

Mangosteen Clinical Abstracts



Antiproliferation, antioxidation and induction of apoptosis by *Garcinia mangostana* (mangosteen) on SKBR3 human breast cancer cell line.

Moongkarndi P, Kosem N, Kaslungka S, Luanratana O, Pongpan N, Neungton N.

Department of Microbiology, Faculty of Pharmacy, Mahidol University, Sri Ayudthaya Road, Rajdhevee, Bangkok 10400, Thailand. pypmk@mahidol.ac.th

This study was designed to determine the antiproliferative, apoptotic and antioxidative properties of crude methanolic extract (CME) from the pericarp of *Garcinia mangostana* (family Guttiferae) using human breast cancer (SKBR3) cell line as a model system. SKBR3 cells were cultured in the presence of CME at various concentrations (0-50 microg/ml) for 48 h and the percentage of cell viability was evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-di phenyl tetrazolium bromide (MTT) assay. CME showed a dose-dependent inhibition of cell proliferation with ED(50) of 9.25+/-0.64 microg/ml. We found that antiproliferative effect of CME was associated with apoptosis on breast cancer cell line by determinations of morphological changes and oligonucleosomal DNA fragments. In addition, CME at various concentrations and incubation times were also found to inhibit ROS production. These investigations suggested that the methanolic extract from the pericarp of *Garcinia mangostana* had strong antiproliferation, potent antioxidation and induction of apoptosis. Thus, it indicates that this substance can show different activities and has potential for cancer chemoprevention which were dose dependent as well as exposure time dependent.

Induction of apoptosis by xanthenes from mangosteen in human leukemia cell lines.

Matsumoto K, Akao Y, Kobayashi E, Ohguchi K, Ito T, Tanaka T, Iinuma M, Nozawa Y.

Gifu International Institute of Biotechnology, 1-1 Naka-Fudogaoka, Kakamigahara, Gifu 504-0838, Japan. kmatsumoto@giib.or.jp

We examined the effects of six xanthenes from the pericarps of mangosteen, *Garcinia mangostana*, on the cell growth inhibition of human leukemia cell line HL60. All xanthenes displayed growth inhibitory effects. Among them, alpha-mangostin showed complete inhibition at 10 microM through the induction of apoptosis.

Antimycobacterial activity of prenylated xanthenes from the fruits of *Garcinia mangostana*.

Suksamrarn S, Suwannapoch N, Phakhodee W, Thanuhiranlert J, Ratananukul P, Chimnoi N, Suksamrarn A.

Department of Chemistry, Faculty of Science, Srinakharinwirot University, Bangkok, Thailand. sunit@swu.ac.th

Prenylated xanthenes, isolated from the fruit hulls and the edible arils and seeds of *Garcinia mangostana*, were tested for their antituberculosis potential. Alpha- and beta-mangostins and garcinone B exhibited strong inhibitory effect against *Mycobacterium tuberculosis* with the minimum inhibitory concentration (MIC) value of 6.25 microg/ml. Tri- and tetra-oxygenated xanthenes with di-C5 units or with a C5 and a modified C5 groups are essential for high activities. Substitution in the A and C rings has been shown to modify the bioactivity of the compounds.

Garcinone E, a xanthone derivative, has potent cytotoxic effect against hepatocellular carcinoma cell lines.

Ho CK, Huang YL, Chen CC.

Department of Medical Research & Education, Veterans General Hospital, Taipei, ROC.

Treatment of hepatocellular carcinomas (HCCs) with chemotherapy has generally been disappointing and it is most desirable to have more effective new drugs. We extracted and purified 6 xanthone compounds from the rinds (peel) of the fruits of *Garcinia mangostana* L., using partitioned chromatography and then tested the cytotoxic effects of these compounds on a panel of 14 different human cancer cell lines including 6 hepatoma cell lines, based on the MTT method. Several commonly used chemotherapeutic agents were included in the assay to determine the relative potency of the potential new drugs. Our results have shown that one of the xanthone derivatives which could be identified as garcinone E has potent cytotoxic effect on all HCC cell lines as well as on the other gastric and lung cancer cell lines included in the screen. We suggest that garcinone E may be potentially useful for the treatment of certain types of cancer.

Inhibitions of histamine release and prostaglandin E2 synthesis by mangosteen, a Thai medicinal plant.

Nakatani K, Atsumi M, Arakawa T, Oosawa K, Shimura S, Nakahata N, Ohizumi Y.

Department of Pharmaceutical Molecular Biology, Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai, Japan.

The fruit hull of mangosteen, *Garcinia mangostana* L. has been used as a Thai indigenous medicine for many years. However, its mechanism of action as a medicine has not been elucidated. The present study was undertaken to examine the effects of mangosteen extracts (100% ethanol, 70% ethanol, 40% ethanol and water) on histamine release and prostaglandin E2 synthesis. We found that the 40% ethanol extract of mangosteen inhibited IgE-mediated histamine release from RBL-2H3 cells with greater potency than the water extract of *Rubus suavissimus* that has been used as an anti-allergy crude drug in Japan. All extracts of mangosteen potently inhibited A23187-induced prostaglandin E2 synthesis in C6 rat glioma cells, while the water extract of *Rubus suavissimus* had no effect. The 40% ethanol extract of mangosteen inhibited the prostaglandin E2 synthesis in a concentration-dependent manner with relatively lower concentrations than the histamine release. In addition, passive cutaneous anaphylaxis (PCA) reactions in rats were significantly inhibited by this ethanol extract as well as by the water extract of *Rubus suavissimus*. These results suggest that the 40% ethanol extract of mangosteen has potent inhibitory activities of both histamine release and prostaglandin E2 synthesis.

Inhibition of cyclooxygenase and prostaglandin E2 synthesis by gamma-mangostin, a xanthone derivative in mangosteen, in C6 rat glioma cells.

Nakatani K, Nakahata N, Arakawa T, Yasuda H, Ohizumi Y.

Department of Pharmaceutical Molecular Biology, Graduate School of Pharmaceutical Sciences, Tohoku University, Aoba, Aramaki, Aoba-ku, 980-8578, Sendai, Japan.

The fruit hull of mangosteen, *Garcinia mangostana* L., has been used for many years as a medicine for treatment of skin infection, wounds, and diarrhea in Southeast Asia. In the present study, we examined the effect of gamma-mangostin, a tetraoxygenated diprenylated xanthone contained in mangosteen, on arachidonic acid (AA) cascade in C6 rat glioma cells. gamma-Mangostin had a potent inhibitory activity of prostaglandin E2 (PGE2) release induced by A23187, a Ca²⁺ ionophore. The inhibition was concentration-dependent, with the IC₅₀ value of about 5 microM. gamma-Mangostin had no inhibitory effect on A23187-induced phosphorylation of p42/p44 extracellular signal regulated kinase/mitogen-activated protein kinase or on the liberation of [¹⁴C]-AA from the cells labeled with [¹⁴C]-AA. However, gamma-mangostin concentration-dependently inhibited the conversion of AA to PGE2 in microsomal preparations, showing its possible inhibition of cyclooxygenase (COX).

In enzyme assay in vitro, gamma-mangostin inhibited the activities of both constitutive COX (COX-1) and inducible COX (COX-2) in a concentration-dependent manner, with the IC₅₀ values of about 0.8 and 2 microM, respectively. Lineweaver-Burk plot analysis indicated that gamma-mangostin competitively inhibited the activities of both COX-1 and -2. This study is a first demonstration that gamma-mangostin, a xanthone derivative, directly inhibits COX activity.

Characterization of acyl-ACP thioesterases of mangosteen (*Garcinia mangostana*) seed and high levels of stearate production in transgenic canola.

Hawkins DJ, Kridl JC.

Calgene, Inc., Davis, CA 95616, USA.

Acyl-acyl-carrier protein (ACP) thioesterases are, at least in part, responsible for the fatty acyl chain length composition of seed storage oils. Acyl-ACP thioesterases with specificity for each of the saturated acyl-ACP substrates from 8:0 through 16:0 have been cloned, with the exception of 18:0, and are members of the FatB class of thioesterases. The authors have determined that the tropical tree species mangosteen (*Garcinia mangostana*) stores 18:0 (stearate) in its seed oil in amounts of up to 56% by weight. Acyl-ACP thioesterase activity as measured in crude mangosteen seed extracts showed a preference for 18:1-ACP substrates, but had significant activity with 18:0 relative to that with 16:0-ACP, suggesting a thioesterase might be involved in the production of stearate. Three distinct acyl-ACP thioesterases were cloned from mangosteen seed cDNA; two representative of the FatA class and one representative of the FatB class. When expressed in vitro, the enzyme encoded by one of the FatAs (Garm FatA1) while preferring 18:1-ACP showed relatively low activity with 16:0-ACP as compared to 18:0-ACP, similar to the substrate preferences shown by the crude seed extract. Expression of Garm FatA1 in Brassica seeds led to the accumulation of stearate up to 22% in seed oil. These results suggest that Garm FatA1 is at least partially responsible for determining the high stearate composition of mangosteen seed oil and that FatA as well FatB thioesterases have evolved for specialized roles.

Immunopharmacological activity of polysaccharide from the pericarb of mangosteen *Garcinia mangostana*: phagocytic intracellular killing activities.

Chanarat P, Chanarat N, Fujihara M, Nagumo T.

Department of Clinical Microscopy, Faculty of Associated Medical Sciences, Chiang Mai University, Thailand.

Polysaccharides from the pericarbs of mangosteen, *Garcinia mangostana* Linn., was obtained by treating the dried ground pericarbs with hot water followed by ethanol precipitation (M fraction). The extract was fractionated by anion exchange chromatography on a DEAE-cellulose column as MDE1-5 fractions.

The fractions of MDE3 and MDE4 composed of mainly D-galacturonic acid and a small amount of neutral sugar (L-arabinose as the major one and L-rhamnose and D-galactose as the minor ones) were studied for immunopharmacological activities by phagocytic test to intracellular bacteria (*Salmonella enteritidis*) and nitroblue tetrazolium (NBT) and superoxide generation tests. The results showed that the number of *S. enteritidis* in cultured monocyte with extract of pericarb of mangosteen (MDE3) was killed. Activating score (mean \pm SD) of NBT test of 100 polymorphonuclear phagocytic cells were 145 \pm 78, 338 \pm 58, 222 \pm 73, 209 \pm 77, 211 \pm 63, 372 \pm 19, 369 \pm 20, 355 \pm 34 in normal saline control, phorbol myristate acetate (PMA), MDE3, MDE4, indomethacin (I), PMA + MDE3, PMA + MDE4 and PMA + I, respectively. Superoxide generation test was also done by color reduction of cytochrome c. Both MDE3 and MDE4 stimulate superoxide production. The number of *S. enteritidis* in cultured monocyte with extract of pericarb of mangosteen was killed. This paper suggests that polysaccharides in the extract can stimulate phagocytic cells and kill intracellular bacteria (*S. enteritidis*).

Histaminergic and serotonergic receptor blocking substances from the medicinal plant *Garcinia mangostana*.

Chairungrilerd N, Furukawa K, Ohta T, Nozoe S, Ohizumi Y.

A crude methanolic extract of the fruit hull of Mangosteen, *Garcinia mangostana* L. inhibited the contractions of isolated thoracic rabbit aorta induced by histamine and serotonin. The extract of the fruit hull has been fractionated by silica gel chromatography, monitoring the pharmacological activity to give alpha- and gamma-mangostin. On the basis of pharmacological data, it is suggested that alpha-mangostin and gamma-mangostin are a histaminergic and a serotonergic receptor blocking agent, respectively.

Study of genotoxic effects of antidiarrheal medicinal herbs on human cells in vitro.

Settheetham W, Ishida T.

Department of Physiology, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand.

The use of medicinal herbs has been a common practice in Asia but their genotoxic properties are little known. In the present study, genotoxic effects of three antidiarrheal herbs, guava leaf, mangosteen peel and pomegranate peel, were examined using established human cell lines, Raji and P3HR-1. Cells were treated with boiled-water extract of the herbs at various concentrations for 24 and 48 hours in vitro. Cell growth and viability were dose dependently reduced. No apparent chromosomal aberrations were induced by the treatment. Administration of pomegranate extract induced apoptotic DNA fragmentation. This genotoxicity test system is simple and convenient for the primary screening.

Inhibition of wheat embryo calcium-dependent protein kinase and other kinases by mangostin and gamma-mangostin.

Jinsart W, Ternai B, Buddhasukh D, Polya GM.

Department of Chemistry, La Trobe University, Bundoora, Victoria, Australia.

The hull of the fruit of the mangosteen tree (*Garcinia mangostana*) contains four inhibitors of plant Ca(2+)-dependent protein kinase. Two of these inhibitors have been purified and identified as the xanthenes 1,3,6-trihydroxy-7-methoxy-2,8-bis(3-methyl-2-butenyl)-9H-xanthen-9-one (mangostin) and 1,3,6,7-tetrahydroxy-2,8-bis(3-methyl-2-butenyl)-9H-xanthen-9-one (gamma-mangostin). Both xanthenes also inhibit avian myosin light chain kinase and rat liver cyclic AMP-dependent protein kinase. This is the first report of inhibition of plant and animal second messenger-regulated protein kinases by plant-derived xanthenes.

Antiproliferative activity of Thai medicinal plant extracts on human breast adenocarcinoma cell line.

Moongkarndi P, Kosem N, Luanratana O, Jongsomboonkusol S, Pongpan N.

Department of Microbiology, Faculty of Pharmacy, Mahidol University, Rajdhevee, Sri Ayudthaya Rd, Bangkok 10400, Thailand. pypmk@mahidol.ac.th

Ethanollic extracts of selected nine Thai medicinal plants were tested for antiproliferative activity against SKBR3 human breast adenocarcinoma cell line using MTT assay. *Garcinia mangostana* showed the most potent activity. However, all plant extracts showed activity in potential range for further investigation on cancer cells.

Alpha-mangostin induces Ca(2+)-ATPase-dependent apoptosis via mitochondrial pathway in PC12 cells.

Sato A, Fujiwara H, Oku H, Ishiguro K, Ohizumi Y.

Department of Pharmaceutical Molecular Biology, Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai, Japan.

We investigated the cell death effects of eight xanthenes on PC12 rat pheochromocytoma cells. Among these compounds, alpha-mangostin, from the fruit hull of *Garcinia mangostana* L., had the most potent effect with the EC(50) value of 4 microM. Alpha-mangostin-treated PC12 cells demonstrated typical apoptotic DNA fragmentation and caspase-3 cleavage (equivalent to activation). The flow cytometric analysis indicated that this compound induced apoptosis in time-and concentration-dependent manners. Alpha-mangostin showed the features of the mitochondrial apoptotic pathway such as mitochondrial membrane depolarization and cytochrome c release. Furthermore, alpha-mangostin inhibited the sarco(endo)plasmic reticulum Ca(2+)-ATPase markedly.

There was a correlation between the Ca(2+)-ATPase inhibitory effects and the apoptotic effects of the xanthone derivatives. On the other hand, c-Jun NH(2)-terminal kinase (JNK/SAPK), one of the signaling molecules of endoplasmic reticulum (ER) stress, was activated with alpha-mangostin treatment. These results suggest that alpha-mangostin inhibits Ca(2+)-ATPase to cause apoptosis through the mitochondrial pathway.

Effect of gamma-mangostin through the inhibition of 5-hydroxytryptamine_{2A} receptors in 5-fluoro-alpha-methyltryptamine-induced head-twitch responses of mice.

Chairungrilerd N, Furukawa K, Tadano T, Kisara K, Ohizumi Y.

Department of Molecular Biology, Faculty of Pharmaceutical Sciences, Tohoku University, Sendai, Japan.

1. Intracerebroventricular (i.c.v.) injection of gamma-mangostin (10-40 nmol/mouse), a major compound of the fruit hull of *Garcinia mangostana* Lin., like ketanserin (10, 20 nmol/mouse, i.c.v.) inhibited 5-fluoro-alpha-methyltryptamine (5-FMT) (45 mg kg⁻¹, i.p.)-induced head-twitch response in mice in the presence or absence of citalopram (a 5-hydroxytryptamine (5-HT)-uptake inhibitor). 2. Neither the 5-FMT- nor the 8-hydroxy-2-(di-n-propylamino)tetralin (5-HT_{1A}-agonist)-induced 5-HT syndrome (head weaving and hindlimb abduction) was affected by gamma-mangostin or ketanserin. 3. The locomotor activity stimulated by 5-FMT through the activation of alpha₁-adrenoceptors did not alter in the presence of gamma-mangostin. 4. 5-HT-induced inositol phosphates accumulation in mouse brain slices was abolished by ketanserin. Gamma-mangostin caused a concentration-dependent inhibition of the inositol phosphates accumulation. 5. Gamma-mangostin caused a concentration-dependent inhibition of the binding of [³H]-spiperone, a specific 5-HT_{2A} receptor antagonist, to mouse brain membranes. 6. Kinetic analysis of the [³H]-spiperone binding revealed that gamma-mangostin increased the K_d value without affecting the B_{max} value, indicating the mode of the competitive nature of the inhibition by gamma-mangostin. 7. These results suggest that gamma-mangostin inhibits 5-FMT-induced head-twitch response in mice by blocking 5-HT_{2A} receptors not by blocking the release of 5-HT from the central neurone. Gamma-mangostin is a promising 5-HT_{2A} receptor antagonist in the central nervous system.

Novel types of receptor antagonists from the medicinal plant *Garcinia Mangostana*

Furukawa K, Chairungsrilerd N, Ohta T, Nozoe S, Ohizumi Y.

Department of Pharmaceutical Molecular Biology, Faculty of Pharmaceutical Sciences, Tohoku University, Sendai, Japan.

A crude methanolic extract of the fruit hull of *Garcinia mangostana* L. inhibited the contraction of the isolated rabbit aorta induced by histamine and serotonin. The extract has been fractionated by silica gel chromatography, monitoring the pharmacological activity to give active compounds. On the basis of physicochemical data, the active substances were identified as alpha-mangostin and gamma-mangostin. To define the pharmacological properties of alpha-mangostin, the effect of alpha-mangostin on both histamine H1 and H2 receptors were examined by monitoring the mechanical responses of smooth muscles and measuring the radioligand binding to cultured vascular smooth muscle cells. The results suggest that alpha-mangostin acts as a selective and competitive histamine H1 receptor antagonist. The pharmacological actions of gamma-mangostin on 5-HT receptors were also investigated by using contractile response of vascular smooth muscle, platelet aggregation and radioligand binding studies. The results provide the evidence that gamma-mangostin is a selective and competitive 5-HT_{2A} receptor antagonist. It is of great interest that the structures of alpha-mangostin and gamma-mangostin free from nitrogen atom are not resemble to the common structures of histamine and serotonin receptor antagonists. alpha-Mangostin and gamma-mangostin may become novel types of lead compounds for histamine and serotonin receptor antagonists.

Gamma-mangostin, a novel type of 5-hydroxytryptamine 2A receptor antagonist.

Chairungsrilerd N, Furukawa KI, Ohta T, Nozoe S, Ohizumi Y.

Department of Pharmaceutical Molecular Biology, Faculty of Pharmaceutical Sciences, Tohoku University, Sendai, Japan.

Gamma-mangostin, purified from the fruit hull of the medicinal plant *Garcinia mangostana* caused a parallel rightwards shift of the concentration/response curve for the contraction elicited by 5-hydroxytryptamine (5-HT) in the rabbit aorta ($pA_2 = 8.2$) without affecting the contractile responses to KCl, phenylephrine (α_1) or histamine (H₁). The perfusion pressure response of rat coronary artery to 5-HT (5-HT_{2A}) was reduced concentration dependently by gamma-mangostin ($IC_{50} = 0.32 \text{ microM}$). 5-HT amplified,

ADP-induced aggregation of rabbit platelets (5-HT_{2A}) was inhibited by gamma-mangostin (IC₅₀ = 0.29 microM), whereas that induced by thrombin was not affected, nor did gamma-mangostin affect 5-HT-induced contraction of the guinea-pig ileum (5-HT₃) in the presence of 5-HT₁, 5-HT₂ and 5-HT₄ receptor antagonists. Furthermore, 5-HT-induced contraction of the rat fundus (5-HT_{2B}) and 5-HT-induced relaxation of the rabbit aorta in the presence of ketanserin (5-HT₁) and carbachol-induced contraction of the guinea-pig ileum (muscarinic M₃) were not affected by gamma-mangostin (5 microM). Gamma-mangostin inhibited [³H]spiperone binding to cultured rat aortic myocytes (IC₅₀ = 3.5 nM). The K_d for [³H]spiperone binding was increased by gamma-mangostin (3 nM) from 11.7 to 27.4 nM without affecting B_{max}. These results suggest that gamma-mangostin is a novel competitive antagonist, free from a nitrogen atom, for the 5-HT_{2A} receptors in vascular smooth muscles and platelets.

Evaluation of the antifungal activity of natural xanthenes from *Garcinia mangostana* and their synthetic derivatives.

Gopalakrishnan G, Banumathi B, Suresh G.

Centre for Agrochemical Research, SPIC Science Foundations, Madras, India.

The antifungal activity of several xanthenes isolated from the fruit hulls of *Garcinia mangostana* and some derivatives of mangostin against three phytopathogenic fungi, *Fusarium oxysporum* var. *vasinfectum*, *Alternaria tenuis*, and *Dreschlera oryzae*, has been evaluated. The natural xanthenes showed good inhibitory activity against the three fungi. Substitution in the A and C rings has been shown to modify the bioactivities of the compounds.

Antibacterial activity of xanthenes from guttiferaceous plants against methicillin-resistant *Staphylococcus aureus*.

Iinuma M, Tosa H, Tanaka T, Asai F, Kobayashi Y, Shimano R, Miyauchi K.

Department of Pharmacognosy, Gifu Pharmaceutical University, Japan.

Extracts of *Garcinia mangostana* (Guttiferae) showing inhibitory effects against the growth of *S. aureus* NIHJ 209p were fractionated according to guidance obtained from bioassay and some of the components with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) were characterized. One active isolate, alpha-mangostin, a xanthone derivative, had a minimum inhibitory concentration (MIC) of 1.57-12.5 micrograms mL⁻¹. Other related xanthenes were also examined to determine their anti-MRSA activity. Rubraxanthone, which was isolated from *Garcinia dioica* and has a structure similar to that of alpha-mangostin, had the highest activity against staphylococcal strains (MIC = 0.31-1.25 micrograms mL⁻¹), an activity which was greater than that of the antibiotic vancomycin (3.13-6.25 micrograms mL⁻¹). The inhibitory effect against strains of MRSA of two of the compounds when used in conjunction with other antibiotics was also studied.

The anti-MRSA activity of alpha-mangostin was clearly increased by the presence of vancomycin; this behaviour was not observed for rubraxanthone. The strong in-vitro antibacterial activity of xanthone derivatives against both methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* suggests the compounds might find wide pharmaceutical use.

The mode of inhibitory action of alpha-mangostin, a novel inhibitor, on the sarcoplasmic reticulum Ca(2+)-pumping ATPase from rabbit skeletal muscle.

Furukawa K, Shibusawa K, Chairungsrilerd N, Ohta T, Nozoe S, Ohizumi Y.

Department of Pharmaceutical Molecular Biology, Faculty of Pharmaceutical Sciences, Tohoku University, Sendai, Japan.

alpha-Mangostin, the principal ingredient of the fruit hull of *Garcinia mangostana*, caused a concentration-dependent decrease in the activities of both Ca(2+)-ATPase and Ca(2+)-transport of the sarcoplasmic reticulum from rabbit skeletal muscle with an IC₅₀ value of 5 microM. Neither Ca²⁺ release nor other enzyme activities were affected by alpha-mangostin. Kinetic analysis of the inhibitory effects of alpha-mangostin on Ca(2+)-ATPase suggests that the inhibition of the ATPase is a noncompetitive-type with respect to ATP or Ca²⁺. alpha-Mangostin may become a useful pharmacological tool for clarifying the physiological functions of Ca(2+)-pumping ATPase and sarcoplasmic reticulum.

Active constituents against HIV-1 protease from *Garcinia mangostana*.

Chen SX, Wan M, Loh BN.

The ethanol extract of *Garcinia mangostana* L. (Guttiferae) showed potent inhibitory activity against HIV-1 protease. The activity-guided purification of the extract resulted in the isolation of two active, known compounds. The chemical structures of the isolated compounds were established by spectroscopic analyses as mangostin (IC₅₀ = 5.12 +/- 0.41 microM) and gamma-mangostin (IC₅₀ = 4.81 +/- 0.32 microM). The type of inhibition by both compounds is noncompetitive.

Mangostin inhibits the oxidative modification of human low density lipoprotein.

Williams P, Ongsakul M, Proudfoot J, Croft K, Beilin L.

University of Western Australia, Department of Medicine, Royal Perth Hospital, Australia.

The oxidation of low density lipoprotein (LDL) may play an important role in atherosclerosis. We investigated the possible antioxidant effects of mangostin, isolated from *Garcinia mangostana*, on metal ion dependent (Cu^{2+}) and independent (aqueous peroxy radicals) oxidation of human LDL. Mangostin prolonged the lagtime to both metal ion dependent and independent oxidation of LDL in a dose dependent manner over 5 to 50 μM as monitored by the formation of conjugated dienes at 234 nm ($P < 0.001$). There was no significant effect of mangostin on the rate at which conjugated dienes were formed in the uninhibited phase of oxidation. Levels of thiobarbituric reactive substances (TBARS) generated in LDL were measured 4 and 24 hours after oxidation with 5 μM Cu^{2+} in the presence or absence of 50 μM or 100 μM mangostin. We observed an inhibition of TBARS formation with 100 μM mangostin at 4 hours ($P = 0.027$) but not at 24 hours ($P = 0.163$). Similar results were observed in the presence of 50 μM mangostin. Mangostin, at 100 μM , retarded the relative electrophoretic mobility of LDL at both 4 and 24 hours after Cu^{2+} induced oxidation. Mangostin (100 μM) significantly inhibited the consumption of alpha-tocopherol in the LDL during Cu^{2+} initiated oxidation over a 75 minute period ($P < 0.001$). From these results, we conclude that mangostin is acting as a free radical scavenger to protect the LDL from oxidative damage in this in vitro system.

Pharmacological profile of mangostin and its derivatives.

Shankaranarayan D, Gopalakrishnan C, Kameswaran L.

Mangostin (M), a naturally occurring xanthone in the rinds of the fruits of *Garcinia mangostana* Linn. (Guttiferae) and its derivatives such as 3-O-methyl mangostin (MM), 3,6-di-O-methyl mangostin (DM), 1-isomangostin (IM), mangostin triacetate (MT), mangostin 3,6-di-O-(tetra acetyl) glucoside (MTG) and mangostin-6,6-di-O-glucoside (MOG) were screened for various pharmacological effects in experimental animals. With the exception of DM all the test compounds produced CNS depression characterised by ptosis, sedation, decreased motor activity, potentiation of pentobarbital sleeping time and ether anaesthesia in mice and rats. None of the compounds exhibited analgesic, antipyretic and anticonvulsant effects. With the exception of MOG, none of the test compounds produced significant effects on the cardiovascular system of frogs and dogs. MOG produced myocardial stimulation and a rise in blood pressure which was partially blocked by propranolol. M, IM and MT produced pronounced antiinflammatory activity both by intraperitoneal and oral routes in rats as tested by carrageenin-induced hind paw oedema, cotton pellet implantation and granuloma pouch techniques. Antiinflammatory activity for M, IM and MT was observed even in bilaterally adrenalectomised rats.

M, IM and MT did not produce any mast cell membrane stabilising effect and the degranulation effect of polymyxin B, diazoxide and Triton X-100 on rat peritoneal mast cells in vitro was not prevented. M, IM and MT did not alter the prothrombin time of albino rats. M alone produced significant antiulcer activity in rats.

Gamma-Mangostin inhibits inhibitor-kappaB kinase activity and decreases lipopolysaccharide-induced cyclooxygenase-2 gene expression in C6 rat glioma cells.

Nakatani K, Yamakuni T, Kondo N, Arakawa T, Oosawa K, Shimura S, Inoue H, Ohizumi Y.

Department of Pharmaceutical Molecular Biology, Graduate School of Pharmaceutical Sciences, Tohoku University, Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan.

We investigated the effect of gamma-mangostin purified from the fruit hull of the medicinal plant *Garcinia mangostana* on spontaneous prostaglandin E(2) (PGE(2)) release and inducible cyclooxygenase-2 (COX-2) gene expression in C6 rat glioma cells. An 18-h treatment with gamma-mangostin potently inhibited spontaneous PGE(2) release in a concentration-dependent manner with the IC(50) value of approximately 2 microM, without affecting the cell viability even at 30 microM. By immunoblotting and reverse-transcription polymerase chain reaction, we showed that gamma-mangostin concentration-dependently inhibited lipopolysaccharide (LPS)-induced expression of COX-2 protein and its mRNA, but not those of constitutive COX-1 cyclooxygenase. Because LPS is known to stimulate inhibitor kappaB (IkappaB) kinase (IKK)-mediated phosphorylation of IkappaB followed by its degradation, which in turn induces nuclear factor (NF)-kappaB nuclear translocation leading to transcriptional activation of COX-2 gene, the effect of gamma-mangostin on the IKK/IkappaB cascade controlling the NF-kappaB activation was examined. An in vitro IKK assay using IKK protein immunoprecipitated from C6 cell extract showed that this compound inhibited IKK activity in a concentration-dependent manner, with the IC(50) value of approximately 10 microM. Consistently gamma-mangostin was also observed to decrease the LPS-induced IkappaB degradation and phosphorylation in a concentration-dependent manner, as assayed by immunoblotting. Furthermore, luciferase reporter assays showed that gamma-mangostin reduced the LPS-inducible activation of NF-kappaB and human COX-2 gene promoter region-dependent transcription. gamma-Mangostin also inhibited rat carrageenan-induced paw edema. These results suggest that gamma-mangostin directly inhibits IKK activity and thereby prevents COX-2 gene transcription, an NF-kappaB target gene, probably to decrease the inflammatory agent-stimulated PGE(2) production in vivo, and is a new useful lead compound for anti-inflammatory drug development.

Biological activities of alpha-mangostin derivatives against acidic sphingomyelinase.

Hamada M, Iikubo K, Ishikawa Y, Ikeda A, Umezawa K, Nishiyama S.

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223-8522, Japan.

Deprenyl and benzofenone-type congeners of alpha-mangostin 1 have been synthesized to understand their role for the inhibitory activity against sphingomyelinase (SMase). While removal of the prenyl group of the right side (11 and 12) caused loss of the selectivity between ASMase (acidic sphingomyelinase) and NSMase (neutral sphingomyelinase), the prenyl group of the left side appeared to increase the inhibitory activities (16 and 17).

Inhibition of lipoprotein oxidation by prenylated xanthenes derived from mangostin.

Mahabusarakam W, Proudfoot J, Taylor W, Croft K.

Chemistry Department, Prince of Songkla University, Hat Yai, Thailand.

Oxidative damage is thought to play a critical role in cardiovascular and other chronic diseases. This has led to considerable interest in the antioxidant activity of dietary compounds. Flavonoids have received the most attention and much is known about the structural requirements for antioxidant activity. However, little is known about the antioxidant activity of other plant derived phenolic compounds such as the xanthenes. We have previously shown that the prenylated xanthone, mangostin, can inhibit the oxidation of low density lipoprotein. In order to examine the effects of structure modification on antioxidant activity of this class of compound we have prepared a number of derivatives of mangostin and tested antioxidant activity in an isolated LDL and plasma assay. The results of this study show that structural modification of mangostin can have a profound effect on antioxidant activity. Derivatisation of the C-3 and C-6 hydroxyl groups with either methyl, acetate, propane diol or nitrile substantially reduces antioxidant activity. In contrast, derivatisation of C-3 and C-6 with aminoethyl derivatives enhanced antioxidant activity, which may be related to changes in solubility. Cyclisation of the prenyl chains had little influence on antioxidant activity.

Inhibition of eukaryote protein kinases and of a cyclic nucleotide-binding phosphatase by prenylated xanthenes.

Lu ZX, Hasmeda M, Mahabusarakam W, Ternai B, Ternai PC, Polya GM.

School of Biochemistry, La Trobe University, Bundoora, Victoria, Australia.

A series of prenylated xanthenes are variously potent inhibitors of the catalytic subunit (cAK) of rat liver cyclic AMP-dependent protein kinase (PKA), rat brain Ca²⁺ and phospholipid-dependent protein kinase C (PKC), chicken gizzard myosin light chain kinase (MLCK), wheat embryo Ca²⁺-dependent protein kinase (CDPK) and potato tuber cyclic nucleotide-binding phosphatase (Pase). The prenylated xanthenes examined are mostly derivatives of alpha-mangostin in which the 3-hydroxyl and 6-hydroxyl are variously substituted with groups R or R', respectively, or derivatives of 3-isomangostin (mangostanol) in which the 9-hydroxyl is substituted with groups R' or the prenyl side chain is modified. The most potent inhibitors of cAK have non-protonatable and relatively small R' and R groups. Conversely, the most potent inhibitors of PKC and MLCK have bulkier and basic R' groups. Some prenylated xanthenes are also potent inhibitors of CDPK. PKC and cAK are competitively inhibited by particular prenylated xanthenes whereas the compounds that are the most potent inhibitors of MLCK and CDPK are non-competitive inhibitors. Prenylated xanthenes having relatively small and non-protonatable R' and R groups inhibit a high-affinity cyclic nucleotide binding Pase in a non-competitive fashion.

Pharmacological properties of alpha-mangostin, a novel histamine H1 receptor antagonist.

Chairungsrilerd N, Furukawa K, Ohta T, Nozoe S, Ohizumi Y.

Department of Pharmaceutical Molecular Biology, Faculty of Pharmaceutical Sciences, Tohoku University, Sendai, Japan.

In the isolated rabbit thoracic aorta and guinea-pig trachea, alpha-mangostin inhibited histamine-induced contractions in a concentration-dependent manner in the presence or absence of cimetidine, a histamine H₂ receptor antagonist. But KCl-, phenylephrine- or carbachol-induced contractions were not affected by alpha-mangostin. The concentration-contractile response curve for histamine was shifted to the right in a parallel manner by alpha-mangostin. In the presence of chlorpheniramine, a histamine H₁ receptor antagonist, alpha-mangostin did not affect the relaxation of the rabbit aorta induced by histamine. In the guinea-pig trachea, alpha-mangostin had no effect on the relaxation induced by dimaprit, a histamine H₂ receptor agonist. alpha-Mangostin caused a concentration-dependent inhibition of the binding of [³H]mepyramine, a specific histamine H₁ receptor antagonist to rat aortic smooth muscle cells. Kinetic analysis of [³H]mepyramine binding indicated the competitive inhibition by alpha-mangostin. These results suggest that alpha-mangostin is a novel competitive histamine H₁ receptor antagonist in smooth muscle cells.