

Clinical Validation of

**MANGOSTEEN**

Includes Scientific Papers, Research Papers,  
University Studies & Articles



# Clinical Studies of Mangosteen

## Study #1

### 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 (IC<sub>50</sub> = 5.12 +/- 0.41 microM) and gamma-mangostin (IC<sub>50</sub> = 4.81 +/- 0.32 microM). The type of inhibition by both compounds is noncompetitive.

## Study #2

### **Immunopharmacological activity of polysaccharide from the pericarb of mangosteen garcinia: 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*).**

### **Study #3**

## **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.

## **Study #4**

### **Preferential target is mitochondria in alpha-mangostin-induced apoptosis in human leukemia HL60 cells.**

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

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

Our previous study has shown that alpha-mangostin, a xanthone from the pericarps of mangosteen, induces caspase-3-dependent apoptosis in HL60 cells. In the current study, we investigated the mechanism of apoptosis induced by alpha-mangostin in HL60 cells. Alpha-mangostin-treated HL60 cells demonstrated caspase-9 and -3 activation but not -8, which leads us to assume that alpha-mangostin may mediate the mitochondrial pathway in the apoptosis. Parameters of mitochondrial dysfunction including swelling, loss of membrane potential (deltapsim), decrease in intracellular ATP, ROS accumulation, and cytochrome c/AIF release, were observed within 1 or 2 h after the treatment. On the other hand, alpha-mangostin-treatment did not affect expression of bcl-2 family proteins and activation of MAP kinases. **These findings indicate that alpha-mangostin preferentially targets mitochondria in the early phase, resulting in indication of apoptosis in HL60 cells. Furthermore, we examined the structure-activity relationship between xanthone derivatives including alpha-mangostin and the potency of deltaprim-loss in HL60 cells. Interestingly, replacement of hydroxyl group by methoxy group remarkably decreased its potency. It was also shown that the cytotoxicity substantially correlated with deltaprim decrease. These results indicate that alpha-mangostin and its analogs would be candidates for preventive and therapeutic application for cancer treatment.**

## **Study #5**

### **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.

## **Study #6**

### **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.

## **Study #7**

### **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](mailto: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. Copyright 2004 Elsevier B.V.

## **Study #8**

### **Inhibitory effects of crude alpha-mangostin, a xanthone derivative, on two different categories of colon preneoplastic lesions induced by 1, 2-dimethylhydrazine in the rat.**

**Nabandith V, Suzui M, Morioka T, Kaneshiro T, Kinjo T, Matsumoto K, Akao Y, Inuma M, Yoshimi N.**

Tumor Pathology Division, Faculty of Medicine, University of the Ryukyus, Okinawa 903-0215, Japan.

The purpose of this study was to examine whether crude alpha-mangostin (a major xanthone derivative in mangosteen pericarp (*Garcinia mangostana*)) has short-term chemopreventive effects on putative preneoplastic lesions involved in rat colon carcinogenesis. The crude preparation was obtained by simple recrystallization of an ethylacetate extract of mangosteen pericarps. A total of 33 five-week-old male F344 rats were randomly divided into 5 experimental groups. Rats in groups 1-3 were given a subcutaneous injection of 1,2-dimethylhydrazine (DMH)(40 mg/kg body weight) once a week for 2 weeks. Starting one week before the first injection of DMH, rats in groups 2 and 3 were fed a diet containing 0.02% and 0.05% crude alpha-mangostin, respectively, for 5 weeks. Rats in group 4 also received the diet containing 0.05% crude alpha-mangostin, while rats in group 5 served as untreated controls. The experiment was terminated 5 weeks after the start. Dietary administration of crude alpha-mangostin at both doses significantly inhibited the induction and/or development of aberrant crypt foci (ACF) ( $P < 0.05$  for 0.02% crude alpha-mangostin,  $P < 0.01$  for 0.05% crude alpha-mangostin), when compared to the DMH-treated group (group 1). Moreover, treatment of rats with 0.05% crude alpha-mangostin significantly decreased dysplastic foci (DF) ( $P < 0.05$ ) and beta-catenin accumulated crypts (BCAC) ( $P < 0.05$ ), to below the group 1 values. The proliferating cell nuclear antigen (PCNA) labeling indices of colon epithelium and focal lesions in groups 2 and 3 were also significantly lower than in group 1 and this effect occurred in a dose dependent manner of the crude alpha-mangostin. This finding that crude alpha-mangostin has potent chemopreventive effects in our short-term colon carcinogenesis bioassay system suggests that longer exposure might result in suppression of tumor development.

## Study #9

### Cytotoxic prenylated xanthenes from the young fruit of *Garcinia mangostana*.

Suksamrarn S, Komutiban O, Ratananukul P, Chimnoi N, Lartpornmatulee N, Suksamrarn A.

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

Three new prenylated xanthenes, mangostenones C (1), D (2), and E (3), together with 16 known xanthenes 4-19, were isolated from the young fruit (7-week maturity stage) of *Garcinia mangostana*. The structural elucidation of the new compounds was mainly established on the basis of 1D and 2D NMR and HR-MS spectroscopic analysis. Compound 1 showed cytotoxic properties against three human cancer cell lines, epidermoid carcinoma of the mouth (KB), breast cancer (BC-1), and small cell lung cancer (NCI-H187), with IC<sub>50</sub> values of 2.8, 3.53, and 3.72 microg/ml, respectively. Among the isolates, alpha-mangostin (12), the major metabolite, exhibited the most potent effects against the BC-1 cells with an IC<sub>50</sub> value of 0.92 microg/ml, an activity greater than that of the standard drug ellipticine (IC<sub>50</sub> = 1.46 microg/ml). Compound 12 also showed the highest activity against KB cells, while gartanin (10) displayed the strongest activity against the NCI-H187 cells at the respective IC<sub>50</sub> values of 2.08 microg/ml and 1.08 microg/ml.

## **Study #10**

### **Alpha-mangostin induces Ca<sup>2+</sup>-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.**

## **Study #11**

### **Activity of medicinal plant extracts against hospital isolates of methicillin-resistant *Staphylococcus aureus*.**

**Voravuthikunchai SP, Kitpipit L.**

Department of Microbiology, Faculty of Science, Prince of Songkla University, Hatyai, Songkla, Thailand. supayang.v@psu.ac.th

Aqueous and ethanolic extracts of ten traditional Thai medicinal plants were investigated for their ability to inhibit 35 hospital isolates of methicillin-resistant *Staphylococcus aureus* (MRSA). Nine medicinal plants displayed activity against all isolates tested. Ethanolic extracts of *Garcinia mangostana*, *Punica granatum* and *Quercus infectoria* were most effective, with MICs for MRSA isolates of 0.05-0.4, 0.2-0.4 and 0.2-0.4 mg/mL, respectively, and for *S. aureus* ATCC 25923 of 0.1, 0.2 and 0.1 mg/mL, respectively. MBCs for MRSA isolates were 0.1-0.4, 1.6-3.2 and 0.4-1.6 mg/mL, and for *S. aureus* ATCC 25923 were 0.4, 3.2 and 1.6 mg/mL, respectively.

## **Study #12**

### **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<sup>-1</sup>. 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<sup>-1</sup>), an activity which was greater than that of the antibiotic vancomycin (3.13-6.25 micrograms mL<sup>-1</sup>). 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.**

### **Study #13**

#### **Antibacterial activity of alpha-mangostin against vancomycin resistant Enterococci (VRE) and synergism with antibiotics.**

**Sakagami Y, Iinuma M, Piyasena KG, Dharmaratne HR.**

Osaka Prefectural Institute of Public Health, Osaka, Japan. sakagami@iph.pref.osaka.jp

alpha-Mangostin, isolated from the stem bark of *Garcinia mangostana* L., was found to be active against vancomycin resistant Enterococci (VRE) and methicillin resistant *Staphylococcus aureus* (MRSA), with MIC values of 6.25 and 6.25 to 12.5 microg/ml, respectively. Our studies showed synergism between alpha-mangostin and gentamicin (GM) against VRE, and alpha-mangostin and vancomycin hydrochloride (VCM) against MRSA. Further studies showed partial synergism between alpha-mangostin and commercially available antibiotics such as ampicillin and minocycline. These findings suggested that alpha-mangostin alone or in combination with GM against VRE and in combination with VCM against MRSA might be useful in controlling VRE and MRSA infections.

## **Study #14**

### **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.

## **Study #15**

### **Antimicrobial effects of Thai medicinal plants against acne-inducing bacteria.**

**Chomnawang MT, Surassmo S, Nukoolkarn VS, Gritsanapan W.**

Department of Microbiology, Faculty of Pharmacy, Mahidol University, 447 Sri Ayudthaya Road, Rachathevi, Bangkok 10400, Thailand. scmtd@mahidol.ac.th

Propionibacterium acnes and Staphylococcus epidermidis have been recognized as pus-forming bacteria triggering an inflammation in acne. The present study was conducted to evaluate antimicrobial activities of Thai medicinal plants against these etiologic agents of acne vulgaris. Crude extracts were tested for antimicrobial activities by disc diffusion and broth dilution methods. The results from the disc diffusion method showed that 13 medicinal plants could inhibit the growth of Propionibacterium acnes. Among those, Senna alata, Eupatorium odoratum, Garcinia mangostana, and Barleria lupulina had strong inhibitory effects. Based on a broth dilution method, the Garcinia mangostana extract had the greatest antimicrobial effect. The MIC values were the same (0.039 mg/ml) for both bacterial species and the MBC values were 0.039 and 0.156 mg/ml against Propionibacterium acnes and Staphylococcus epidermidis, respectively. In bioautography assay, the Garcinia mangostana extract produced strong inhibition zones against Propionibacterium acnes. Antimicrobial activity from fractions of column chromatography revealed one of the active compounds in Garcinia mangostana could be mangostin, a xanthone derivative. Taken together, our data indicated that Garcinia mangostana had a strong inhibitory effect on Propionibacterium acnes and Staphylococcus epidermidis. Therefore, this plant would be an interesting topic for further study and possibly for an alternative treatment for acne.

## **Study #16**

### **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.

## **Study #17**

### **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.**

## **Study #18**

### **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.

## **Study #19**

### **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 Ca<sup>2+</sup> ionophore. The inhibition was concentration-dependent, with the IC<sub>50</sub> 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 [<sup>14</sup>C]-AA from the cells labeled with [<sup>14</sup>C]-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 IC<sub>50</sub> 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.

## **Study #20**

### **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 #21**

### **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 ( $\text{Cu}^{2+}$ ) 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  $\mu\text{M}$  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  $\mu\text{M}$   $\text{Cu}^{2+}$  in the presence or absence of 50  $\mu\text{M}$  or 100  $\mu\text{M}$  mangostin. We observed an inhibition of TBARS formation with 100  $\mu\text{M}$  mangostin at 4 hours ( $P = 0.027$ ) but not at 24 hours ( $P = 0.163$ ). Similar results were observed in the presence of 50  $\mu\text{M}$  mangostin. Mangostin, at 100  $\mu\text{M}$ , retarded the relative electrophoretic mobility of LDL at both 4 and 24 hours after  $\text{Cu}^{2+}$  induced oxidation. Mangostin (100  $\mu\text{M}$ ) significantly inhibited the consumption of alpha-tocopherol in the LDL during  $\text{Cu}^{2+}$  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.

## **Study #22**

### **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.

## **Study #23**

### **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.

## **Study #24**

### **Three xanthenes and a benzophenone from *Garcinia mangostana*.**

**Huang YL, Chen CC, Chen YJ, Huang RL, Shieh BJ.**

National Research Institute of Chinese Medicine, No. 155-1, Sec. 2, Li Nung Street Peitou, Taipei, Taiwan, Republic of China.

Investigation of the constituents of *Garcinia mangostana* has led to the isolation of four new compounds: three minor xanthenes, garcimangosone A (1), garcimangosone B (2), and garcimangosone C (3), and a benzophenone glucoside, garcimangosone D (4). The structures of these four compounds were established by spectral (NMR and MS) and chemical methods.

## **Study #25**

### **Xanthones from the green fruit hulls of *Garcinia mangostana*.**

**Suksamrarn S, Suwannapoch N, Ratananukul P, Aroonlerk N, Suksamrarn A.**

Department of Chemistry, Faculty of Science, Srinakharinwirot University, Bangkok 10110, Thailand. [sunit@psm.swu.ac.th](mailto:sunit@psm.swu.ac.th)

Three new xanthones, mangostenol (1), mangostenone A (2), and mangostenone B (3), were isolated from the green fruit hulls of *Garcinia mangostana*, along with the known xanthones, trapezifolixanthone, tovophyllin B (4), alpha- and beta-mangostins, garcinone B, mangostinone, mangostanol, and the flavonoid epicatechin. The structures of the new xanthones were elucidated by analysis of their spectroscopic data.

## **Study #26**

### **Antioxidant xanthenes from the pericarp of *Garcinia mangostana* (Mangosteen).**

**Jung HA, Su BN, Keller WJ, Mehta RG, Kinghorn AD.**

Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210, USA.

As part of ongoing research on cancer chemopreventive agents from botanical dietary supplements, *Garcinia mangostana* L. (commonly known as mangosteen) was selected for detailed study. Repeated chromatography of a CH<sub>2</sub>Cl<sub>2</sub>-soluble extract of the pericarp led to the isolation of two new highly oxygenated prenylated xanthenes, 8-hydroxycudraxanthone G (1) and mangostingone [7-methoxy-2-(3-methyl-2-butenyl)-8-(3-methyl-2-oxo-3-butenyl)-1,3,6-trihydroxyxanthone, 2], together with 12 known xanthenes, cudraxanthone G (3), 8-deoxygartanin (4), garcimangosone B (5), garcinone D (6), garcinone E (7), gartanin (8), 1-isomangostin (9), alpha-mangostin (10), gamma-mangostin (11), mangostinone (12), smeathxanthone A (13), and tovophyllin A (14). The structures of compounds 1 and 2 were elucidated by spectroscopic data analysis. Except for compound 2, which was isolated as a minor component, the antioxidant activities of all isolates were determined using authentic and morpholinosydnonimine-derived peroxyxynitrite methods, and compounds 1, 8, 10, 11, and 13 were the most active. Alpha-mangostin (10) inhibited 7,12-dimethylbenz[alpha]anthracene-induced preneoplastic lesions in a mouse mammary organ culture assay with an IC<sub>50</sub> of 1.0 microg/mL (2.44 microM).

## **Study #27**

### **Xanthones and benzophenones from *Garcinia griffithii* and *Garcinia mangostana*.**

**Nguyen LH, Venkatraman G, Sim KY, Harrison LJ.**

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Republic of Singapore.

A new polyisoprenylated benzophenone, guttiferone I, together with the known compounds cambogin, 1,7-dihydroxyxanthone, 1,3,6,7-tetrahydroxyxanthone and 1,3,5,6-tetrahydroxyxanthone were isolated from the stem bark of *Garcinia griffithii*. The acetone extract of the heartwood of *Garcinia mangostana* contained one new diprenylated xanthone (mangoxanthone) and a new benzophenone (3',6-dihydroxy-2,4,4'-trimethoxybenzophenone) as well as the known xanthoness dulxanthone D, 1,3,7-trihydroxy-2-methoxyxanthone, 1,3,5-trihydroxy-13,13-dimethyl-2H-pyran[7,6-b]xanthen-9-one. Their structures were established on the basis of spectroscopic studies and chemical correlation.

## **Recent Antioxidant News**

- Antioxidant Diminishes Birth Defects, in Mice (07/01/2004, Reuters Health)

## **Antioxidants as explained by the National Cancer Institute**

Antioxidants neutralize free radicals as the natural by-product of normal cell processes. Free radicals are molecules with incomplete electron shells which make them more chemically reactive than those with complete electron shells.

Exposure to various environmental factors, including tobacco smoke and radiation, can also lead to free radical formation. In humans, the most common form of free radicals is oxygen. When an oxygen molecule (O<sub>2</sub>) becomes electrically charged or "radicalized" it tries to steal electrons from other molecules, causing damage to the DNA and other molecules. Over time, such damage may become irreversible and lead to disease including cancer.

Antioxidants are often described as "mopping up" free radicals, meaning they neutralize the electrical charge and prevent the free radical from taking electrons from other molecules. Considerable laboratory evidence from chemical, cell culture, and animal studies indicates that antioxidants may slow or possibly prevent the development of cancer.

## **How Antioxidants Work - as Explained by a Major health Publication**

As cells function normally in the body, they produce damaged molecules — called free radicals. These free radicals are highly unstable and steal components from other cellular molecules, such as fat, protein, or DNA, thereby spreading the damage.

This damage continues in a chain reaction, and entire cells soon become damaged and die. This process is called peroxidation. Peroxidation is useful because it helps the body destroy cells that have outlived their usefulness and kills germs and parasites. However, peroxidation, when left unchecked, also destroys or damages healthy cells.

Antioxidants help prevent widespread cellular destruction by willingly donating components to stabilize free radicals. More importantly, antioxidants return to the surface of the cell to stabilize rather than damage other cellular components.

When there are not enough antioxidants to hold peroxidation in check, free radicals begin damaging healthy cells which, in turn, can lead to problems. For example, free radical damage to immune cells can lead to an increased risk of infections.

## The Science of Xanthonenes

Xanthonenes have been the subject of intense research for several decades. They are found in a select number of rain forest plants, but nowhere are they found in more abundance than in the *pericarp*, or rind, of the Mangosteen fruit. This smooth, purple covering that was ground with ancient mortars and used to treat infection turns out to be the mother lode of beneficial xanthonenes.

The two most beneficial xanthonenes found in the Mangosteen have been named *Alpha Mangostin* and *Gamma Mangostin*. When isolated and thoroughly tested by researchers, these two xanthonenes have been found to carry a host of benefits. According to professional journals such as *Free Radical Research*, *Journal of Pharmacology*, and the *Indian Journal of Experimental Biology*, these xanthonenes have a remarkable effect on cardiovascular health; are naturally antibiotic, antiviral, and anti-inflammatory; and are some of the most powerful antioxidants to be found in nature.

What are Xanthonenes? Xanthonenes are a class of plant derived nutrients or “phytonutrients.” They have been demonstrated in numerous scientific studies to hold tremendous nutritional value. Found to exhibit strong antioxidant activity xanthonenes disarm free radicals in the body and enhance and support your body's immune system. Although xanthonenes exist in small amounts throughout nature, it is found in concentrated amounts in the pericarp of the Mangosteen fruit.

There are over 40 known forms of xanthonenes naturally occurring in the pericarp, the two most widely studied are Alpha Mangostin and Gamma Mangostin.

The xanthonenes that have been studied were extracted from the pericarp in a process somewhat analogous to digestion. The undigestible cellulose of the rind is of course not digested by the human GI tract and passes on through you. To render the chemically active substances available to the body in the most elementary way the fruit is simply pulped and the digestive enzymes do their thing to let the chemicals get across the gut wall to the bloodstream.

The human body has no problem absorbing the nutrients from the pericarp. In fact, the process is identical to what happens to the greens you eat that are also more than 80% fiber as well.

## Understanding Antioxidants

*To begin with Xanthonenes are among the most powerful Antioxidants known to science. Of the 200 known Xanthonenes, More than 40 exist in the Mangosteen. This is a greater concentration of Xanthonenes than can be found in any other substance on earth.*

In recent years there has been intensive research into the phenomenon of aging. Until the 1950s, the predominate thinking in science was that aging is exclusively a phenomenon programmed into the genes, a kind of genetic clock with just so many ticks and, at the last tick, your time would be up, and there would be nothing to be done about it.

That paradigm has been replaced with the idea that aging is a complex phenomenon affected by many variables.

Your body burns food for fuel just as a fireplace burns wood for fuel. In both cases it is literally a burning process. In the case of a fireplace the fire is more obvious. In your body, this burning occurs molecule by molecule, so that a fire does not erupt.

Both processes — that in a fireplace and that in the cells of your body — burn oxygen, a process called "oxidation." In a fireplace, there are ashes left over after the fire. In your body, free radicals are left over. These are molecules which have an extra unpaired electron. This extra electron makes the free radical molecule highly reactive. These molecules act like flaming torches in relationship to the tissues of your body.

Free radicals, at a molecular level, burn everything they touch, and are damaging to cellular structures, particularly the cell membrane which holds the cell together.

Because free radicals are so damaging to the body, nature has designed a system to neutralize them. The body produces substances called "antioxidants," which convert free radicals into harmless molecules. Antioxidants are produced within the cells. The cells' ability to produce adequate amounts of antioxidants is determined by age, inheritance, nutrition and stress. People who produce higher than usual levels of natural antioxidants enjoy greater health and longevity. This connection has been researched and proven.

Free radicals affect the body as CFCs affect ozone in the upper atmosphere—a little goes a long way. When a free radical does its damage, it is not neutralized but able to continue doing further damage, creating more free radicals. If unchecked by antioxidants, free radicals act like a fire out of control.

In a young, healthy, well-nourished, non-stressed individual, sufficient amounts of antioxidants are produced in the cells to handle the challenge of free radicals. As a person grows older, the cells are less able to produce sufficient amounts of antioxidants.

Free radicals attack the tissues and cause cell breakdown and inflammation. The most obvious result is arthritis and myositis (joint and muscle inflammation), but most experts believe that excess free radicals play an important part in cancer, heart disease, cataracts and aging itself. It may be that free radicals attack the very systems which produce antioxidants and thus, over a period of years, weaken the body's

ability to deal with free radicals. Most investigators believe that a constant barrage of free radicals damages the chromosomes themselves and may, in this way, speed up the aging process.

Whatever the cause, the production of antioxidants begins to decline at age twenty and, interestingly, this also is the time when visible aging begins. Until very recently, aging and the degenerative changes which go along with aging were thought to be inevitable. This may turn out not to be the case.

**Dr. Duke's  
Phytochemical and Ethnobotanical Databases**

---

Biological Activities in: *Garcinia mangostana* L. (Clusiaceae) -- Mangosteen, Mangostin

---

**Activities**

Acidulant *FEMA 6,000*  
Aldose-Reductase-Inhibitor  
Allergenic  
Alpha-Amylase-Inhibitor  
**Analgesic 1-4 g/day 5-10 g/day**  
Androgenic?  
Angiotensin-Receptor-Blocker  
Antiacne  
Antiasthmatic  
**AntiAGE 2,000 mg/day**  
Antiaggregant  
**Antiaging 400 mg/day**  
Antiakathisic  
Antialcoholic  
**Antiallergic 50 mg/2x/day 500 mg/day**  
**Antialzheimeran 100-3,000 mg/day**  
Antiamblyopic  
Antianemic  
Antianginal  
Antianorectic  
Antianxiety  
**Antiaphthic 20,000 ppm**  
**Antiarabiflavinotic 2-10 mg orl/day**  
Antiarrhythmic  
**Antiarthritic 1 g/day**  
**Antiasthmatic 1,000 mg/day**  
**Antiatheromic 15 g/man/day**  
**Antiatherosclerotic 500 mg/day**  
**Antibackache 1-4 g/day**  
**Antibacterial 100 ug/ml**  
Antiberiberi  
Anticalculic  
Anticancer  
Anticarcinomic  
Anticardiospasmic  
**Anticarpal-Tunnel 50 mg/day**  
**Anticataract 15 mg/day 350 mg/day 400 mg/day**  
Anticheilitic  
Antichilblain

Anticoagulant  
**Anticold 1-2 g/man/day**  
Anticolitic  
**Anticonvulsant 3 g/day**  
**Anticoronary 50 mg/man/2 days**  
**AntiCrohn's 50-100 mg/day/orl/man**  
**Antidecubitic 500 mg/man/2x/day**  
Antideliriant  
**Antidepressant 2,000 mg/day**  
Antidermatitic  
**Antidiabetic 10 g/man/day/orl**  
Antidiarrheic  
Antidote (Aluminum)  
Antidote (Cadmium)  
Antidote (Lead)  
Antidote (Paraquat)  
Antidysphagic  
**Antieczemic 3.5-5 g/day**  
**Antiedemic 1 g/man/day**  
Antiencephalitic  
Antiencephalopathic  
**Antiepileptic 3 g/day**  
Antifatigue  
Antifeedant  
Antiflu  
Antigastritic  
Antigingivitic  
**Antiglaucomic 2 g/day**  
Antiglossitic  
Antiheartburn  
**Antihemorrhagic 1 g/man/day**  
**Antihepatitic 2-6 g/man/day**  
Antihepatotoxic  
**Antiherpetic 1-5 g/day**  
**Antihistaminic 2 g/day orl man 50 mg/2x/day**  
**AntiHIV 6.1 uM**  
**Antihyperactivity 1.5-6 g/day**  
Antihyperkeratotic  
Antihyperkinetic  
Antihypertensive  
Antiichthyotic  
**Antiinfertility 1 g/day**  
Antiinflammatory  
Antiinsomniac  
Antiinsomnic  
Antikeratitic

**Antileptic 1.5 g/man/day**  
Antileukoplakic  
**Antilupus 150 mg/man/day/2 mos**  
Antimastitic  
Antimeasles  
AntiMeniere's  
**Antimenorrhagic 100 mg/day/wmn/orl**  
Antimigraine  
Antimutagenic  
Antimyocarditic  
**Antineuralgic 1-4 g/day**  
Antineurasthenic  
Antineuritic  
**Antineuropathic 50 mg**  
**Antinitrosic 1 g/man/day**  
**Antiobesity 1 g 3 x/day**  
Antiorchitic  
**Antiosteoarthritic 1 g 2 x/day**  
**Antiosteoporotic 500 mg/day**  
**Antioxidant 100 ppm**  
Antioxidant Synergist  
Antiozenic  
**Antiparkinsonian 1 g 2 x/day 100 mg/day**  
Antiparotitic  
Antipellagic  
**Antiperiodontitic 1 g 2 x/day 750 mg/day**  
**Antiphotophobic 30-300 mg/man/day**  
Antipityriasic  
**AntiPMS 1 g/day**  
Antipneumonic  
Antipodriac  
Antipoliomyelitic  
**Antiporphyrin 30-300 mg/man/day**  
Antiproliferant  
Antipsoriac  
Antipyretic  
Antiradicular  
**Antiscorbutic 10 mg/man/day**  
Antiscotomic  
Antiseborrheic  
**Antiseptic 4-8 g/day MIC=3.3-217 mg/ml**  
Antishingles  
**Antispasmodic 100 mg/2x/day**  
Antistress  
**Antisyndrome-X 1-4 g/day**  
Antitic

Antitubercular  
Antitumor  
Antitumor (Colon)  
Antitumor (Lung)  
Antitussive  
**Antiulcer 12 mg 3x/day/man/orl**  
Antivertigo  
**Antiviral 1-5 g/day 6.1 uM**  
Antixerophthalmic  
Aphidifuge  
**Apoptotic 1-10 mM**  
**Asthma-preventive 1,000 mg/day/orl**  
Beta-Adrenergic Receptor Blocker  
Beta-Blocker  
**Beta-Glucuronidase-Inhibitor 1.5 g/day/man**  
Calcium-Antagonist  
Calcium-Channel-Blocker  
**Cancer-Preventive 22 ppm**  
Cardioprotective  
**Cardiotoxic 18,000 mg/man/day**  
Chemopreventive  
**Cold-preventive 1-2 g/day**  
Collagenic  
Colorant  
**Cytotoxic 600 ppm 8.6 uM**  
Demulcent  
Detoxicant  
Disinfectant  
**Diuretic 700 mg/man/orl**  
Dye  
Fistula-Preventive  
**FLavor FEMA 3-25 FEMA 370-4,400**  
Fungicide  
Hemostat  
Hepatoprotective  
Hypertensive  
**Hypocholesterolemic 300-1,000 mg/day 500 mg/day**  
Hypoglycemic  
Hypolipemic  
Hypolipidemic  
**Hypotensive 1 g/day 1,000 mg/man/day 10 g/man/day/orl**  
Hypouricemic  
**Immunostimulant 180 mg/man/day/orl**  
**Insectifuge 75-150 mg/man/day**  
Interferon-Synergist  
Interferonogenic

Irritant  
Laxative  
Laxative  
Lithogenic  
Litholytic  
Mucogenic  
**Mucolytic 1 g/woman/day**  
Mycobactericide  
Odontolytic  
Osteogenic  
Peristaltic  
Pesticide  
Phagocytotic  
**Prooxidant 20 ug/g**  
**Prostaglandin-Synthesis-Inhibitor IC50=119 uM**  
Refrigerant  
Sedative  
Serotonergic  
Thymoprotective  
**Topoisomerase-II-Inhibitor IC50=38.6 uM**  
Ubiquitot  
**Uricosuric 4 g/man/day**  
Urinary-Acidulant  
Vasodilator  
Vulnerary

---

## References

---

ppm = parts per million  
tr = trace

---

*Phytochemical Database, USDA - ARS - NGRL, Beltsville Agricultural Research Center, Beltsville, Maryland*

Wed Oct 15 22:36:20 EDT 2003

### References:

1. *Planta Med.* 1996 Aug;62(4):381-2.
2. *J Med Assoc Thai.* 1997 Sep;80 Suppl 1:S149-54.
3. *Planta Med.* 2002 Nov;68(11):975-9.
4. *Bioorg Med Chem.* 2004 Nov 15;12(22):5799-806.
5. *J Nat Prod.* 2003 Aug;66(8):1124-7.
6. *J Ethnopharmacol.* 2004 Jan;90(1):161-6.
7. *Fitoterapia.* 2004 Jun;75(3-4):375-7
8. *Asian Pac J Cancer Prev.* 2004 Oct-Dec;5(4):433-8.
9. *Chem Pharm Bull (Tokyo).* 2006 Mar;54(3):301-5.

10. J Pharmacol Sci. 2004 May;95(1):33-40.
11. Clin Microbiol Infect. 2005 Jun;11(6):510-2.
12. J Pharm Pharmacol. 1996 Aug;48(8):861-5.
13. Phytomedicine. 2005 Mar;12(3):203-8.
14. Chem Pharm Bull (Tokyo). 2003 Jul;51(7):857-9.
15. J Ethnopharmacol. 2005 Oct 3;101(1-3):330-3.
16. J Nat Prod. 1997 May;60(5):519-24.
17. Mol Pharmacol. 2004 Sep;66(3):667-74.
18. Biol Pharm Bull. 2002 Sep;25(9):1137-41.
19. Biochem Pharmacol. 2002 Jan 1;63(1):73-9.
20. Planta Med. 1996 Oct;62(5):471-2.
21. Free Radic Res. 1995 Aug;23(2):175-84.
22. Southeast Asian J Trop Med Public Health. 1995;26 Suppl 1:306-10.
23. Arch Int Pharmacodyn Ther. 1979 Jun;239(2):257-69.
24. J Nat Prod. 2001 Jul;64(7):903-6.
25. J Nat Prod. 2002 May;65(5):761-3.
26. J Agric Food Chem. 2006 Mar 22;54(6):2077-82.
27. Phytochemistry. 2005 Jul;66(14):1718-23.
28. Antioxidant Diminishes Birth Defects, in Mice (07/01/2004, Reuters Health)
29. Phytochemical Database, USDA – ARS – NGRL, Beltsville Agricultural research Center, Beltsville, Maryland