Recent developments in the pharmacology of prenylated xanthones

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Prenylated xanthones are secondary metabolites that are particularly common in plants belonging to the Clusiaceae family. Such compounds have been the focus intensive research because of their potential as biologically active agents. Here, we survey data published over the past decade relating to the properties of prenylated xanthones to provide a more detailed view of the potential of these naturally occurring compounds as therapeutic agents.

Introduction

Xanthones are an important class of natural and semisynthetic compounds with a range of pharmacological activities [1]. Such secondary metabolites are found in plants (mainly in Clusiaceae, Gentianaceae, Moraceae, and Polygalaceae families), fungi, ferns, and lichens, and are classified into five main subclasses: (i) simple oxygenated and nonoxygenated xanthones; (ii) xanthone *O*- and *C*-glycosides; (iii) *O*- and *C*-prenylated xanthones; (iv) polycyclic xanthones; and (v) xanthone dimers [1]. Several recent reviews of the phytochemistry and the pharmacognosy of xanthones focused mainly on xanthones, glycosides [1–3], polycyclic xanthones [4], and bis-xanthones [5]. Less attention has been dedicated to prenylated xanthones, although they represent the most abundant group of xanthones in terms of the number of structures isolated from natural sources. To our knowledge, the only review of prenylated xanthones was published in 2009 [6], focusing on data from 1963 to 2006. However, these compounds have been gaining increasing interest from the research community because of the discovery of novel, valuable, and promising biological effects. Bibliographic searches of common online publication databases, such as Scifinder, Medline, ISI, and Scopus, revealed that of the total number of publications on prenylated xanthones reported in the literature from 1973 to 2016, more than 60% were published over the past 10 years. Thus, here we provide an update on the main literature data published over the past decade and highlight the new opportunities and future challenges for research activities in this field. The chemical structures of the prenylated xanthones discussed in this review are illustrated in Fig. 1.

Xanthones from *Anaxagorea* spp.

Research over the past two decades has demonstrated *Anaxagorea* spp. (Annonaceae) to be promising sources of prenylated xanthones [7]. In particular, much interest has focused on the Thai medicinal plant *Anaxagorea luzonensis* Merr, with Sabphon and coworkers recently reporting the isolation of 1,3,5-trihydroxy-4-prenylxanthone **1** from *A. luzonensis* heartwood extracts [8]. The authors assayed the phosphodiesterase type 5 (PDE5) inhibitory activity of this novel isolate, recording an IC_{50} value of 3.0 μM. They also highlighted the importance of the prenyl side chain in position 4 as a determinant of the observed activity of this molecule [8]. PDE5 has a well-recognized role in several human syndromes, including erectile dysfunction. It is a well-known target of sildenafil, vardenafil, tadalafil, and avanafil, which are all drugs currently used in the treatment of male sexual dysfunction [9]. It has also a definite role in the pathogenesis of hypertension [11]. Although preliminary, the investigations by Sabphon and coworkers on the pharmacological properties of 1,3,5-trihydroxy-4-prenylxanthone **1** are the first on the inhibitory effects of a xanthone on PDE5. Thus, compound **20** might represent a lead compound for a new generation of PDE5 inhibitors, with therapeutic potential for male infertility, hypertension, and related disorders.

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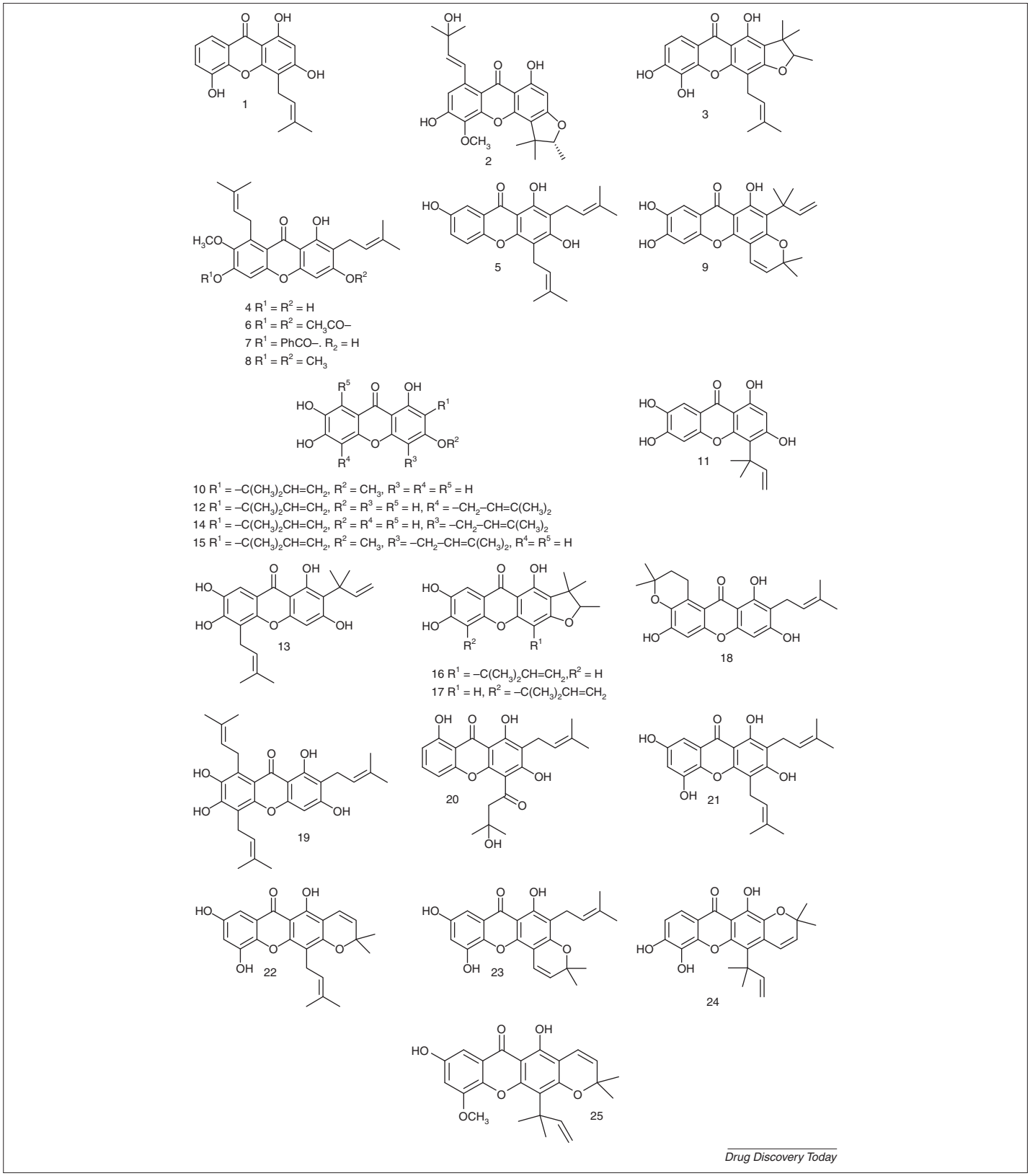

FIGURE 1

Structures of prenylated xanthones.

Xanthones from *Calophyllum* spp.

Several plants from the genus *Calophyllum* are rich sources of prenylated xanthones. Over the past decade, several reports of the isolation and pharmacological activity of such secondary metabolites from *Calophyllum* spp. have been published. For example, Dai and coworkers isolated caloxanthone N **2** and geronthoxanthone C **3** from the ethanolic extract of twigs of *Calophyllum inophyllum* L. [10]. Both isolates were shown *in vitro*

to be growth inhibitory agents against the K562 (human chronic myelogenous leukemia) cancer cell line, with IC_{50} values of 7.2 μg/mL and 6.3 μg/mL respectively [11]. Thus, caloxanthone N **2** and geronthoxanthone C **3** show promise as anticancer agents *in vitro*, although future studies will need to test both compounds against a wider panel of cancer and 'normal' cell lines to confirm their anticancer potential, to investigate more deeply their mechanism of action, and, finally, to determine their selectivity index.

Xanthones from *Cratoxylum* spp.

Cratoxylum spp. are a well-known natural source of prenylated xanthones. As a continuation of their ongoing studies on the phytochemical composition of the medicinal plant *Cratoxylum cochinchinense* (Lour.) Bl., Ren and coworkers published an extensive study of the composition of its prenylated xanthones and of structurally related analogs obtained by chemical synthesis [12]. The authors first isolated several prenylated xanthones from the chloroform-soluble fraction of the methanol extract of dried and ground stems, among which were α-mangostin **4** and 1,3,7-trihydroxy-2,4-diisoprenylxanthone **5**. Only α-mangostin was active in a preliminary assay of its effectiveness as a cytotoxic agent against the HT-29 (human colon cancer) cancer cell line. Thus, α-mangostin has since been used as a lead compound to obtain via acetylation, methylation, benzoylation, and cyclization reactions 13 semisynthetic derivatives, all assayed under the same experimental conditions. 3,6-Di-*O*-acetyl-α-mangostin **6** and 6-*O*-benzoyl-α-mangostin **7** were found to be the most active agents, with IC_{50} values of 1.0 μM and 1.9 μM, respectively. However, such activity was not reproducible *in vivo* using the hollow fiber assay at the highest dose tested (20 mg/kg i.p.). Nevertheless, these chemicals have only been tested *in vitro* and *in vivo* using one assay and so additional *in vitro* and *in vivo* tests should be carried out in the near future to shed more light on their potential as anticancer agents. Natural and semisynthetic products have been also assayed as anti-inflammatory agents in the nuclear factor (NF)-κB inhibition test, with 1,3,7-trihydroxy-2,4-diisoprenylxanthone **5** shown to be the most effective compound (IC_{50} = 2.9 μM). This last set of results is important because it indicates that the mechanism of action underlying the *in vitro* growth inhibitory effects on colon cancer cells recorded for α-mangostin and its semisynthetic derivatives do not involve the NF-κB signaling pathway, although this pathway is known to have a pivotal role in colon cancer pathogenesis [13]. An alternative putative mechanism of action can be hypothesized from data obtained from the mitochondrial transmembrane assay for which IC_{50} values of 3.3 μM and 0.9 μM were recorded for α-mangostin **4** and 3,6-di-*O*-methyl-α-mangostin **8**, respectively.

In 2014, Ibrahim and coworkers isolated α-mangostin **4** from the stem bark extract of *Cratoxylum arborescens* (Vahl) Blume and extensively studied the mechanism behind its apoptotic effect on the MDA-MB-231 (human breast cancer) cancer cell line [14]. The authors first recorded the effects of α-mangostin on cell viability using the MTT-test (IC_{50} = 9.2 μg/mL). Subsequent fluorescence microscopy studies revealed that this compound was able to induce deep morphological changes in a dose-dependent manner. The apoptotic induction began after exposure to an initial concentration of 5.0 μg/mL. Factors contributing to the observed apoptosis in MDA-MB-231 cells triggered by α-mangostin included disruption of matrix metalloproteinases, translocation of cytochrome c from mitochondria to the cytosol, regulation of Bcl-2 and Bax expression, induction of caspases 3/7, 8, and 9 following an increase in cleavage of the respective procaspases, suppression of PCNA and PARP expression, enhancement of reactive oxygen species production, and, finally, inhibition of tumor necrosis factor (TNF)-α. Considered together, these data enabled the authors to establish the anticancer efficacy of selected prenylated xanthones, and to gain further insights into their mechanism of action, to identify specific targets in the endocellular environment, and to determine a preliminary structure–activity relation for α-mangostin as a lead compound. In terms of the latter, Ren and coworkers preliminarily showed that an increase in the lipophilicity of the α-mangostin core contributed to the overall growth inhibitory activity of this compound. Further synthetic studies to obtain differently functionalized esters and ethers (e.g., fatty acids, functionalized benzoic acids, or ethers with longer chains) should be carried out to collect more information concerning the contribution of a decrease in the polarity of α-mangostin to its overall activity.

Xanthones from *Cudrania* spp.

Plants from the genus *Cudrania* (sin. *Maclura*) (Moraceae) were recently demonstrated to be a valuable source of prenylated xanthones. Fractionation of root extracts of *Cudrania tricuspidata* resulted in the isolation of nine prenylated xanthones: cudratricusxanthone N **9**, 1,6,7-trihydroxy-2-(1,1-dimethylallyl)-3-methoxyxanthone **10**, cudratricusxanthone L **11**, cudratricusxanthone A **12**, cudraxanthone L **13**, macluraxanthone B **14**, cudracuspixanthone A **15**, cudraxanthone D **16**, and cudraxanthone M **17** [15]. Subsequently, the inhibitory effects of these phytochemicals on protein tyrosine phosphatase 1B (PTP1B), an enzyme known to have a pivotal role in several human chronic and acute diseases, including type 2 diabetes mellitus, obesity, and breast, colon, and ovarian cancers, have been evaluated. Of the natural products isolated so far, apolar flavonoids have been shown to be the most effective inhibitory agents of PTP1B. The pioneering work by Quang and coworkers highlighted, for the first time, prenylated xanthones as novel inhibitors of PTP1B. Data obtained from experiments on the isolated enzyme are also promising. IC_{50} values for all the nine phytochemicals ranged from 1.9 μM to 4.6 μM and, in most cases, the inhibitory effects of prenylated xanthones from *C. tricuspidata* were higher than for those obtained for the prenylated flavonoids used as controls. Using cudratricusxanthone N **9** as a model, Quang and coworkers also reported preliminary insights into its mechanism of action, namely the noncompetitive inhibition of PTP1B [15]. This study provided the rationale to continue investigations aimed at characterizing prenylated xanthones from *C. tricuspidata* as potential antidiabetic and antiobesity agents, and as novel lead compounds of a new generation of drugs able to interfere with sugar and lipid metabolism. Moreover, experiments performed by Quang and coworkers might encourage further assays both *in vitro* (e.g., inhibition of α-glucosidase) and *in vivo* (e.g., use of animal models, such as alloxan-induced hyperglycemic rats) to better define the pharmacological potential of prenylated xanthones. Finally, results from this latter study also provide an explanation for the occurrence of hypoglycemia as an adverse effect associated with the traditional use of roots of *C. tricuspidata* in Korea, China, and Japan.

Xanthones from *Garcinia* spp.

Garcinia mangostana (Clusiaceae) is well recognized as the richest natural source of prenylated xanthones. Mangosteen fruits are consumed as food worldwide and other parts of this plant are also used as ethnomedicine in South East Asia. In 2011, Zhang *et al.* reported the isolation of several prenylated xanthones from mangosteen fruits extracts, among which were mangostenone D **18** and garcinone E **19** [16]. These two phytochemicals were assayed for their *in vitro* growth inhibitory effects against the MCF-7 (human breast cancer), A549 (human lung carcinoma), and HepG2 (human hepatoma) cancer cell lines. The IC_{50} values ranged from 1.2 μM to 2.1 μM and 1.0 μM to 11.7 μM, respectively. Moreover, garcinone E was shown to be more active compared with doxorubicin, which was used as reference drug [15]. These *in vitro* studies, although limited to only three cancer cell lines, represent a solid base on which further studies could be carried out to reveal the growth inhibitory properties of mangostenone D **18** and garcinone E **19** in more detail. Thus, it would be relevant to study their selectivity towards both cancer and 'normal' cell lines. Moreover, the finding that garcinone E is more effective than doxorubicin should prompt investigations to reveal the biomolecular basis of its mechanism of action as well as, more interestingly, the effect of this xanthone on cancer cell lines that are known to be resistant to proapoptotic stimuli. Some studies using natural compounds have been published. For example, Ryu *et al.* reported that γ-mangostin and smeathxanthone from fruits of *G. mangostana* showed good inhibitory activity against α-glucosidase, with IC_{50} values of 1.5 μM and 6.9 μM, respectively [17,18]. As *in vivo* confirmation of their potential to interfere with glucose metabolism, the same authors assayed a fraction of the ethanolic extract of mangosteen fruits enriched with these two xanthones in hyperglycemic Sprague-Dawley rats and found it to have the same antihyperglycemic effect after oral administration of maltose as the known α-glucosidase inhibitor acarbose, which was used as the reference drug [18]. Data from Ryu *et al.* also provide rationale for the widespread use of mangosteen fruits as a traditional antidiabetic remedy by local populations of South East Asia. In 2014, Xu *et al.* reported the isolation of 1,3,8-trihydroxy-2-prenyl-4-(3-hydroxy-3-methylbutanoyl)xanthone **20** from mangosteen fruits . This compound was tested as a growth inhibitory agent against a panel of eight human cancer cell lines comprising CNE1, CNE2, SUNE1, HONE1 (nasopharyngeal carcinoma), A549, GLC82 (lung cancer), MCF-7, and Bal7402 (hepatoma), and was shown to have IC_{50} values ranging from 0.73 μM to 9.77 μM [19]. However, these data must be confirmed and validated by comparing the effect of this phytochemical on 'normal' cell lines to calculate its selectivity index as well as on cancer cell lines that are resistant to proapoptotic stimuli.

Several polyphenols (e.g., flavonoids) have been reported to modulate the functionality of cholinesterases. Nevertheless, few data have been reported in the recent literature in relation to prenylated xanthones [20]. In this context, Khaw *et al.* described the anticholinesterase activity of α-mangostin, γ-mangostin, and garcinone C [21]. Such secondary metabolites were seen to efficiently inhibit acetyl-cholinesterase with IC_{50} values of 1.31 μM, 2.14 μM, and 1.24 μM respectively. γ-Mangostin also inhibited butyryl cholinesterase (IC_{50} = 1.78 μM) with equal potency [21]. Such data, although preliminary, might represent a valid stimulus for further studies to better characterize prenylated xanthones as anticholinesterase agents.

Fatmawati and coworkers described the aldose reductase inhibitory properties of α-mangostin, γ-mangostin, and 3-isomangostin isolated from mangosteen fruits [22]. Similar to glucosidases, aldose reductase is also involved in glucose metabolism and its dysfunction is one of the main causes of diabetes [23]. 3-Isomangostin was shown to be a potent negative modulator of the enzyme, with an IC_{50} value of 3.48 μM, similar to that recorded for quercetin, which was used as a control [22]. These data, together with those obtained by Ryu *et al.*, enforce the potential of prenylated xanthones as antidiabetic agents and should prompt further studies to better characterize their effects as well as to look for more potent and effective samples.

Few data have been reported over the past decade on the antimicrobial properties of prenylated xanthones from mangosteen, although the latter has been used as a traditional remedy for several kinds of bacterial infection for many years [24]. In 2009, Chomnawang and coworkers reported that the main constituent of mangosteen fruits, α-mangostin, is a potent bactericidal agent against methicillin-resistant *Staphylococcus aureus* (MRSA) [25]. Other antimicrobial properties of α-mangostin were determined by Al-Massarini and coworkers. α-Mangostin exerted good to potent effects *in vitro* against a panel of bacteria, including *Bacillus subtilis* (MIC = 3.9 μM), *Mycobacterium smegmatis* (MIC = 3.7 μM), *Mycobacterium chelonae* (MIC = 3.7 μM), *Mycobacterium xenopi* (MIC = 3.7 μM), and *Mycobacterium intracellulare* (MIC = 3.7 μM), and protozoa, such as *Plasmodium falciparum* (IC_{50} = 2.2 μM), *Leishmania infantum* (IC_{50} = 8.0 μM), *Trypanosoma cruzi* (IC_{50} = 8.9 μM), and *Trypanosoma brucei* (IC_{50} = 7.9 μM) [26]. Based on these promising results, further studies are required to investigate the antimicrobial activity of α-mangostin in more detail.

In 2009, Ngoupayo and coworkers isolated three new prenylated xanthones, staudtiixanthones A-C **21**, **22**, and **23**, from the methanol extract of twigs of *Garcinia staudtii* Engl. [27]. Staudtiixanthone A was found to exert a potent immunosuppressive effect on neutrophils and mononuclear cells (73% inhibition) when tested at a concentration of 3.1 μg/mL. All the isolates had a marked antiproliferative effect on T cells pretreated with phytohemagglutinin, with IC_{50} values of 6.2 μg/mL, 6.4 μg/mL, and 12.7 μg/mL respectively. Staudtiixanthone A was the most effective agent, with 97.1% inhibition of cell proliferation at a dose of 12.5 μg/mL. Furthermore, the three staudtiixanthones strongly inhibited interleukin (IL)-2, IL-4, and interferon (IFN)-γ release from phytohemagglutinin-treated cells in a dose-dependent manner, with staudtiixanthone A again the most potent compound, with 68.2% and 62.5% inhibition of IL-2 and IFN-γ release, respectively at a concentration of 0.5 μg/mL, and 88.1% for IL-4 at 1.0 μg/mL. Finally, all three staudtiixanthones exerted a marked suppressive effect on the chemotaxis of polymorphonuclear cells [27]. All these observed effects occurred at doses that were nontoxic to the cells, as highlighted by *in vitro* treatment of MDBK cells at doses up to 50 μg/mL; thus, staudtiixanthones should be considered as lead compounds for the development and design of a novel category of immunomodulatory agents.

The above-mentioned data support the renewed interest in *Garcinia* spp. as a valuable source of biologically active prenylated

xanthones. Mainly because of their well-described food and ethnomedical properties, most studies have focused on *G. mangostana* fruits. Over the past decade, a plethora of data has contributed to the better definition of the safety and biological properties of mangosteen fruits and their phyto- and food preparations. Thus, *G. mangostana* can be considered as a nutraceutical with beneficial effects for human wellbeing. Although several other *Garcinia* spp. have been investigated, the resulting data are very preliminary, especially from a pharmacological point of view. Only *in vitro* tests have been carried out and only on the antimicrobial or growth inhibitory capacities of isolated compounds against cancer cell lines. Such tests were also performed on panels of both bacteria and tumor cell lines comprising a relatively restricted number of strains. Given that effects on normal cells have not yet been examined, the selectivity indices for these compounds have yet to be calculated. Thus, more studies on compounds from *Garcinia* spp. are required to not only reveal the presence of novel phytochemical entities, but also, more interestingly, to increase our understanding of the pharmacological properties of these secondary plant metabolites.

Xanthones from *Mesua* spp.

In 2013, Teh and coworkers isolated several compounds from stem bark extracts of *Mesua beccariana* (Baill.) Kosterm., root bark of *Mesua ferrea* L., and roots of *Mesua congestiflora* P.F. Stevens, including mesuaferrin A 24, macluraxanthone 25, and α-mangostin 4 [28].

The authors tested these compounds as *in vitro* cytotoxic agents against a panel of human and murine 'normal' and cancer cell lines comprising Raji cells, SNU-1 (gastric carcinoma), K562, LS1747 (colon adenocarcinoma), SKMEL-28 (murine melanoma), IMR-32 (human neuroblastoma), HeLa, HepG2, and NCI H23 (lung carcinoma). All three compounds showed good to excellent effects against all cell lines with IC_{50} values ranging from 0.36 μM to 3.68 μM, 1.4 μM to 18.25 μM, and 6.1 μM to 11.44 μM, respectively [28]. Although this was the only study published during the past decade on prenylated xanthones from *Mesua* spp., it highlighted the potential of prenylated xanthones from *Mesua* spp. Thus, more investigations aimed at better deciphering the phytochemical and pharmacognostic profile of this genus should be performed.

Concluding remarks

Here, we have examined reports relating to prenylated xanthones published from 2007 to early 2016. Whereas studies on extraction, isolation, and structural analyses were numerous during this period, there were relatively few pharmacological investigations. In addition, most assays were performed using *in vitro* tests mainly in bacterial and cancer cell cultures, and few studies were carried out on isolated enzymes. In most studies, isolated prenylated xanthones showed great potential as therapeutic agents. However, other than a single study, there have been no other *in vivo* studies performed to validate and confirm the promising data from *in vitro* tests. This is the main drawback associated with the pharmacological studies on prenylated xanthones published to date. Although all the plant species discussed here are well-known ethnobotanicals. There is a poor correlation between the traditional medicine uses of such plants and their phytochemical composition, in particular the activity of the prenylated xanthones that they contain. There are now hundreds of prenylated xanthones available with known structures and significant therapeutic potential that could act as lead compounds for new generations of anticancer, antibacterial, immunomodulatory, antidiabetic, and antiobesity agents; however, such potential must be validated by *in vivo* studies using appropriate animal models.

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