2,8-bis(isoprenyl)-9H-xanthen-9-one	
5-Hydroxy-8-methoxy-9-(*N*,*N*-dimethylaminoethoxy)-7-(isoprenyl)-2,2-dimethyl-pyrano[3,2-*b*]xanthen-6-one	
5-Hydroxy-8-methoxy-9-(3-*N*,*N*-dimethylaminopropoxy)-7-(isoprenyl)-2,2-dimethyl-pyrano[3,2-*b*]xanthen-6-one	
5-Hydroxy-8-methoxy-9-(2-hydroxy-3-*N*,*N*-dimethylaminopropoxy)-7-(isoprenyl)-2,2-dimethyl-pirano[3,2-*b*]xanton-6-one	
5-Hydroxy-8-methoxy-9-(2-hydroxy-3-*N*-isopropilaminopropoxi)-7-(isoprenyl)-2,2-dimethyl-pyrano[3,2-*b*]xanthen-6-one	
5-Hydroxy-8-methyl-(3-cyanobutoxy)-7-(isoprenyl)-2,2-dimethyl-pyranol[3,2-*b*]xanthen-6-one	
Bicyclomangostin	
Di-*O*-methylamangostin	Gopalakrishnan et al. (1997)
Di-*O*-ethylmangostin	
Di-*O*-butylmangostin	
Di-*O*-isopropylmangostin	
Di-*O*-all Di-*O*-methallylmangostin ylmangostin	
Di-*O*-acethylmangostin	
3-Isomangostin	

Table 7
Antioxidant properties of *G. mangostana*

G. mangostana extracts and/or xanthone	References
The methanol extract of the fruit hulls of GML showed DPPH scavenging activity	Yoshikawa et al. (1994)
α-Mangostin inhibited copper-induced LDL oxidation *in vitro*	Williams et al. (1995)
α and γ-Mangostin showed antioxidant activity using the ferric thiocyanate method	Fan and Su (1997)
The copper-induced LDL oxidation *in vitro* was inhibited by α-mangostin and by prenylated xanthones derived from this xanthone	Mahabusarakam et al. (2000)
Methanolic extract of the edible portion of GML exhibited antioxidant activity using DPPH and ABTS assays	Leong and Shui (2002)
The crude methanol extract of pericarp from GML ameliorated the intracellular production of ROS in SKBR3 cells	Moongkarndi et al. (2004a)
The pericarp extract of GML was able to scavenge $HO^{\cdot}$ and effective to inhibit lipid peroxidation	Garcia et al. (2005)
Several xanthones showed scavenging $ONOO^{-}$ ability *in vitro*	Jung et al. (2006)
The aqueous and ethanolic extracts of the pericarp of GML present DPPH scavenging activity and protects neuroblastoma cell line NG108-15 from H_2O_2 citotoxicity	Weecharangsan et al. (2006)
The ethanolic extract of GM showed antioxidant activity against DPPH radicals and reduced the ROS production of PML	Chomnawang et al. (2007)
Mangosteen-fruit showed antioxidant activity against DPPH and ABTS radicals and prevents the decrease in antioxidant activity induced by a cholesterol supplemented diet in rats	Haruenkit et al. (2007)
α-Mangostin showed protective effect against isoproterenol-induced oxidative damage and myocardial injury in rats	Devi Sampath and Vijayaraghavan (2007)
γ-Mangostin showed $HO^{\cdot}$-scavenging activity	Chin et al. (2008)

3. Xanthones from whole fruit, trunk, branches, and leaves of GML

Three new xanthones were isolated from the whole mangosteen-fruit: mangostenone C, D and E (Suksamrarn et al., 2006) (Table 3). In total, 18 xanthones have been isolated from the whole mangosteen-fruit. In addition, 21 xanthones have been isolated from trunk and branches of GML (Holloway and Scheinmann, 1975; Nilar et al., 2005; Nilar and Harrison, 2002; Ee et al., 2006) (Table 4). On the other hand, 1,6-dihydroxy-3-methoxy-2-isoprenyl-xanthone, 1-hydroxy-6-acetoxy-3-methoxy-2-isoprenylxanthone and gartanin were isolated from mangosteen leaves (Parveen and Khan, 1988) (Table 5). Chin et al. (2008) isolated and identificated two new compounds of mangosteen powder fruit 1,2-dihydro-1,8,10-trihydroxy-2-(2-hydroxypropan-2-yl)-9-(3-methylbut-2-enyl)furo[3,2-*a*]xanthen-11-one and 6-deoxy-7-demethylmangostanin.

Also, 31 synthetic derivatives have been obtained from α-mangostin, and they have been used to perform several studies (Table 6).

4. Main biological and medicinal properties of GML

4.1. Antioxidant properties

In the Table 7 the antioxidant properties of mangosteen-fruit extracts and some xanthones that have been studied are summarized.

The antioxidant activity of extracts and xanthones isolated from GML has been shown using the following methods: 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity (Yoshikawa et al., 1994; Leong and Shui, 2002; Weecharangsan et al., 2006; Chomnawang et al., 2007; Haruenkit et al., 2007), the ferric thiocyanate method (Yoshikawa et al., 1994; Fan and Su, 1997), and the 2,20-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid (ABTS) assay (Leong and Shui, 2002; Haruenkit et al., 2007).

Yoshikawa et al. (1994) found that the methanolic extracts of GML hulls showed DPPH radical scavenging activity. α and γ-mangostins showed antioxidant activity using the ferric thiocyanate method (Yoshikawa et al., 1994; Fan and Su, 1997). Williams et al. (1995) found that α-mangostins decreases the human low density lipoproteins (LDL) oxidation induced by copper or peroxyl radical. They found that α-mangostin (i) prolonged lag time of conjugated dienes at 234 nm in a dose-dependent manner, (ii) diminishes thiobarbituric reactive substances (TBARS) production, and (iii) decreases the α-tocopherol consumption induced by LDL oxidation. Consistently, Mahabusarakam et al. (2000) also found that α-mangostin and their synthetic derivatives prevent the decrease of the α-tocopherol consumption induced by LDL oxidation. These authors found that the structural modifications of α-mangostin modify the antioxidant activity. For example, substitution of C-3 and C-6 with aminoethyl derivatives enhanced the activity; whereas substitution with methyl, acetate, propanediol or nitrile reduced the antioxidant activity (Mahabusarakam et al., 2000).

On the other hand, Leong and Shui (2002) compared the total antioxidant capacity of twenty-seven fruits available in the Singapore market, including mangostan, using the ABTS and DPPH assays. They showed that the GML extract had the eighth place in antioxidant efficiency.

Weecharangsan et al. (2006) studied the antioxidant and neuroprotective properties of four extracts obtained from mangosteen-fruit pericarp (water, 50% ethanol, 95% ethanol and ethyl acetate). The antioxidant capacity was evaluated by the DPPH method using 1, 10, 50 and 100 μg/mL of each extract. Water and ethanolic (50%) extracts showed high antioxidant capacity (inhibitory concentration at 50% (IC_{50}) = 34.98 ± 2.24 and 30.76 ± 1.66 μg/mL, respectively). The antioxidant capacity of these extracts was tested on a neuroblastoma cell line (NG108-15) exposed to hydrogen peroxide (H_2O_2); both extracts exhibited neuroprotective activity when they used concentration of 50 μg/mL. The 50% ethanolic extract had higher neuroprotective activity than the water extract. More recently, Chomnawang et al. (2007) showed that GML ethanolic extract possesses a significant antioxidant activity, as measured by the inhibition of the formation of DPPH radicals by 50%. This extract displayed an IC_{50} of 6.13 μg/mL in comparison with ethanolic extracts of *Houttuynia cordata*, *Eupatorium odoratum* and *Senna alata* (IC_{50} of 32.53, 67.55 and 112.46 μg/mL, respectively). In addition, the extract of *G. mangostana* significantly reduced the reactive oxygen species (ROS) production of polymorphonuclear leucocytes (PML) with 77.8% of superoxide anion ($O_2^{\cdot-}$) inhibition ratio (62.6%, 44.9% and 35.18% for *H. cordata*, *E. odoratum*, and *S. alata*, respectively). Haruenkit et al. (2007) showed the antioxidant activity of mangosteen measured with DPPH and ABTS assays. They found values of 79.1 and 1268.6 μM trolox equivalents/100 g of fresh weight for DPPH and ABTS assays, respectively. In addition, in rats fed with basal diet supplemented with 1% of cholesterol plus 5% of mangosteen the increase in plasma lipids and decrease in antioxidant activity seen with cholesterol alone was prevented.

Moongkarndi et al. (2004a) showed that a GML extract significantly diminished intracellular ROS production, which was measured using 2,7-dichlorofluorescein diacetate (DCFH-DA) in SKBR3 cell line. In a similar study, Garcia et al. (2005) studied the antioxidant capacity of several fruits and vegetables from the

Philippines by measurement of lipoperoxidation (linoleic acid system) and hydroxyl radical ($HO^{\cdot}$) scavenging (deoxyribose method). They found that the extract obtained from the mangosteen-fruit pericarp had one of the highest antioxidant activities. On the other hand, Jung et al. (2006) measured the peroxynitrite ($ONOO^-$) scavenging capacity of 13 xanthones by monitoring the oxidation of dihydrorhodamine 123 (DHR-123). $ONOO^-$ is the oxidant specie produced by the reaction between nitric oxide ($NO^{\cdot}$) and $O_2^{\cdot-}$ (Chirino et al., 2006). The IC_{50} (μM) value for $ONOO^-$ scavenging was determined for several compounds. Xanthones with the highest capacity to scavenge $ONOO^-$ were smeathxanthone A (2.2), 8-hydroxycudraxanthone G (4.6), γ-mangostin (8), gartanin (9.1), α-mangostin (12.2), garcinone E (14.1), garcimangosone B (15.9), 1-isomangostin (19.2) and garcinone D (26). They also studied the $ONOO^-$ scavenging capacity of cudraxanthone G, 8-deoxygartanin, mangostinone and tovophyllin A, but it was lower (IC_{50} > 30 μM). DL-penicillamine was used as a positive control and its IC_{50} was 3.1 μM. Devi Sampath and Vijayaraghavan (2007) evaluated the effect of α-mangostin on the antioxidant defense system and on lipid peroxidation during isoproterenol-induced myocardial infarction in rats. Treatments of rats with isoproterenol (150 mg/kg for 2 days) showed a significant decrease of the antioxidant enzymes glutathione-*S*-transferase (GST), glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH); as well as marked elevation in serum enzymes such as lactate dehydrogenase (LDH), creatine phosphokinase (CPK), glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT) and lipid peroxides. The histological examination of rats treated with isoproterenol showed necrotic changes in the tissue with intense infiltration of neutrophils. Pretreatment with α-mangostin (200 mg/kg) for 6 days prior and 2 days concurrently with isoproterenol administration significantly attenuated these changes. This xanthone showed a protective effect against lipid peroxidation and antioxidant defense system during injury-induced myocardial infarction in rats.

Chin et al. (2008) studied the $HO^{\cdot}$-scavenging activity of several xanthones isolated from the fruit powder of GML. Only γ-mangostin from the 16 xanthones tested showed $HO^{\cdot}$-scavenging activity (IC_{50} = 0.2 μg/mL). In addition, Chin et al. (2008) tested the same xanthones for the induction of quinone reductase (QR, phase II drug-metabolizing enzyme), using murine hepatoma cells (Hepa 1c1c7) *in vivo*. All the xanthones, with the exception of α-mangostin, were found to induce QR activity. The concentration required to double QR induction activity (CD) values of compounds were 1.3, 2.2, 0.68 and 0.95 μg/mL for 1,2-dihydro-1,8,10-trihydroxy-2-(2-hydroxypropan-2-yl)-9-(3-methylbut-2-enyl)furo[3,2-*a*]xanthen-11-one, 6-deoxy-7-demethylmangostanin, 1,3,7-trihydroxy-2,8-di-(3-methylbut-2-enyl)xanthone and mangostanin, respectively.

In our laboratory, we found that α-mangostin (pericarp isolated), mangosteen extract and commercial mangosteen juice, are able to scavenge directly ROS and prevent neurotoxicity and ROS production induced by 3-nitropropionic acid in cultured neurons (unpublished observations and Guzman-Beltran et al., submitted to publication).

The above data indicate that the antioxidant properties of extracts and some xanthones isolated from GML warrant additional studies to further examine their antioxidant properties in supplementary experimental models.

4.2. Antitumoral properties

Several studies have been designed to examine the anticancer activities of xanthones isolated from mangosteen-fruit pericarp (Table 8). Hepatocellular carcinoma (Ho et al., 2002), SKBR3 human breast cancer (Moongkarndi et al., 2004a) and human leukemia (Matsumoto et al., 2003) cell lines have been used.

Ho et al. (2002) found that garcinone E has a potent cytotoxic effect on hepatocellular carcinoma cell lines. They studied the cytotoxic effect of 6 xanthones isolated from mangosteen-fruit pericarp and found that garcinone E was the most toxic. Therefore, garcinone E was tested against HCC36, TONG, HA22T, Hep3B, HEpG2 and SK-Hep-1 hepatocellular carcinoma cell lines; NCI-Hut 125, CH27 LC-1, H2891 and Calu-1 lung carcinoma cell lines; and AZ521, NUGC-3, KATO-III and AGS gastric carcinoma cell lines. Garcinone E exhibited a very broad spectrum of dose- and time-dependent cytotoxic effects against various cancer cell lines; with the exception of lung carcinoma cell line CH27 LC-1, all cell lines tested were killed. The values for garcinone lethal dose 50% (LD_{50}) against the cell lines studied were between 0.1 and 5.4 μM. Garcinone E had an antitumoral effect in the following order: SK-Hep-1 > HA22T > HEpG2 > Hep3B > HCC36.

Matsumoto et al. (2003) studied the effect of 6 xanthones (α, β and γ-mangostins, mangostinone, garcinone E and 2-isoprenyl-1,7-dihydroxy-3-methoxy xanthone) isolated from mangosteen-fruit pericarp on the cell growth inhibition of human leukemia cell line HL60. They examined cytotoxic effects 72 h after cell incubation with xanthone at 5 or 40 μM. All xanthones showed a significant inhibition effect, but α, β and γ-mangostins were particularly effective from 10 μM. The most abundant compound in the extract was α-mangostin, and it showed the highest inhibitory activity (IC_{50} 10 μM). Later, the α-mangostin effect was shown in other leukemia cell lines: K562, NB4 and U937. Cell growth of all these leukemia cell lines was inhibited by α-mangostin at 5–10 μM.

Nabandith et al. (2004) investigated whether the administration of α-mangostin in the diet had short-term chemopreventive effects on putative preneoplastic lesions involved in rat colon carcinogenesis, induced by a subcutaneous injection of

Table 8
Antitumoral properties of xanthones isolated from *Garcinia mangostana*

Effect	References
Garcinone E has a cytotoxic effect on hepatoma cells lines as well as on the gastric and lung cancer cell lines	Ho et al. (2002)
Six xanthones from the pericarp of GML showed antiproliferative activity against human leukemia HL60 cells. In addition, α-mangostin induced caspase 3-dependent apoptosis in HL60	Matsumoto et al. (2003)
The treatment with dietary α-mangostin inhibits cells proliferation in the colon lesions in rats injected with DMH	Nabandith et al. (2004)
Aqueous extract of the fruit rind GML showed antileukemic activity in four cells lines	Chiang et al. (2004)
α-Mangostin induced apoptosis in human leukemia cell lines	Matsumoto et al. (2004)
Ethanolic and methanolic extracts of GML showed antiproliferative effect on human breast cancer SKBR3 cells	Moongkarndi (2004a, 2004b)
The antiproliferative effect of α- and γ-mangostins, was associated with apoptosis in human colon cancer DLD-1 cells	Matsumoto et al. (2005)
α-Mangostin inhibited DMBA-induced preneoplastic lesions in a mouse mammary organ culture	Jung et al. (2006)
Mangostenone C, mangostenone D, demethylcalabaxanthone, β-mangostin, gartanin, garcinone E, α-mangostin, mangostinone, γ-mangostin, garcinone D, and garcinone C showed cytotoxic effect on the three human cancer cell lines	Suksamrarn et al. (2006)
α-Mangostin showed antitumoral activity against DLD-1 cells	Nakagawa et al. (2007)

1,2-dimethylhydrazine, DMH (40 mg/kg body weight once a week for 2 weeks). They found that dietary administration of α-mangostin significantly inhibited the occurrence of biomarkers for short-term colon carcinogenesis (aberrant crypt foci, dysplastic foci and β-catenin accumulated crypt) induced by DMH.

In another study, Chiang et al. (2004) investigated the antileukemic activity of hot water and juice extracts of 17 most used fruits in Taiwan in K562, P3HR1, Raji and U937 leukemia cells. Only the hot water extract of mangosteen-fruit pericarp exhibited a potent antileukemic activity, with an IC_{50} of 61 ± 9.9 and 159 ± 12 μg/mL against K562 and Raji cells, respectively. This extract also had a moderate activity against U937 cells, but it was less effective against P3HR1 cells.

Matsumoto et al. (2004) studied the mechanism of cell death induced by α-mangostin treatment in human leukemia cell line HL60. They found that this xanthone induces apotosis in HL60 cells, which was mediated by mitochondrial dysfunctions in the early phase. They found that α-mangostin induces caspases 9 and 3 activation, loss of mitochondrial membrane potential, and, release of ROS and cytochrome C. They also showed that neither bcl-2 family proteins nor activation of mitogen-activated protein kinases are involved in α-mangostin-induced cell death.These results indicated that mitochondria play a pivotal role in induction of apoptosis by α-mangostin.

Moongkarndi et al. (2004b) tested the antiproliferative activity of 9 Thai medicinal plants against SKBR3 human breast adenocarcinoma cell line. The extract obtained from GML had the most potent activity with an IC_{50} value of 15.45 ± 0.5 μg/mL.

In another study performed by the same authors (Moongkarndi et al., 2004a), the antiproliferation, apoptosis and antioxidant activity of crude methanolic extract from mangosten-fruit pericarp was evaluated using SKBR3 human breast cancer cell line as a model. This methanolic extract had a significant antiproliferation activity (ED_{50} = 9.25 ± 0.64 μg/mL) by inducing apoptotic cell death. Also, the methanolic extract showed antioxidant activity by inhibiting the intracellular ROS production.

Matsumoto et al. (2005) studied the antiproliferative effect of 4 prenylated xanthones (α, β, and γ-mangostins and methoxy-β-mangostin) in human colon cancer DLD-1 cells. Except for methoxy-β-mangostin, the other three xanthones strongly inhibited cell growth at 20 μM at 72 h and their antitumor efficacy was correlated with the number of hydroxyl groups. Apoptosis was associated with antiproliferative effect of α and γ-mangostins, but not of β-mangostin. The affected expression of cyclins cdc2 and p27 shown that cell-cycle arrest was related with the antiproliferative effect of α, β (G1 arrest) and γ-mangostin (S arrest).

Recently, the following authors have investigated the antitumoral properties of GML:

Jung et al. (2006) isolated from mangosteen-fruit pericarp two new xanthones (8-hydroxycudraxanthone G and mangostinone) as well as 12 known xanthones. They determined their antitumoral properties in preneoplastic lesions induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) in a mouse mammary organ culture. α-mangostin inhibited DMBA-induced preneoplastic lesions with an IC_{50} of 1.0 μg/mL (2.44 μM).

Suksamrarn et al. (2006) isolated from mangosteen-fruit pericarp three new prenylated xanthones (mangostenones C, D and E) as well as 16 known xanthones. The cytotoxic properties of these xanthones were determined against three different human cancer cell lines: epidermoid carcinoma of mouth (KB), breast cancer (BC-1), and small cell lung cancer (NCI-H187). Mangostenone C exhibited a cytotoxic effect against the three cell lines proved, with IC_{50} values of 2.8, 3.53, and 3.72 μg/mL, respectively. However, α-mangostin exhibited the most potent effect against BC-1 cells with an IC_{50} value of 0.92 μg/mL, an activity that was greater than the standard drug ellipticine (IC_{50} = 1.46 μg/mL); α-mangostin also had a cytotoxic effect against KB cells (IC_{50} = 2.08 μg/mL); and gartanin was able to inhibit the NCI-H187 growth (IC_{50} = 1.08 μg/mL). Laphookhieo et al. (2006) found that α- and γ-mangostins have a cytotoxic effect against NCI-H187.

Nakagawa et al. (2007) evaluated α-mangostin for *in vitro* cytotoxicity against DLD-1 cells. They demonstrated that the number of viable cells was decreased by the treatment with mangostin 20 μM. They also showed the synergistic growth suppression in the cells by the combination treatment with 2.5 μM of mangostin and 2.5 μM of 5-fluorouracil (5-FU), a chemotherapeutic agent for colorectal adenocarcinoma.

In summary, the results suggest that α-mangostin and its analogs would be candidates for preventive and therapeutic application for cancer treatment.

4.3. Anti-inflammatory and antiallergy properties

There is evidence about antiallergy and anti-inflammatory properties of GML in differerent *in vitro* models, such as RBL-2H3 cells (Nakatani et al., 2002b) and C6 rat glioma cells (Nakatani et al., 2002a,b, 2004; Yamakuni et al., 2006), rabbit thoracic aorta and guinea-pig trachea (Chairungsrilerd et al., 1996b,c) and several models *in vivo* in rats (Shankaranarayan et al., 1979; Nakatani et al., 2004) (Table 9).

Shankaranarayan et al. (1979) made up xanthone synthetic derivatives (3-*O*-methyl mangostin, 3,6-di-*O*-methyl mangostin, mangostin triacetate, 1-isomangostin, mangostin-3,6-di-*O*-(tetra acethyl)-glucoside and mangostin-3,6-di-*O*-glucoside) from α-mangostin to be used in pharmacologic studies as well as α-mangostin. Oral and intraperitoneal administration (50 mg/kg) of α-mangostin, 1-isomangostin and mangostin triacetate exhibited anti-inflammatory activity in rats tested by the carrageenan-induced hind paw edema (M, 1M and MT showed 66.6%, 63.19% and 59.03% of reduction, respectively), cotton pellet granuloma (M, 1M and MT showed 56.99%, 52.81% and 52.63% of reduction, respectively) and granuloma pouch techniques (M, 1M and MT showed 65.6%, 63.3% and 58.3% of reduction, respectively). As positive control, dexamethazone treated rats (1 mg/kg) were used; and as negative control, acacia-gum treated rats (2 mL/kg) were used. The anti-inflammatory activity of these compounds was also shown in adrenalectomised rats. In addition, Gopalakrishnan (1980) showed that α-mangostin isolated from the rinds of the mangosteen inhibited systemic anaphylaxis, immunocytoadherence in guinea pigs and rats, and inhibited the primary and secondary responses of adjuvant-induced arthritis in rats.

Chairungsrilerd et al. (1996c) demonstrated that methanolic extract of mangosteen-fruit pericarp inhibits the contractions of isolated thoracic rabbit aorta induced by histamine and serotonin. They suggested that α- and γ-mangostins are histaminergic and serotonergic receptor blocking agents, respectively. This same research group studied the effect of α-mangostin on histamine-induced contractions in rabbit thoracic aorta and guinea-pig trachea (Chairungsrilerd et al., 1996a). α-mangostin inhibited histamine-induced contractions in a dose-dependent manner with or without cimetidine, an antagonist of the H_2-histamine receptor. Also, α-mangostin inhibited contractions mediated by the histamine H_1 receptor. Furthermore, α-mangostin competitively inhibits [^{3}H]mepyramine (specific antagonist of histamine H_1 receptor) binding to rat aortic smooth muscle cells. Chairungsrilerd et al. (1998b) also showed that 0.03–5 μM of γ-mangostin purified from the GML caused a parallel rightwards shift of the concentration/response curve for the contraction elicited by 0.5 mM of 5-hydroxytryptamine (5-HT) in the rabbit aorta without affecting the contractile responses to 30 mM of KCl, 3 μM of phenylephrine or histamine. The perfusion pressure response of rat coronary artery to 5-HT_{2A} was reduced concentration dependently by γ-mangostin

Table 9
Anti-inflammatory and antiallergy properties of *G. mangostana*

Effect	References
α-Mangostin, 1-isomangostin, and mangostin triacetate showed antiiflamatory activity in several experimental models in rats	Shankaranarayan et al. (1979)
α-Mangostin, i.p. has anti-inflammatory effects in several experimental models of inflammation in rats and guinea pigs	Gopalakrishnan et al. (1980)
α-Mangostin ameliorates the histamine-induced contraction of aorta and trachea from male guinea pigs	Chairungsrilerd et al. (1996a)
The crude methanol extract of GM hulls blocked the histaminergic and serotonergic response in isolated rabbit aorta strips. α-mangostin blocked the histaminergic response and γ-mangostin blocked the serotonergic response	Chairungsilerd et al. (1996b)
γ-Mangostin is $5HT_{2A}$ receptor antagonist in vascular smooth muscles and platelets	Chairungsrilerd et al. (1998a)
γ-Mangostin inhibits 5-FMT-induced head-twitch response in mice by blocking $5\text{-}HT_{2A}$ receptors	Chairungsrilerd et al. (1998b)
Extracts of mangosteen hulls inhibited histamine release in RBL-2H3 cells and decreased A23187 induced PGE_2 synthesis in C6 rat glioma cells	Nakatani et al. (2002b)
γ-Mangostin inhibited A2318 induced PGE_2 release in C6 cells and arachidonic acid conversion to PGE_2 in isolated microsomes as well as the activities of both constitutive COX-1 and inducible COX-2	Nakatani et al. (2002b)
γ-Mangostin (a) inhibited COX-1 and -2 activity and PGE_2 synthesis in C_6 rat glioma cells, (b) inhibited LPS-induced expression of COX-2 protein and its mRNA, (c) reduced the LPS-inducible activation of NF-kB, and (d) inhibited rat carrageenan-induced paw edema	Nakatani et al. (2004)
Garcinone B reduced A23187-induced PGE_2 release and LPS-induced transcription of NF-kB-mediated in C6 rat glioma cells	Yamakuni et al. (2006)
α- and γ-mangostins inhibited LPS-stimulated citotoxicity, $NO^{\cdot}$ and PGE_2 production, and iNOs induction in RAW 264.7 cells. α-Mangostin showed a potent inhibition on paw oedema in mice	Chen et al. (2008)
α-Mangostin inhibits human 12-LOX	Deschamps et al. (2007)

(IC_{50} = 0.32 μM). 5-HT amplified, ADP-induced aggregation of rabbit platelets was inhibited by γ-mangostin (IC_{50} = 0.29 μM). This xanthone (5 μM) also affected 5-HT-induced contraction of the guinea-pig ileum (3 μM of $5\text{-}HT_3$) in the presence of $5\text{-}HT_1$, $5\text{-}HT_2$ and $5\text{-}HT_4$ receptor antagonists and inhibited [^{3}H]spiperone binding to cultured rat aortic myocytes (IC_{50} = 3.5 nM). Chairungsrilerd et al. (1998a) showed that γ-mangostin (10–40 nmol/mouse) inhibited 5-fluoro-α-methyltryptamine (5-FMT, 45 mg/kg i.p.) induced head-twitch response in mice by blocking $5\text{-}HT_{2A}$ receptors, not by blocking the release of 5-HT from the central neurone. γ-mangostin is a promising $5\text{-}HT_{2A}$ receptor antagonist in vascular smooth muscle, platelets and the central nervous system (Chairungsrilerd et al., 1998a,b).

Nakatani et al. (2002b) examined the effect of extracts from mangosteen-fruit (water and ethanol 40%, 70% and 100%) on histamine release and prostaglandin-E_2 (PGE_2) synthesis. They found that 40% ethanol extract (100 and 300 μg/mL) inhibits the histamine release induced by IgE in RBL-2H3 cells. This effect was higher than aqueous extract of *Rubus suavissimus*, which has been used in Japan as antiallergic drug; whereas 70% and 100% extracts showed only weak inhibition. A 40% ethanol extract of GML extracts (3, 10, 30 and 100 μg/mL) potently inhibited A23187 (a calcium ionophore)-induced PGE_2 release in C6 rat glioma cells, while the water extract of *R. suavissimus* had no effect. In addition, passive cutaneous anaphylaxis reactions in rats were significantly inhibited by this ethanol extract.

This same group examined the effect of γ-mangostin isolated from mangosteen-fruit pericarp on arachidonic acid cascade in C6 rat glioma cells. They found that γ-mangostin has a potent inhibitory activity on A23187-induced PGE_2 release. This inhibition was concentration-dependent, with an IC_{50} of about 5 μM. Conversion of arachidonic acid to PGE_2 was inhibited by γ-mangostin, which also inhibited the activities of both constitutive cyclooxygenase-1 and inducible cyclooxygenase-2 (COX-1 and COX-2, respectively) in a concentration-dependent manner (IC_{50} of about 0.8 and 2 μM, respectively) (Nakatani et al., 2002a).

Nakatani et al. (2004) studied the effect of γ-mangostin on spontaneous release of prostaglandin E_2 and COX-2 gene expression using C6 rat glioma cells. After 18 h of γ-mangostin treatment, spontaneous release of PGE_2 was inhibited in a concentration-dependent manner (IC_{50} of about 2 μM). Furthermore, γ-mangostin prevents (in a concentration-dependent manner) the lipopolysaccharide-induced expression of COX-2 protein and its mRNA, but not those of constitutive COX-1. In this work, the effect of γ-mangostin on nuclear factor κB activation was also examined. It was found that γ-mangostin suppressed the inhibitor κB kinase activity to inhibit lypopolisaccharide-induced nuclear factor κB activation and thereby decreases COX-2 induction.

Yamakuni et al. (2006) found that garcinone B (10 μM) reduced by 30% the increase of PGE_2 release induced by A23187 in C6 rat glioma cells. Garcinone B (20 μM) also diminished approximately 30% of lypopolisaccharide-induced nuclear factor κB activation. These results suggest that garcinone B may be a pharmacological tool to investigate intracellular signaling pathways involved in inflammation.

Recently, Chen et al. (2008) demonstrated that α- and γ-mangostins significantly inhibited lipopolysaccharide-stimulated $NO^{\cdot}$ production and cytotoxicity to RAW 264.7 cells. The amount of $NO^{\cdot}$ production at 3 to 25 μM was continously measured, and the IC_{50} values were 12.4 and 10.1 μM for α- and γ-mangostins. The α- and γ-mangostins also significantly reduced PGE_2 production in lipopolysaccharide-activated RAW 264.7 cells with IC_{50} values of 11.08 and 4.5 μM, respectively. The effects of these xanthones were probed by measuring the induction of inducible nitric oxide synthase (iNOS) and COX enzyme expressions. The two xanthones concentration-dependently reduced the induction of iNOS. The RAW 264.7 cells were activated with lipopolysaccharide (1 μg/mL) for 12 h and the treatment with α- or γ-mangostins (5 μg/mL) for 24 h weakly inhibited iNOS activity in activated RAW 264.7 macrophages.

The anti-inflammatory effects of α- and γ-mangostins were evaluated by carrageenan-induced paw edema in mice. The α-mangostin and sulindac (reference compound) treatment showed a potent inhibition of paw edema at 3 h and 5 h, respectively. The action of α-mangostin was more rapid than that of sulindac. However, γ-mangostin did not significant inhibit the paw oedema in mice. This demonstrated that *in vivo* α-mangostin has more anti-inflammatory activity than γ-mangostin. In addition, Deschamps et al. (2007) demonstrated that α-mangostin inhibited 12-human lipoxygenase (12-LOX) with an IC_{50} of 0.58 μM.

The IgE receptor activates intracellular signal transductions resulting in the release of inflammatory signal mediators such as histamine and this is the primary event in several allergic responses. Based on this information, Itoh et al. (2008) demonstrated that xanthones isolated from mangosteen (α, β and γ-mangostins) suppressed the degranulation in Ag-mediated activation of IgE

receptors in rat basophilic leukemia RBL-2H3 cells. These authors suggest that the inhibitory mechanism of degranulation by xanthones was mainly due to suppression of the SYK/PLCγs/PKC pathway.

All the data above indicate that xanthones isolated from mangosteen could be a novel target of anti-inflammatory and antiallergic compounds.

4.4. Antibacterial, antifungal and antiviral properties

Several studies have demonstrated antibacterial, antifungal and antiviral properties of xanthones and extracts obtained from GML (Tables 10 and 11).

Sundaram et al. (1983) studied the antibacterial and antifungal properties of α-mangostin and four of its derivatives. They found that bacteria *S. aureus*, *P. aeruginosa*, *Salmonella typhimurium* and *Bacillus subtilis* were highly susceptible to xanthones, whereas *Proteus* sp., *Klebsiella* sp. and *Escherichia coli* were only moderately susceptible to them. About fungi, *Epidermophyton floccosum*, *Alternaria solani*, *Mucor* sp., *Rhizupus* sp. and *Cunninghamella echinulata* were also highly susceptible to xanthones, whereas *Trichophyton mentagrophytes*, *Microsporum canis*, *Aspergillus niger*, *Aspergillus flavus*, *Penicillium* sp., *Fusarium roseum* and *Curvularia lunata* were only moderately susceptible to them. The minimum inhibitory concentration (MIC, the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation) of α-mangostin was between 12.5 and 50 μg/mL for bacteria and between 1 and 5 μg/mL for fungi. The order of the antibacterial and antifungal efficiency was as follows: α-mangostin > isomangostin > 3-*O*-methyl mangostin > 3,6-di-*O*-methyl mangostin. Mangostin triacetate had no activity.

Mahabusarakam et al. (1986) investigated the antimicrobial activities of mangostin, gartanin, γ-mangostin, 1-isomangostin and 3-isomangostin isolated from GML against *S. aureus*, both normal and penicillin-resistant strains. The order of the efficacy determined by the MIC (μg/mL) was found to be methicillin (3.9) > α-mangostin (15.6) > γ-mangostin (31.2) > 1-isomangostin (62.5) > 3-isomangostin (125) > gartanin (250) against normal strain, and for penicillin-resistant strains α-mangostin (1.56–12.5) > methicillin (1.56–12.5) > 1-isomangostin (125) > 3-isomangostin (250), γ-mangostin (250) and gartanin (250). In addition, the activities of mangostin, gartanin and γ-mangostin against *Candida albicans*, *Cryptococcus neoformans*, *T. mentagrophytes* and *Microsporum gypseum* were tested. All of the components showed moderate activities against *T. mentagrophytes* and *M. gypseum* but exhibited no activity against *C. albicans* and *C. neoformans*.

Iinuma et al. (1996) studied the inhibitory effect of several xanthones, isolated from mangosteen-fruit pericarp, against the growth of methicillin-resistant *S. aureus* (MRSA). α-mangostin exhibited high efficacy, with MIC values of 1.57–12.5 μg/mL.

Chanarat et al. (1997) found that polysaccharides obtained from mangosteen-fruit pericarp can stimulate activity of polymorphonuclear phagocytic cells against *Salmonella enteritidis*.

Suksamrarn et al. (2003) studied the antituberculosis potential of prenylated xanthones obtained from mangosteen-fruit pericarp. Among them α-, and β-mangostins and garcinone B exhibited the most potent inhibitory effect against *Mycobacterium tuberculosis*, with an MIC of 6.25 μg/mL; whereas demethylcalabaxanthone and trapezifolixanthone had an MIC value of 12.5 μg/mL and γ-mangostin, garcinone D, mangostanin, mangostenone A and tovophyllin B had an MIC value of 25 μg/mL. The xanthones with low antituberculosis potential were mangostenol and mangostanol with MIC values of 100 μg/mL and 200 μg/mL, respectively.

Chomnawang et al. (2005) evaluated the antibacterial activity of 19 medicinal plants from Thailand against *Staphylococcus epidermidis* and *Propionibacterium acnes*, which have been recognized as pus-forming bacteria triggering an inflammation in acne. Only 13 Thai medicinal plants were able to inhibit the growth of both bacteria. Among these, GML exhibited the most potent inhibitory effect, with an MIC value of 0.039 μg/mL for both bacteria.

Table 10
Antibacterial properties of *G. mangostana*

Effect	References
α-Mangostin strongly inhibited *S. aureus*, *P. aeruginosa*, *S. thypimurium*, *B. Subillis*	Sundaram et al. (1983)
It was showed the antibacterial activity of the α- and γ-mangostins in 49 species of methicillin-resistant *Staphylococcus aureus* (MRSA) and the antibacterial activity of α-mangostin in 50 species of MRSA and 13 species of *Enterococcus* spp.	Phongpaichit et al. (1994)
Six xanthones including α-mangostin, garcinone E, gartanin, and γ-mangostin showed antibacterial activity against MRSA	Iinuma et al. (1996)
Polysaccharides form the pericarp of GML enhanced the ability of phagocytic cells to kill *Salmonella enteritidis in vitro*	Chanarat et al. (1997)
α and γ-mangostins and garcinone B exhibited strong inhibitory effect against *Mycobacterium tuberculosis*	Suksamrarn et al. (2003)
Extract of GML ihibited the growth of *Propionibacterium acnes* and *Staphylococcus epidermidis*	Chomnawang et al. (2005)
α-Mangostin is active against vancomycin resistant Enterococci (VRE) and MRSA	Sakagami et al. (2005)
Ethanolic extracts of GML inhibited MRSA and *S. aureus* ATCC25923	Voravuthikunchai and Kitpipit (2005)
The herbal mouthwash containing the pericarp extract of GML may be used as an adjunct in treating oral malodor	Rassameemasmaung et al. (2007)

Table 11
Antifungal and antiviral properties of *G. mangostana*

Effect	References
α-Mangostin showed antifungal activity against *Epidermdophyton floccosum*. *Alternaria solani*, *Mucor* sp., *Rhizopus* sp., *Cunninghamella echinulata*	Sundaram et al. (1983)
α-Mangostin, gartanin, γ-mangostin, 1-isomangostin and 3-isomangostin showed activity against *Staphylococcus aureus* both normal and penicilline-resistan strains. Mangostin, γ-mangostin and gartanin showed moderate activities against *Trichophyton mentagrophytes* and *Microsporum gypseum*	Mahabusarakam et al. (1986)
Ethanolic extract of GM, and α and β-mangostins have a potent inhibitory activity against HIV-1 protease (proteolytic cleavage)	Chen et al. (1996) and Vlietinck et al. (1998)
α-mangostin, BR-xanthone A, gartanin, 8-deoxygartanin, garcinone D, γ-mangostin, and euxanthone showed antifungal activity against *F. oxysprum vasinfectum*, *A. tenuis*, and *D. oryzae*	Gopalakrishnan et al. (1997)

Gopalakrishnan et al. (1997) demonstrated that A and B rings of xanthones are important to antifungal activity.

Furthermore, the GML minimal bactericidal concentration, that is the lowest concentration to kill bacteria, was 0.039 and 0.156 μg/mL against *P. acnes* and *S. epidermidis*, respectively. In addition, the same author showed that *G. mangostana* ethanolic extract could significantly reduce TNF-α production generated from peripheral blood mononuclear cells by stimulating with *P. acnes* (Chomnawang et al., 2007).

Sakagami et al. (2005) found that α-mangostin had inhibitory activity against vancomycin resistant *Enterococci* (VRE) and MRSA with MIC values of 6.25 and 12.5 μg/mL, respectively. Synergy between α-mangostin and gentamicin against VRE; and α-mangostin and vancomycin hydrochloride against MRSA was shown. Furthermore, partial synergy between α-mangostin and ampicillin or minocycline was also shown.

Voravuthikunchai and Kitpipit (2005) studied aqueous an ethanolic extracts obtained from 10 traditional Thai medicinal plants for their ability to inhibit MRSA from 35 hospitals. Nine Thai plants had activity against these bacteria. Ethanolic extracts from GML, *Punica granatum* and *Quercus infectoria* were highly efficient at inhibiting bacterial growth, with MIC values of 0.05, 0.2 to 0.4 and 0.1 to 1.6 μg/mL, respectively.

Phongpaichit et al. (1994) studied the antibacterial activity of α- and γ-mangostins and a mangostin mixture on 49 strains of MRSA isolated from patients in Songklanagarind Hospital. They also studied the antibacterial activity of α-mangostin on 50 strains of MRSA and 13 strains of *Enterococcus* spp. isolated from patients in Maharaj Nakorn Chiang Mai Hospital. Mangostin mixture had the most potent effect against MRSA, with an MIC value of 1.48 μg/mL, which was the same value as vancomycin, an antimicrobial agent used as a positive control. Penicillin G was also used as control and its MIC was >50 μg/mL. Furthermore, α- and γ-mangostins also had an effect against MRSA, with MIC values of 3.12 and 2.26 μg/mL, respectively. The MIC value of α-mangostin against MRSA was 8 μg/mL. Mangostin inhibited the growth of all *Enterococcus* spp. with an MIC value of 1 μg/mL.

Gopalakrishnan et al. (1997) demonstrated the antifungal activity of several xanthones isolated from mangosteen-fruit pericarp and some α-mangostin-derivatives against three phytopathogenic fungi (*Fusarium oxysporum vasinfectum*, *Alternaria tenuis* and *Dreschlera oryzae*). α-mangostin, γ-mangostin, gartanin, garcinone D, BR-xanthone and euxanthone showed high inhibitory activity against the three fungi; they used 1, 10, 100 and 1000 ppm in the culture medium. Substitution in A and C rings has been shown to modify the bioactivities of the compounds.

Several natural products have been identified because of their capacity to inhibit different stages in the replication cycle of human immunodeficiency virus (HIV-1). Among them, xanthones have been shown to inhibit proteolytic cleavage by protease inhibition (reviewed in Vlietinck et al., 1998).

Chen et al. (1996) showed that ethanolic extract of GML effectively inhibited HIV-1 protease. Two xanthones were isolated from the ethanolic extract: α- and γ-mangostins, which exhibited an IC_{50} value of 5.12 ± 0.41 and 4.81 ± 0.32 μM, respectively. Pepstatin A (IC_{50} = 76 ± 5.5 nM) was used as positive control.

Recently, Rassameemasmaung et al. (2007) showed that a herbal mouthwash containing the pericarp extract of GML has some effect against volatile sulfur compounds, plaque and papillary bleeding in sixty subjects who were diagnosed as having mild or moderate chronic gingivitis, so the pericarp extract may be used as an adjunct in treating oral malodor.

4.5. Antimalarial properties

Several xanthones isolated from GML have shown antimalaria activity *in vitro* against *Plasmodium falciparum*. β-mangostin and α-mangostin exhibited a comparable IC_{50} value (7 and 5.1 μM respectively), whereas mangiferina, a xanthone-glucoside, exhibited an IC_{50} value higher than 50 μM (Riscoe et al., 2005). In the other hand, Mahabusarakam et al. (2006) found that α-mangostin exhibited an IC_{50} value of 17 μM against *P. falciparum*.

Laphookhieo et al. (2006) found that β-mangostin isolated from roots of *C. cochinchinense* had an IC_{50} value of 7.2 μg/mL against *P. falciparum*.

5. Medicinal properties of xanthones isolated from sources other than *G. Mangostana*

The following medicinal properties have been described about xanthones that are isolated from sources other than GML: antimalarial (Pinto et al., 2005; Laphookhieo et al., 2006; Riscoe et al., 2005; Mahabusarakam et al., 2006; Azebaze et al., 2006; Likhitwitayawuid et al., 1998a,b); antidiabetes, antihiperlipidemic and antiatherogenic (Muruganandan et al., 2005; Pinto et al., 2005); antibacterial (Pinto et al., 2005; Azebaze et al., 2006; Dharmaratne and Wijesinghe, 1999), anticancer (Pedro et al., 2002), antitumoral (Pinto et al., 2005; Laphookhieo et al., 2006; Liou et al., 1993), cardioprotective (Pinto et al., 2005; Jiang et al., 2004) and hepatoprotective, immunomodulator, anti-inflammatory, antiulcer, antiviral and antifungal (reviewed in Pinto et al., 2005).

6. Conclusions

Following the discovery of medicinal properties in components of *G. mangostana*, many studies have been conducted. These studies include both natural extracts and synthetic derivatives. In this review, the potential beneficial effect of GML in both acute and chronic disease has been discussed. This suggests possible therapeutic applications that relate to GML. Nevertheless, further studies need to be done in order to investigate the effects of GML extracts in humans.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgements

This work was supported by Programa de Apoyo a Proyectos de Investigación e Innovación Teconológica, Direccion General de Asunto del Personal Académico (DGAPA, Grant No. IN207007) from Universidad Nacional Autónoma de México (UNAM).

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