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XANTHONOIDS OF TROPICAL PLANTS†

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During the past 20 years, a large number of xanthones have been isolated from the higher plants and their natural occurrence has gained considerable importance. The reviews by Roberts in 1961[1] and by Dean in 1963[2] refer to the natural occurrence of 11 or 12 xanthones in higher plants and of 4 xanthones which had been described as fungal metabolites. In 1968, Gottlieb[3] mentioned the isolation of 60 xanthones from higher plants and 7 fungal metabolites and in 1969 Carpenter *et al.*[4] listed 82 xanthones from higher plants. Ollis[5] in a lecture in Brazil in 1970 has given a concise survey of xanthonoids, polyisoprenylated xanthonoids and benzophenones. Gunasekera[6] in 1976 recorded 183 xanthones from 5 families of tracheophyta and the numbers are rising rapidly partly due to the use of modern methods for their isolation and structure elucidation.

These results are of considerable chemotaxonomic interest. The natural xanthones from higher plants have been obtained mainly from about 150 plants associated with four families: Guttiferae, Gentianaceae, Moraceae and Polygalaceae. More recently isolated examples from other families (e.g. Lytheraceae,[7] Loganiaceae,[8] etc. have been reported. Even the two families Moraceae and Polygalaceae have so far been limited to a few species, but comparatively extensive studies have been made in the Guttiferae, and Gentianaceae. Hence this review will attempt mainly to cover the results from these two families.

Guttiferae

Majority of these plants are trees or shrubs and some of them yield useful timber (e.g. *Clusia*, *Garcinia* and *Calophyllum*). There are 40 genera and over 1000 species generally confined to the warm humid tropics. Some of these genera and species are found to be endemic to certain land masses, e.g. *Kielmeyera* is confined to the South American continent, *Symphonia* L. and *Pentadesma* Sabine are confined to Africa.

In the early classification[9a] (1907) the family had been divided into 6 sub-families and 10 tribes whereas in a recent revised classfication[9b] given in Table 1 the sub-family Endodesmioideae has been incorporated into the sub-family Calophylloideae and a new sub-family Lorostermonoideae has been described.

In Sri Lanka there are 27 species listed in Table 2 belonging to the sub families Calophylloideae and Clusioideae and of these 13 species are endemic.[10]

A number of plants, mainly non endemic species belonging to the family have been reported to be used in medicine.[11] Table 3 gives the species and parts of some of the Sri Lanka plants used in the indigenous Ayurvedic system of medicine.

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†Based on a Plenary Lecture delivered on 4 April 1979 at the ACS/CSJ Chemical Congress in Honolulu, Hawaii.

Table 1. Family Clusiaceae (Guttifierae)

Sub family	**Kielmeyeroideae**	
	Kielmeyereae:	*Kielmeyera* (20 species) (Trop. S. America)
		Marila (7)
	Caraipeae:	*Caraipa* (12)
Sub family	**Calophylloideae**	
	Calophylleae:	*Mesua* (3 species) (Indo Mal.)
		Mammea (4) (Trop. America)
		Ochrocarpus (25) Palaeo trop.
		Calophyllum (80) Palaeo trop.
		Kayea (25)
	Endodesmieae:	*Endodesmia* (1)
Sub family	**Clusioideae**	
	Clusieae:	*Clusia* (200 species)
		Tovomita (40)
		Chrysochlamys (10)
	Garcinieae:	*Allanblackia* (6)
		Rheedia (30)
		Garcinia (220)
Sub family	**Moronoboideae:**	*Pentadesma* (5 species) (Trop. Afr.)
		Moronobea (5) (South Amer.)
		Montrouziera (6) New Caledonia
		Platonia (1 or 2)
		Symphonia (17) Mostly Madagascar
Sub family	**Lorostemonoideae:**	
		Lorostemon (1 species) Amazon

Table 2. Clusiaceae (Guttiferae)

Calophyllum L.
- **C. bracteatum* Thw. (Walu kina–S)
- **C. calaba* L. (Guru kina–S, Chiru punnai–T)
- **C. cordato-oblongum* Thw. (Kalu kina–S)
- **C. cuneifolium* Thw.
- *C. inophyllum* L. (Domba–S, Punnai–T)
- *C. pulcherrimum* Wall ex Choisy
- **C. soulattri* Burm. f.
- **C. thwaitesii* Planch and Triana (Batu kina–S)
- *C. tomentosum* Wight
- **C. trapezifolium* Thw.
- **C. walkeri* Wight (Kina–S)
- **C. zeylanicum* Kosterm.

Clusia L.
- *C. rosea* Jacq.

Garcinia L.
- *G. echinocarpa* Thw. (Madol–S)
- **G hermonii* Kosterm.
- *G. mangostana* L.
- *G. morella* (Gaertn.) Desr.
- *G. quaesita* (Ratu–goraka–S)
- *G. spicata* (Wight and Arn) Hooker f.
- **G. terpnophylla* (Thw.) Thw. (Kokatiya–S)
- *G. thwaitesii* Pierre
- *G. xanthochymus* Hooker f. (Rata goraka–S)
- *G. zeylanica* Roxb. (Kaha goraka–S)

Kayea Wall
- **K. stylosa* Thw. (Suwanda–S)

Mesua L.
- *M. ferrea* L. (Na–S)
- *M. ferrea* L. (form *M. salicina* Pl. and Tr.)
- **M. thwaitesii* Planch and Triana (Diya Na–S)

(*Endemic); S = Sinhala; T = Tamil.

Table 3.

Plant	Part of the plant used
Calophyllum calaba L.	Bark
Calophyllum inophyllum L.	Resins, bark, roots, leaves and seed oil
Calophyllum tomentosum Wright	Seeds
Garcinia echinocarpa Thw.	Seed oil
Garcinia cambogia (Gaertn.) Desv.	Bark
Garcinia mangostana L.	Pericarp
Garcinia morella Desv.	Resin
Mesua ferrea L.	Bark, flowers

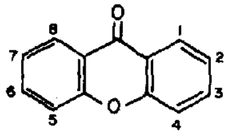
The types of xanthone structures (over 100 at the moment) that have come out from the different Guttiferae species which number about 90 investigated so far, are summarised below according to their oxygenation pattern. It may be mentioned that the parent xanthone molecule has not been found as a natural product.

In the following Tables and figures the names of the xanthones and the plants from which they have been isolated are given under the oxygenation types.

Mono-oxygenated xanthones

Only three mono-oxygenated xanthones have been isolated from five genera (Table 4). One is the methyl ether of 2-hydroxyxanthone.

Table 4. Mono-oxygenated xanthones



2-Hydroxyxanthone
Calophyllum cordato-oblongum Thw.[29]
Calophyllam trapezifolium Thw.[46]
Kielmeyera excelsa Camb[99]
Kielmeyera rubriflora Camb[104]
Kielmeyera speciosa St. Hill[106]
Mammea acuminata[46]
Mammea americana L.[109,110]
Mesua salicina Pl. and Tr.[116]
Ochrocarpus odoratus[119]

4-Hydroxyxanthone
Calophyllum brasiliense Camb[23,24]
Calophyllum cordato-oblongum Thw.[29]
Mammea acuminata[46]
Mammea americana L.[109,110]
Mesua salicina Pl. and Tr.[116]

2-Methoxyxanthone
Kielmeyera coriacea Mart[97]
Kielmeyera corymbosa (Spr.) Mart[98]
Mammea acuminata[46]
Mammea americana L.[111]
Mesua salicina Pl. and Tr.[116]

Dioxygenated xanthones

The free hydroxyxanthones are 1,5- 1,7- and 2,6-dihydroxyxanthone. The 1,5- and 1,7-dihydroxyxanthones are found fairly extensively. Six methyl ethers and one methylene dioxy derivative have been reported from 11 genera as in Table 5.

Table 5. Dioxygenated xanthones

1,5-Dihydroxyxanthone
Allanblackia floribunda Oliver[12]
Calophyllum bracteatum Thw.[20]
Calophyllum pulcherrimum Wall. ex Choisy[47]
Calophyllum thwaitesii Planch and Triana[54]
Calophyllum tomentosum Wight[46]
Calophyllum trapezifolium Thw.[56]
Calophyllum walkeri Wight[54]
Garcinia buchananii Baker[64]
Garcinia echinocarpa Thw.[70]
Garcinia hermonii Kosterm.[74]
Garcinia terpnophylla Thw.[70]
Mammea acuminata[46]
Mammea africana G. Don[108]
Mammea americana L.[110]
Mesua ferrea L.[113]
Mesua salicina Pl. and Tr.[116]
Mesua thwaitesii Planch and Triana[117]
Ochrocarpus odoratus[119]
Rheedia gardneriana Pl. and Tri.[123]

1,7-Dihydroxyxanthone
Allanblackia floribunda Oliver[12]
Calophyllum bracteatum Thw.[20]
Calophyllum calaba L.[20]
Calophyllum cuneifolium Thw.[31]
Calophyllum fragrans Ridley[32]
Calophyllum inophyllum L.[39]
Calophyllum pulcherrimum Wall. ex Choisy[47]
Calophyllum ramiflorum Schwarz.[48]
Calophyllum sclerophyllum Vesq.[50]
Calophyllum soulattri Burm. f.[31]
Calophyllum thwaitesii Planch and Triana[54]
Calophyllum tomentosum Wight[46]
Calophyllum trapezifolium Thw.[56]
Calophyllum walkeri Wight[54]
Garcinia eugenifolia Wall[72]
Garcinia hermonii Kosterm.[74]
Garcinia terpnophylla Thw.[70]
Harungana madagascariensis[93]
Kielmeyera candidissima[95]
Kielmeyera excelsa Camb[100]
Mammea acuminata[46]
Mammea africana G. Don[108]
Mammea americana L.[111]
Mesua ferrea L.[114]
Mesua salicina Pl. and Tr.[116]
Mesua thwaitesii Planch and Triana[117]

Table 5. (*Contd*)

Platonia insignis[122]
Rheedia gardneriana Pl. and Tri.[123]
Symphonia globulifera L.[124]

2,6-Dihydroxyxanthone
Mammea acuminata[46]

1-Hydroxy-5-methoxyxanthone
Calophyllum soulattri Burm. f.[31]
Mesua salicina Pl. and Tr.[116]

1-Hydroxy-7-methoxyxanthone
Kielmeyera corymbosa (Spr.) Mart[98]
Kielmeyera excelsa Camb[99]
Mammea acuminata[46]
Mesua ferrea L.[113]
Mesua salicina Pl. and Tr.[116]

2-Hydroxy-1-methoxyxanthone
Kielmeyera excelsa Camb[99]

Kielmeyera rupestris A. P. Duarte[105]
Kielmeyera speciosa St. Hill[106]

3-Hydroxy-2-methoxyxanthone
Mammea acuminata[46]
Ochrocarpus odoratus[119]

3-Hydroxy-4-methoxyxanthone
Calophyllum cordato-oblongum Thw.[29]
Mesua salicina Pl. and Tri.[116]

5-Hydroxy-1-methoxyxanthone
Mammea acuminata[46]
Mammea africana G. Don.[108]
Pentaphalangium solomonse Warb[121]

1,2-Methylenedioxyxanthone
Kielmeyera excelsa Camb[99]

Trioxygenated xanthones

The free hydroxyxanthones are 1,3,5-, 1,5,6-, 1,6,7- and 2,3,4-trihydroxyxanthones. Over 17 methyl ethers and two methylene dioxy derivatives have been reported from 9 genera as in Table 6.

Table 6. Trioxygenated xanthones

1,5-Dihydroxy-3-methoxyxanthone
Kielmeyera coriacea Mart[96]
Kielmeyera corymbosa (Spr.) Mart[98]
Kielmeyera rupestris A. P. Duarte[105]
Kielmeyera speciosa St. Hill[63]
Mesua ferrea L.[114]

1,6-Dihydroxy-5-methoxyxanthone
(Buchanoxanthone)
Calophyllum calaba L.[20]
Calophyllum cordato-oblongum Thw.[29]
Calophyllum cuneifolium Thw.[31]
Calophyllum fragrans Ridley[32]
Calophyllum inophyllum L.[39]
Calophyllum soulattri Burm. f.[31]
Calophyllum tomentosum Wight[46]
Calophyllum trapezifolium Thw.[46]
Calophyllum walkeri Wight[54]
Garcinia buchananii Baker[64]
Rheedia gardneriana Pl. and Tri.[123]

1,7-Dihydroxy-3-methoxyxanthone
(Gentisin)
Calophyllum brasiliense Camb[24]
Garcinia eugenifolia Wall[72]
Mesua ferrea L.[114]

1,7-Dihydroxy-8-methoxyxanthone
Kielmeyera excelsa Camb[101]
Kielmeyera petiolaris (Spr.) Mart[101]

2,3-Dihydroxy-1-methoxyxanthone
Kielmeyera speciosa St. Hill[106]

2,8-Dihydroxy-1-methoxyxanthone
Calophyllum calaba L.[20]
Kielmeyera excelsa Camb[99,101]
Kielmeyera ferruginea A. P. Duarte[102]
Kielmeyera petiolaris (Spr.) Mart[103]

3,4-Dihydroxy-2-methoxyxanthone
Kielmeyera coriacea Mart[96]
Kielmeyera corymbosa (Spr.) Mart[98]

1,2-Dimethoxy-3-hydroxyxanthone
Kielmeyera rupestris A. P. Duarte[105]
Kielmeyera speciosa St. Hill[106]

1,2-Dimethoxy-8-hydroxyxanthone
Calophyllum fragrans Ridley[32]
Kielmeyera petiolaris (Spr.) Mart[103]

1,3-Dimethoxy-5-hydroxyxanthone
Kielmeyera candidissima[95]
Kielmeyera coriacea Mart[96,97]
Kielmeyera corymbosa (Spr.) Mart[98]
Kielmeyera ferruginea A. P. Duarte[102]
Kielmeyera rupestris A. P. Duarte[105]
Kielmeyera speciosa St. Hill[63]
Mesua thwaitesii Planch and Triana[117]

1,7-Dimethoxy-3-hydroxyxanthone
Kielmeyera rupestris A. P. Duarte[105]

1,7-Dimethoxy-8-hydroxyxanthone
Kielmeyera excelsa Camb[101]
Kielmeyera petiolaris (Spr.) Mart[101]

1,8-Dimethoxy-2-hydroxyxanthone
Calophyllum calaba L.[20]

2,3-Dimethoxy-4-hydroxyxanthone
Kielmeyera coriacea Mart[96]
Kielmeyera corymbosa (Spr.) Mart[98]
Kielmeyera ferruginea A. P. Duarte[102]
Kielmeyera rubriflora Camb[104]
Kielmeyera rupestris A. P. Duarte[105]
Kielmeyera speciosa St. Hill[63,106]

2,4-Dimethoxy-3-hydroxyxanthone
Kielmeyera coriacea Mart[97]
Kielmeyera rubriflora Camb[104]
Kielmeyera speciosa St. Hill[106]

Table 6. (*Contd*)

3,7-Dimethoxy-1-hydroxyxanthone
Calophyllum brasiliense Camb[23,24]

6,7-Dimethoxy-1-hydroxyxanthone
Calophyllum ramiflorum Schwarz[48]

2,3-Methylenedioxy-4-hydroxyxanthone
Kielmeyera coriacea Mart[96]
Kielmeyera corymbosa (Spr.) Mart[98]
Kielmeyera rubriflora Camb[104]
Kielmeyera speciosa St. Hill[63,106]

2,3-Methylenedioxy-4-methoxyxanthone
Kielmeyera coriacea Mart[97]
Kielmeyera corymbosa (Spr.) Mart[98]
Keilmeyera rubriflora Camb[104]
Kielmeyera rupestris A. P. Duarte[105]
Kielmeyera speciosa St. Hill[106]

1,3,5-Trihydroxyxanthone
Allanblackia floribunda Oliver[12]

1,5,6-Trihydroxyxanthone
Calophyllum calaba L.[20]
Calophyllum cordato-oblongum Thw.[29]
Calophyllum fragrans Ridley[32]
Calophyllum inophyllum L.[39]
Calophyllum scriblitifolium Hend and Wyatt Smith[51]
Garcinia buchananii Baker[64]
Garcinia eugenifolia Wall[72]
Mammea africana G. Don[108]
Mesua ferrea L.[114]
Mesua salicina Pl. and Tr.[116]
Mesua thwaitesii Planch and Triana[117]
Ochrocarpus odoratus[119]
Symphonia globulifera L.[124]

1,6,7-Trihydroxyxanthone
Garcinia eugenifolia Wall[72]
Mammea africana G. Don[108]

2,3,4-Trihydroxyxanthone
Ochrocarpus odoratus[119]

Tetraoxygenated xanthones

The free hydroxyxanthones are 1,3,5,6-, 1,3,5,7- and 1,3,6,7-tetrahydoxyxanthones. Over 16 methyl ethers have been reported from 11 genera as in Table 7.

Table 7. Tetraoxygenated xanthones

1,3-Dihydroxy-2,5-dimethoxyxanthone
Kielmeyera candidissima[95]

1,5-Dihydroxy-2,3-dimethoxyxanthone
Calophyllum walkeri Wight[54]

1,5-Dihydroxy-3,4-dimethoxyxanthone
Tovomita pyrifolium Pl. and Tr.[130]

1,6-Dihydroxy-5,7-dimethoxyxanthone
Caraipa densiflora[13a]

1,6-Dihydroxy-7,8-dimethoxyxanthone
Caraipa densiflora[13]

1,7-Dihydroxy-3,6-dimethoxyxanthone
Calophyllum inophyllum L.[40]

3,8-Dihydroxy-1,2-dimethoxyxanthone
Calophyllum trapezifolium Thw.[56]

3-Hydroxy-1,5,6-trimethoxyxanthone
Kielmeyera rupestris A. P. Duarte[105]

1-Methoxy-3,5,6-trihydroxyxanthone
Calophyllum sclerophyllum Vesq.[58]

2-Methoxy-1,3,5-trihydroxyxanthone
(Tovopyrifolin C)
Calophyllum bracteatum Thw.[20]
Kayea stylosa Thw.[74]
Pentadesma butyracea Sabine[120]
Tovomita pyrifolium Pl. and Tr.[130]

3-Methoxy-1,4,7-trihydroxyxanthone
Garcinia eugenifolia Wall[72]

7-Methoxy-1,3,8-trihydroxyxanthone
Kielmeyera speciosa St. Hill[106]

1,3,5,6-Tetrahydroxyxanthone
Calophyllum sclerophyllum Vesq.[50]
Mammea africana G. Don[108]
Ochrocarpus odoratus[119]
Symphonia globulifera L.[124,127]

1,3,5,7-Tetrahydroxyxanthone
Garcinia pedunculata[89]

1,3,6,7-Tetrahydroxyxanthone
Allanblackia floribunda Oliver[12]
Garcinia echinocarpa Thw.[70]
Garcinia hermonii Kosterm.[74]
Garcinia multiflora Champ.[78]
Garcinia pedunculata[89]
Mammea africana G. Don[108]
Ochrocarpus odoratus[119]
Pentaphalangium solomonse Warb[121]
Symphonia globulifera L.[124,127]

Pentaoxygenated xanthones

Four partially methylated 1,2,3,7,8- and 1,3,5,6,7-pentaoxygenated compounds have been isolated from 3 genera as in Table 8.

Table 8. Pentaoxygenated xanthones

1,8-Dihydroxy-2,3,7-trimethoxyxanthone *Calophyllum bracteatum* Thw.[20]	**1,7-Dihydroxy-2,3,8-trimethoxyxanthone** *Kielmeyera rubriflora* Camb[104]
3,7-Dihydroxy-1,5,6-trimethoxyxanthone *Mesua salicina* Pl. and Tr.[116,212]	**5,6-Dimethoxy-1,3,7-trihydroxyxanthone** *Mesua salicina* Pl. and Tr.[116,212]

The structure of the above simple oxygenated xanthones have been established mainly from the UV, IR and NMR data of these compounds.

The UV spectrum varies in a characteristic manner depending on the oxygenation pattern and with the availability of a considerable amount of data, assignments can be readily made. Besides use of $AlCl_3$ shifts for chelated –OH, sodium acetate, sodium hydroxide and boric acid shifts, considerable information of the position of –OH groups in other locations can be obtained. Such data have been very valuable for a preliminary assignment which can then be substantiated from NMR chemical shifts for remaining aromatic protons, whose coupling patterns provide additional and definitive information about their location. More recently ^{13}C NMR data[212] have become available for a large number of xanthones and its use is rapidly increasing.

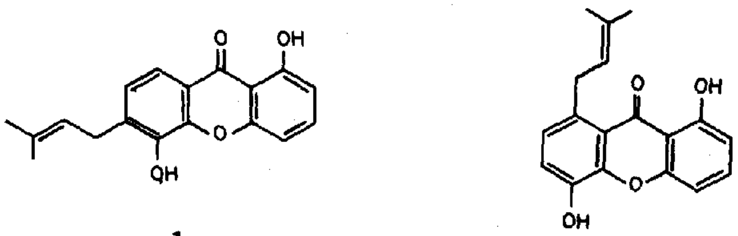
Prenylated and geranylated xanthones

The presence of prenyl and geranyl groups in the nucleus can be of chemotaxonomic value and a large number of them have been characterised in the last decade. Mono-, di- and tri-prenylated compounds have been isolated and in some of them the prenyl group has in certain cases undergone further change. The most characteristic of which is its oxidative cyclisation with an *ortho*-OH group to a chromene ring. Characterisation of these compounds and their structure elucidation has been simplified by the characteristic NMR patterns that these prenylated groups manifest. On account of which structures of some resulting complex molecules have been more rapidly established no doubt with other supplementary data. The next few figures summarise the information on these compounds.

There are no mono-oxygenated prenylated xanthones reported so far.

Dioxygenated monoprenylated xanthones

Guanandin (1) and Isoguanandin (2) are two examples with the prenyl group intact and in scriblitifolic acid (3) the prenyl group has been reduced and a terminal Me group converted to a –COOH group as shown in Fig. 1. These have been obtained from 7 *Calophyllum* species.



1

Guanandin

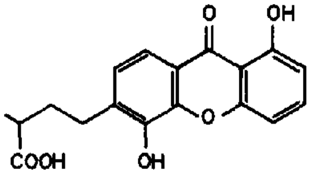
Calophyllum bracteatum Thw.[20]
Calophyllum brasiliense Camb[23,25]
Calophyllum calaba L.[20]
Calophyllum cuneifolium Thw.[31]
Calophyllum inophyllum L.[40]
Calophyllum scriblitifolium
Hend and Wyatt Smith[51]
Calophyllum walkeri Wight[54]

2

Isoguanandin

Calophyllum brasiliense Camb[23,25]

Fig. 1.



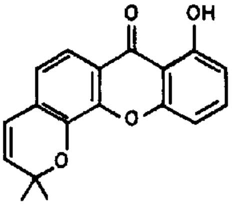
Calophyllum calaba L.[30]
Calophyllum cordato-oblongum Thw.[29]
Calophyllum cuneifolium Thw.[31]
Calophyllum scriblitifolium
Hend and Wyatt Smith[51]

3
Scriblitifolic acid

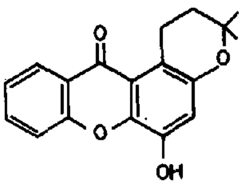
Fig. 1. Dioxygenated monoprenylated xanthones.

Dioxygenated chromenoxanthones and chromanoxanthones

Dehydrocycloguanandin (4) is a dioxygenated chromenoxanthone and cordato oblonguxanthone is a rare example of a chromanoxanthone. They are found in 2 *Calophyllum* species. Structures are given in Fig. 2.



4
Dehydrocycloguanandin
Calophyllum brasiliense Camb[28]

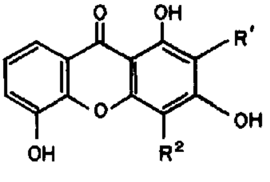


5
Cordato oblonguxanthone
Calophyllum cordato-oblongum Thw.[29]

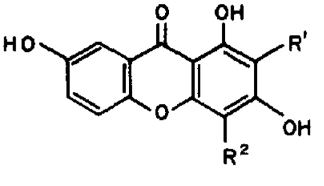
Fig. 2. Dioxygenated chromenoxanthones and chromanoxanthones.

Trioxygenated monoprenylated xanthones

2- or 4- Prenylated xanthones **6a,b**, **7a,b** and 1,1-dimethylallylxanthones (**8**) (Globuxanthone) from *Symphonia globulifera* L. and **8a** isolated from *Allanblackia floribunda* Oliver as the 3,7-dimethyl ether are the examples of this type (Fig. 3) and they are found in 5 genera. The presence of the 1,1-dimethylallyl group can be readily identified from the NMR spectrum.



6
a: R^1 = 3-methylbut-2-enyl, R^2 = H
b: R^1 = H, R^2 = 3-methylbut-2-enyl



7
a: R^1 = 3-methylbut-2-enyl, R^2 = H
b: R^1 = H, R^2 = 3-methylbut-2-enyl

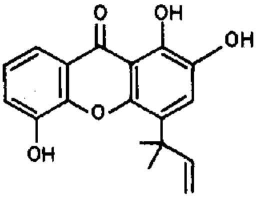
1,3,5-Trihydroxy-2(3-methylbut-2-enyl)xanthone 6a
Calophyllum cuneifolium Thw.[31]
Calophyllum scriblitifolium
Hend and Wyatt Smith[51]
Calophyllum soulattri Burm. f.[31]
Calophyllum tomentosum Wight[46]
Calophyllum walkeri Wight[54]

1,3,5-Trihydroxy-4(3-methylbut-2-enyl)xanthone 6b
Pentaphalangium solomonse Warb.[121]

1,3,7-Trihydroxy-2(3-methylbut-2-enyl)xanthone 7a
Allanblackia floribunda Oliver[12]
Calophyllum canum Hook[27]
C. neo-ebudicum Guillaumin[44]
C. scriblitifolium Hend and Wyatt Smith[51]
Garcinia hermonii Kosterm.[74]
Pentaphalangium solomonse Wart[121]

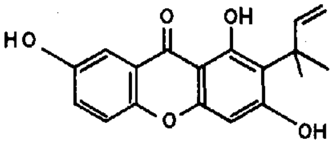
1,3,7-Trihydroxy-4(3-methylbut-2-enyl)xanthone 7b
Symphonia globulifera L.[37]

Fig. 3.



8

Globuxanthone 8
Symphonia globulifera L.[128]



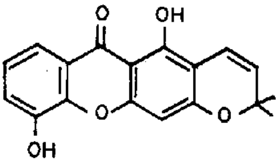
8a

1,3,7-Trihydroxy-2(1,1-dimethyl-prop-2-enyl)xanthone 8a
Allanblackia floribunda Oliver[12]

Fig. 3. Trioxygenated monoprenylated xanthones.

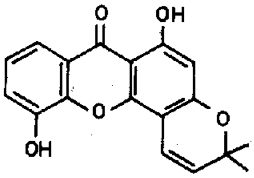
Trioxygenated chromenoxanthones

The four compounds 6-deoxyjacareubin (**9**), 6-deoxyisojacareubin (**9a**), tovoxanthone (**10**) and osajaxanthone (**11**) have the prenyl group oxidatively cyclised to a chromene ring. These compounds (Fig. 4) have been isolated from five different genera.



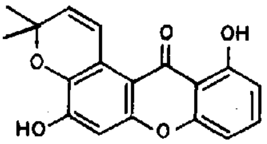
9

6-Deoxyjacareubin 9
Calophyllum bracteatum Thw.[20]
Calophyllum brasiliense Camb[25]
Calophyllum calaba L.[20]
Calophyllum cuneifolium Thw.[31]
Calophyllum fragrans Ridley[32]
Calophyllum inophyllum L.[39,40]
Calophyllum neo-ebudicum Guillaumin[44]
Calophyllum scriblitifolium
Hend and Wyatt Smith[51]
Calophyllum soulattri Burm. f.[31]
Calophyllum tomentosum Wight[46]
Calophyllum trapezifolium Thw.[46]
Kielmeyera corymbosa (Spr.) Mart.[98]
Kielmeyera ferruginea A. P. Duarte[102]
Kielmeyera speciosa St. Hill[63]



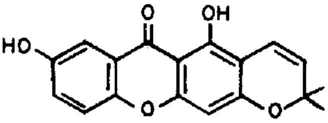
9a

6-Deoxyisojacareubin 9a
Pentaphalangium solomonse Warb[121]



10

Tovoxanthone 10
Tovomita choisyana Pl. and Tr.[128]



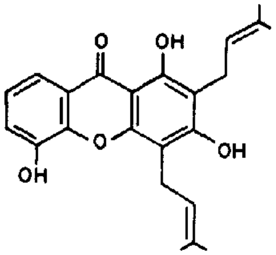
11

Osajaxanthone 11
Calophyllum brasiliense Camb[25]
Calophyllum canum Hook.[27]
Kielmeyera coriacea Mart[97]
Kielmeyera corymbosa (Spr.) Mart[98]
Kielmeyera ferruginea A. P. Duarte[102]
Pentadesma butyracea Sabine[129]

Fig. 4. Trioxygenated chromenoxanthones.

Trioxygenated diprenylated xanthones

The only example is 8-deoxygartanin (**12**) isolated from the fruit of *Garcinia magostana* whose structure is given in Fig. 5.



12

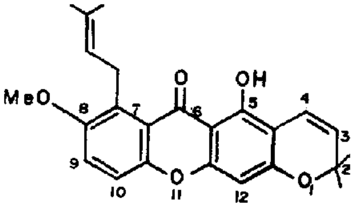
8-Deoxygartenin

Garcinia mangostana L.[84]

Fig. 5. Trioxygenated diprenylated xanthones.

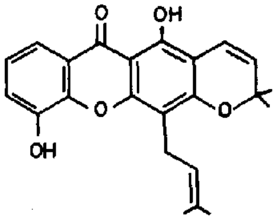
Trioxygenated prenylated chromenoxanthones and dichromenoxanthones

From the bark extracts of 7 *Calophyllum* species studied in Sri Lanka two prenylated chromenoxanthones (calabaxanthone (**13**), trapezifolixanthone (**14**), and one di-chromenoxanthone, thwaitesixanthone (**15**) have been isolated (Fig. 6). Besides other evidence, studies on the chemical shift differences[190] in the NMR between, e.g. calabaxanthone and its acetate have shown a positive diamagnetic shift for the C_4–H protons and a negative paramagnetic shift for the C_3–H protons for a linear 2H-pyrano ring. Trapezifolixanthone structure has been confirmed by synthesis by Jain *et al.*[132]



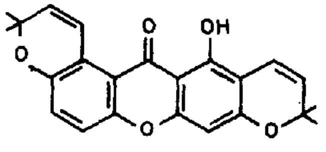
13

Calabaxanthone (13)
Calophyllum bracteatum Thw.[20]
Calophyllum calaba L.[20]
Calophyllum cuneifolium Thw.[31]
Calophyllum tomentosum Wight[46]
Calophyllum trapezifolium Thw.[55]
Calophyllum walkeri Wight[54]



14

Trapezifolixanthone (14)
Calophyllum cuneifolium Thw.[31]
Calophyllum trapezifolium Thw.[55]



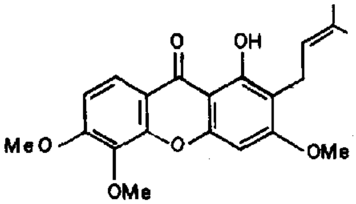
15

Thwaitesixanthone (15)
Calophyllum cuneifolium Thw.[31]
Calophyllum Thwaitesii Planch and Triana[54]

Fig. 6. Trioxygenated chromenoxanthones.

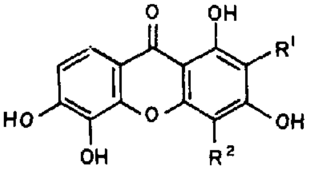
Tetraoxygenated monoprenylated xanthones

Four monoprenylated tetraoxygenated xanthones (**16**, **17a**, **17b** and **18**) and one 1,1-dimethylallyl xanthone (**19**) (symphoxanthone) have been described from 3 genera and their structures are given below in Fig. 7.



16

1-Hydroxy-3,5,6-trimethoxy-2(3-methylbut-2-enyl)xanthone (16)
Calophyllum ramiflorum Schwarz[48]

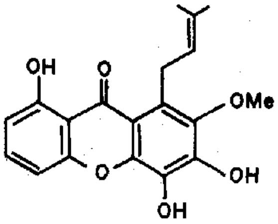


17

a: R^1 = 3-Methylbut-2-enyl, R^2 = H
b: R^1 = H, R^2 = 3-Methylbut-2-enyl

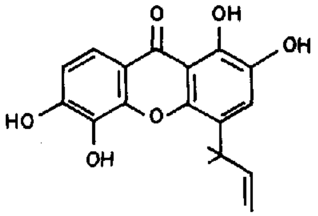
1,3,5,6-Tetrahydroxy-2(3-methylbut-2-enyl)xanthone (17a)
Calophyllum canum Hook[27]
Calophyllum fragrans Ridley[32]
Calophyllum inophyllum L.[39]
Calophyllum neo-ebudicum Guillaumin[44]
Calophyllum sclerophyllum Vesq.[50]
Calophyllum scriblitifolium Hend and Wyatt Smith[51]

1,3,5,6-Tetrahydoxy-4(3-methylbut-2-enyl) xanthone (Ugaxanthone) 17b
Symphonia globulifera L.[125]



18

Celibixanthone 18
Cratoxylon celibicum Blume[61]



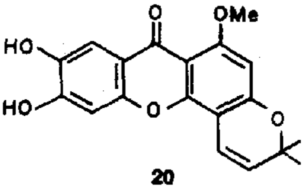
19

Symphoxanthone 19
Symphonia globulifera L.[126]

Fig. 7. Tetraoxygenated monoprenylated xanthones.

Tetraoxygenated chromenoxanthones

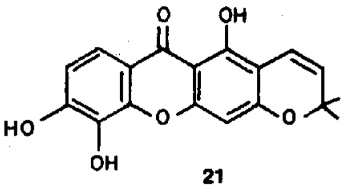
There are two xanthones (Lorostemin (**20**) and Jacareubin (**21**)) from 4 genera (Fig. 8). Jacareubin (**21**) has been found in a large number (16 species) of ***Calophyllum*** and is considered as a chemotaxonomic marker for this genus.



20

Lorostemin 20
Lorostemon coelhoi Paula[107]
Lorostemon negrensis Fross[107]

Fig. 8.



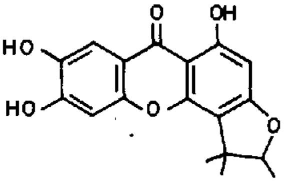
21

Jacareubin 21
Calophyllum bracteatum Thw.[20]
Calophyllum brasiliense Camb[26]
Calophyllum calaba L.[20]
Calophyllum canum Hook.[27]
Calophyllum cordato-oblongum Thw.[29]
Calophyllum cuneifolium Thw.[31]
Calophyllum fragrans Ridley[32]
Calophyllum inophyllum L.[38]
Calophyllum neo-ebudicum Guillaumin[44]
Calophyllum ramiflorum Schwarz[48]
Calophyllum sclerophyllum Vesq.[50]
Calophyllum scriblitifolium Hend and Wyatt Smith[51]
Calophyllum thwaitesii Planch and Triana[54]
Calophyllum tomentosum Wight[46]
Calophyllum trapezifolium Thw.[55]
Calophyllum walkeri Wight[54]
Kielmeyera ferruginea A. P. Duarte[102]
Pentadesma butyracea Sabine[120]

Fig. 8. Tetraoxygenated chromenoxanthones.

Tetraoxygenated furanoxanthone

Only one compound has been described from *Allanblackia floribunda* (4′,5′-dihydro-1,6,7-trihydroxy-4′,4′,5′-trimethylfurano (2′,3′ : 3,4) xanthone (**22**) (Fig. 9).



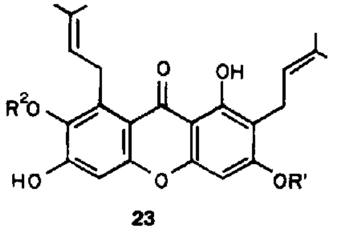
22
(4′,5′-dihydro-1,6,7-trihydroxy-4′,4′,5′-trimethylfurano
(2′,3′ : 3,4) xanthone

Allanblackia floribunda Oliver[12]

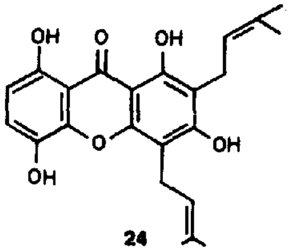
Fig. 9. Tetraoxygenated furanoxanthones.

Tetraoxygenated diprenylated xanthones

This group contains mangostins (**23a, b, c**) and gartenin (**24**) isolated from two *Garcinia* species. Mangostin was isolated in 1855 but its structure elucidation was carried out by Stout and Yates in 1958. Their structures are given in Fig. 10.



23
a: $R^1 = H, R^2 = Me$
b: $R^1 = Me, R^2 = Me$
c: $R^1 = H, R^2 = H$



24

Mangostin 23a
Garcinia mangostana L.[81]
Garcinia terpnophylla Thw.[70]

β-Mangostin 23b
Garcinia mangostana L.[82]

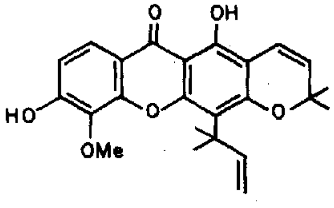
γ-Mangostin 23c
Garcinia mangostana L.[83]

Gartanin 24
Garcinia magostana L.[84]

Fig. 10. Tetraoxygenated diprenylated xanthones.

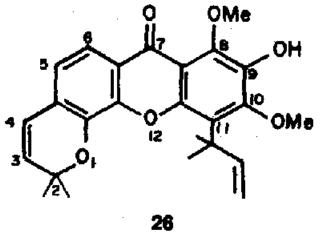
Tetraoxygenated prenylated chromenoxanthones

10-O-Methylmacluraxanthone (25) and kayeaxanthone (26) were isolated from *Kayea stylosa* Thw. in Sri Lanka. The structure of kayeazanthone was established by comparing the NMR signals at position 4- and 5- with similarly constituted known compounds owing to the small amount of material that was available. From a *Tovomita* species tovopyrifolin (27) has been isolated. They are shown in Fig. 11.



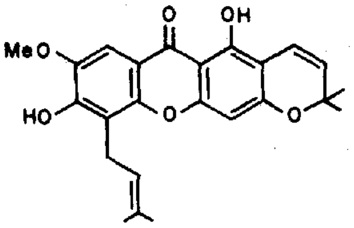
25

10-O-Methylmacluraxanthone 25
Kayea stylosa Thw.[74]



26

Kayeaxanthone 26
Kayea stylosa Thw.[74]



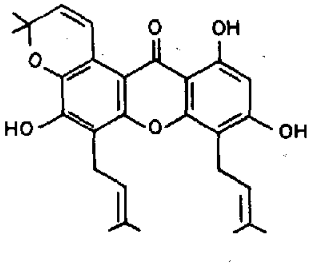
27

Tovopyrifolin A 27
Tovomita choisyana Pl. and Tr.[128]
Tovomita pyrifolium Pl. and Tr.[130]

Fig. 11. Tetraoxygenated diprenylated chromenoxanthones.

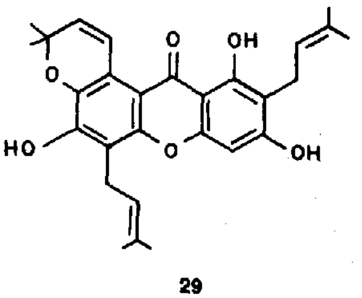
Tetraoxygenated diprenylated chromenoxanthones and prenylated dichromenoxanthones

Three compounds pentadesmaxanthone (28), tovophyllin A (29) and tovophyllin B (30) have been isolated from two species and structures established as in Fig. 12.



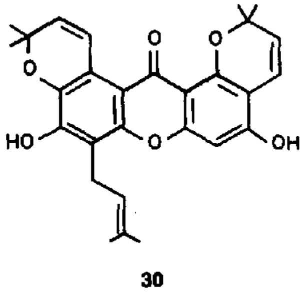
28

Pentadesmaxanthone 28
Pentadesma butyracea Sabine[120]



29

Tovophyllin A 29



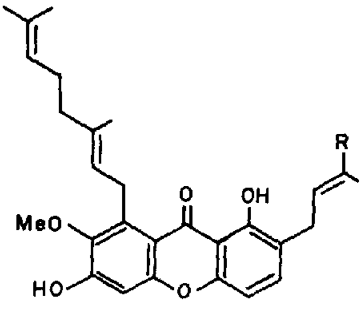
30

Tovophyllin B 30
Tovomita macrophylla
(Pl. and Tr.) Walp[129]
Tovomita pyrifolium
Pl. and Tr.[130]

Fig. 12. Tetraoxygenated triprenylated chromenoxanthones.

Trioxygenated geranylated xanthones

Cowanin (31) and cowanol (32) have been isolated from *Garcinia cowa* and structures are given in Fig. 13.



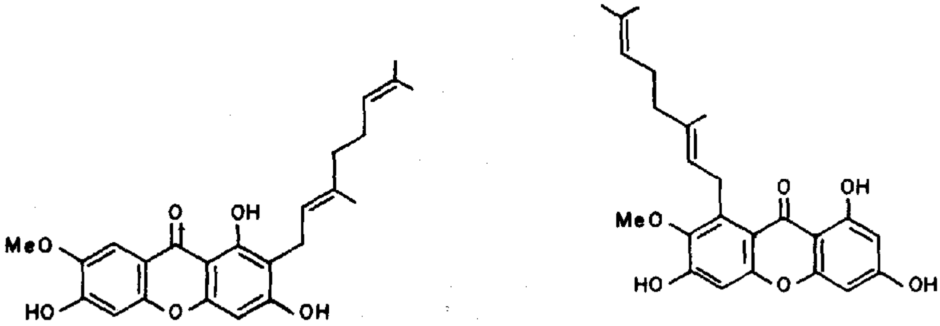
Cowanin R = CH_3 **31**
Cowanol R = CH_2OH **32**

Garcinia cowa Khran[66]

Fig. 13. Trioxygenated geranylated xanthones.

Tetraoxygenated geranylated xanthones

Cowaxanthone (33) and rubraxanthone (34) have been isolated from two *Garcinia* species and structures are in Fig. 14.



33
Cowaxanthone
Garcinia cowa Khran[66]

34
Rubraxanthone
Garcinia cowa Khran[66]
Garcinia rubra Merill[67]

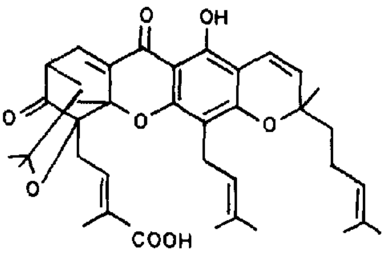
Fig. 14. Tetraoxygenated geranylated xanthones.

Polyisoprenylated xanthonoids

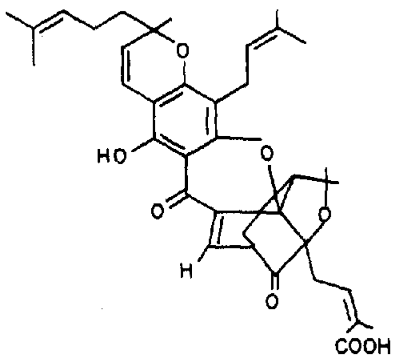
The classic member of this class is gambogic acid (35) as structural work on it started in 1809 but its correct molecular formula was first reported in 1963. The first polyisoprenylated xanthoniod structure to be elucidated was that of morellin. This was achieved after a detailed and extensive chemical investigation by Venkataraman and his group over a period of years. The special feature in the proposed morellin structure was that one of the benzene rings of the "xanthone type" precursor had been modified during the biosynthetic sequence by transformations leading to a bicyclo [2,2,2] octenone skeleton. This structure was subsequently established by an X-ray crystallographic study.

Meanwhile the structural studies on gambogic acid, $C_{38}H_{44}O_8$[86,87,133-139,142,143] was being independently studied in several laboratories and the view that this compound contained a xanthonoid residue (C_{13}) in association with five isoprenoid units (5 × C_5) became established with the elucidation of its constitution (Venkataraman,[86] Yates[87] and Ollis[136]).

Gambogic acid has been isolated from *G. morella*[140] and *G. hanburyi*. Its structure can be represented as shown in formulae (**35**) and (**35a**). (see Fig. 15).



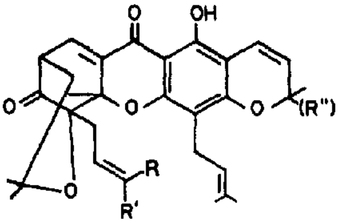
35
Gambogic acid



35a
Gambogic acid

Fig. 15.

In addition to morellin (**36**) Venkataraman *et al.* have also isolated from the seeds of *Garcinia morella*, isomorellin, morellic acid, isomorellic acid, deoxymorellin, morellinol and dihydroisomorellin (Fig. 15a). The compounds all, have closely related structures and 7 related natural polyisoprenylated xanthonoids are recognised at present.



	R'	R
Morellin **36**	CHO	Me
Isomorellin **37**	Me	CHO
Morellic acid **38**	Me	COOH
Isomorellic acid **39**	COOH	Me
Deoxyisomorellin **40**	Me	Me
Morellinol **41**	CH_2OH	Me
Dihydroisomorellin **37a**	CHO	Me
	(no d.b. in cyclohexane ring)	
Gambogic acid **35**	Me	CO_2H Prenyl (R'')

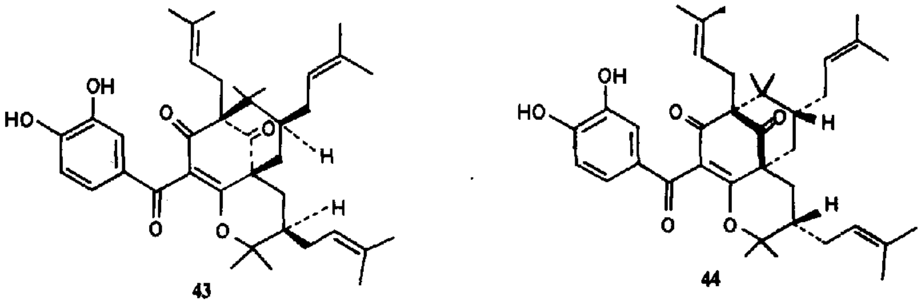
Fig. 15(a).

Prenylated benzophenones

It will be appropriate in this review to include three polyisoprenylated benzophenones isolated from *Garcinia* and *Clusia* species. Venkataraman *et al.* obtained xanthochymol (**42**) lemon yellow needles, m.p. 135°, $[\alpha]_D^{29}$ + 143.5°($CHCl_3$) and isoxanthochymol (**43**) pale yellow cubes m.p. 242°, $[\alpha]_D$ + 208°(MeOH) from *G. xanthochymus* fruits[79a,b,c] (also isolated by Dreyer from the fruits of *Clusia rosea* Jacq.) and more recently from *G. indica* and *G. cambogia* fruits. The major pigment xanthochymol was shown to be a catechol derivative and structure, assigned from spectral analysis, indicated a β-diketone, capable of enolization, whereas isoxanthochymol was similar in all respects except the ability to enolize. Xanthochymol (**42**) has been converted to isoxanthochymol (**43**) by treatment of a benzene solution at room temperature with HI or trifluoroacetic acid. X-ray analysis of the di-*p*-bromobenzene sulphonate of isoxanthochymol enabled them to fix the structure of both.

Pai *et al.* at Madras[79c] have isolated from the roots of *G. cambogia* another compound called cambogin (**44**), m.p. 242°, $[\alpha]_D - 212.6°$(MeOH). It has been shown to be an enantiomer of isoxanthochymol by X-ray structure determination by Rogers *et al.* (Fig. 16a).

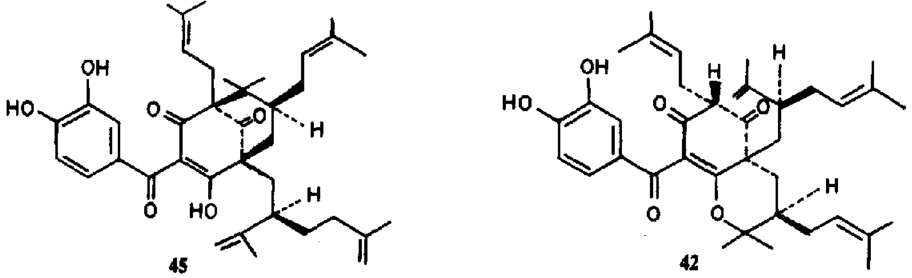
Venkataraman *et al.* determined the structure of isoxanthochymol from an X-ray crystallographic analysis of its di-*p*-dibromobenzene sulphonate whereas the structure of xanthochymol was deduced from isoxanthochymol by a comparison of the physical and chemical data of the two compounds. Blount and William[141] have shown by X-ray analysis that the compound isolated from *G. xanthochymus* by Dr. Basa, had the structure **45** (Fig. 16(b)).



43
Isoxanthochymol

44
Cambogin

Fig. 16(a).



45
Xanthochymol
(Basa)

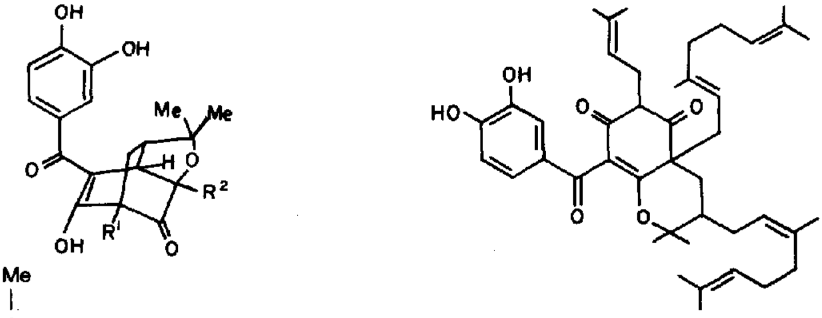
42
Xanthochymol
(Venkataraman)

Fig. 16(b).

Direct comparison of this **45** with the xanthochymol (**42**) of Venkataraman by NMR, m.p. and mixed m.p. has conclusively confirmed their identity.

These results again emphasize the need to supplement structural assignment from chemical and spectral data by synthesis or X-ray determination. In the case of more complex molecules X-ray method in the future will be the more rapid one.

Ollis *et al.* had obtained from the stemwood of *G. hombroniana*[75] a deep yellow oil and assigned it a structure **46a**. In the light of xanthochymol structure, Venkataraman *et al.*[86] have proposed the alternative structure **46** in keeping with that of xanthochymol (Fig. 17).



46a

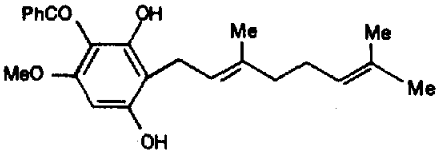
$R' = (CH_2CH{=}\overset{Me}{C}{-}CH_2)_2CH_2CH{=}CMe_2$

$R^2 = CH_2CH{=}\overset{Me}{C}\ CH_2{\cdot}CH_2CH{=}CMe_2$

46
Bronianone

Fig. 17.

From *Monobea pulchra* a geranylated benzophenone, marupone (47) has been isolated by Gottlieb[118] (Fig. 17a).



47
Marupone

Fig. 17(a).

From *Clusia congestiflora*, Stout *et al.*[59] have isolated clusianone.

Although diphenyl derivatives have been reported, e.g. aucuparins (Gottlieb[144]) and diphenyls (Scheinmann[145]), the first example from the Guttiferae where the polyketide chain undergoes an aldol type of condensation to give a diphenyl carboxylic acid as in Fig. 18 has recently been reported from *Garcinia hermonii* Kosterm.[6]

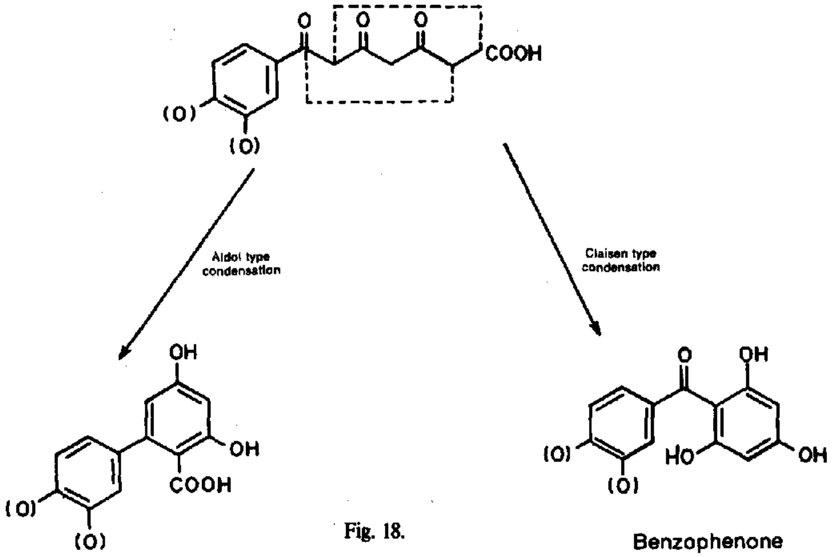
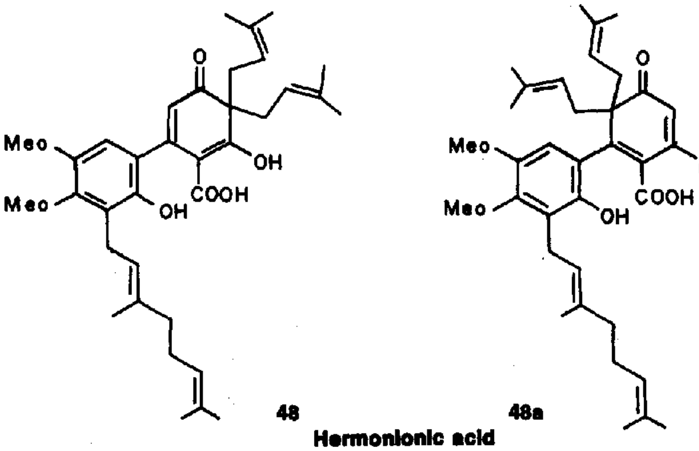


Fig. 18.

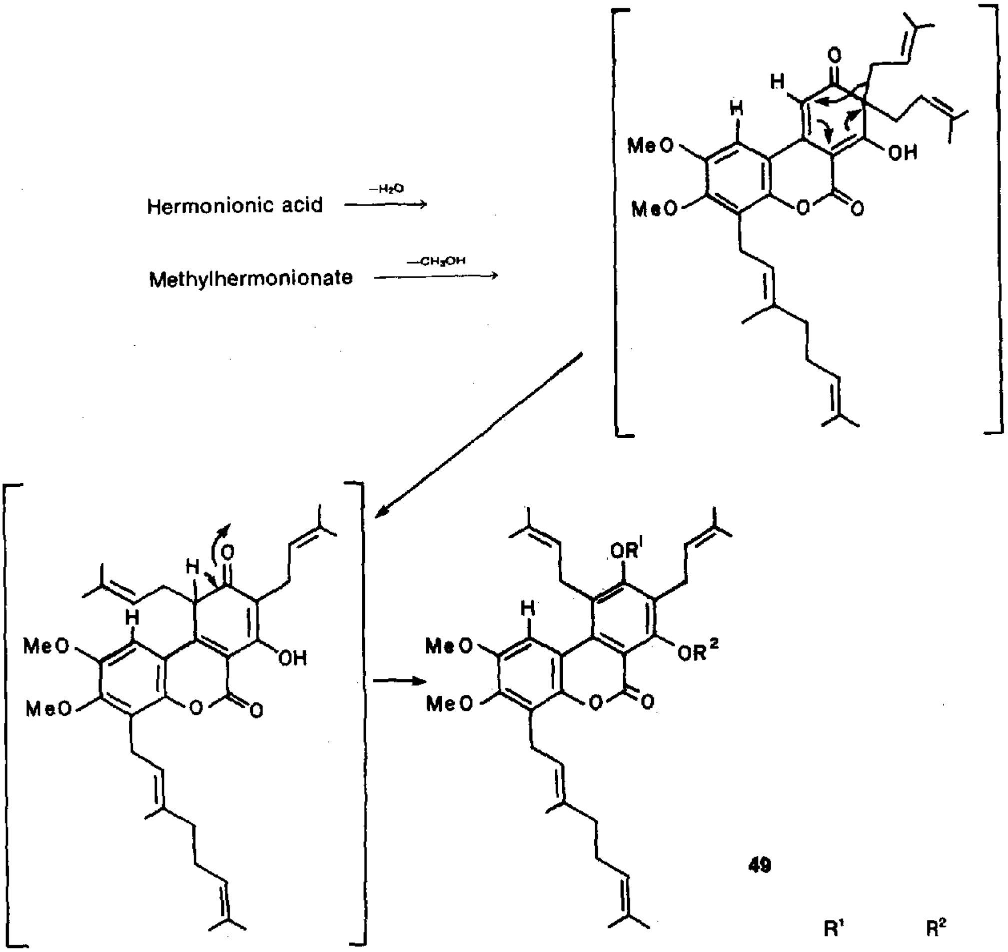
It can be represented by two structures 48 and 48a to accomodate all the chemical evidence available (Fig. 18a).



48 **48a**
Hermonionic acid

Fig. 18(a).

The free acid (hermonionic acid) or its methyl ester on heating undergoes a 1,5-sigmatropic change to give a lactone hermoniolic acid lactone (**49**) which has been shown to have the structure given in the sequence in Fig. 19.

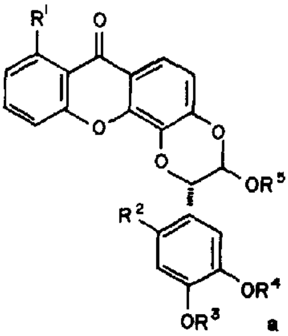


49

	R^1	R^2
a: Hermoniolic acid lactone	H	H
b: Monomethylhermoniolic acid lactone	H	Me
c: Dimethylhermoniolic acid lactone	Me	Me

Fig. 19.

Gottlieb *et al.* have recently described the isolation and structure assignment of three xantholignoids from *Kielmeyera coriacea* and *Caraipa densiflora*[146] which have been called respectively kielcorin (**50**), cadensin A (**51**) and cadesin B (**52**) (Fig. 20). ^{13}C NMR data which has now become available for a number of natural xanthonoids[212] was used effectively in the structure assignment.



	R^1		R^2	R^3	R^4	R^5
Kielcorin H	H	**50**	H	H	Me	H
Cadensin A	OH	**51**	H	Me	H	H
Cadensin B	OH	**52**	OMe	Me	H	H

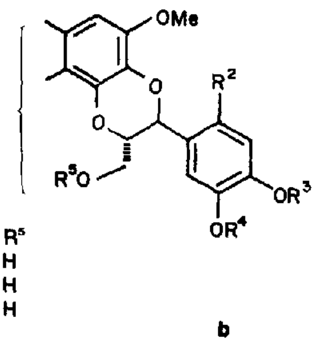
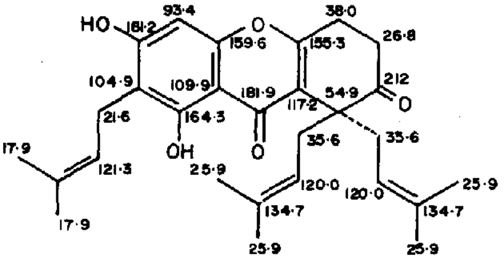


Fig. 20.

Nielson and Arends[147] have shown that Kielcorin has structure **50b** by hydrolysis with NaOH aq and establishing the structure of the product.

The bark benzene extractives of *Calophyllum zeylanicum* Kosterm.[57], gave a new tetrahydroxanthone named zeyloxanthonone (0.04%) m.p. 137°, which has been shown to be 6,8-dihydroxy-1,1,7-tri (3-methylbut-2-enyl)-2-oxo-1,2,3,4-tetrahydroxanthen-9-one (**53**). The complete data on which this structure was assigned has just appeared[148] and the ^{13}C NMR data for the compound is given in Fig. 21.



53

^{13}C-NMR (25.15 MHz) data (ppm) of zeyloxanthonone in $CDCl_3$

Fig. 21.

This is the first report of the isolation of a triprenylated tetrahydroxanthone as a natural product. Hostettmann *et al.*[150] have recently reported the isolation of a tetrahydroxanthone glucoside from *Gentiana campestris*. The isolation of a tetrahydroxanthone should be of biogenetic and chemotaxonomic interest.

A list of the Guttiferae species that have been investigated so far is given in Appendix.

Gentianaceae

Plants belonging to the family Gentianaceae are classified into five sub families[9c] as given below in Table 9 and are found in all parts of the world. The tropical plants are generally found at a higher elevation, and they have been widely used in local medicine. Simple polyoxygenated xanthones have been isolated from most of the plants that have been investigated and no attempt will be made to tabulate all the simple xanthones that have been isolated except to draw some very broad generalisation from the data available.

Table 9.

Tribe 1.	*Gentianeae*		
	Sub-tribe 1.1	Erythraeineae:	*Enicostema* (2)
			Cicendia (2)
			Exaculum (1)
		(Erythraea) =	*Centaurium* (40)
			Curtia (10)
			Sabbatia (10)
			Blackstonia (5)
			Bartonia (5)
			Canscora (20)
	Sub-tribe 1.2	Exacinae:	*Exacum* (35)
			Cotlanthera (4)
			Sebaea (100)
	Sub-tribe 1.3	Chironiinae:	*Chironia* (35)
			Orphium (1)
			Gentianothamnus (1)
	Sub-tribe 1.4	Gentiainae:	*Gentiana* (200)
			Gentianella (250)
			Ixanthus (1)
			Lomatogonium (10)
			Swertia (including *Frasera* 90)
	Sub-tribe 1.5	Tachiinae:	*Lisianthus* (30)
			Tachia (3)
			Macrocarpaea (30)
			Chorisepalum (4)

Table 9. (*Contd*)

Tribe 2.	*Rusbyantheae*: Monotypic (i.e. one genus and one species)	*Rusbyanthus* (1)
Tribe 3.	*Helieae*:	*Prepusa* (5) *Schultesia* (20) *Chelonanthus* (15) *Symbolanthus* (10) *Helia* (10)
Tribe 4.	*Voyrieae*:	*Voyria* (8)
Tribe 5.	*Leiphaimeae*:	*Voyriella* (2) *Leiphaimos* (40)

From about 50 plants belonging to this family about a 100 xanthones have been isolated. If the xanthone glycosides, about which some account in greater detail will be given below, are not included the majority of the natural xanthones are tetra and penta-oxygenated ones showing a wide variety of oxygenation patterns. They have been found in the free form or as their methyl ethers. The Table 10 below summarises some generalisations from the data available from 29 plant species[151,152] in 4 genera.

Table 10.

Genus	No. plants in genera	No. of different compounds isolated	Position at which oxygenation is absent
Canscora	1	20	2- and 4-
Frasera	2	17	6-
Gentiana	9	19	2- and 6-
Swertia	17	20	2-, 4- and 6-
		S. bimaculata	6- only
		S. purpurescens	2- and 6-

Besides in 12 species the oxygenation pattern 1,3,5,8- and 1,3,7,8- only have been found.

It should be observed that oxygenation at position 6- is absent in 28 species in three genera and at position 2- in 26 species in 2 genera. This information may be of value from a chemotaxonomic point of view although negative information is generally considered to be of less value.

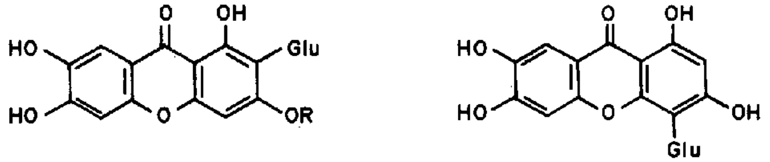
With recognition of the occurrence of xanthone glycosides in some species extensive investigations are in progress with their characterisation and structure elucidation.

Naturally occurring xanthone glycosides

Hostettamann and Wagner[153] have recently reviewed the xanthone glycosides. A distinction has to be made between C-glycosides and O-glycosides. In C-glycosides a C–C bond links the sugar moiety to the xanthone nucleus and they are therefore resistant to acidic and enzymic hydrolysis whereas the O-glycosides have typical glycosidic linkage.

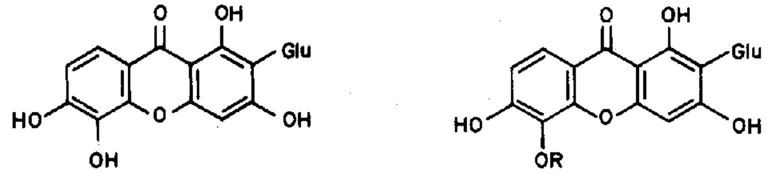
C-Glycosides

Mangiferin (**51a**) was isolated first by Wiechowski in 1908 from *Mangifera indica* L. (Anacardiaceae). It is of widespread occurrence in angiosperms and has also been identified in ferns. Its structure has been established as 2-C-β-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone.[154–157] An isomer, isomangiferin (**52**) has been isolated from the aerial parts of *Anemarrhena asphodeloides* Bunge (Liliaceae) and identified as 4-C-β-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone.[158] Another C-glycoside isolated from the bark of *Mangifera indica* L. has been shown to be 2-C-β-D-glucopyranosyl-3-methoxy-1,6,7-trihydroxyxanthone and is generally referred to as homomangiferin (**51b**)[159] (Fig. 22).



mangiferin 51a R = H
homomangiferin 51b R = Me

52
isomangiferin



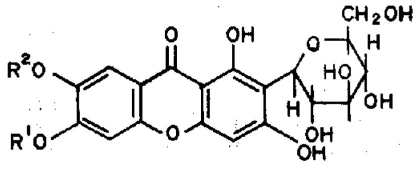
53

54
Irisxanthone R = Me

Fig. 22.

From roots of *Canscora decussata* Schult[160] a new glycoxanthone with an oxidation pattern different to mangiferin was isolated in 1973 and its structure has been established by chemical transformation and spectral (UV, IR, NMR and MS) data as 2-C-β-D-glucopyranosyl-1,3,5,6-tetrahydroxyxanthone (**53**). In the same year another glycoxanthone isolated from the rhizome of *Iris florentina* L. (Iridaceae)[161] has been shown to be 2-C-β-D-glucopyranosyl-5-methoxy-1,3,6-trihydroxyxanthone and called irisxanthone (**54**).

In the fern *Asplenium montanum* Willd. (Aspleniaceae)[162] two hydrolysable derivatives of the xanthone-C-glycosides, mangiferin and isomangiferin were described. Both are O-glycosides and the hydrolysable sugar moiety is attached to the C-glycosyl moiety in an unidentified point. Two new O-glucosides of mangiferin have been isolated by Goetz and Jacot-Guillarmod[163] from the leaves of *Gentiana aslepiadea*[163] and shown to be mangiferin-7-O-β-D-glucoside and mangiferin-6-O-β-D-glucoside **55a** and **55b** (Fig. 23).



55a R¹ = H, R² = β-D-glucosyl
55b R¹ = β-D-glucosyl, R² = H

Fig. 23.

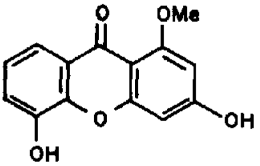
A number of similar flavones have been recently recognised and therefore corresponding xanthones too may soon be described.

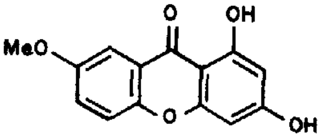
Xanthone C-glycosides seem to be a unique taxonomic marker in the plants and seem to be more closely related to flavonoids than to xanthones in their distribution and biogenesis.

O-Glycosides

In 1969 only three O-glycosides gentiacauloside (**75**) from *Gentiana acaulis*,[188] Gentioside (**57**) from *G. lutea*, Swertianolin (**62**) from *Swertia japonica* had been reported. But within the last 10 years more than 20 xanthone O-glycosides have been described and their natural occurrence has so far been restricted to the Gentianaceae as given in the Tables 11–14.[153]

Table 11. Trioxygenated xanthones

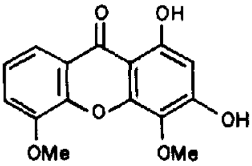


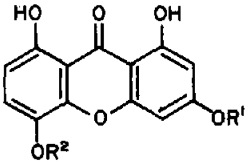


Glycoside	Oxidation pattern			Natural sources
	1	3	5	
56	OMe	O-rut.	OH	*Canscora decussata*[164]
	1	3	7	
57	OH	O-prim.	OMe	*Gentiana lutea*[165,166] *Gentiana pannonica*[167] *Gentiana punctata*[167] *Gentiana purpurea*[167]

rut. rutinose; prim. primeverose.

Table 12. Tetraoxygenated xanthones.



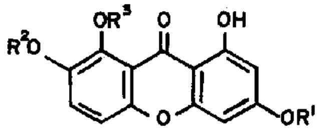


Desmethylbellidifolin $R^1 = R^2 = H$
Bellidifolin $R^1 = Me$, $R^2 = H$
$R^1 = R^2 = Me$

Glycoside	Oxidation pattern				Natural sources
	1	3	4	5	
58	O-glc.	OH	OMe	OMe	*Swertia bimaculata*[168]
59	O-glyc.	OH	OMe	OMe	*Swertia bimaculata*[169]
60	OH	O-glc.	OMe	OMe	*Swertia bimaculata*[168]
	1	3	5	8	
61	O-glc.	OH	OH	OH	*Swertia purpurascens*[170] *Swertia racemosa*[171] *Swertia randaiensis*[172]
62	O-glc.	OMe	OH	OH	*Swertia purpurascens*[170] *Swertia racemosa*[171] *Swertia japonica*[171]
63	O-glc.	OMe	OMe	OH	*Swertia bimaculata*[169] *Frasera caroliniensis*[173]
64	OH	OH	OH	O-glc.	*Gentiana campestris*[174] *Gentiana germanica*[175] *Gentiana ramosa*[175]
65	OH	OMe	OH	O-glc.	*Gentiana campertris*[174] *Gentiana germanica*[175] *Gentiana ramosa*[175] *Swertia perennis*[176] *Swertia purpurascens*[170]

glc.: glucose; glyc.: unidentified sugar.

Table 13. Tetraoxygenated xanthones

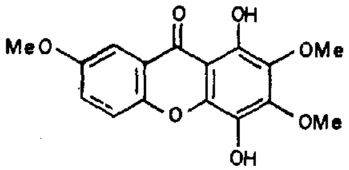


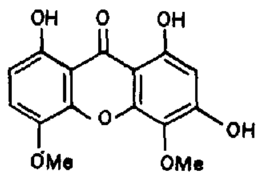
Norswertianin R¹ = R² = R³ = H
Swertianin R¹ = Me, R² = R³ = H
Swertiapernin R¹ = R³ = Me, R² = H
Gentiacaulein R¹ = R² = Me, R³ = H
Decussatin R¹ = R² = R³ = H

Glycoside	Oxidation pattern				Natural sources
	1	3	7	8	
66	O-glc.	OH	OH	OH	*Swertia dilatata*[171] *Swertia gracilescens*[171] *Swertia perennis*[176] *Gentiana bavarica*[177]
67	O-prim.	OH	OH	OH	*Gentiana bavarica*[177] *Gentiana verna*[178]
68	O-prim.	OMe	OH	OH	*Gentiana bavarica*[177] *Gentiana verna*[178] *Gentiana nivalis*[179]
69	OH	OMe	O-rut.	OH	*Gentiana bavarica*[180]
70	OH	OMe	O-(Ac) rut.	OH	*Gentiana bavarica*[177,180]
71	OH	OMe	OH	O-glc.	*Gentiana verna*[178]
72	OH	OMe	OH	O-prim.	*Gentiana alpina*[181] *Gentiana ciliata*[181] *Gentiana kochiana*[182]
73	O-prim.	OMe	OMe	OH	*Swertia perennis*[176]
74	O-prim.	OMe	OH	OMe	*Gentiana bavarica*[177] *Gentiana nivalis*[179] *Gentiana verna*[178] *Gentiana acaulis*[188]
75	OH	OMe	O-prim.	OMe	*Gentiana alpina*[181] *Gentiana angustifolia*[181] *Gentiana ciliata*[181] *Gentiana clusii*[181] *Gentiana kochiana*[181]
76	OMe	O-prim.	OMe	OH	*Gentiana alpina*[181] *Gentiana angustifolia*[181] *Gentiana clusii*[181] *Gentiana ciliata*[181] *Gentiana kochiana*[182]
77	O-prim.	OMe	OMe	OMe	*Gentiana alpina*[181] *Gentiana bavarica*[177] *Gentiana ciliata*[181] *Gentiana clusii*[181] *Gentiana nivalis*[179] *Gentiana verna*[178,183] *Swertia perennis*[176]

glc. glucose; prim. primeverose; rut. rutinose.

Table 14. Pentaoxygenated xanthones





Glycoside	Oxidation pattern					Natural sources
	1	2	3	4	7	
78	O-glyc.	OMe	OMe	OH	OMe	*Swertia bimaculata*[184]
	1	3	4	5	8	
79	O-glyc.	OH	OMe	OMe	OH	*Gentiana campestris*[185] *Gentiana germanica*[175] *Gentiana ramosa*[175]

glc. glucose; glyc. unidentified sugar.

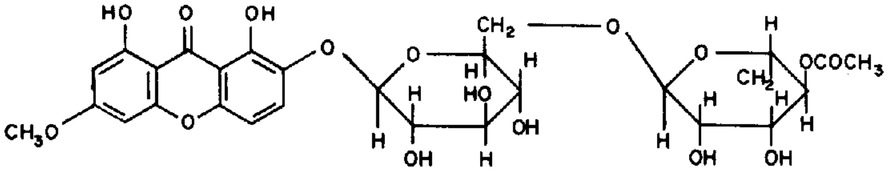
However with the available new isolation techniques more and more glycosides would be isolated from families containing polyoxygenated xanthones. So far O-monosides and O-biosides have been isolated. In the former β-D-glucose is the only monosaccharide so far recognised whereas in the analogous flavones other sugars like D-galactose, L-rhamnose, L-arabinose and D-apiose have been frequently found. Of the two disaccharides discovered to date primeverose or 6-O-(β-D-xylopyranosyl)-β-D-glucopyranose is the more common and rutinose or 6-O-(α-L-rhamnopyranosyl)-β-D-glucopyranose is the rarer one. The latter sugar has been found in a tetraoxygenated xanthone of *Canscora decussata* Schult and in a tetraoxygenated xanthone of *Gentiana bavarica* L. On the other hand Wagner[184] has described 25 disaccharides in various flavonoid glycosides. A diglucoside norswertianin-1-O-glucosyl-3-O-glucoside has been described for the first time from *Swertia perennis.*[187]

The aglycones have tri-, tetra- or penta-oxygenation pattern. 1,3-oxygenation pattern is found in each compound with further oxygenation in the 4-, 5-, 7- or 8-position. So far substitution at 6-position has not been encountered in keeping with the earlier observations on free xanthones.

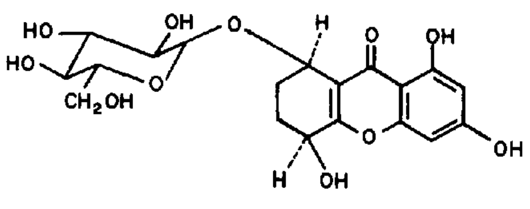
Upto date only two trioxygenated glycosides have been identified as 1-hydroxy-7-methoxy-3-O-primeverosylxanthone (**57**) in the roots of several *Gentiana* species[165,189] and 5-hydroxy-1-methoxy-3-O-rutinosylxanthone (**56**) in the aerial parts of *Canscora decussata* Schult.[164] On the other hand several tetraoxygenated xanthones have been isolated with 1,3,4,5-; 1,3,5,8- and 1,3,7,8-oxygenation pattern and the last one having the largest number so far (Table 13). A pentaoxygenated compound from the leaves of *Gentiana campestris* L.[183] has been characterised, as 1-O-β-D-glucopyranosyl-3,8-dihydroxy-4,5-dimethoxyxanthone (**79**).

An acyl-O-glucoside (**80**) was isolated by Hostettmann *et al.* from the aerial parts of *Gentiana bavarica* L.[177] With ^{13}C NMR data the acyl group has now been assigned to position 4 of rhamnose. In contrast several acylated flavone glycosides have been recorded.

A glycoside isolated from *Gentiana campestris*[150] needs special mention as it is the first example of a tetrahydroxyxanthone glycoside. Such xanthones are rare as natural products and the occurrence of such a compound in *Calophyllum zeylanicum* Kosterm.[148] has already been mentioned. Its structure was elucidated by spectral analysis including ^{13}C data as 1,3,5-trihydroxy-8-β-D-glucopyranosyl 5,6,7,8-tetrahydroxyxanthone (**81**). Its occurrence is of great biogenetic significance because the corresponding xanthone glucoside, possessing the same oxidation pattern and carrying the hydrolysable sugar at the same position is present in relatively high concentration.



80
Gentiabavarutinoside



81
1,3,5-Trihydroxy-8-β-D-glucopyranosyl-5,6,7,8-tetrahydroxanthone

Fig. 23(a).

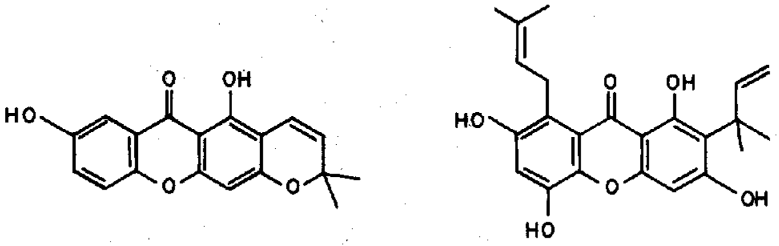
An O-glycoside found in the urine of cows fed on mango leaves is euxanthic acid (1-Hydroxy-7-O-glucoronylxanthone).

From a consideration of the above table it should be noted that 13 xanthones carry their glycosidic group at position 1. This is somewhat surprising owing to its closeness to the CO group. Besides the corresponding position in the flavone nucleus (i.e. position 5) is rarely glycosylated. Therefore the study of the biosynthetic pathway of these glycosides should be of particular interest.

Hostettmann has carried out detailed investigation on the occurrence of the glycosides in the Gentianaceae and has attempted to provide chemical information about the sub-genera[192] and sections of this family.

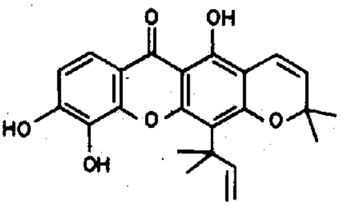
Moraceae

Plants of the family Moraceae have been intensively investigated by Venkataraman *et al.*[193] and a variety of flavonoids and in particular prenylated flavonoids have been characterised. Xanthones have been reported from a few species. From *Maclura pomifera* root bark Wolfrom *et al.*[94] characterised the three prenylated xanthones osajaxanthone (**11**), alvaxanthone (**82**) and macluraxanthone (**83**) as in Fig. 24, and more recently 1,3,6,7-tetrahydroxyxanthone. This species is known as *Toxylon pomiferum* Rafin and a specimen obtained from U.S.A. has been investigated by Venkataraman in 1973.[195] They showed the presence of the above three prenylated xanthones and in addition isolated 6-deoxyjacareubin (**9**), 8-deoxygartanin (**12**) and another called toxylxanthone A which is in fact trapezifolixanthone (**14**) isolated earlier from *Calophyllum trapezifolium* (Fig. 25). The last three constituents and osajaxanthone have been isolated from Guttiferae species as mentioned earlier. In addition they recorded the presence of three other xanthones, toxylxanthone B (**84**), toxylxanthone C (**85**) and toxylxanthone D (**86**) (Fig. 26). The structure of toxylxanthone B (**84**) has been revised by Kirtany and Paknik[196] and confirmed by Scheinmann and Cotterill[197] and this is shown.



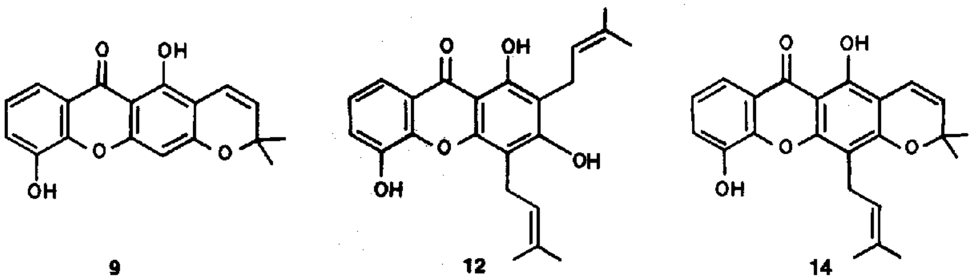
11
Osajaxanthone

82
Alvaxanthone



83
Macluraxanthone

Fig. 24.

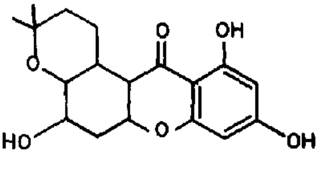


9
6-Deoxyjacareubin

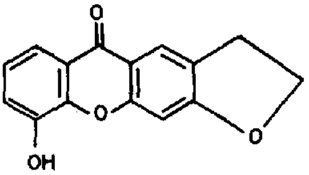
12
8-Deoxygartanin

14
Trapezifolixanthone

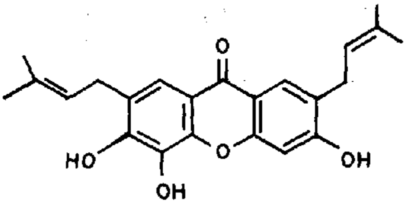
Fig. 25.



84
Toxylxanthone B



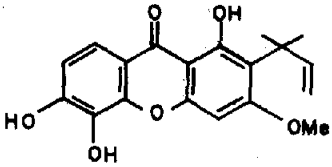
85
Toxylxanthone C



86
Toxylxanthone D

Fig. 26.

From two other moraceae species *Clarisia racemosa* R. and P.[197] and *Chlorophora tinctoria* Gand[198] the presence of 1,3,6,7-tetrahydroxyxanthone has been established. Seshadri *et al.* isolated cudraniaxanthone (**87**) from *Cudrania javanensis*[199] (Fig. 26a).

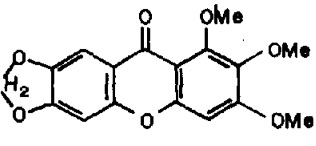


87
Cudraniaxanthone

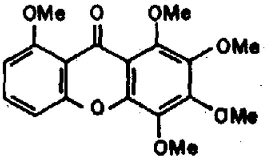
Fig. 26(a).

Polygalaceae

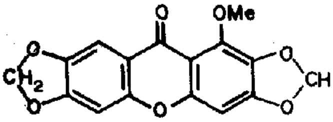
Polonsky *et al.* reported for the first time the isolation of two xanthones, polygalaxanthone A (**88**) and B (**89**) from *Polygala paenea* L.[200] The structure of the polygalaxanthone A was corrected later by Stout and Fries[201] as 1,2,3-trimethoxy-6,7-methylenedioxyxanthone (**88**). Polygalaxanthone B is 1,2,3,4,8-pentamethoxyxanthone (**89**). Both are pentaoxygenated xanthones. Dreyer has reported from *Polygala macradenia* Gray,[202] the above polygalaxanthone A, 1-methoxy-2,3 : 6,7-bis (methylenedioxy) xanthone (**90**) (Fig. 27) and 1,2,3,4,6,7-hexamethoxyxanthone (**91a**). Gottlieb *et al.* have reported from *Polygala spectabilis* DC[203] the presence of three 1,2,3,7,8-pentaoxygenated xanthones: 1,2,3,7,8-pentamethoxyxanthone (**91b**), 2-hydroxy-1,3-dimethoxy-7,8-methylenedioxyxanthone (**92a**) and 1,2,3-trimethoxy-7.8-methylenedioxyxanthone (**92b**) (Fig. 28).



88
Polygalaxanthone A

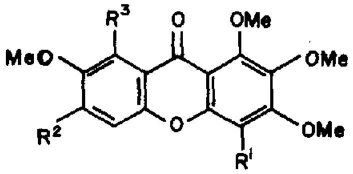


89
Polygalaxanthone B

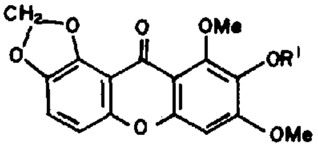


90

Fig. 27.



91a $R^1 = R^2 = OMe$, $R^3 = H$
91b $R^1 = R^2 = H$, $R^3 = OMe$



92a $R^1 = H$
92b $R^1 = Me$

Fig. 28.

From *polygala tennuifolia* Willdenow, Ito *et al.* in 1977[204] have reported the presence of 1,2,3,7-tetramethoxyxanthone (**93a**), 1,2,3,6,7-pentamethoxyxanthone (**93b**) and 6-hydroxy-1,2,3,7-tetramethoxyxanthone (**93c**), reporting a tetraoxygenated xanthone for the first time from this family. Ghosal *et al.* also in 1977[205] have reported for the first time several trioxygenated xanthone derivatives as 1-hydroxy-2,3-dimethoxyxanthone (**94a**), 1,2,3-trimethoxyxanthone (**94b**), 1-hydroxy-2,3-methylenedioxyxanthone (**94c**) and 1-methoxy-2,3-methylenedioxyxanthone (**94d**) (Fig. 29).

The occurrence of methyl ethers and methylenedioxy derivatives and pentaoxygenated compounds seems to be characteristic of this family. All the xanthones so far reported from the Polygalaceae show oxygenation at positions 1-, 2- and 3-. Four Polygala species investigated by us did not show the presence of xanthones.

93
a: $R = H$
b: $R = OMe$
c: $R = OH$

94
a: $R^1 = H$, $R^2 = R^3 = Me$
b: $R^1 = R^2 = R^3 = Me$
c: $R^1 = H$, $R^2 = R^3 = —CH_2—$
d: $R^1 = Me$, $R^2 = R^3 = —CH_2—$

Fig. 29.

Biosynthesis of xanthones

The biosynthetic pathways to xanthones have been discussed in recent years. Initially these attempted to interrelate the observed oxygenation pattern of natural xanthones and correlate them with recognised oxygenation patterns. If the xanthones from the Guttiferae are examined, it is seen that ring A and the attached CO group (C_7 unit) are provided by the shikimic acid pathway whereas ring B (C_6 unit) arises via the acetate-malonate polyketide route. Therefore polyhydroxy benzophenones or their biogentically equivalents could be intermediates in the formation of xanthones. These ideas[5] are summarised in Fig. 30 in which the most frequently encountered sites of mono (a), di-(b,b) and tri-(c,c,c) for the shikimate derived ring A are shown.

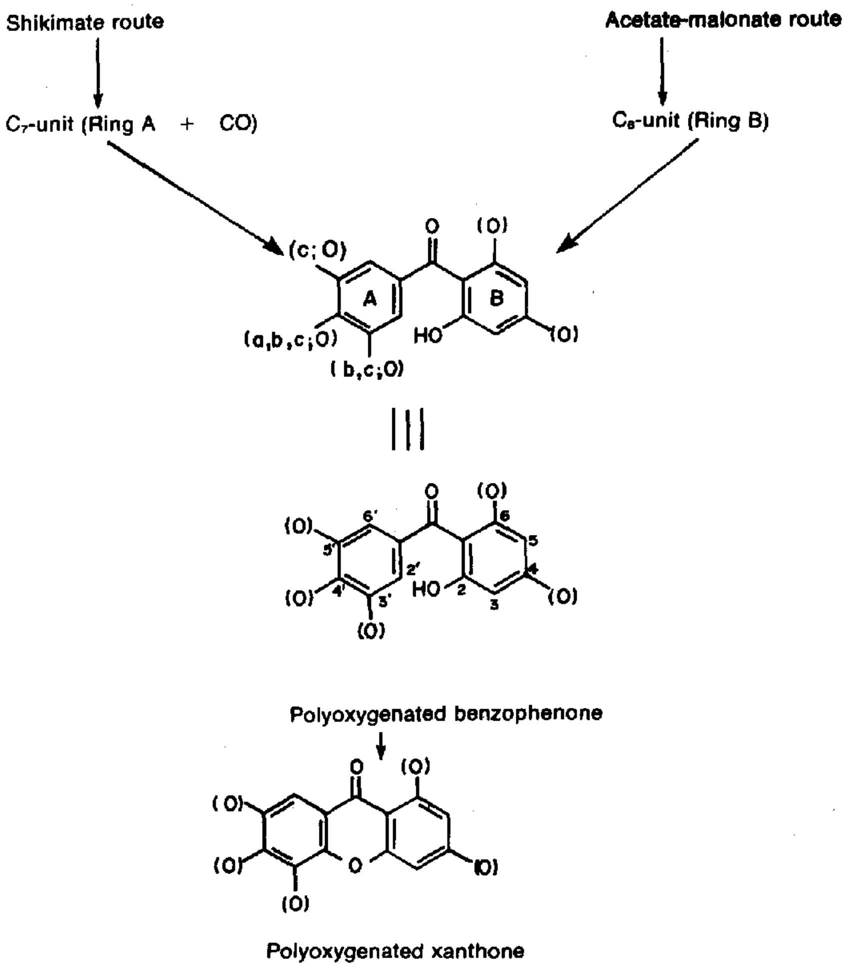


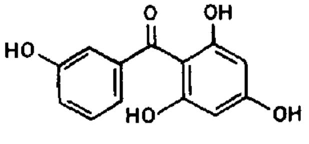
Fig. 30. Biosynthesis of xanthones in higher plants.

The above biosynthetic pathway has been supported by the following experimental data:

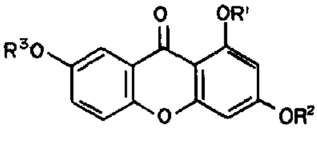
(a) The radio labelled acetate studies of Floss and Retting[206] have shown acetate incorporation in ring B of xanthones.

(b) Atkinson, Gupta and Lewis[207] have confirmed the above results by showing 0.53% incorporation of 2-^{14}C-acetate into the xanthones formed in the rhizomes of *Gentiana lutea* shown below:

(c) Lewis *et al.* [207] have also shown that (i) the ^{14}C-labelled phenylalanine was incorporated into ring A (ii) tritiated 2,3',4,6-tetrahydroxybenzophenone (**95**) was biosynthetically transformed into gentisein (**96a**), gentisin (**96b**) and isogentisin (**96c**) as in Fig. 31.



95



96

	R¹	R²	R³	
a:	H	H	H	Gentisein
b:	H	Me	H	Gentisin
c:	H	H	Me	Isogentisin
	H	Me	Me	
	Me	Me	Me	

Fig. 31.

A number of mechanisms have been suggested for the transformation of polyoxygenated benzophenones to polyoxygenated xanthones.

(a) Direct oxidative coupling of 2,2′-dihydroxy benzophenone via radical intermediate (Lewis, 1963) as in Fig. 32.[127,198,208-211]

(b) Intramolecular addition of hydroxy groups in quinonoid intermediates (Whalley,[211] 1968) as in Fig. 33.

(c) Dehydration between the OH groups of the acetate and shikimate derived moieties (2,2′-dihydroxy-benzophenone) via suitably activated intermediates such as O-phosphates (Seshadri,[213] 1961; Markham,[214] 1965) as in Fig. 34.

(d) Via spiro cyclohexadienone intermediate (Gottlieb,[215] 1968) as in Fig. 35.

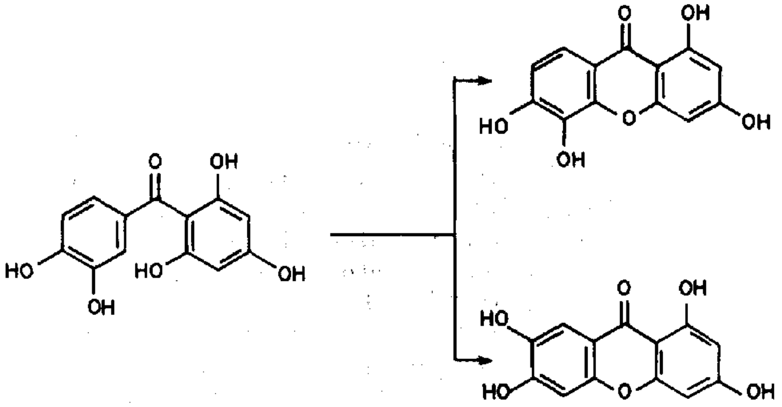


Fig. 32.

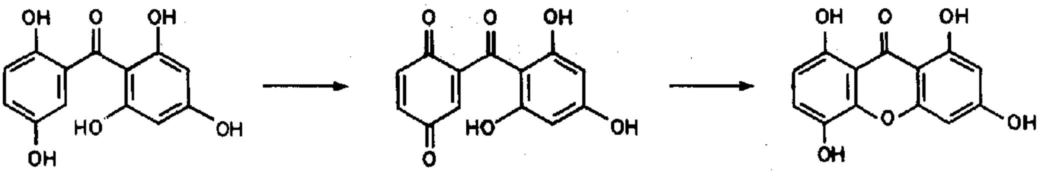


Fig. 33.

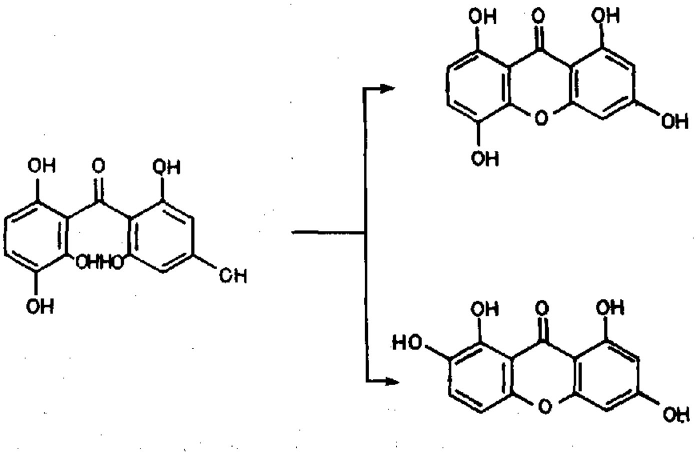


Fig. 34.

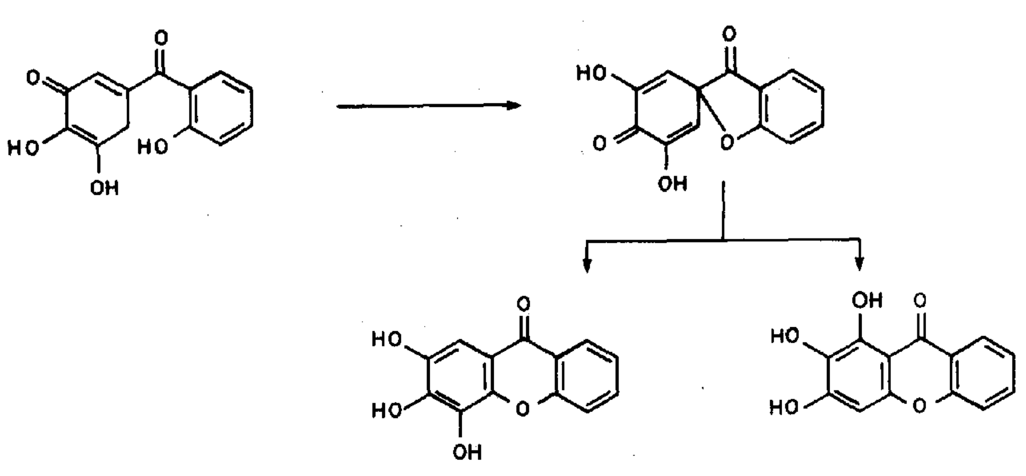
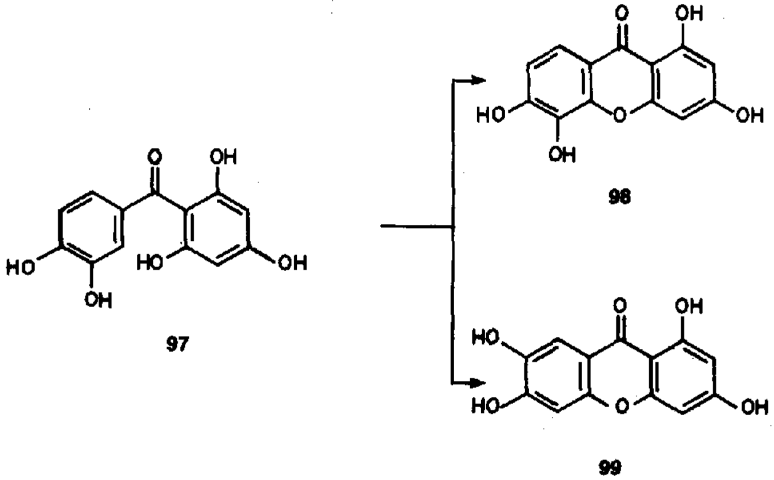


Fig. 35.

The above mechanisms have been discussed by Scheinmann *et al.*[4] (1969) and they conclude that "direct oxidative coupling of the benzophenones leads to a simpler explanation of the wide variety of oxidative patterns in (natural) 'xanthones'". They have also emphasised the frequent co-occurrence of pairs of corresponding xanthones like 5- and 7-monoxyxanthones, 1,5- and 1,7-dioxyxanthones, 1,5,6- and 1,6,7-trioxyxanthones and 1,3,5,6- and 1,3,6,7-tetraoxyxanthones as evidence of such a mechanism. An alternative explanation for this has been presented[224] (see below).

Formation of naturally occurring xanthones by oxidation of polyhydroxy benzophenones with a variety of oxidising[216–218] agents like potassium permanganate, potassium ferricyanide, manganese dioxide and quinone has been studied. Good yields of xanthones (40–70%) sometimes as isomeric xanthones corresponding to *o*- and *p*-coupling were observed. These studies have been extended[216,217] with enzyme systems of the laccase and peroxidase types which too produced xanthones from polyhydroxy benzophenones.

There are only two known cases of the co-occurrence of benzophenones and xanthones. These are the results from *Gentiana* lutea (Fig. 31)[219] and *Symphonia globulifera*[124–127] in which maclurin (97) and the two oxidative cyclisation products 1,3,5,6-tetrahydroxyxanthone (98) and 1,3,6,7-tetrahydroxyxanthone (99) were obtained as in Fig. 36.



97

98

99

Fig. 36.

Other transformations associated with the biosynthesis of natural xanthones are connected with the presence of methoxy, methylene dioxy groups, C_5 and C_{10} residues. The biogenetic origin[220] of the C_5 and C_{10} units is definitely 3,3-dimethylallyl pyrophosphate and geranyl pyrophosphate and these units would enter the *ortho*- or *para*- position to the phenolic OH groups to give the respective products.

Gottlieb *et al.*[5] first observed the natural co-occurrence of xanthones and aucuparins. These have been extended by the isolation of the first diphenyl carboxilic acid, hermonionic acid[6] (**48**) from *Garcinia hermonii* Kosterm given earlier. This can be related to the two main routes of aldol condensation and acylation proposed by Birch in polyketide biosynthesis as in Fig. 37.

The correlation of the biosynthesis of flavonoids and stilbenes from cinnamoyl polyketide and the corresponding route with the 3,4,5-trioxybenzoylpolyketide to benzophenones or the diphenyl skeleton is shown in Figs. 37 and 38.

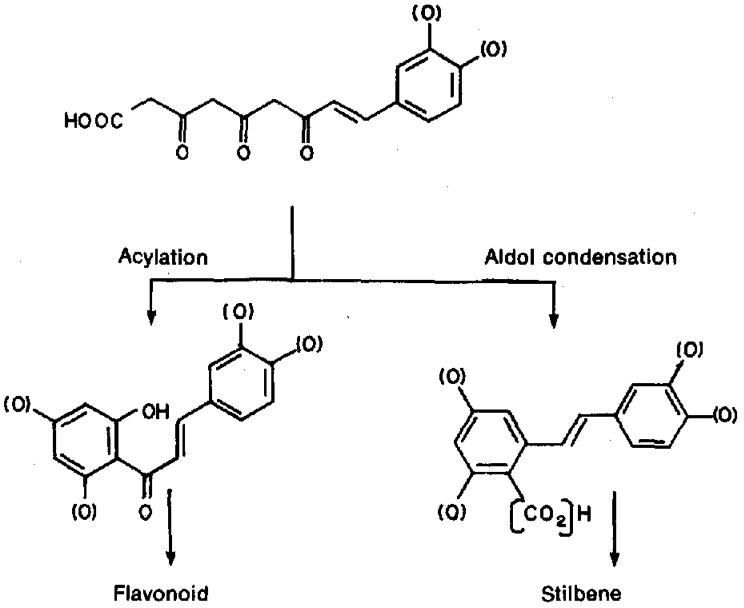


Fig. 37.

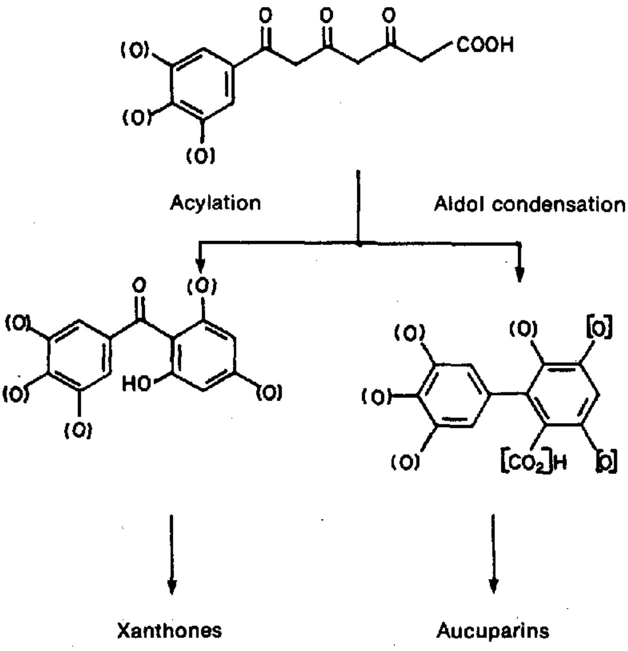
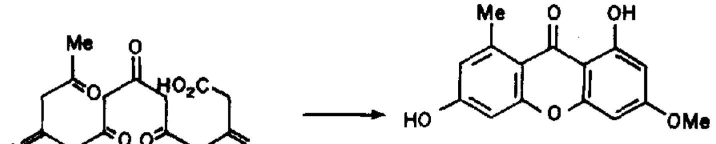


Fig. 38.

It will be useful to emphasise the clear distinction in xanthone biosynthesis in higher plants and the biosynthetic pathway for the xanthones from fungal metabolites. This can be illustrated by the synthesis of griseoxanthone (**100**)[221] by the acetate-malonate polyketide route as in Fig. 39.



100
Griseoxanthone

Fig. 39.

Biogenesis of polyisoprenylated xanthonoids

Although there is no experimental data on the biosynthesis of polyisoprenylated xanthonoids, these compounds can be considered to be formed by polyisoprenylation of xanthone precursor. Ollis[222] has carried out a biogenetic analysis for gambogic acid, which exemplified this approach, and is therefore given in outline here. In gambogic acid the C_{36} skeleton is derived from xanthone (C_{13}) in association with one geranyl (C_{10}) and three isoprenoid ($3 \times C_5$) units. Following the postulated route to 2,2-dimethyl chromenes from O-3,3-dimethylallylphenol, the oxidative cyclisation of the *o*-hydroxy-geranyl grouping to the 2-methyl-2-(4-methylpent-3-enyl) chromene residue of gambogic acid becomes apparent. An internal Prins type of addition to a C=C double bond of a 3,3-dimethylallyl group, may account for the formation of the bridged bicyclo [2,2,2]-octenone. Ollis has postulated the following reactions for the formation of gambogic acid from the biogenetically acceptable 1,3,5,6-tetrahydroxyxanthone.

(i) C-alkylation by geranyl pyrophosphate and 3,3-dimethylallyl pyrophosphate.

(ii) Protonation of the intermediate ketol to give an oxonium cation.

(iii) Neutralisation of this intermediate by an internal Prins addition. All these mechanistically reasonable processes are summarised in his biognetic proposal given below in Fig. 40 for gambogic acid and related polyisoprenoids.

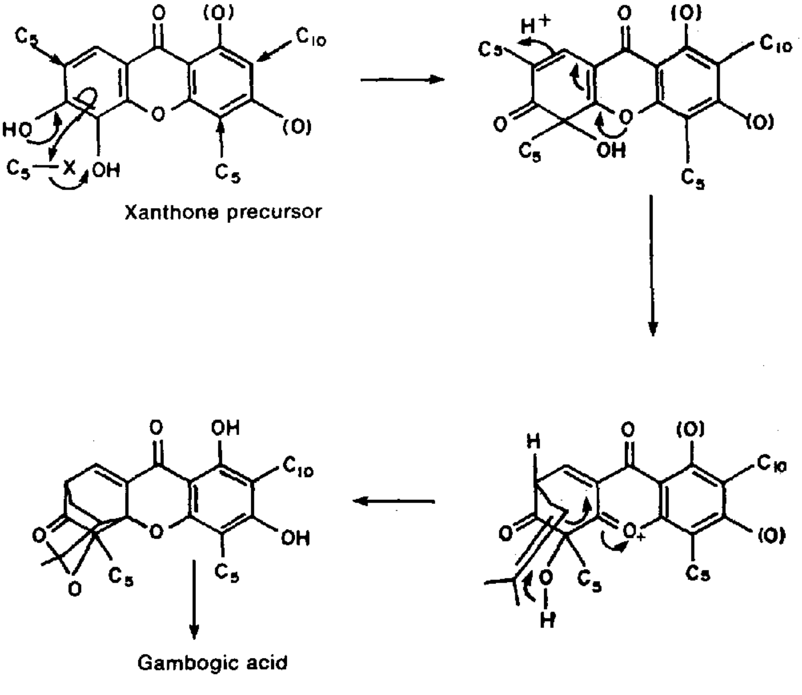


Fig. 40.

Venkataraman[140] in his Seshadri, 70th Birthday lecture (1973) has proposed a modified biosynthetic pathway. He considers that the suggestion of Ollis *et al.* that the pyrone oxygen initiates the step which lead to the bicyclo-octane ring system as improbable. According to him in keeping with the original scheme the pyrone CO is much more likely to trigger the concerted series of reactions as shown in Fig. 41.

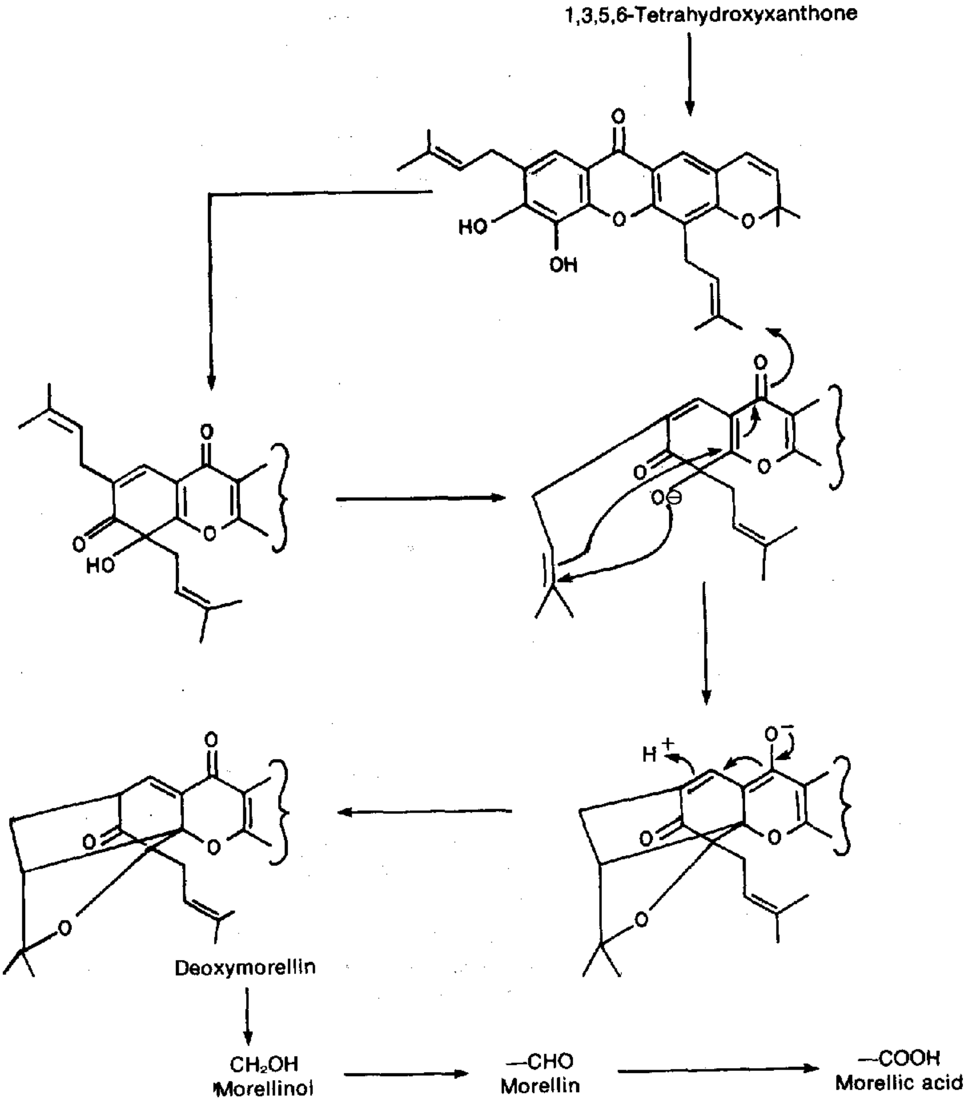


Fig. 41.

In this scheme deoxymorellin is the first pigment formed in the biosynthesis and the progressive oxidation of a Me group then leads to morellinol, morellin and morellic acid.

Although polyhydroxy-benzophenones have been shown to give rise to xanthones both under enzymic conditions and with chemical reagents, the question of the co-occurrence of a large variety of polyhydroxyxanthones has not yet found a satisfactory answer. Carpenter *et al.* in their 1969 review postulated the formation of 15 standard xanthones resulting from the oxidative coupling of 9 benzophenone precursors. They also observed that whenever an oxygen function occurs at other than "standard positions they would be at position *ortho-* or *para-* to the standard oxygen function and attempted to explain these observations". Within the last 10 years a large number of xanthones have been isolated from ***Mammea, Calophyllum, Mesua*** and other Guttiferae genera and Gentianaceae species. These would require the co-occurrence of several benzophenone precursors. However there are only two examples where it has been experimentally established that benzophenones and xanthones co-occur. One in the Guttiferae species, *Symphonia globulifera*[124-127] where maclurin (2,2′,3,5′,6-pentahydroxy-benzophenone) was isolated in a yield of 1.5% along with 1,3,5,6- and 1,3,6,7-tetrahydroxyxanthone (Fig. 36). The other in the Gentianaceae species, *Gentiana lutea*[74] where the fresh rhizomes were shown to contain 0.0003% of 2,3′,4,6-tetrahydroxybenzophenone, 0.002% of 1,3,7-trihydroxyxanthone and 0.014% of a mixture of gentisin and isogentisin (Fig. 31).

Rezende and Gottlieb[223] consider 1,3,5,6- and 1,3,6,7-tetraoxygenation patterns as primitive characters in xanthone biosynthesis, as oxygen functions are always present at *para*-position in hydroxylated shikimate derived atomatic rings (ring A). Besides they have carried a frequency count on the number of different xanthones and shown 1,3-dioxygenation for the acetate derived ring B and 5,6- and 6,7-dioxygenation for the shikimate derived ring A. Xanthones, which contain more or less oxygen function are said to be formed by oxidative or reductive steps as shown in Fig. 42.

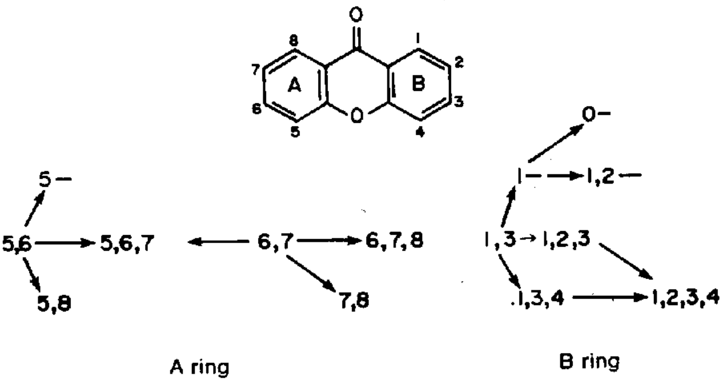


Fig. 42. Changes in oxygenation of xanthones with evolutionary advancement.

From the frequency counts it is apparent that the Guttiferae and Gentianaceae contain different enzyme systems. They have attempted to relate the oxygenation pattern to the oxidation or reduction of the xanthone precursor. However it is possible to account for xanthone distribution in both the Guttiferae and Gentianaceae by dehydroxylation and/or hydroxylation mechanism on the xanthone molecule from the polyoxygenated xanthone itself.[148,224]

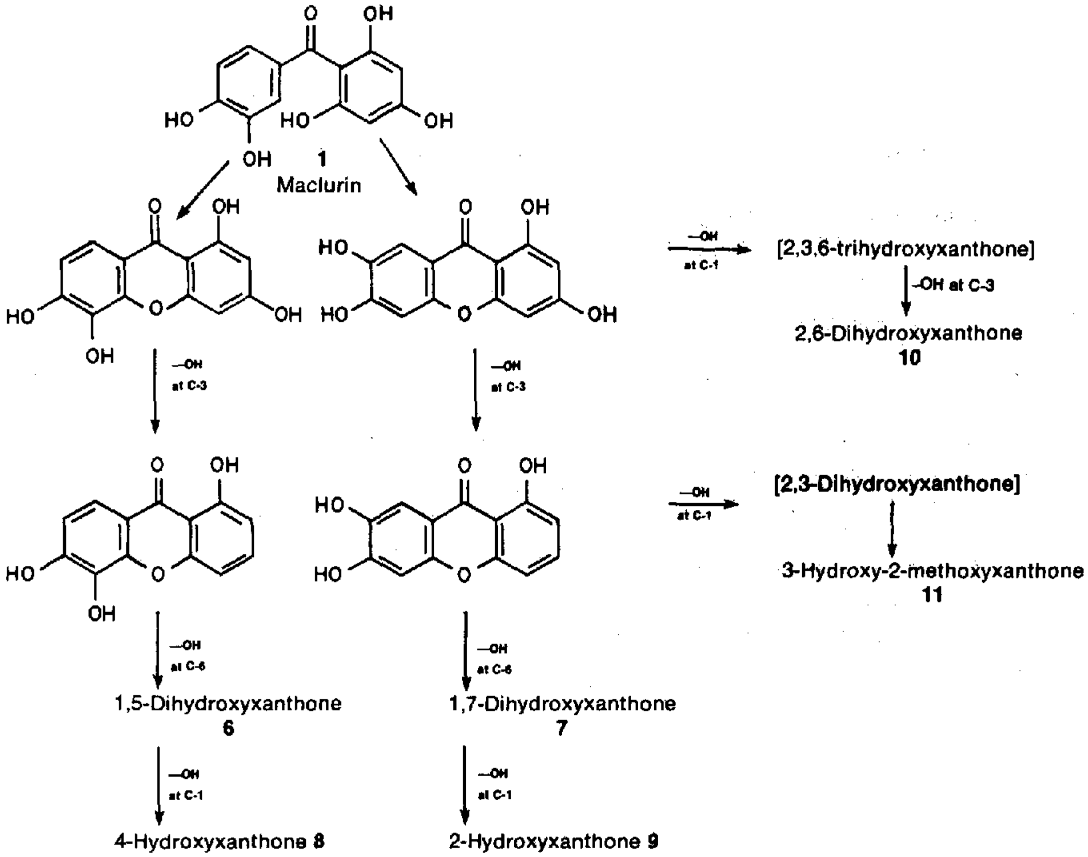
Of the three *Mammea* species, studied, to date, the above mentioned tetraoxygenated xanthones were isolated from *M. africana*. The other two *Mammea* species had only mono- and di-oxygenated xanthones as in Table 15. Without postulating several hydroxybenzophenones, the *Mammea* xanthones

Table 15. Xanthones from *Mammea* species (% dry weight with respect to plant parts)

	M. acuminata (timber)	*M. africana* (timber)	*M. americana* (seeds)
2-Methoxyxanthone	2.65×10^{-3}	—	+[b]
2-Hydroxyxanthone	5.86×10^{-3}	—	1.1×10^{-3}
4-Hydroxyxanthone	4.0×10^{-3}	—	0.7×10^{-3}
1-Hydroxy-7-methoxyxanthone	8.0×10^{-3}	—	—
1,5-Dihydroxyxanthone	4.7×10^{-3}	+ 2.4×10^{-2}[a]	0.6×10^{-3}
1,7-Dihydroxyxanthone	6.9×10^{-3}	+	0.6×10^{-3}
1-Methoxy-5-hydroxyxanthone	3.2×10^{-3}	1.0×10^{-2}	—
3-Hydroxy-2-methoxyxanthone	8.0×10^{-4}	—	—
2,6-Dihydroxyxanthone	3.8×10^{-4}	—	—
1,5,6-Trihydroxyxanthone	—	+ 7.2×10^{-2}[a]	—
1,6,7-Trihydroxyxanthone	—	+	—
1,3,6,7-Tetrahydroxyxanthone	—	+ 1.2×10^{-2}[a]	—
1,3,5,6-Tetrahydroxyxanthone	—	+	—

[a] No separate percentages were available.
[b] No yield available.

can be considered to be formed by the nuclear reductions[224] of 1,3,5,6- and 1,3,6,7-tetraoxygenated xanthones derived from maclurin as in Scheme given in Fig. 43. The scheme requires the removal of one or more aromatic OH groups and this is not uncommon. Mechanistically the removal of the aromatic OH groups would be even greater if they are situated at either *ortho*- or *para*- to the CO group as in Scheme given in Fig. 44[225]. Gottlieb's survey has shown that a number of xanthones with nuclear reduction at position 3 are common. This was found to be so *in vitro*.[226] The other alternative to nuclear reduction in the xanthone biogenesis is the nuclear oxygenation of the simple xanthones, 2- and 4-hydroxyxanthones, derived from 2,3′-dihydroxy-benzophenone. Even though this would explain the biosynthesis of all the xanthones isolated from the *Mammea* species, 2,3′-dihydroxy-benzophenone would require an initial dehydroxylation of the acetate and shikimate units, or to recognise hydroxylation on an unactivated benzene nucleus for the conversion of, e.g. 4-hydroxyxanthone to 1,5-dihydroxyxanthone. The nuclear reductions of tetraoxygenated xanthones appear to be a more plausible biogenetic scheme for the formation of the xanthones in *Mammea*. The different oxygenation pattern of xanthones isolated from *Calophyllum*, *Mesua*, *Garcinia* and other genera can thus be the result of nuclear reductions and similar oxygenation as will be discussed next.



a: **2**, **3**, **4** and **5** in *M. africana* only.
b: **6** and **7** in all three species
c: **8** and **9** in *M. americana* and *M. acuminata* only
d: **10** and **11** in *M. acuminata* only

Fig. 43. Biogenetic scheme for the synthesis of xanthones of *Mammea*.

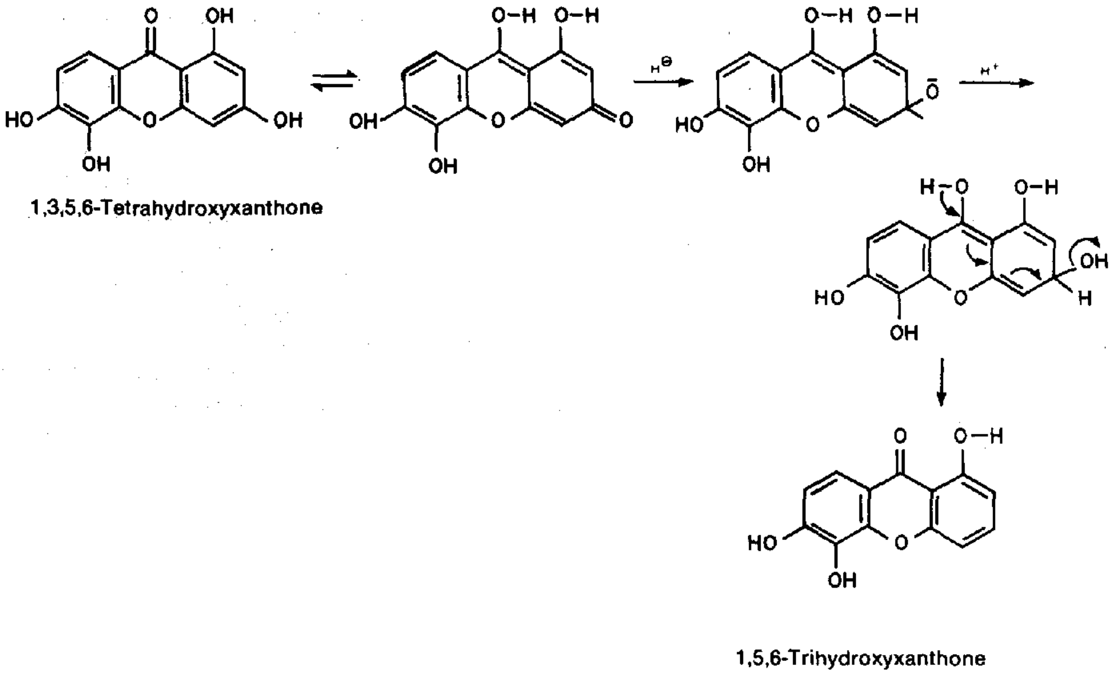


Fig. 44. Mechanism of the nuclear reduction of -OH group either *para*- or *ortho*- to the CO group.

From *Gentiana lutea* 2,3′,4,6-tetrahydroxybenzophenone has been isolated together with 1,3,7-trihydroxyxanthone (Fig. 31).

So far only from *Canscora decussata* that 1,3,5-xanthone derivatives have been isolated. From other species a large number of 1,3,7,8- or 1,3,5,8-derivatives or compounds with hydroxylation at other *ortho*- or *para* position have been reported. These can readily arise by the indicated mechanism[227] (in Fig. 45) without the need for other benzophenone precursors as follows:

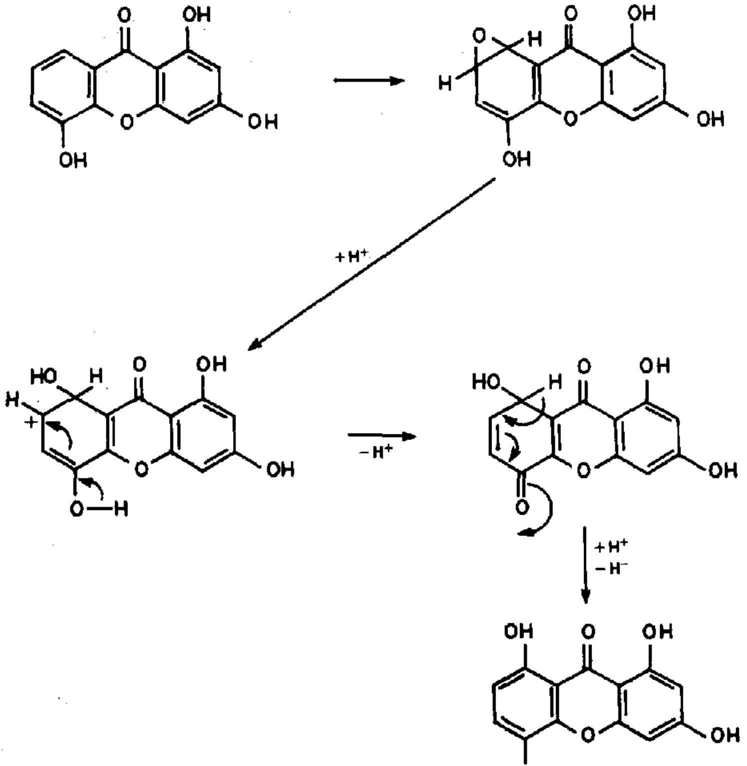


Fig. 45.

In certain cases both mechanisms may be occurring, i.e. some being formed by a dehydroxylation process and the other by a hydroxylation. The former being more characteristic of the Guttiferae and the latter that of the Gentianaceae.

During the past few decades there has been considerable experimental examination of biogenetic theory which has led to some detailed understanding of many of the processes that are actually involved in the biosynthesis of natural products. Carpenter *et al.* in a review had referred to the co-occurrence of xanthones with 4-arylcoumarin and biflavonoids, but could not see a relationship among them. However Ollis has pointed to the fact that 4-arylcoumarins and 4-alkylcoumarins co-occur and has suggested that they may be formed by analogous biosynthetic pathway involving an aldol type of condensation of a polyketide with a β-keto acid. On this biogenetic hypothesis Ollis[5] has directly correlated many of the natural products isolated from the Guttiferae. This hypothesis brings together not only the xanthones, benzophenones and aucuparin but also the 4-alkyl and 4-aryl coumarins. These can be derived from polyketide precursors by chain extension of oxygenated benzoic and cinnamic acids with one or three acetate residues.

Likewise biflavones isolated from the Guttiferae can be correlated on the basis that oxidative radical coupling in higher plants can take place between enols and phenols as well as between phenols. Ollis[5] has given the following polketide routes (Fig. 46) to various classes of phenolic compounds isolated from the Guttiferae.

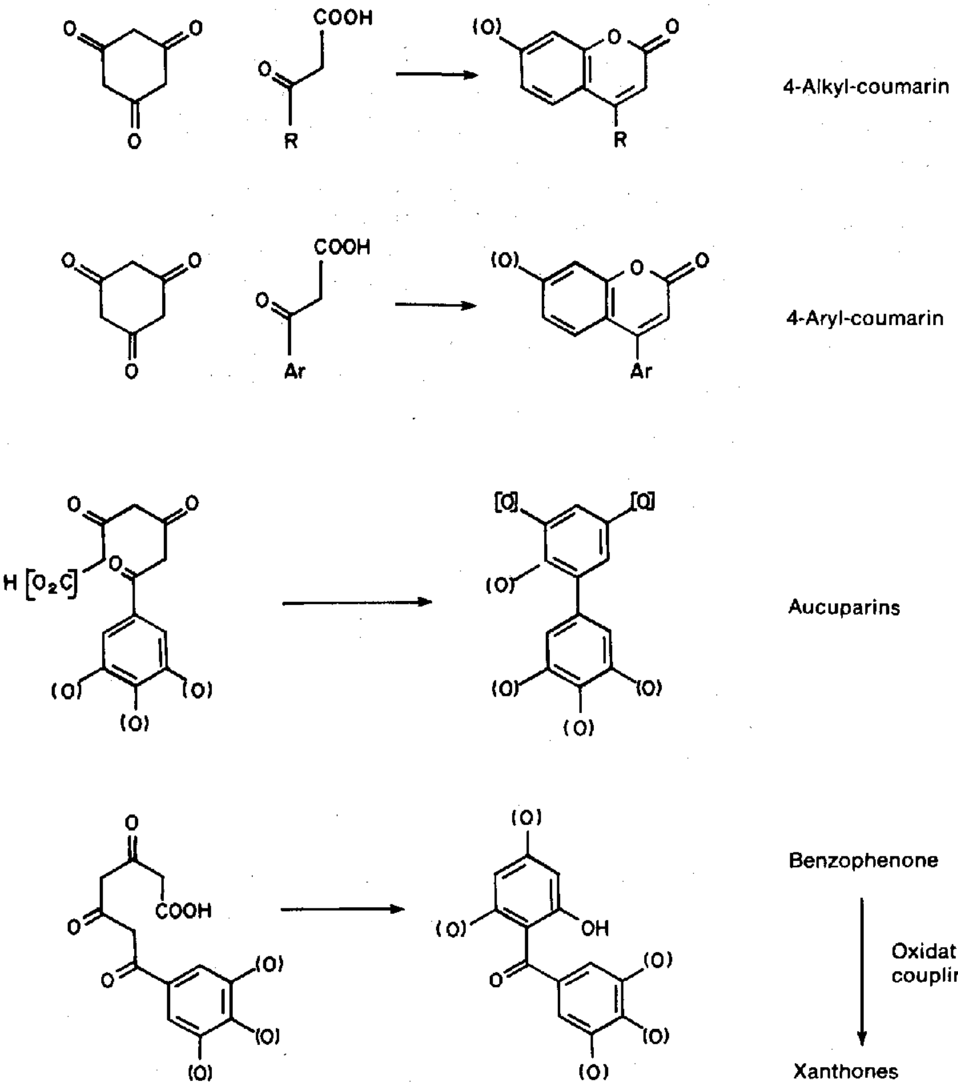


Fig. 46.

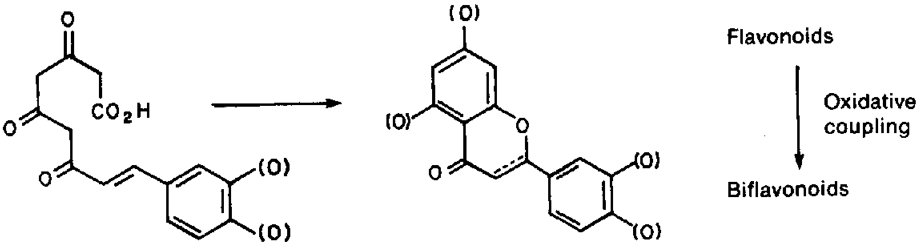


Fig. 46.

Pharmacology

Xanthone derivatives have been shown to be effective as an allergy inhibitor, bronchodilator in the treatment of asthma etc.[228] and synthetic work is in progress in several pharmaceutical firms. In the Ayurvedic systems of medicine plants belonging to the Gentianaceae find wide application, e.g. the use of *Canscora decussata*[229] in some mental disorders like melancholia or the tuberculostatic acivity that has been reported for xanthones. Besides free xanthones show a higher tuberculostatic acitivity than the xanthone glycosides, e.g. the minimum inhibitory concentration for the aglycone was 10 μg/ml in comparison with mangiferin which required 200 μg/ml.

Pharmacological investigations were first carried on the xanthone glycoside mangiferin. The early result of Finnegan[230] on the diuretic and cardiotonic action of mangiferin in animals could not be fully confirmed. However by studying the extracts, fractions and pure compounds of *Canscora decussata* a remarkable CNS stimulating effect of mangiferin in 50–100 mg/kg has been observed. This could be blocked by pretreatment with chloropromazine. This effect manifested itself by hyperactivity, fine tremors, piloerection, increased spontaneous motility, sedation etc. The corresponding free xanthones either did not show the above properties or showed them to a much lower extent. In vitro experiments showed that the above was through a monoaminooxidase inhibition.[231]

On the other hand Ghosal *et al.*[232] have observed in mice and rats the opposite CNS depressant or antipsychotic effect for xanthen-O-glycosides. This has interested an Italian group[233] who have started investigation with model compounds.

These studies will gain greater importance in the future with the recognition of xanthones as an important group of secondary plant metabolites whose role is very little understood at the moment.

In this report the reviewer has tried to indicate the variety of xanthone structures found in the Guttiferae, the types of simple xanthones and their glycosides found in the Gentianaceae with a brief account of the xanthones found in Moraceae and Polygalaceae. Next the biogenesis of these compounds is discussed and lastly their potential pharmacological value has been indicated.

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APPENDIX

Plant species studied in the family Guttiferae

Genus:	*Allanblackia* Oliver	
	A. floribunda Oliver	12
Genus:	*Caraipa* Aubl.	
	C. densiflora	13, 13*a*
	C. grandiflora	13
Genus:	*Calophyllum* L.	
	C. apetalum Willd.	14–17
	C. australianum P. M. Vesq.	18
	C. blancoi Pl. and Tr.	19
	C. bracteatum Thw.	20
	C. brasiliense Camb	21–26
	C. calaba L.	20
	C. canum Hook.	27
	C. chapelieri Drake	28
	C. cordato-oblongum Thw.	29
	C. costatum Bill	30
	C. cuneifolium Thw.	31
	C. fragrans Ridley	32
	C. inophyllum L.	22, 33–42
	C. longifolium Wild.	43
	C. neo-ebudicum Guillaumin	44
	C. papuanum Lauterb	55
	C. pulcherrimum Wall	46, 47
	C. ramiflorum Schwarz	48
	C. recedens Jumella and Perrier	49
	C. sclerophyllum Vesq.	50
	C. scriblitifolium Hend and Wyatt Smith	51–53
	C. soulattri Burm. f.	31
	C. thwaitesii Planch and Triana	54
	C. tomentosum Wight	15,16,46
	C. trapezifolium Thw.	55, 56
	C. walkeri Wight	54
	C. zeylanicum Kosterm.	57
Genus:	*Clusia* L.	
	C. rosea Jacq.	58
	C. congestiflora	59
	Clusia species	60
Genus:	*Cratoxylon* Blume	
	C. celibicum Blume	61,62
Genus:	*Garcinia* L.	
	G. buchananii Baker	63–65
	G. cambogia Dear.	68
	G. cowa Khran	66, 67
	G. dulcis (Roxb.) Kurz	69
	G. echinocarpa Thw.	70
	G. eugenifolia Wall	65, 71, 72
	G. hanburyi Hook. f.	73
	G. hermonii Kosterm.	74
	G. hombroniana Pierre	75, 76
	G. indica	77
	G. kola Heckel	77*a*
	G. linii Chang	78, 79
	G. livingstonii	80
	G. mangostana L.	81–85
	G. mannii Oliv.	85a
	G. morella Desr.	86–87
	G. multiflora	78,79
	G. pedunculata	88, 89
	G. rubra Merrill	66
	G. spicata Hook. f.	90
	G. talboti Reiz	91
	G. terpnophylla Thw.	70
	G. volkensii Engl.	92
	G. xanthochymus Hook. f.	79
Genus	*Harungana* Thou	
	H. madagascariensis Poir	93
Genus:	*Kayea* Wall	
	K. stylosa Thw.	94
Genus:	*Kielmeyera* Mart	
	K. candidissima	95
	K. coriacea Mart	38, 96,97
	K. corymbosa (Spr.) Mart	96, 98
	K. excelsa Camb	99–101
	K. ferruginea A. P. Duarte	102
	K. petiolaris (Spr.) Mart	101, 103
	K. rosea	38
	K. rubriflora Camb	104
	K. rupestris A. P. Duarte	105
	K. speciosa St. Hill	63, 106
Genus:	*Lorostemon* Duck	
	L. coelhoi Paula	107
	L. negrensis Fross	107
Genus:	*Mammea* L.	
	M. acuminata	46
	M. africana G. Don	108
	M. americana L.	109–111
	M. longifolia (Wight) Planch and Triana	112
Genus:	*Mesua* L.	
	M. ferrea L.	113, 114
	M. myrtifolia	115
	M. salicina Pl. and Tr.	116
	M. thwaitesii Planch and Triana	117
Genus:	*Moronobea*	
	M. pulchra	118
Genus:	*Ochrocarpus* Thou.	
	O. odoratus	119
Genus:	*Pentadesma* Sabine	
	P. butyracea Sabine	120

Genus:	*Pentaphalangium*	
	P. solomonse Warb.	121
Genus:	*Platonia* Mart	
	P. insignis Mart	122
Genus:	*Rheedia* L.	
	R. gardneriana Pl. and Tr.	123
Genus:	*Symphonia* L.	
	S. globulifera L.	124–127
Genus:	*Tovomita* Auble	
	T. choisyana Pl. and Tr.	128
	T. macrophylla (Pl. and Tr.) Walp	129
	T. pyrifolium	130
	T. mangle	131