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Retraction

Retracted: Naturally Occurring Xanthones: Chemistry and Biology

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Journal of Applied Chemistry has retracted the article titled "Naturally Occurring Xanthones: Chemistry and Biology" [1]. The article was found to contain a substantial amount of overlapping material from previously published articles, including the following sources cited as [2–5]:

(i) Kurt Hostettmann, Hildebert Wagner, "Xanthone glycosides," *Phytochemistry*, Volume 16, Issue 7, 1977, Pages 821–829, ISSN 0031-9422, doi: 10.1016/S0031-9422(00)86673-X [2].

(ii) L. M.M. Vieira, A. Kijjoa, Naturally-occurring xanthones: recent developments, *Current Medicinal Chemistry*, Volume 12, Issue 21, 2005, doi: 10.2174/092986705774370682 [3].

(iii) S. R. Jensen, J. Schripsema, Chemotaxonomy and pharmacology of *Gentianaceae*. In: Lena Struwe, Victor A. Albert (eds.), *Gentianaceae*, 573-632, January 2001. doi: 10.1017/cbo9780511541865.007 [4].

(iv) Ozlem Demirkiran, (2007) Xanthones in *Hypericum*: synthesis and biological activities. In: Khan M. T. H. (eds) Bioactive Heterocycles III. Topics in Heterocyclic Chemistry, vol. 9. Springer, Berlin, Heidelberg, Germany, doi: 10.1007/7081_2007_079 [5].

Additionally, 507 words were reproduced from the authors earlier review article [6], cited as reference 108 in the article.

The article is being retracted due to this overlap, with the agreement of the editorial board. The authors did not respond to these concerns.

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[1] S. Negi, V. K. Bisht, P. Singh, M. S. M. Rawat, and G. P. Joshi, "Naturally occurring xanthones: chemistry and biology," *Journal of Applied Chemistry*, vol. 2013, Article ID 621459, 9 pages, 2013.

[2] H. Kurt and H. Wagner, "Xanthone glycosides," *Phytochemistry*, vol. 16, no. 7, pp. 821–829, 1977.

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Review Article

Naturally Occurring Xanthones: Chemistry and Biology

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Xanthones are one of the biggest classes of compounds in natural product chemistry. A number of xanthones have been isolated from natural sources of higher plants, fungi, ferns, and lichens. They have gradually risen to great importance because of their medicinal properties. This review focuses on the types, isolation, characterization, biological applications, and biosynthesis of naturally occurring xanthones isolated so far. Different physicochemical and instrumental methods such as liquid-solid and liquid-liquid extraction, TLC, flash chromatography, column chromatography, IR, ^{1}H NMR and ^{13}C NMR spectroscopy, GLC, HPLC, GC, and LCMS have been widely used for isolation and structural elucidation of xanthones. Hepatoprotective, anticarcinogenic, antileprosy, antimalarial, antioxidant, anticholinergic, mutagenicity, radioprotective, immunomodulatory, antibone resorption, antiparasitic, neuraminidase inhibitory, anticomplement, antibacterial, antifungal, algicidal, anti-HIV, cardioprotective, antitumoral, antidiabetes, antihyperlipidemic, antiatherogenic, anti-inflammatory, antiulcer, antidiabetic, hypolipidemic, analgesic, antiasthmatic, antihistaminic, antiamoebic, diuretic, antidiarrheal, larvicidal, and ovicidal activities have been reported for natural occurring xanthones. To a certain extent, this review provides necessary foundation for further research and development of new medicines.

1. Introduction

Xanthones are secondary metabolites commonly occurring in higher plant families, fungi, and lichen [1]. Their pharmacological properties have raised great interest. Structures of xanthones are related to that of flavonoids and their chromatographic behaviours are also similar. Flavonoids are frequently encountered in nature, whereas xanthones are found in limited number of families. Xanthones always occur in the families Gentianaceae, Guttiferae, Moraceae, Clusiaceae, and Polygalaceae. Xanthones are sometimes found as the parent polyhydroxylated compounds but most are mono- or polymethyl ethers or are found as glycosides [2]. Unlike iridoids, xanthones are apparently not present in all plant species investigated in the family Gentianaceae. This is documented by the systematic work of Hostettmann et al. [3]. Natural occurrence of 12 xanthones in higher plants and 4 in fungi has been reviewed by Roberts in 1961 and by Dean in 1963 [4, 5]. Gottlieb [6] mentioned the isolation of 60 xanthones from higher plants and 7 from fungi, whereas Carpenter et al. [7] listed 82 xanthones from higher plants. Gunasekera [8] recorded 183 xanthones from 5 families of tracheophyta. According to Vieira and Kijjoa [9], out of total 515 xanthones, 278 were reported from natural sources. These xanthones have been isolated from 20 families of higher plants (122 species in 44 genera), fungi (19 species), and lichens (3 species). In this period, the xanthones from higher plants appear to be associated mainly with the families Clusiaceae (55 species in 12 genera) and Gentianaceae (28 species in 8 genera). Bo and Liu [10] have reviewed separation methods used for pharmacologically active xanthones. Jose Pedraza-Chaverri et al. [11] reviewed the isolated chemical constituents and medicinal properties of *C. Garcinia* (mangostana). Some of the plants, ferns, and fungus species which contain xanthones are *Artocarpus, Anthocleista, Allanblackia, Andrographis, Aspergillus, Bersama, Blackstonia, Calophyllum, Canscora, Centaurium, Chironia, Cratoxylum, Comastoma, Garcinia, Cudrania, Eustoma, Emericella, Frasera, Garcinia, Gentiana, Gentianella, Gentianopsis, Halenia, Hoppea, Hypericum, Ixanthus, Lomatogonium, Mesua, Morinda, Macrocarpaea,* Mangrove fungi, *Orphium, Peperomia, Pentadesma, Polygala, Penicillium, Phoma*, *Phomopsis, Rheedia,*

Rhus, Securidaca, Symphonia, Schultesia, Swertia, Tripterospermum, Vismia, Veratrilla, and *Xylaria*.

2. Classification

Xanthones isolated from natural sources are classified into six main groups, namely, simple xanthones, xanthone glycosides, prenylated xanthones, xanthonolignoids, bisxanthones, and miscellaneous xanthones.

2.1. Simple Oxygenated Xanthones. Simple oxygenated xanthones are subdivided according to the degree of oxygenation into non-, mono-, di-, tri-, tetra-, penta-, and hexaoxygenated substances [9, 12, 13]. In these xanthones the substituents are simple hydroxy, methoxy, or methyl groups. About 150 simple oxygenated xanthones have been reported.

2.1.1. Nonoxygenated Simple Xanthones. The nonoxygenated xanthones, namely, methylxanthones (1-,2-,3-,4-methylxanthone), were reported in crude oils from off-shore Norway [14]. This was the first description of xanthones in fossil organic matter. These xanthones might have been generated as diagenetic products, formed by oxidation of xanthenes in the reservoir, or might have originated by biosynthesis from aromatic precursors.

2.1.2. Monooxygenated Xanthones. Besides, six monooxygenated xanthones from *Swertia*, 2-hydroxyxanthone, 4-hydroxyxanthone, and 2-methoxyxanthone have been isolated from four genera, namely, *Calophyllum*, *Kielmeyera*, *Mesua,* and *Ochrocarpus*.

2.1.3. Dioxygenated Xanthones. More than fifteen dioxygenated xanthones were reported from plants of the families Clusiaceae and Euphorbiaceae. 1,5-Dihydroxyxanthone, 1,7-dihydroxyxanthone, and 2,6-dihydroxyxanthone are found fairly extensively. Other deoxygenated xanthones such as 1-hydroxy-5-methoxyxanthone, 1-hydroxy-7-methoxyxanthone, 2-hydroxy-1-methoxy-xanthone, 3-hydroxy-2-methoxyxanthone, 3-hydroxy-4-methoxyxanthone, 5-hydroxy-1-methoxyxanthone, and 1,2-methylenedioxyxanthone have been reported from eleven plants genera.

2.1.4. Trioxygenated Xanthones. Forty-five trioxygenated xanthones have been reported; out of these fifteen were described as new. Among these, only two natural sulfonated xanthones, namely, 1,3-dihydroxy-5-methoxyxanthone-4-sulfonate and 5-O-β-D-glucopyranosyl-1,3-dihydroxyxanthone-4-sulfonate, are reported from *Hypericum sampsonii*. These sulfonated xanthones were found to exhibit significant cytotoxicity against cancer cell line [15, 16]. 1,3,5-, 1,5,6-, 1,6,7-, and 2,3,4-trihydroxyxanthone, seventeen methyl ethers, and two methylenedioxy derivatives from nine genera have been reported.

2.1.5. Tetraoxygenated Xanthones. Among the 53 tetraoxygenated xanthones identified so far, 21 were found to be new natural products. These xanthones were mainly reported from plants of the families Gentianaceae, Clusiaceae, and Polygalaceae. Interestingly, 7-chloro-1,2,3-trihydroxy-6-methoxyxanthone isolated from *Polygala vulgaris* [17] appeared to be the first chloroxanthone of the family Polygalaceae. This compound exhibited antiproliferative activity against the human intestinal adenocarcinoma cell line. The free hydroxyxanthones are 1,3,5,6-, 1,3,5,7-, and 1,3,6,7-tetrahydroxyxanthone [18].

2.1.6. Pentaoxygenated Xanthones. Twenty-seven pentaoxygenated xanthones have been identified. Four partially methylated pentaoxygenated xanthones, namely, 1,8-dihydroxy-2,3,7-trimethoxyxanthone, 5,6-dihydroxy-1,3,7-trimethoxyxanthone, 1,7-dihydroxy-2,3,8-trimethoxyxanthone, 3,8-dihydroxy-1,2,6-trimethoxyxanthone [19], and 3,7-dihydroxy-1,5,6-trimethoxyxanthone, have been isolated from three plants genera.

2.1.7. Hexaoxygenated Xanthones. Two hexaoxygenated xanthones, 8-hydroxy-1,2,3,4,6-pentamethoxyxanthone [15, 20] and 1,8-dihydroxy-2,3,4,6-tetramethoxyxanthone [21], are isolated from two *Centaurium* species and 3-hydroxy-1,2,5,6,7-pentamethoxyxanthone was isolated from the roots of *Polygala japonica*. The natural occurrence of pentaoxygenated, hexaoxygenated, and dimeric xanthones has been reviewed by Peres and Nagem [22].

2.2. Xanthone Glycosides. Sixty-one naturally occurring glycosylated xanthones, thirty-nine of which are new compounds, have been reported predominantly in the families Gentianaceae and Polygalaceae as C- or O-glycosides. The details of naturally occurring xanthone glycosides have been reviewed [2] and distinction between C-glycosides and O-glycosides has also been made. In C-glycosides, C–C bond links the sugar moiety to the xanthone nucleus and they are resistant to acidic and enzymatic hydrolysis whereas the O-glycosides have typical glycosidic linkage.

2.2.1. C-Glycosides. C-glycosides are rare; thus, only seven C-glycosides were mentioned in Sultanbawa's review [13] and 17 in Al-Hazimi's review [23]. Mangiferin and isomangiferin are the most common C-glycosides. Mangiferin (2,-C-β-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone) is of widespread occurrence in angiosperms and ferns and was first isolated from *Mangifera indica* [24–26]. An isomer, isomangiferin (4-C-β-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone), has been isolated from the aerial parts of *Anemarrhena asphodeloides* [27]. Homomangiferin (2-C-β-D-glucopyranosyl-3-methoxy-1,6,7-trihydroxyxanthone) has also been isolated from the bark of *Mangifera indica* [28]. In 1973, another glycoxanthone (2-C-β-D-glucopyranosyl-1,3,5,6-tetrahydroxyxanthone) with an oxidation pattern other than that of mangiferin was found in *Canscora decussate* [29]. Arisawa and Morita [30] have isolated tetraoxygenated xanthone glycoside 2-C-β-D-glucopyranosyl-5-methoxy-1,3,6-trihydroxyxanthone from *Iris florentina*.

2.2.2. O-Glycosides. More than 20 xanthone O-glycosides are known. A few are from natural sources, namely, gentiacauloside from *Gentiana acaulis*, gentioside from *G. lutea*, and swertianolin from *Swertia japonica* [31]. Their natural occurrence is restricted to the family Gentianaceae. The first xanthone O-glycoside, norswertianin-1-O-glucosyl-3-O-glucoside, was isolated from *S. perennis* [2]. A tetraoxygenated xanthone O-glycoside (3,7,8-trihydroxyxanthone-1-O-β-laminaribioside) was isolated from the fern species [32]. 1-Hydroxy-7-methoxy-3-O-primeverosylxanthone [33] and 1-methoxy-5-hydroxyxanthone-3-O-rutinoside [34] have been isolated from *Gentiana* species and *Canscora decussata*.

2.3. Prenylated and Related Xanthones. Among 285 prenylated xanthones, 173 were described as new compounds. The occurrence of prenylated xanthones is restricted to the plant species of the family Guttiferae. The major C_5 unit of the substituents included the commonly found 3-methylbut-2-enyl or isoprenyl group as in isoemericellin and the less frequent 3-hydroxy-3-methylbutyl as in nigrolineaxanthone P and 1,1-dimethylprop-2-enyl as in globuxanthone, respectively [35–37]. Prenylated xanthones, caloxanthone O and caloxanthone P, were isolated from *Calophyllum inophyllum* [38] and polyprenylated xanthones and benzophenones from *Garcinia oblongifolia* [39].

2.4. Xanthonolignoids. Naturally occurring xanthonolignoids are rare, so only five compounds are known. The first xanthonolignoid was isolated from Kielmeyera species by Castelão Jr. et al. [40]. They also isolated two other xanthonolignoids named Cadensins A and B from *Caraipa densiflora*. A xanthonolignoid Kielcorin was obtained from *Hypericum* species [41]. Recently, kielcorin was also isolated from *Vismia guaramirangae* [42], *Kielmeyera variabilis* [43], and *Hypericum canariensis* [44], whereas cadensin C and cadensin D from *Vismia guaramirangae* and *Hypericum canariensis* have been reported [45].

2.5. Bisxanthones. A total of twelve bisxanthones, five from higher plants, one from lichen, and six from fungi, have been reported to date. These include jacarelhyperols A and B [46], from the aerial parts of *Hypericum japonicum* and dimeric xanthone, and globulixanthone E, from the roots of *Symphonia globulifera* [47]. Three C_2-C_2' dimeric tetrahydroxyxanthones dicerandrols A, B, and C, are also isolated from the fungus *Phomopsis longicolla* [48].

2.6. Miscellaneous. Xanthones with substituents other than those mentioned above are included in this group. Xanthofulvin and vinaxanthone were isolated from *Penicillium* species [49]. A polycyclic substance (xanthopterin) with the ability to inhibit the HSP47 (heat shock protein) gene expression was isolated from the culture broth of a *Streptomyces* species [50]. Xantholiptin is a potent inhibitor of collagen production induced by treatment with TGF-b in human dermal fibroblasts. Xanthones have been synthesized by different methods. The elements of synthetic methods such as building blocks, Diels-Alder reaction, and heterogeneous catalysts have also been reviewed [51].

3. Methods for Isolation and Characterization of Xanthones

Plants xanthones are commonly isolated by column chromatography on silica gel using different solvent mixtures with increasing polarity [52–55]. Xanthone glycosides are usually crystallized from MeOH. They may also be separated and identified using TLC [56] and HPLC [57–61] by comparison with authentic samples. The structure of xanthones has been established on the basis of UV, IR, MS, and NMR data [13, 62–72]. Preparative TLC on silica gel using AcOEt, MeOH, and H_2O (21 : 4 : 3) as mobile phase has been used in instances of difficult separation. Frequently used solvents in TLC are on polyamide, MeOH-H_2O (9 : 1) and MeOH-H_2O-AcOH (90 : 5 : 5); on cellulose, HOAc (5–30%); on silica gel, Py-H_2O-AcOEt-MeOH (12 : 10 : 80 : 5) and AcOEt-MeOH-H_2O (21 : 4 : 3) and chromatoplates are viewed in UV light. In certain cases, spraying with 5% KOH in MeOH or 5% aqueous H_2SO_4 has been advantageous [33]. Polyamide columns are frequently applied for the separation of xanthone glycosides. Purification of xanthones on Sephadex LH20 column has also been carried out [2]. Xanthones are also isolated from resin of *Garcinia hanburyi* [73] and from the fermentation products of an endophytic fungus *Phomopsis* [74].

HPLC has been proved as the best technique for separation, identification, and quantification of xanthones. Several HPLC methods have been developed for naturally occurring xanthones using microporous chemically bonded silica gel (Micropak CN column), solvent hexane-chloroform (13 : 7, v/v), isooctane-$CHCl_3$ (3 : 17, v/v), or dioxane-dichloromethane (1 : 9) detected at 254 nm by UV detector [60]. Polar aglycones as well as glycosides of xanthones are also resolved on reversed phase column (C_8 and C_{18}) using acetonitrile-water as mobile phase [75, 76]. High-speed counter current chromatography (HSCCC) and high performance centrifugal partition chromatography (HPCPC) were also used for the separation and isolation of mangiferin and neomangiferin from an extract of *Anemarrhena asphodeloides* [77] and α-mangostins and γ-mangostins from mangosteen pericarp, respectively [78].

3.1. Ultraviolet Visible Spectroscopy (UV). Ultraviolet visible spectroscopy technique is useful for locating free hydroxyl groups in xanthones. In particular, the OH group at position 3 is easily detected by addition of NaOAc which results in a bathochromic shift of the 300–330 nm bands with increased intensity. Three or four bands of maximum absorption are always found in the region 220–410 nm and it is noteworthy that all bands show high intensity. Most of the substances show a marked absorption in the 400 nm regions, which accounts for their yellow colour [79].

3.2. Infrared Spectroscopy (IR). The carbonyl group in xanthones is always easily detectable in IR spectra as a strong band (stretching frequency) in the region of 1657 cm^{-1} [53].

The presence of a hydroxyl group in the l or 8 position lowers the frequency to about 1650 cm^{-1} by hydrogen bonding. Substituents in the 3 or 6 position of the xanthone nucleus may have a marked effect upon the carbonyl stretching frequency [80].

3.3. Proton Nuclear Magnetic Resonance Spectroscopy (^1H NMR). 1D and 2D-NMR spectra (^1H, ^{13}C, DEPT, COSY, TOCSY, HROESY, HSQC, HMBC, and NOESY) have been used for characterization of the xanthones. The ^1H NMR spectrum appears predominantly in the range of 0–12 ppm downfield from the reference signal of TMS. The integral of the signals is proportional to the number of protons present. ^1H NMR gives information about the substitution pattern on each ring. Acetylated derivatives have been utilised in the structure determination of glycosides [81]. The number and relative position of acetyl and methoxy groups can be determined by observing the shift for the position of absorption for the aromatic protons which occurs upon replacing methoxy group by an acetyl group. Signals between δ 2.40–2.50 are indicative of acetylation at peri-position to the carbonyl group (1 or 8 position) since for other positions the acetyl signals fall between δ 2.30 and 2.35. In nonacetylated xanthones the presence of hydrogen bonded OH at δ 12-13 also confirms hydroxyl substitution at 1 or 8. But when these positions are unsubstituted, then absorption for the aromatic protons appears at δ 7.70–8.05 [82]. Tetraoxygenated xanthones, namely, 1,3,7,8- and 1,3,5,8-, showed two meta- and two ortho-coupled protons in the ^1H NMR spectrum. They can also be distinguished by the fact that the presence for the ortho-coupled proton in the 1,3,7,8- system appears at lower field [83] than that for 1,3,5,8- (bellidifolin) system [84]. The signals of 2″-O-acetyl methyl protons of 8-C-glucosyl flavone acetate are found at higher field than those of corresponding 6-C-glucosyl flavone acetate [85]. In a similar manner, 2-C and 4-C isomeric glycosyl xanthones can be distinguished.

3.4. Carbon Nuclear Magnetic Resonance Spectroscopy (^{13}C NMR). The number of signals in the ^{13}C NMR spectrum indicates the number of different types of C atoms. It gives the information about the total number of the C atoms present in the molecule. It is particularly diagnostic for determining the sugar linkage in di- or polysaccharides; the signal of the carbon carrying the primary alcohols appears at δ 62 in glucose. This signal is shifted to δ 67 in disaccharides possessing a 1–6 linkage [60, 61]. The chemical shift for carbonyl carbon is δ 184.5 when positions 1 and 8 are substituted by hydroxyl groups. But when one of these positions is occupied either by a methoxy or a sugar moiety, the carbonyl signal is shifted upfield by about 4 ppm. If both positions are occupied by a methoxy group or sugar moieties, the upfield shift is about 10 ppm. When methoxy groups are located in position 1 or 8, the corresponding absorption appears at δ 60-61, whereas they appear at about δ 56 when the methoxy group is located in the remaining positions on xanthone nucleus [53].

3.5. Mass Spectrometry (MS). Mass spectrometry is also a useful tool in the structure elucidation of xanthone glycosides. Prox [86] established the fragmentation pattern of mangiferin and related C-glycosides. Aritomi and Kawasaki [27, 28] obtained satisfactory results using peracetylated derivatives of the same and analogous compounds. In mass spectrum of O-glycosides, no discernible molecular ion peak can be observed, but an important fragment ion peak due to the aglycone moiety appears, followed by further fragmentation. Significant fragment ions from the loss of OH, H_2O, and CHO are typical for xanthones and related compounds with a methoxy substituent peri to the carbonyl group [34, 53, 87].

4. Biological Activities of Xanthones

Plants belonging to the family Gentianaceae are best known for their bitter taste due to the presence of xanthones and are used in traditional remedies against loss of appetite and fever and are still included in many "tonic" formulations [88]. Some specific activities have been reported for xanthones and iridoids from Gentianaceae. Xanthones (especially mangiferin) are reported to give CNS stimulation [89, 90] and have anti-inflammatory activity [12]. For bellidifolin and swerchirin, a strong hypoglycemic activity has been reported [91–93]. A crude extract of *Swertia* has been reported to display insect repellent activity [94]. The extracts of most of the *Swertia* species show mutagenic activity [95]. An extract from *S. paniculata* is used in the Indian System of Medicine as a bitter tonic and in the treatment of some mental disorders [96]. *S. hookeri* extract is used in the treatment of microbial infections and as a mood elevator [97]. Swertifrancheside isolated from *S. franchetiana* was found to be potent inhibitor of the DNA polymerase activity of human immunodeficiency virus-1 reverse transcriptase [98]. Naturally occurring xanthones have emerged as an important class of organic compounds in view of their remarkable pharmacological and other biological activities. It has now been observed that a number of plant products which are in regular use as chemotherapeutic agents contain xanthones as active constituents. Mangiferin was the first xanthone to be investigated pharmacologically and has been found to exhibit a broad spectrum of biological activities. It shows monoamine oxidase inhibition, cardiotonic, convulsant, and choleretic activities [29, 89]. Pronounced anti-inflammatory activity has also been observed for mangiferin [99]. Oral and topical compounds containing mangiferin are useful for the treatment of diseases caused by herpes virus. Mangiferin has been found to protect the liver of the rats from high altitude hypoxia. On the other hand, Ghosal and Chaudhuri [100] have observed the opposite CNS depressant effect for xanthone-O-glycosides in mice and rats. The antimalarial drug AYUSH-64 contains *S. chirata* as one of the ingredients. Xanthones from *S. chirata* are reported to produce CNS depression [29]. The total extract of *S. chirata* showed significant antifeedant activity against *Jute semilooper* [101]. Norswertianolin, an O-glycoside, has been reported to produce antitubercular activity. The O-glycosides of *S. purpurascens* are known to produce CNS depression in albino rats and mice [102]. Xanthones of *Mammea americana* exhibited inhibitory

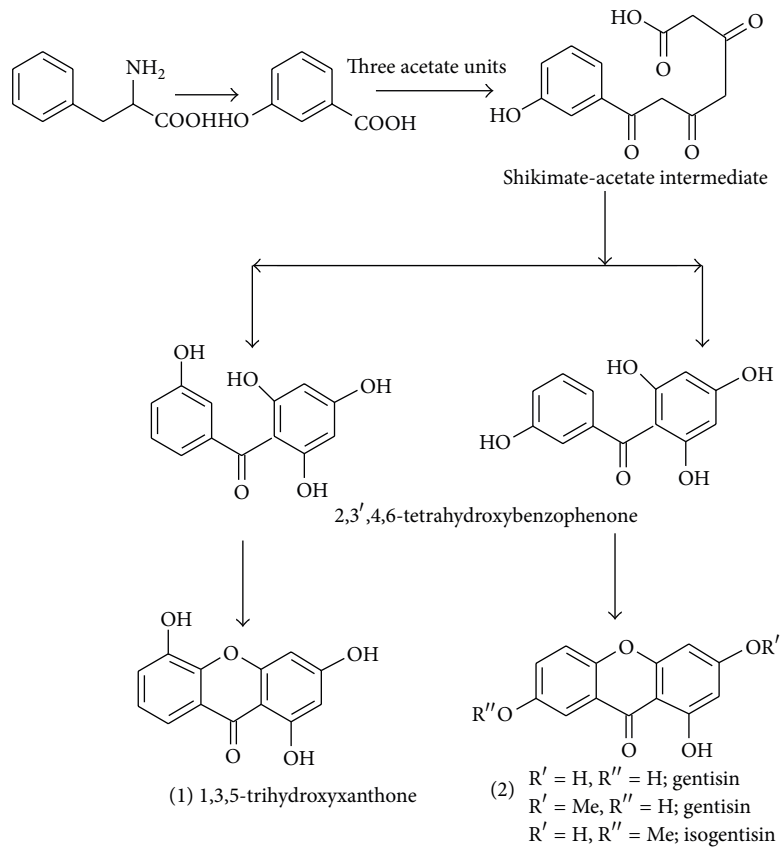

Figure 1: Biosynthetic pathways leading to the xanthones (1) and (2).

activity against sarcoma 180 tumor cell [103]. 1,8-Dihydroxy-3,5-dimethoxyxanthone (swerchirin), isolated from the hexane fraction from *Swertia chirayita,* has a very significant blood sugar lowering effect in fasted, fed, glucose loaded, and tolbutamide pretreated albino rats. The ED_{50} for 40% glycaemia lowering in CF male albino rats was 23.1 mg/kg when orally administered [104]. *Swertia* species have also been investigated for the presence of essential elements [105–107]. Xanthones have been reported to display hepatoprotective, antimicrobial, anticarcinogenic, antileprosy, antioxidant, anticholinergic, mutagenicity [108, 109], and radioprotective effect [110], immunomodulatory effect [111], antibone resorption [112], and antiparasitic effects [113], neuraminidase inhibitory [114], antimalarial [115], anticomplement [116], antifungal and algicidal [117], and anti-HIV activity [118], and cardioprotective, antitumoral, antibacterial, antidiabetes, antihyperlipidemic, antiatherogenic, immunomodulator, anti-inflammatory, antiulcer, antiviral, antifungal [119], antidiabetic, hypolipidemic [120], analgesic, antiasthmatic, antihistaminic, antiamoebic, diuretic, antidiarrheal, larvicidal, ovicidal, antiprotozoal, antileptospiral, anti-TMV, and anticancer activities [121–124]. Xanthones from *S. mussotii* were evaluated for their anti-hepatitis B virus activity on HepG 2.2.15 cells line; they exhibited significant activity inhibiting hepatitis B virus DNA replication with IC_{50} values from 0.01 mM to 0.13 mM [125].

5. Biosynthesis of Xanthones

Biosynthetically xanthones are of mixed shikimate and acetate origin (Figure 1). Thus, phenylalanine, which is formed from shikimate, loses two carbon atoms from the side-chain and is oxidized to form *m*-hydroxybenzoic acid. This combines with three units of acetate (via malonate) to give the intermediate. The shikimate-acetate intermediate undergoes ring-closure to give substituted benzophenone, which by an oxidative phenol coupling generates the central ring of the xanthone moiety. This oxidative coupling can take place in two ways depending on the folding of the benzophenone either in the *ortho* or in the *para* position to the hydroxyl substituent in the potential B-ring to give 1,3,5-trihydroxyxanthone (1) or the 1,3,7-substituted analogue gentisin (2), respectively. Thus, depending on the orientation of the intermediate, two different hydroxylation patterns can be found. Experimental proof for the overall pathway has been obtained from experiments performed using *Gentiana lutea* [126, 127].

When plants were fed ^{14}C-labeled phenylalanine, the label was recovered solely in the B-ring (Figure 1). Conversely, feeding of ^{14}C-labeled acetate gave incorporation of the main part in the A-ring. The alternative ring closure to (1) has recently been shown to take place in cultured cells of *Centaurium erythraea*, where 2,3′,4,6-tetrahydroxybenzophenone

is the precursor for 1,3,5-trihydroxyxanthone [128]. Furthermore, in these cell cultures, compound (1) is selectively oxidized by a xanthone 6-hydroxylase to 1,3,5,6-tetrahydroxyxanthone [129]. Explored methods for synthesis of simple oxygenated xanthones have been documented by Sousa and Pinto [130].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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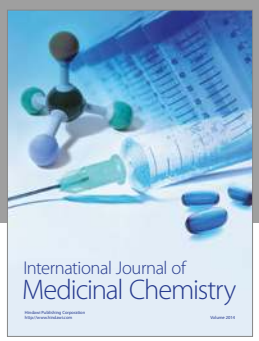

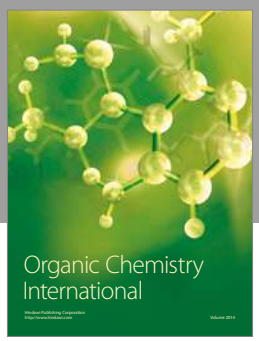

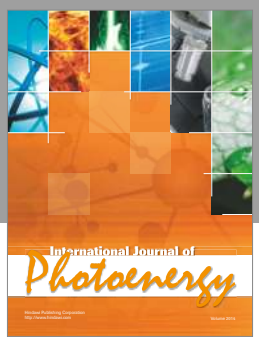

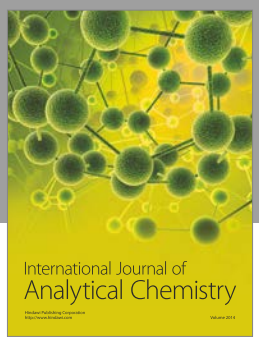

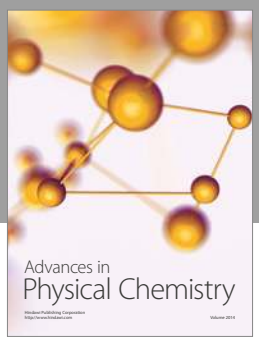

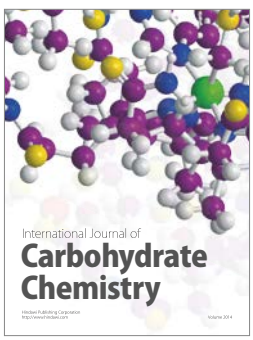

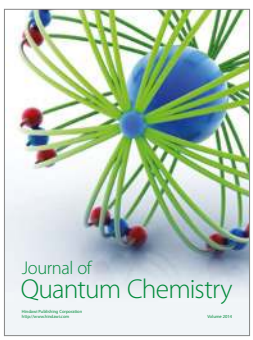

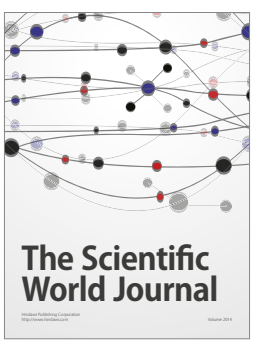

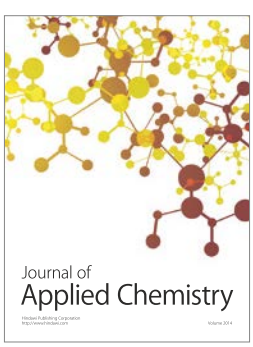

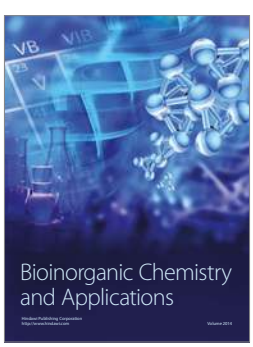

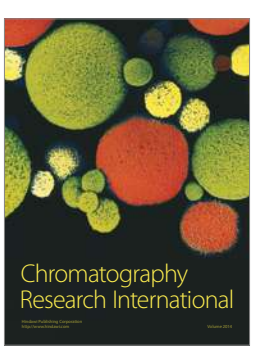

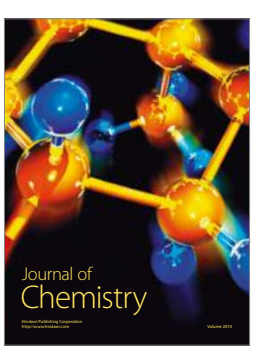

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