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Review

Recent cancer drug development with xanthone structures

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Abstract

Objectives Xanthones are simple three-membered ring compounds that are mainly found as secondary metabolites in higher plants and microorganisms. Xanthones have very diverse biological profiles, including antihypertensive, antioxidative, antithrombotic and anticancer activity, depending on their diverse structures, which are modified by substituents on the ring system. Although several reviews have already been published on xanthone compounds, few of them have focused on the anticancer activity of xanthone derivatives. In this review we briefly summarize natural and synthetic xanthone compounds which have potential as anticancer drugs.

Key findings The interesting structural scaffold and pharmacological importance of xanthone derivatives have led many scientists to isolate or synthesize these compounds as novel drug candidates. In the past, extensive research has been conducted to obtain xanthone derivatives from natural resources as well as through synthetic chemistry. Xanthones interact with various pharmacological targets based on the different substituents on the core ring. The anticancer activities of xanthones are also dramatically altered by the ring substituents and their positions.

Summary The biological activities of synthetic xanthone derivatives depend on the various substituents and their position. Study of the biological mechanism of action of xanthone analogues, however, has not been conducted extensively compared to the diversity of xanthone compounds. Elucidation of the exact biological target of xanthone compounds will provide better opportunities for these compounds to be developed as potent anticancer drugs. At the same time, modification of natural xanthone derivatives aimed at specific targets is capable of expanding the biological spectrum of xanthone compounds.

Keywords anticancer agents; drug development; xanthones

Introduction

Cancer is the leading cause of death in modern society and there is an urgent need to find better cures for cancer-related diseases. Although enormous efforts have been dedicated to developing novel drugs for cancer treatment, cancer remains a major life-threatening disease. In order to develop more potent anticancer drugs, many tools have been employed, including chemical and biological methods.

Using chemical tools, numerous structural scaffolds have been created for disease treatments. Among these scaffolds, xanthones are simple three-membered heterocyclic ring compounds mainly found as secondary metabolites in higher plants and microorganisms. Xanthones have diverse biological profiles, including antihypertensive, antioxidative, antithrombotic and anticancer activities, depending on their diverse structures modified by substituents on the ring system.[1] The notable structural scaffold and pharmacological importance of xanthone derivatives have attracted many scientists to isolate or synthesize xanthone compounds as novel drug candidates. The major two sources of xanthone derivatives are synthesis and isolation from natural resources, either plant or marine materials. Generally applicable and simple xanthone core construction methods are well established.[2]

Although several reviews have already been published on xanthone compounds,[3–7] few of them have focused on the anticancer activity of xanthone derivatives. In this review, we provide a summary of xanthones that have recently shown potential as novel anticancer drug candidates. This review is based on the origins, natural resources and synthesis of the various xanthones. Table 1 lists some biological action targets of anticancer xanthones.[8]

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Table 1 Xanthone compounds with biological targets

Origin	Biological action	Structures
1) Synthesis	Topoiosmerase II	1) Thioxanthones,[37] epoxyxanthones,[36] acylxanthones[8]
2) Nature		2) Gambogic acid[22]
Synthesis	DNA intercalation	Bisxanthones[26]
1) Nature	DNA alkylation	1) Psorospermin[13,15,16]
2) Synthesis		2) Bisfuranoxanthones[31]
Synthesis	DNA cross-linking	Bisepoxyxanthones[36]
Nature	KDR/Flk-1 phosphorylation	Gambogic acid[20]
Nature	Apoptosis	Gambogic acid[19,24]
Synthesis	α-Glucosidase	Extended xanthones,[28] oxygenated xanthones[28]
Synthesis	Aromatase	Imidazolylxanthones[30]

Anticancer active xanthones from natural resources

Most xanthones identified from natural resources are of plant origin. Recently, however, some cancer-preventive xanthone derivatives have been isolated from marine fungus species. Chemopreventive agents are known to act on the enzymes related to the metabolic activation and excretion process of xenobiotics. Enzymes specifically involved in phase I metabolism transform xenobiotics to more hydrophilic species for detoxification, but some of these enzymes also increase the risk of producing carcinogens, which can interact with DNA, leading to carcinogenesis. Monodictyxanthone analogues isolated from marine algicolous fungus *Monodictys putredinis* are shown in Figure 1 and some of them showed effective inhibition on the cytochrome P450 (CYP) 1A isoenzyme converting xenobiotics to carcinogens.[9] These findings suggest that marine organisms or algae might also be a good source of chemopreventive xanthone derivatives.

A xanthone, α-mangostin (Figure 1), separated from the pericarps of mangosteen, *Garcinia mangostana*, efficiently inhibited cell growth of a human leukaemia cell line by inducing caspase-3 dependent apoptosis.[10,11] Further studies revealed that the cellular target of α-mangostin was the mitochondria.[12]

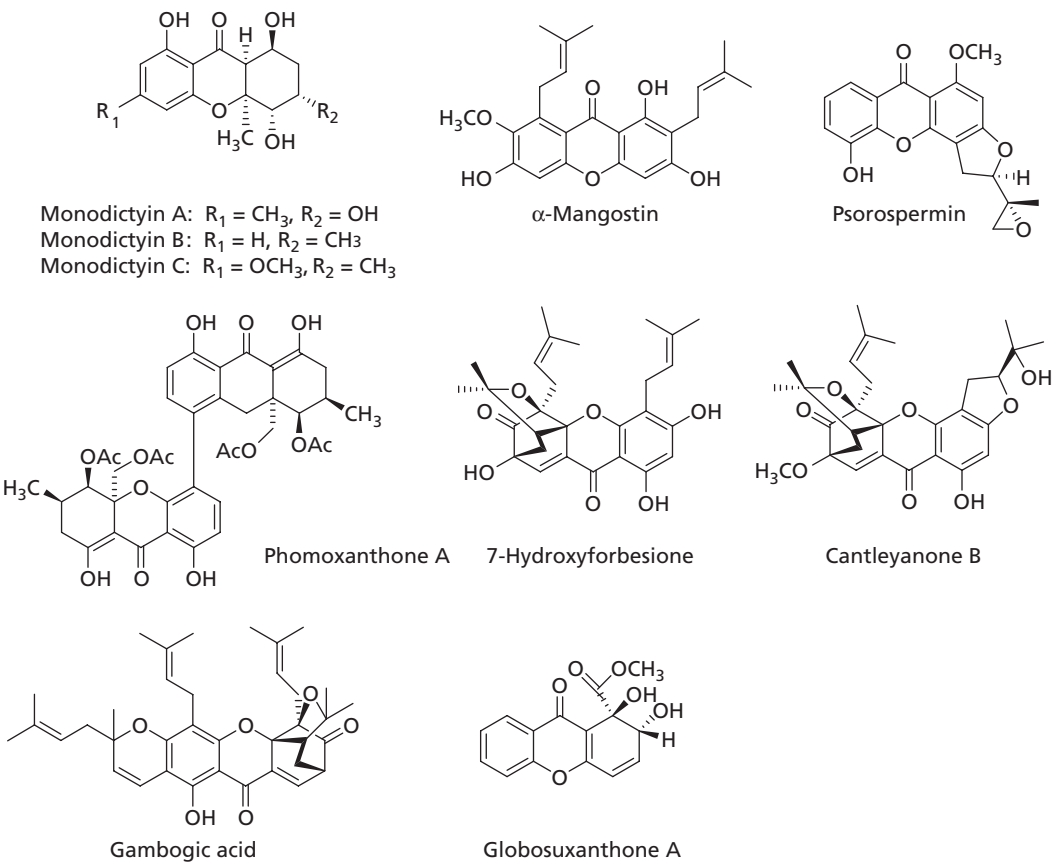

Figure 1 Diverse xanthones isolated from natural resources

Another impressive natural xanthone analogue is psorospermin (Figure 1), an ingredient of the African plant *Psorospermum febrifugum*.[13] This compound showed excellent anticancer activity against human and murine cancer cell lines. Because of the superb NCI 60 panel screening test results, psorospermin advanced to clinical trials but further development for the commercial market suffered from limited resources. Recently, stereoselective total synthesis for psorospermin was reported.[14] Hopefully, this accomplishment will pave the road to clinical trials with this compound. Psorospermin has shown biological activities via intercalation of the xanthone group with DNA base pairs and alkylation of epoxide by N7-guanine in the presence of topoisomerase II.[15,16]

Phomoxanthones (Figure 1) are structurally unique xanthone dimers obtained from the endophytic fungus *Phomopsis* species. These xanthone dimer analogues have shown excellent cytotoxic activity against tested tumor cell lines.[17]

Another naturally abundant type of xanthones in plants are prenylated xanthones; only two classes of prenylated xanthones will be discussed here. Several new polyprenylated xanthone derivatives were isolated from *Garcinia cantleyana*, which is found in the Malaysian Peninsula. These analogues are structurally caged polyprenylated derivatives. Among these analogues (Figure 1), 7-hydroxyforbesione, cantleyanone B and cantleyanone C were found to be potent cytotoxic agents. The caged structure on ring B and the peri-hydroxyl group on ring A are important for their biological activities.[18] Another interesting prenylated xanthone is gambogic acid (Figure 1), which is isolated from the resin of the *Garcinia hurbury* tree. This compound was identified as a potent anticancer agent during high-throughput screening (HTS) to determine whether this apoptosis-inducing agent could be used as a novel anticancer agent.[19] Several studies have examined the mechanism of action of gambogic acid. One reported pathway is the inhibition of angiogenesis by suppressing vascular endothelial growth factor (VEGF)-induced tyrosine phosphorylation of VEGF-A receptor-2 (KDR/Flk-1).[20] VEGF is highly expressed in human cancer tissues. It was also found that the ability of gambogic acid to induce apoptosis was not related to cell cycle arrest, a common pathway for many current natural anticancer drugs, including paclitaxel. Another study showed that gambogic acid reversed docetaxel resistance in gastric cancer cells by downregulation of survivin, an inhibitor of apoptosis protein.[21] Topoisomerase, a crucial enzyme for the DNA cycle, is another target for gambogic acid.[22] The catalytic activity of human topoisomerase IIα was efficiently inhibited by gambogic acid through binding to the ATP domain in the enzyme. Topoisomerase IIα inhibiting agents recently invoked interest due to their ability to synergize with other anticancer agents, further supporting the potential of gambogic acid as a prospective anticancer drug candidate. Several gambogic acid derivatives were synthesized and tested for their tumour-suppressing activities.[23,24]

Lastly, globosuxanthone A (Figure 1) isolated from fungal strain *Chaetomium globosum* exhibited efficient anticancer activity against human solid cancer cell lines.[25]

Although the naturally isolated xanthones discussed here have shown potential as new anticancer drug candidates, like most other natural products the quantities and structural limitations of xanthones create a bottle-neck for commercial development. Developing efficient synthetic methods of modifying xanthones and calibrating their pharmacologically active structures may solve these problems.

Synthetic xanthones

The biological activities of xanthones are known to be dependent on the position and types of substituents on the ring core. Since structural modifications with side chain substituents on the oxygenated xanthone core provide a wide spectrum of biological activity, most synthetic xanthone derivatives have focused on the introduction of various substituents on the aromatic ring moieties in the xanthone core. In this section, synthetic xanthones, in particular oxygenated xanthones, are discussed (Figure 2).

Due to their planar structure, xanthones are recognized as efficient DNA intercalators and many xanthone derivatives have shown anticancer activities via non-covalent DNA interaction. Using this property, a few compounds conjugated with two xanthone rings through proper linkers have been developed. Bisxanthone (Figure 2) tethered by a 6-carbon unit effectively inhibited a central nervous system cancer cell line and it was expected that including a lipophilic linker in its structure would enhance the blood–brain barrier penetration efficiently.[26] Oxime- and methyloxime-coupled xanthones were prepared and tested for cytotoxic activity. The results showed that these compounds were efficient cancer cell growth inhibitors.[27] Some synthetic oxygenated xanthones were efficient α-glucosidase inhibitors and simple polyhydroxyxanthones seem to be effective leads for new anticancer agents by α-glucosidase inhibition.[28] Protein kinase C (PKC) is also a pharmacological target of some xanthone compounds. Indeed, 3,4-dihydroxy- and 1-formyl-4-hydroxy-3-methoxyxanthones (Figure 2) have been reported as efficient and selective PKC inhibitors.[29]

Aromatase, a P450 enzyme that catalyses the conversion of androgen to estrogen via aromatization of the steroid A ring moiety, is a key enzyme for breast cancer occurrence. Synthetic xanthones modified with imidazole substituents showed superior aromatase inhibitory activity compared to the known aromatase inhibitor drug fadrozole.[30] These results implied that elegantly calibrated xanthones could be developed as aromatase inhibitor drug candidates for inhibiting breast cancer relapse.

Some xanthones, such as bisfuranoxanthones (Figure 2), have been modified from the naturally isolated bio-potent psorospermin mentioned above[31] and are comparable with psorospermin in the cytotoxicity test. However, they were not efficient as topoisomerase II mediated DNA alkylators, which is a characteristic property of psorospermin. This finding was attributed to the close positioning of the methylene (CH_2) group to N7 of guanine by the rigid bisfuran group and molecular modelling studies confirmed this observation.

One of the best-known xanthone anticancer drug candidates is 5,6-dimethylxanthenone-4-acetic acid (DMXAA; (Figure 2)). This compound has attracted scientific interest

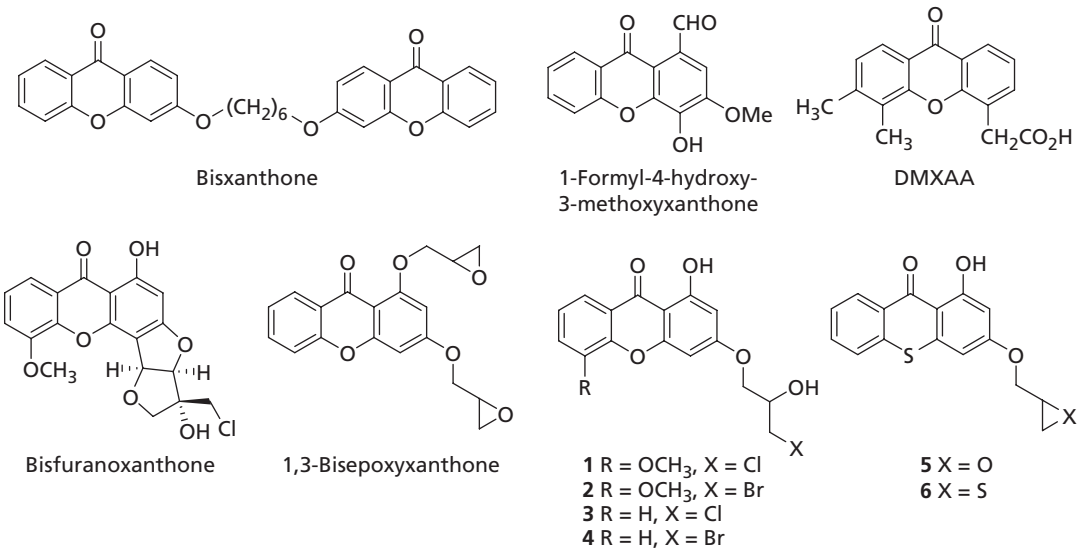

Figure 2 Various oxygenated and epoxy xanthones, and their ring epoxy opened xanthones derived by synthesis

because of its excellent pharmacological profile since its discovery.[32] Although DMXAA has advanced to phase II clinical trials and shown promising activity against malignant tumours, its exact mechanism of action has not yet been elucidated. It is thought to be a vascular disrupting agent that leads to the collapse of tumour vasculature and subsequent tumour cell death. Experimental observation has suggested that DMXAA could specifically activate the TBK1 (TANK-binding kinase 1)–IRF-3 (interferon regulatory factor 3) signalling cascade.[33]

As mentioned above, the xanthone ring is a DNA intercalator. When DNA alkylating or binding groups are incorporated in the xanthone structure, the resulting compounds might show enhanced DNA interacting capacity by a synergic effect from the two combined properties, DNA intercalation and DNA alkylation or groove binding. For this purpose several synthetic xanthones were prepared and tested for their anticancer activities. Xanthones with an epoxy group effectively inhibited cancer growth. When the two epoxy groups were tethered to the 3,5-position of xanthone, its cytotoxic activity was dramatically increased.[34] Although the mechanism of action of these compounds was not systematically studied, it was suggested that increased DNA interaction might contribute to this observation. Epoxide seems to have an important role in the biological action of these series of xanthones since epoxide ring-opened dihydroxy compounds lost some of their cytotoxic activities.[35]

Recently, further epoxyxanthone compounds have been synthesized in order to elucidate the mechanism of action and pharmacological targets for these derivatives. Some epoxyxanthones and their ring-opened halohydrin xanthones, as well as 1,3-bisepoxyxanthone, have been prepared and tested for cytotoxicity and topoisomerase II inhibition (Figure 2). Among these compounds, 1,3-bisepoxyxanthone showed the most active cell growth inhibition capacity.[36] The synthetic method for obtaining representative epoxyxanthones and their ring-opened compounds is described in Figure 3. This observation supported the previous report that a two-epoxy group substitution on xanthone generated better cytotoxic activity than a single epoxy substitution, even though the locations of the two epoxypropoxy groups were different.

To elucidate the possible mechanism of action and pharmacological target of these xanthones, topoisomerase II inhibition tests were conducted. In the test, 1,3-bisepoxyxanthone and monoepoxy ring-opened bromohydrin xanthone (**4**) exhibited excellent inhibition activity for topoisomerase II. 1,3-Bisepoxyxanthone also showed concentration-dependent DNA cross-linking activity.[36] These observations implied that both DNA and topoisomerase II could be action targets of xanthones depending on the substituents and their positions on the xanthone core. Some thioxanthone analogues were also synthesized and tested for their cytotoxicity and topoisomerase II inhibition.[37] Among these, thioxanthone **5** (Figure 2), which contains an epoxy group, showed the greatest inhibitory activity against cancer cell growth. On the other hand, the epoxide ring-opened chlorohydrin xanthone was the most effective inhibitor for topoisomerase II.

Conclusions

Cancer continues to be a major cause of human mortality and morbidity in spite of tremendous progress in anticancer drug development. Although proteomics and genomics are considered to be powerful tools for the development of new cancer treatments, small molecules possessing potent anticancer activities are still attractive as novel cancer drug candidates. Xanthones are among the oldest structures found in the chemical world, and their structural diversity and biological aspects are attracting researchers to search for new and potent cancer drug candidates.

The biological activities of synthetic xanthone derivatives depend on the various substituents and their position. The biological mechanism of action of xanthone analogues, however, has not been investigated as thoroughly as the

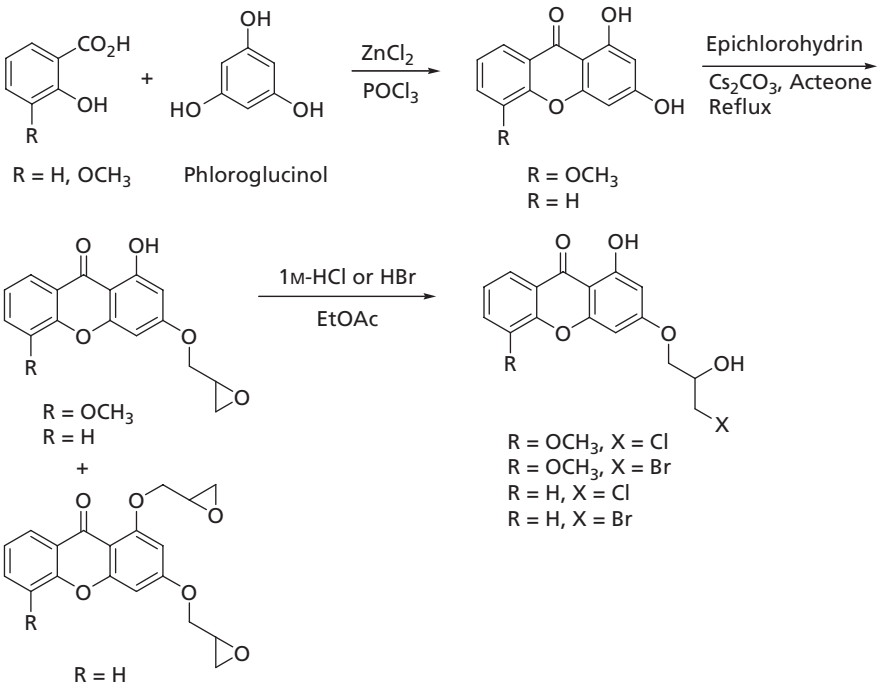

Figure 3 Synthetic pathway for epoxyxanthone derivatives.

diversity of xanthone compounds. Elucidation of the exact biological target of xanthone compounds will provide better opportunities for these compounds to be developed as potent anticancer drugs. At the same time, modification of natural xanthone derivatives aimed at specific targets is capable of expanding the biological spectrum of xanthone compounds. This can be achieved by elaborate design of new xanthone analogues, with help from modern medicinal techniques, including molecular modelling.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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