

1: *Planta Med* 2002 Nov;68(11):975-9

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

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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.

PMID: 12451486 [PubMed - indexed for MEDLINE]

2: *Biol Pharm Bull* 2002 Sep;25(9):1137-41

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

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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.

PMID: 12230104 [PubMed - in process]

3: *Biochem Pharmacol* 2002 Jan 1;63(1):73-9

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

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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.

PMID: 11754876 [PubMed - indexed for MEDLINE]

4: J Med Assoc Thai 1997 Sep;80 Suppl 1:S149-54

Immunopharmacological activity of polysaccharide from the pericarb of mangosteen garcinia: phagocytic intracellular killing activities.

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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 +/- SD) of NBT test of 100 polymorphonuclear phagocytic cells were 145 +/- 78, 338 +/- 58, 222 +/- 73, 209 +/- 77, 211 +/- 63, 372 +/- 19, 369 +/- 20, 355 +/- 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*).

PMID: 9347663 [PubMed - indexed for MEDLINE]

5: *Planta Med* 1996 Oct;62(5):471-2

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

Chairungsrierd 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.

Publication Types:

Letter

PMID: 8923814 [PubMed - indexed for MEDLINE]

6: *Southeast Asian J Trop Med Public Health* 1995;26 Suppl 1:306-10

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

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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.

PMID: 8629131 [PubMed - indexed for MEDLINE]

7: Phytochemistry 1992 Nov;31(11):3711-3

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

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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.

PMID: 1368866 [PubMed - indexed for MEDLINE]

8: Bioorg Med Chem 2003 Apr;11(7):1215-1225

Inhibition of protein kinase C by synthetic xanthone derivatives.

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The modulatory activity of two xanthenes (3,4-dihydroxyxanthone and 1-formyl-4-hydroxy-3-methoxyxanthone) on isoforms alpha, betaI, delta, eta and zeta of protein kinase C (PKC) was evaluated using an in vivo yeast phenotypic assay. Both xanthenes caused an effect compatible with PKC inhibition, similar

to that elicited by known PKC inhibitors (chelerythrine and NPC 15437). PKC inhibition caused by xanthenes was confirmed using an in vitro kinase assay. The yeast phenotypic assay revealed that xanthenes present differences on their potency towards the distinct PKC isoforms tested. It is concluded that 3,4-dihydroxyxanthone and 1-formyl-4-hydroxy-3-methoxyxanthone may become useful PKC inhibitors and xanthone derivatives can be explored to develop new isoform-selective PKC inhibitors.

PMID: 12628649 [PubMed - as supplied by publisher]

9: Acta Pharmacol Sin 2003 Feb;24(2):175-180

Protective effects of xanthenes against myocardial ischemia-reperfusion injury in rats.

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AIM: To investigate the protective effect of xanthenes against myocardial ischemia-reperfusion injury in rats. **METHODS:** Ischemia-reperfusion injury was induced by 20 min of global ischemia and 40 min of reperfusion in isolated rat hearts or 60-min coronary artery occlusion and 180-min reperfusion in vivo, respectively. Heart rate, coronary flow, left ventricular pressure (LVP), and its first derivative (dp/dt_{max}) were recorded, and the activity of creatine kinase in coronary effluent and malondialdehyde contents in myocardial tissues were measured in vitro. The activity of serum creatine kinase and myocardium infarct size were measured in vivo. **RESULTS:** Xanthenes (90 or 300 μ g/L) caused a significant improvement of cardiac function (LVP and $\pm dp/dt_{max}$) and a decrease in the release of creatine kinase in coronary effluent as well as the level of malondialdehyde in myocardial tissues. Xanthenes (0.5 or 1.0 mg/kg) also markedly decreased infarct size and the release of creatine kinase in vivo. **CONCLUSION:** Xanthenes protect the myocardium against the damages induced by ischemia-reperfusion in rats, and the effect of xanthenes may be related to the inhibition of lipid peroxidation.

PMID: 12546727 [PubMed - as supplied by publisher]

10: Mol Biochem Parasitol 2003 Jan;126(1):43-9

Antileishmanial drug development: exploitation of parasite heme dependency.

Kelly JX, Ignatushchenko MV, Bouwer HG, Peyton DH, Hinrichs DJ, Winter RW, Riscoe M.

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A rational approach in the search for new antiparasitic drugs is the exploitation of biochemical differences between the parasite and its mammalian host. One specific example in the case of *Leishmania* relates to the biosynthesis of heme, a critical prosthetic group for proteins involved in metabolism and electron transport. Like all Trypanosomatids, *Leishmania* parasites require heme or pre-formed porphyrins for survival because they lack several key enzymes in the heme biosynthetic pathway. Considering their specific nutritional requirements, we speculated that they would be particularly sensitive to the effects of heme-complexing xanthenes. In this report, we document the antileishmanial activity of selected nitrogenated xanthenes and correlate drug potency with heme affinity. In vitro tests demonstrated that 3,6-bis-omega-diethylaminoamyloxyxanthone, C5, was at least 100 times more active than pentamidine against intracellular amastigotes of *Leishmania mexicana*. Our findings provide practical guidance for optimizing the antileishmanial activity of the xanthone pharmacophore to better exploit parasite heme salvage processes.

PMID: 12554083 [PubMed - in process]

11: Bioorg Med Chem 2002 Dec;10(12):3725-30

Xanthenes as inhibitors of growth of human cancer cell lines and their effects on the proliferation of human lymphocytes in vitro.

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Twenty-seven oxygenated xanthenes have been assessed for their capacity to inhibit in vitro the growth of three human cancer cell lines, MCF-7 (breast cancer), TK-10 (renal cancer) and UACC-62 (melanoma). The effect of these xanthenes on the proliferation of human T-lymphocytes was also evaluated. Differences on their potency towards the effect on the growth of the human cancer cell lines as well as on the proliferation of human T-lymphocytes can be ascribed to the nature and positions of the substituents on the xanthonic nucleus.

PMID: 12413829 [PubMed - in process]

12: Bioorg Med Chem 2002 Oct;10(10):3219-27

Synthesis and in vivo modulatory activity of protein kinase C of xanthone derivatives.

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The modulatory activity of a series of 20 simple xanthenes on isoforms alpha, betaI, delta, eta and zeta of protein kinase C (PKC) was evaluated using an in vivo yeast phenotypic assay. Hydroxy and/or methoxyxanthenes were synthesised. The majority of these compounds caused an effect compatible with activation of PKC and some showed to be more effective than the standard PKC activator (PMA or arachidonic acid). The xanthenes tested differ in their efficacy and potency towards individual PKC isoforms and some showed higher selectivities for PKC-delta, -eta or -zeta, suggesting that xanthone derivatives can become valuable research tools to elucidate the physiological roles of these isoforms.

PMID: 12150867 [PubMed - in process]

13: Mol Biochem Parasitol 2002 Aug 7;123(1):47-54

The kinetics of uptake and accumulation of 3,6-bis-omega-diethylamino-amyloxyxanthone by the human malaria parasite Plasmodium falciparum.

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Malarial parasites rely on the digestion of hemoglobin during the intra-erythrocytic stage. The enzymatic degradation of hemoglobin yields amino acids for parasite survival, and free heme which is detoxified by conversion to an aggregate of dimeric heme known as hemozoin. Xanthenes have been found to subvert this process by formation of soluble drug-heme complexes. We have optimized the simple hydroxyxanthone structure to include side chains with protonatable nitrogen atoms to enhance interaction with the propionate groups of heme and to target the drug to the parasite digestive vacuole. One member of this optimized class of compounds, 3,6-bis-omega-diethylaminoamyloxyxanthone (C5), was used as a prototype for mechanistic studies. By HPLC analysis we demonstrate that the drug accumulates in the digestive vacuole from 5 to approximately 33,000 microM within 1 h of exposure to parasitized red cells. Confocal fluorescence microscopy was used to visualize the accumulation process directly and to document the colocalization of the drug with the acidophilic dye, LysoTracker Red. Copyright 2002 Elsevier Science B.V.

PMID: 12165388 [PubMed - indexed for MEDLINE]

14: Eur J Med Chem 2002 Mar;37(3):237-53

(2-Arylhydrazonomethyl)-substituted xanthenes as antimycotics: synthesis and fungistatic activity against *Candida* species.

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A series of arylhydrazones derived from various 6,8-diacetoxy- or 6,8-dihydroxy-9-oxo-9H-xanthene carboxaldehydes were synthesized and evaluated for their in vitro antifungal properties against two human pathogenic yeasts (*Candida albicans* and *C. krusei*) according to a diffusion method. The activity was strongly dependent from the position of the

(1-arylhydrazinyl-2-ylidene)methyl chain in the xanthone molecular skeleton. Compounds having the nitrogen side chain in the 4-position, with a further halogen substitution on the terminal phenyl ring showed fungistatic effects. Within this series, the 4-fluorophenylhydrazinyl derivative 13g exhibited the highest activity, particularly against *C. krusei*, with a greater efficacy than that of econazole, used as reference.

PMID: 11900868 [PubMed - indexed for MEDLINE]

15: Antimicrob Agents Chemother 2002 Jan;46(1):144-50

Optimization of xanthenes for antimalarial activity: the 3,6-bis-omega-diethylaminoalkoxyxanthone series.

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Hydroxyxanthenes have been identified as novel antimalarial agents. The compounds are believed to exert their activity by complexation to heme and inhibition of hemozoin formation. Modification of the xanthone structure was pursued to improve their antimalarial activity. Attachment of R-groups bearing protonatable nitrogen atoms was conducted to enhance heme affinity through ionic interactions with the propionate side chains of the metalloporphyrin and to facilitate drug accumulation in the parasite food vacuole. A series of 3,6-bis-omega-diethylaminoalkoxyxanthenes with side chains ranging from 2 to 8 carbon atoms were prepared and evaluated. Measurement of heme affinity for each of the derivatives revealed a strong correlation ($R(2) = 0.97$) between affinity and antimalarial potency. The two most active compounds in the series contained 5- and 6-carbon side chains and exhibited low nanomolar 50% inhibitory concentration ($IC(50)$) values against strains of chloroquine-susceptible and multidrug-resistant *Plasmodium falciparum* in vitro. Both of these xanthenes exhibit stronger heme affinity ($8.26 \times 10(5)$ and $9.02 \times 10(5) M(-1)$, respectively) than either chloroquine or quinine under similar conditions and appear to complex heme in a unique manner.

PMID: 11751125 [PubMed - indexed for MEDLINE]

16: J Inorg Biochem 2001 Sep;86(2-3):617-25

A spectroscopic investigation of the binding interactions between 4,5-dihydroxyxanthone and heme.

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In order to investigate one possible mechanism by which xanthenes inhibit growth of malaria-causing Plasmodium parasites, optical and NMR spectroscopic studies were performed on a prototypic xanthone, 4,5-dihydroxyxanthone (45X2), upon its complexation to heme. The 45X2 x heme complex stoichiometry in aqueous solution was found to be 1:2; this interaction was non-cooperative, and exhibited a very similar heme complex dissociation constant ($K(d)=5.1 \times 10(-6)$) as observed for the common antimalarial agents, chloroquine and quinine. The 45X2 x heme(2) complex formation was found to be both pH- and solvent-dependent, with clear evidence of the xanthone carbonyl moiety coordinating with the iron of heme. Hydrogen bonding between the hydroxyl groups of 45X2 and the propionate side chains of heme, as well as pi-pi stacking between both aromatic systems appeared to contribute to the overall stability of the 45X2 x heme(2) complex, as judged by ¹H NMR. It was concluded that 45X2 forms a complex with a heme dimer in aqueous solution, and that this interaction can be generalized to account for its in vivo detrimental effect of parasite growth through an effective inhibition of hemozoin aggregate formation.

PMID: 11566335 [PubMed - indexed for MEDLINE]

17: J Nat Prod 2001 Jul;64(7):903-6

Three xanthenes and a benzophenone from *Garcinia mangostana*.

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

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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.

PMID: 11473420 [PubMed - indexed for MEDLINE]

18: J Ethnopharmacol 2001 May;75(2-3):287-90

Inhibitory effects of xanthenes on platelet activating factor receptor binding in vitro.

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Nine naturally occurring xanthenes were investigated for their platelet activating factor (PAF) receptor binding inhibitory effects using rabbit platelets. 2-(3-methylbut-2-enyl)-1,3,5-trihydroxyxanthone, macluraxanthone, 1,3,5-trihydroxy-6,6'-dimethylpyrano(2',3':6,7)-4-(1,1-dimethylprop-2-enyl)xanthone, 6-deoxyjacareubin and 2-(3-methylbut-2-enyl)-1,3,5,6-tetrahydroxyxanthone showed strong inhibition with IC₅₀ values of 4.8, 11.0, 21.0, 29.0 and 44.0 microM, respectively. The prenyl group at C-2, the dimethylprop-2-enyl group at C-4 and the hydroxyl group at C-5 are all beneficial to the binding of xanthenes to the PAF receptor. The results revealed that xanthenes can represent a new class of natural PAF receptor antagonists.

PMID: 11297865 [PubMed - indexed for MEDLINE]

19: Free Radic Res 2000 Nov;33(5):643-59

Inhibition of lipoprotein oxidation by prenylated xanthenes derived from mangostin.

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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.

PMID: 11200095 [PubMed - indexed for MEDLINE]

20: *Fitoterapia* 2000 Sep;71(5):607-9

Two novel xanthenes from *Garcinia mangostana*.

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The isolation of two novel xanthenes isolated from the fruit hulls of *Garcinia mangostana* is reported. The structures were elucidated by means of spectroscopic analysis.

PMID: 11449524 [PubMed - indexed for MEDLINE]

21: *Am J Trop Med Hyg* 2000 Jan;62(1):77-81

Xanthones as antimalarial agents: stage specificity.

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The erythrocytic development of *Plasmodium falciparum* is divided into the ring, trophozoite, and schizont stages based on morphologic assessment. Using highly synchronous ring and trophozoite cultures of *P. falciparum*, we observed considerable differences in their sensitivity to hydroxyxanthones: trophozoites were much more sensitive to the drugs than ring-stage parasites. Trophozoites treated with a prototypic xanthone, the 2,3,4,5,6-pentahydroxy derivative (X5), were arrested in their development and became degenerate in appearance within 24 hr of drug exposure. These morphologic changes appeared to reflect the cytotoxic nature of the action of the drug against the parasite, since daughter ring-stage forms were not observed following addition of the drug. That X5 was more active against parasites in the later stages of intraerythrocytic development is consistent with the proposed mode of action, inhibition of heme polymerization. Knowledge of the structure-activity relationships for xanthones as antimalarial agents has also been expanded. Xanthones with a hydroxyl group in the peri-position exhibited decreased antimalarial activity, possibly due to intramolecular hydrogen bonding with the carbonyl and consequent reduced affinity for heme. Paired hydroxyls attached to the lower half of the xanthone greatly enhanced drug potency.

PMID: 10761728 [PubMed - indexed for MEDLINE]

22: Chem Biol Interact 1998 Jul 3;114(1-2):121-40

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

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

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A series of prenylated xanthones 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.

PMID: 9744560 [PubMed - indexed for MEDLINE]

23: Arch Pharm (Weinheim) 1998 May;331(5):193-7

Erratum in:

Arch Pharm (Weinheim) 1998 Jun;331(6):230

Substituted xanthenes as antimycobacterial agents, Part 2: Antimycobacterial activity.

Pickert M, Schaper KJ, Frahm AW.

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A series of substituted xanthenes was tested for their activity against four mycobacterial strains (*Mycobacterium tuberculosis*, *M. avium*, *M. lufu*, *M. smegmatis*) by determination of the minimum inhibitory concentrations (MIC values). For the most active compounds, supplementary characterisation was performed by bacterial growth kinetics, which allows a more precise interpretation of their antimycobacterial effects. From the test set, 1-methyl-2,4,7-trinitroxanthone (8a) showed the highest antimycobacterial activity with a MIC value of 3 micrograms/mL against *M. tuberculosis*, which is comparable to the effect of well known drugs used in the treatment of

tuberculosis. For all other compounds, the MIC values could not be determined, due to the comparatively low activity and to the poor solubility of the compounds, respectively. The semiquantitative evaluation of activity against the different strains of mycobacteria resulted in a classification into three activity classes, which will be used as dependent parameter in QSAR investigations, to be published in Part 3 of this series.

PMID: 9691249 [PubMed - indexed for MEDLINE]

24: *Planta Med* 1998 Feb;64(1):70-2

Antimalarial xanthenes from *Garcinia cowa*.

Likhitwitayawuid K, Phadungcharoen T, Krungkrai J.

Five xanthenes from the bark of *Garcinia cowa*, namely 7-O-methylgarcinone E (1), cowanin (2), cowanol (3), cowaxanthone (4), and beta-mangostin (5), were found to possess in vitro antimalarial activity against *Plasmodium falciparum* with IC₅₀ values ranging from 1.50 to 3.00 micrograms/ml. Complete ¹H- and ¹³C-NMR assignments of these compounds are also reported.

Publication Types:

Letter

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25: *J Nat Prod* 1997 May;60(5):519-24

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 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.

PMID: 9213587 [PubMed - indexed for MEDLINE]

26: J Pharm Pharmacol 1996 Aug;48(8):861-5

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

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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.

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27: J Pharm Pharmacol 1996 May;48(5):539-44

Xanthone derivatives as potential anti-cancer drugs.

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Xanthone derivatives have been shown to be potent inhibitors of tumour growth. Oxygenated xanthenes and [3-(dialkylamino)-2-hydroxypropoxy]xanthenes have been prepared and tested for in-vitro inhibition of human PLC/PRF/5, KB and 212 cells. Structure-activity analysis indicated epoxidation of the hydroxyxanthone increased cytotoxicity against tumour cells but ring-opening of the epoxide group with dialkylamine did not enhance the anti-tumour activity. Further evaluation of three of the most active compounds 2, 6-, 3, 6-, and 3, 5-di(2,3-epoxypropoxy)xanthone (compounds 10a, 11a, and 12a, respectively) in DNA, RNA and protein synthesis of tumour cells showed potent inhibitory activity. The 3,5-di(2,3-epoxypropoxy)xanthone also showed potent inhibitory activity against 212 cells, a Ha-ras oncogene-transformed NIH 3T3 cell line. The results indicated that compounds 10a and 12a are potent anti-tumour agents which not only suppressed cellular DNA, RNA and protein synthesis but also specifically inhibited the Ha-ras oncogene in 212 cells.

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28: Pharm Res 1995 Nov;12(11):1756-60

Hepatoprotective activity of xanthenes and xanthonolignoids against tert-butylhydroperoxide-induced toxicity in isolated rat hepatocytes--comparison with silybin.

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PURPOSE. Synthesize and evaluate the protective activity against tertbutylhydroperoxide-induced toxicity in freshly isolated rat hepatocytes of trans-kielcorin, trans-isokielcorin B, as well as their respective building blocks 3,4-dihydroxy-2-methoxyxanthone and 2,3-dihydroxy-4-methoxyxanthone. **METHODS.** Wistar rats, weighing 200-250g were used. Hepatocyte isolation was performed by collagenase perfusion. Incubations were performed at 37 degrees C,

using 1 million cells per milliliter in modified Krebs--Henseleit buffer. The protective activity was evaluated by measuring reduced and oxidized glutathione, lipid peroxidation and cell viability after inducing toxicity with tert-butylhydroperoxide (1.0 mM, 30 min), with or without the studied compounds in the concentrations of 0.025, 0.050, 0.100 and 0.200 mM. Silybin was tested in the same experimental conditions to serve as a positive control. RESULTS. Using these concentrations, the tested compounds prevented tert-butylhydroperoxide-induced lipid peroxidation and cell death in freshly isolated rat hepatocytes. All compounds were also effective in preventing perturbation of cell glutathione homeostasis in some extent. 3,4-Dihydroxy-2-methoxyxanthone and 2,3-dihydroxy-4-methoxyxanthone were more effective than trans-kielcorin and trans-isokielcorin B respectively. Silybin was less effective in protecting cells against lipid peroxidation and loss of cell viability than the four xanthonic derivatives. CONCLUSIONS. The tested compounds protected the freshly isolated rat hepatocytes against tert-butylhydroperoxide-induced toxicity.

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29: J Nat Prod 1993 Jun;56(6):929-34

Antiplatelet effects and vasorelaxing action of some constituents of Formosan plants.

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Various xanthenes as well as quercetin have been shown to exhibit antiplatelet activity. A series of anthraquinones analogues structurally related to xanthenes and a series of quercetin-related compounds were tested for their antiplatelet effects. Emodin, frangulin B, kaempferol tetraacetate, quercetin-3-O-galactoside octaacetate, rhamnazin triacetate, and rhamnetin tetraacetate were found to be potent antiplatelet agents, and 1,8-dihydroxy-6-methoxy-3-methylanthraquinone 8-O-rhamnosyl-(1-->2)-glucoside, rhamnustrioxide undecaacetate, rutin decaacetate, and quercetin-3-O-(6-O-alpha-L-arabinopyranosyl)-beta-D-galactopyranoside decaacetate showed significant antiplatelet effects. Quercetin showed vasorelaxing action in rat thoracic aorta.

PMID: 8350094 [PubMed - indexed for MEDLINE]

30: *Phytochemistry* 1992 Nov;31(11):3711-3

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

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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.

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31: *Agents Actions* 1980 Jun;10(3):252-7

Inhibition of rat intestinal anaphylaxis by various anti-inflammatory agents.

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Adverse reactions to food may, in some cases, be due to IgE-mediated immune reactions to the ingested antigens. A mast cell protector has been shown to protect patients against challenge with food to which they are sensitive. An IgE-mediated intestinal anaphylaxis reaction in the rat has been developed as a model of some aspects of human food allergy. Using this model, a number of xanthenes and other anti-inflammatory agents were tested for activity in inhibiting intestinal anaphylaxis. The compounds were also tested for inhibitory activity against the IgE-mediated rat passive cutaneous anaphylaxis reactions. The xanthenes protected against both reactions, as did isoproterenol and

cyproheptadine, while aspirin, indomethacin, and dexamethasone inhibited the intestinal but not the cutaneous reaction. This suggests that while IgE-triggered mediator release from mast cells is important in both reactions, other mechanisms may also be operative in the intestinal reaction. Furthermore, the use of xanthenes and other anti-inflammatory compounds may be a useful mode of therapy in human food allergy.

PMID: 7405752 [PubMed - indexed for MEDLINE]