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Review on Chemistry, Biological Activity and Biosynthesis of Naturally Occurring Compounds of Cadalene Type Sesquiterpenoids from Malvaceae

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ABSTRACT

The Malvales is one of the widely distributed worldwide by about 230 genera and 2,700 species. The economic use of Malvaceous plants is as a source of many biologically active principles like caffeine, theobromine, vanillin, ephedrine, pseudoephedrine, corchorin, capsularin, tiliacin, kolatin, quercimeritrin, isoquercitrin, choline, gossypol, lacinilene C, heliocides, mansonones, etc. Cadalene has the cadinane skeleton and is present in essential oils and in many plants. It is used as a biomarker in paleobotanic studies. In this review, we report brief information on the chemistry, biological activity and biosynthesis of naturally occurring compounds derived from cadalene of the Malvales is made.

Keywords: Cadalene, Malvaceous plants, Paleobotanic studies

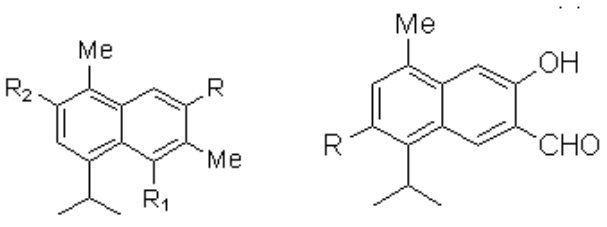
INTRODUCTION

The order Malvales is one of the widely distributed worldwide taxon represented by about 230 genera and 2,700 species and constitutes one of the dominant floristic elements in the Indian subcontinent [1]. It constitutes several important medicinal plants like *Althaea* sp, *Malva* sp, *Sida* sp, *Abutilon* sp, *Hibiscus* sp, *Thespesia* sp, *Gossypium* sp, *Ceiba* sp, *Sterculiaceae* sp, *Helictreres* sp, *Abroma* sp, *Ochroma* sp, *Ceiba* sp, *Gravia* sp, *Corchorous* sp, and *Eleocarpus* sp, which form a good source of many biologically active principles like caffeine, theobromine, vanillin, ephedrine, pseudoephedrine, corchorin, capsularin, tiliacin, kolatin, quercimeritrin, isoquercitrin, choline, gossypol, lacinilene C, heliocides, mansonones, etc.

The genus *Bombax* which belongs to the family *Bombacaceae* of the N.O. Malvales consists of 10 species of large deciduous trees mostly found in tropical America and extending to Asia and Africa [2]. Out of 10 species only three species like *B. malabaricum*, *B. insignis*, and *B. scopulorum* occur in India [3]. *B. malabaricum* is widely used in indigenous medicine as demulcent, diuretic, aphrodisiac, emetic [4], and for curing impotence [5]. In view of this, a brief review on the chemistry, biological activity and biosynthesis of naturally occurring compounds derived from cadalene of the Malvales is made.

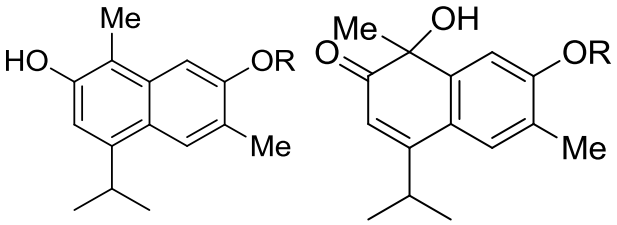
Chemistry of naturally occurring cadalene derivatives

Cadalene (1) was reported to be present in the cade oil [6], 7-hydroxycadalene* (2) was isolated along with the aldehydes 3 and 4 and related compounds from the Elm wood [7].



1 R = R_1 = R_2 = H
2 R =OH , R_1 = R_2 =H
3 R = H
4 R = OMe

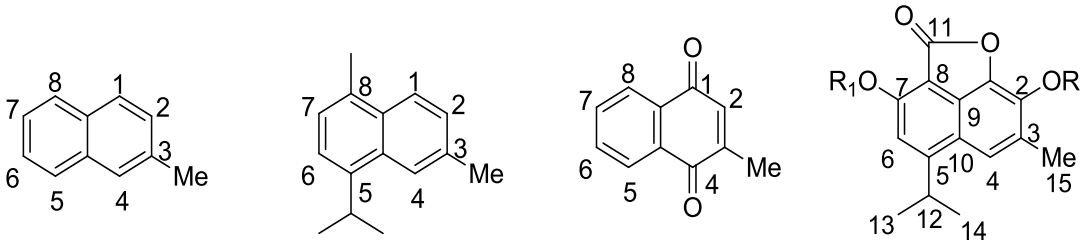
Two related sesquiterpenoids derivatives 5 and 6, and lacinilene C (7) and lacinilene C 7-methyl ether (8) have been isolated from green and field dried cotton bracts of *Gossypium hirsutum* [8] (Malvaceae).



5 R = H
6 R = Me

7 R = H
8 R = Me

Note: The positions of the substituents of the naphthalene and naphthoquinone derivatives reported in this article are numbered in the following manner.



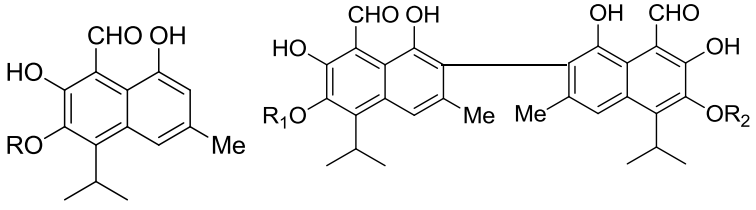
*Nomenclature followed as per "Encyclopedia of the Terpenoids", John Wiley & sons, New York, 1982

On the basis of spectral and chemical transformation studies Stipanovic et al. [9], have assigned the revised structure 7 for lacinilene C in preference to structure 9 assigned to it earlier [10].

9 **10**

A notable feature in the ^{1}H-NMR spectrum of lacinilene C is the appearance of the methyl signals of the isopropyl group as a doublet of doublet with a chemical shift difference of 1.5 Hz as excepted for an isopropyl group separated from an asymmetric center by four bonds [11]. The UV absorption maxima of lacilene C at 370 nm underwent a bathochromic shift of 73 nm as excepted for a phenyl group situated in a position *para*-vinylogous to a carbonyl group in changing from a neutral to a basic solution [12]. As excepted, the UV spectrum of its methyl ether (8) was unaltered on the addition of the base. On oxidation with sodium periodate it gave the excepted methyl keto acid (10). Thus finally structure 7 was preferred to structure 9 for lacinilene C.

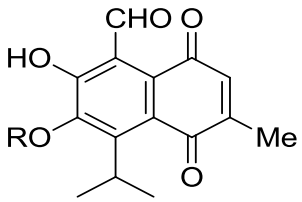
Compounds 5 and 6 are rapidly autoxidize on silica gel to 7 and 8, respectively. The occurrence of 7 and 8 in optically active forms indicates that they are produced enzymatically from naphthols 5 and 6, respectively. The structures of these compounds have been finally confirmed by synthesis [13,14]. The sesquiterpenoid aldehydes, hemigossypol (11) and 6-*O*-methylhemigossypol (12), and the triterpenoid aldehydes gossypol (13), 6-*O*-methygossypol (14), and 6,6'-di-*O*-methylgossypol (15) were reported from the roots of *Gossypium hirsutum* and *G. barbadense* [15].



11 R = H
12 R = Me

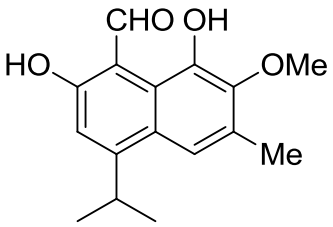
13 $R_1 = R_2$ = H
14 R_1 = Me; R_2 = H
15 $R_1 = R_2$ = Me

The structure of gossypol was determined by Adams et al. [16] and it was subsequently confirmed by synthesis [17]. Gossypol was shown to exhibit optical activity. It occurs predominantly in (+) form in *Thespesia populnea* (Malvaceae), whereas both (±) and (+) gossypol occur in *Gossypium* seeds [18-20]. The optical activity has been attributed to restricted rotation over the binaphthyl linkage [21]. Seshadri et al. [22,23], have reported 6-*O*-methylhemigossypol (12) and two naphthoquinones like hemigossypolone (16) and hemigossypolone-6-*O*-methyl ether (17) from the root bark of *Bombax malabaricum* (Bombacaceae). Bell et al. [24,25], have isolated 11 and 12 from the diseased stele tissues of *Gossypium barbadense* who reported that the melting point, UV, and ^{1}H NMR spectra of their compound 12 was slightly different from the compound of Sheshadri et al. [23], reported from *B. malabaricum*.



16 R = H
17 R = Me

Subsequently, in another report Bell et al. [26], while discussing the dissimilarity of terpenoids in Gossypium and *Bombax* suggested that Sheshadri's hemigossypol-6-methyl ether (12), hemigossypolone (16) and hemigossypolone-6-O-methyl ether (17) were probably 18, 19 and 20 isolated by them from *Gossypium* species as compared to the compounds isolated by Seshadri et al., 22, 23 from *B. malabaricum*.



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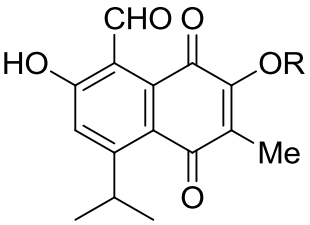
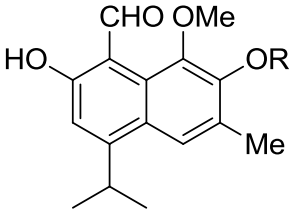
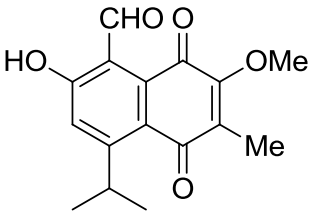


19 R = H
20 R = Me

Later Sankaram et al. [27], have reported three new sesquiterpenoids from the root bark of *B. malabaricum* and were characterized as isohemigossypol-1-methyl ether (21), isohemigossypol-1,2-dimethyl ether (22) and 8-formyl-7-hydroxy-5-isopropyl-2-methoxy-3-methyl-1,4-naphthoquinone (23). They showed that the naphthol 12 reported by Seshadri et al. [23], from the same source was not a hemigossypol derivative but a isohemigossypol derivative identical to the naphthol 21 isolated by them.

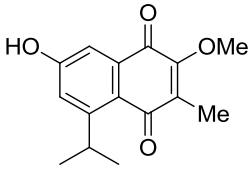


21 R = H
22 R = Me



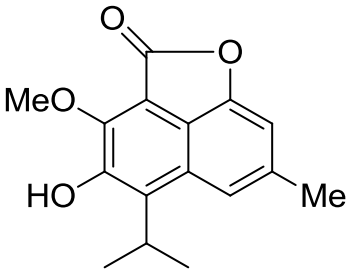
23

Sankaram et al. [27], have also pointed out that the quinone 23 reported by them from *B. malabaricum* closely resembled the naphthoquinone 17 of Seshadri et al. [23], reported from the same source. The major difference was in the ^{1}H-NMR spectrum of 23, wherein the methyl signal appeared as a singlet at δ=7.27 (J=0.5 Hz) which were reported as a double and a quartet at δ=2.06 and 7.32, respectively, by Seshadri et al. [23]. Sreeramulu et al. [28], have isolated a new naphthoquinone derivative from the heartwood of *B. malabaricum* and its structure was established as 7-hydroxy-5-isopropyl-2-methoxy-3-methyl-1,4-naphthoquinone (24).

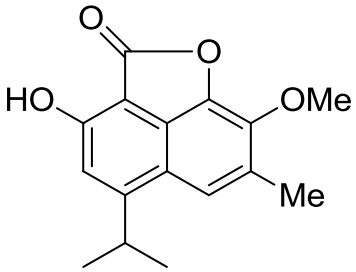


24

A cadalene type sesquiterpene latone, structurally allied to hemigossypol (12) isolated from the roots of *B. malabaricum* by Sheshadri et al. [29] and Sood et al. [30] was characterized as 6-hydroxy-5-isopropyl-7-methoxy-3-methyl-8,1-naphthalene carbolactone (25). Based on extensive 2D-NMR experiments Puck Haber and Stipanovic [31] have revised the structure of sesquiterpene lactone, 25 and they showed that the correct structure for this compound is actually isohemigossypol acid lactone-2-methyl ether (26).

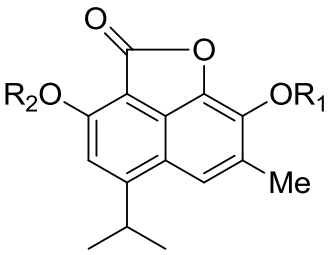


25

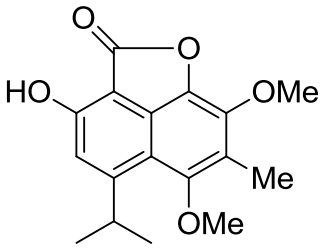


26

Rao et al. [32], have reported two new sesquiterpene lactones from the root bark of *Ceiba pentandra* (Bombacaceae) and they were reported as 2-hydroxy-5-isopropyl-7-methoxy-3-methyl-8,1-naphthalene carbolatone (27) and 2,7-dimethoxy-5-isopropyl-8,1-naphthalene carbolatone (28).

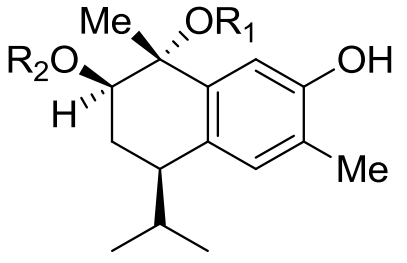


27 R_1= H; R_2 = Me
28 R_1 = R_2 = Me



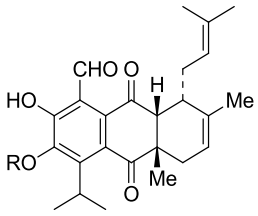
27a

M.V.B. Reddy et al. [32], Reported a new A new sesquiterpene lactone, 5-isopropyl-3-methyl-2,4,7-trimethoxy-8,1-naphthalene carbolactone (27a) together with a known naphthoquinone, 8-formyl-7-hydroxy-5-isopropyl-2-methoxy-3-methyl-1,4-naphthoquinone (18) were isolated from the root bark of *B. malabaricum*. Zhang et al. [33], have reported two new sesquiterpene glycosides from Cotton oil cake (*Gossypium hirsutum*). They were characterized as 5,6,7,8-tetrahydro-2,7*β*, 8*α*-trihydroxy-3,8*β*-dimethyl-5*β*-isopropylnaphthalene-7-O-*β*-D-glucoside (29) and 5,6,7,8-tetrahydro-2,7*β*, 8*α*-trihydroxy-3,8*β*-dimethyl-5*β*-isopropylnaphthalene-8-O-*β*-D-glucoside (30).

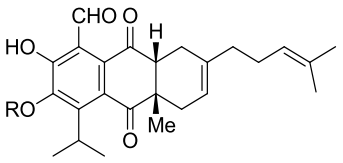


29 R1 = H; R_2 = Glc
30 R = Glc; R2 = H

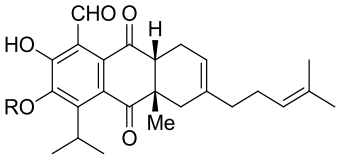
Certain *Heliothis* resistant cotton varieties possessing pigment glands were shown to contain the sesquiterpenoids, hemigossypolone [34] (16) and hemigossypolone-6-methyl ether [35] (17) and the derived sesquiterpenoid heliocides H_1 [36] (31), H_2 [37] (32), H_3 [38] (33), H_4 [36] (34), B_1[35] (35), B_2 [39] (36), B_3 [39] (37) and B_4 [35] (38). The H and B designation indicates that these compounds were first found in *G. hirsutum* and *G. barbadense*, respectively. The resistance of cotton varieties to insect attack has been attributed in part to the terpene aldehydes found in the pigment glands.



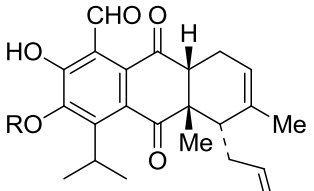
31 R = H
35 R = Me



32 R = H
36 R = Me

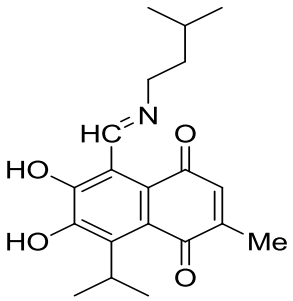


33 R = H
37 R = Me



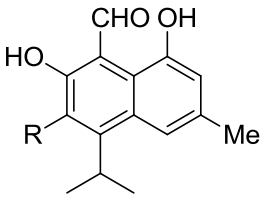
34 R = H
38 R = Me

A dark pigment, gossyrubilone, present in the glands of the young leaves of *G. hirsutum* and *G. barbadense* [35] has been identified as the isopentylimine of hemigossypolone (39). Similarly red imined formed from the sesquiterpenoid quinone 16 and amino acids, resembled the red coloration of the envelope cells surrounding the gland sac.

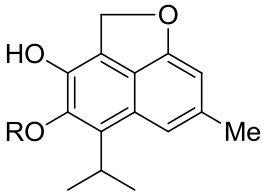


39

Hemigossypol (11), 6-*O*-methylhemigossypol (12), 6-deoxyhemigossypol (40), desoxyhemigossypol (41) and desoxy-6-*O*-methylhemigossypol (42) were isolated and identified from *Verticillium* infected stele tissue of *G. barbadense* and these have been considered as phytoalexins [40].

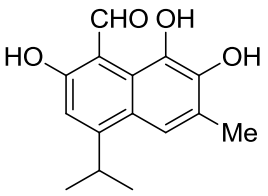


11 R = H
12 R = OMe
40 R = H



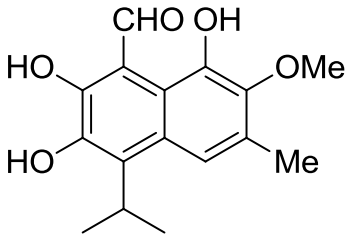
41 R = H
42 R = Me

Sanykov et al. [41], isolated a phytoalexin from similarly infected *Gossypium* species and assigned isohemigossypol structure 43 to it. Veech et al., [42] however, showed it to be hemigossypol (11) by the observation of the increase in intensities of both the aromatic protons due to the nuclear Overhauser effect when the aromatic methyl protons were irradiated. The structure was confirmed by conversion to gossypol (13).



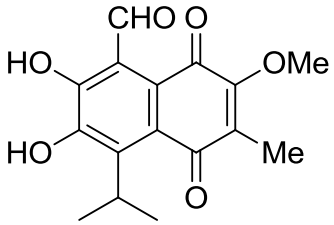
43

A new sesquiterpenoid, isolated from the pigment of the leaves and the immature bolls of *G. raimondii* [43], has been designated as raimondal and it was identified as 5-isopropyl-2-methoxy-3-methyl-1,6,7-trihydroxy-8-naphthaldehyde (44). The assignment of the hydroxyl and methoxyl groups at C-6 and C-2, respectively, were determined by a study of the proton-coupled ^{13}C-NMR spectra before and after the deuterium exchange. Raimondal (44**)** has been shown to the highest toxicity of any cotton terpenoid tested against *Heliothis virescens* cell [44].



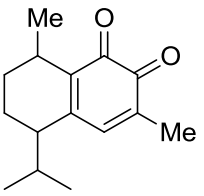
44

Stipanovic et al.[45] have reported a new sesquiterpenoid namely, raimandalone from the foliage of a progeny plant obtained by self-pollination of a hexaploid parent derived from a *G. hirsutum* × *G. raimondii* hybrid. Raimandalone was characterized as 8-formyl-6,7-dihydroxy-5-isopropyl-2-methoxy-3-methyl-1,4-naphthoquinone (45).



45

A mixture of ten closely related naphthoquinones derived from cadalene have been reported from the heartwood of *Mansonia altissima* [46-49], (Sterculiaceae) whose sawdust frequently causes violent sneezing, vertigo and eczema [46]. These naphthoquinones have been characterized as mansonone A (46), B (47), C (48), D (49), E (50), F (51), G (52), H (53), I (54) and L (55). The names mansonone denotes that they have been derived from *Mansonia* species. It is interesting to note that mansonone C (48) occurs in the Elm wood together with other compounds having a cadalene skeleton [7,50].



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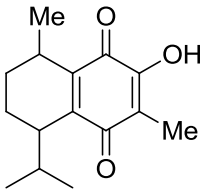
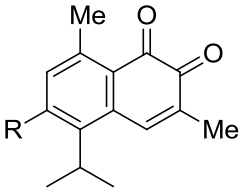
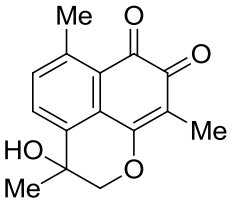


47



48 R = H
52 R = OH



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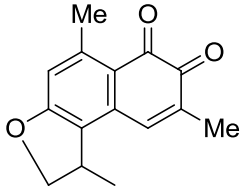
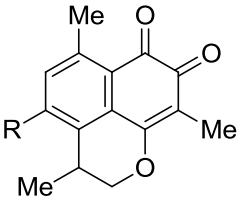
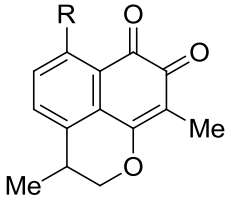


49

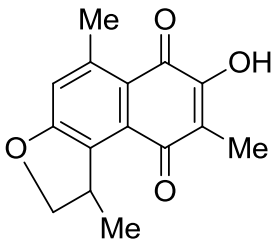


50 R = H
53 R = OH

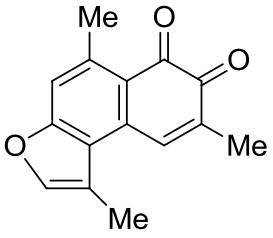


51 R = Me
55 R = CH_2OH

Mansonones C, D, E and F have also been reported from *T. populnea* [51] along with two new sesquiterpenoids, thespesone (56) and thespone (57), structurally related to mansonone D (49).

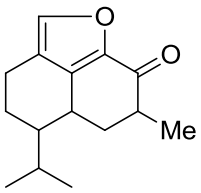


56



57

A group of colourless sesquiterpenoid ketones, hibiscone A (58), B (59), C (60) and D (61) and the ortho-naphthoquinones, hibiscoquinone A (62), B (63), C (64) and D (65), based on cadalene skeleton have been reported from the heartwoods of *Hibiscus elatus* [52] and *H. tiliaceus* [53]. The structures of hibiscoquinones A, B, C and D were determined from the consideration of their UV, IR, ^{1}H-NMR and mass spectral data.



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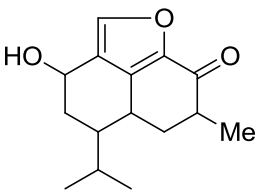

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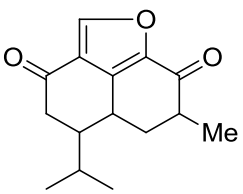

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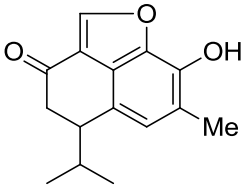

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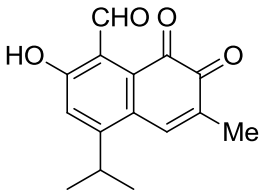

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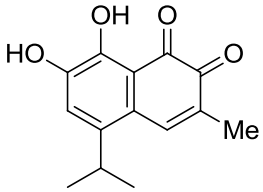

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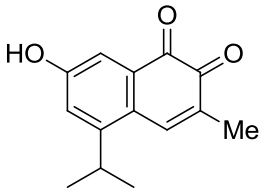

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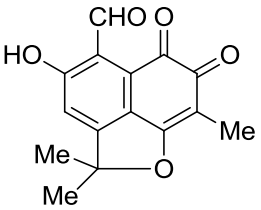
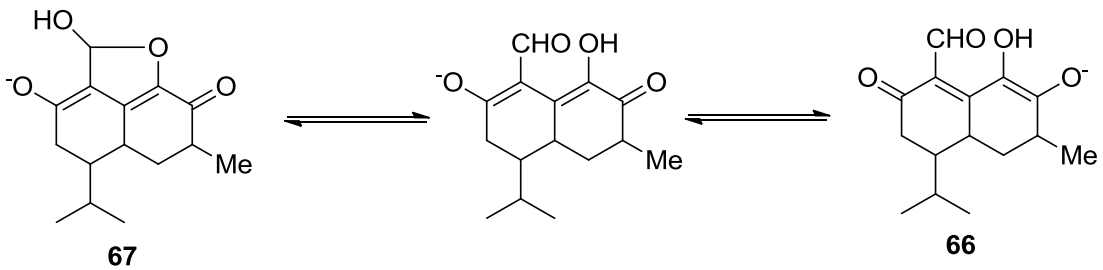


65

Hibiscone C (60) was found to be identical with gmelofuran found in the heartwood of *Gmelina arborea* [54] and the structure has been confirmed by X-ray crystallographic analysis. A bright yellow solution has been obtained on addition of sodium hydroxide to hibiscone C (60) in alcohol, the λ max shifting from 267 nm to 414 nm with increased intensity whereas hibiscones A (58) and B (59) did not produce the alkali shift. It is unlikely that such a change would result merely from the formation of an anion of hibiscone C (60). Moreover, the furan proton signal shifts downfield from δ=8.34 (in CD_3OD) to 9.11 (in CD_3OD + OD^-). The new chromophore was probably the mesomeric anion 66 which arises by nucleophilic attack on the furan ring of hibiscone A, activated by the two carbonyl groups to give 67 followed by the opening of the lactol ring to form the aldehyde function which accounts for the ^{1}H-NMR singler δ=9.11. The whole process was reversed if the solution was acidified after a short time.



67 **66**

The structure of hibiscone B (59) was determined by a consideration of its UV, IR and ^{1}H-NMR spectral data and oxidation with 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to hibiscone C (60). The structure of hibiscone A (58) was determined by a comparison of ^{1}H-NMR and mass spectral data with those of hibiscone B (59).

Biological activity of cadalene derivatives

Gossypol has been claimed as a safe reversible male contraceptive by the Chinese [55,56]. However, there is not much significant work concerning the structure-activity relationships. It has been noticed that purification of gossypol or gossypol-carboxylic acid reduced the contraceptive effect and there is a view that a trace impurity in gossypol may be the active principle. It has also been shown that gossypol works by inhibiting an enzyme that has a crucial role in the metabolism of sperm generating cells. The target enzyme has been shown to be Lactate Dehydrogenase X (LDH-X) which was found only in the sperm and testis cells. *In vitro* studies have shown that gossypol is a selective in activator of sperm specific LDH-X from mouse, rat and human [57,58]. The degree of LDH-X inactivation by gossypol was found to be depend on the enzyme concentration, despite the fact that gossypol concentration is also always in great excess compared to that of LDH-X, suggesting

that the presence of minor components in gossypol could be responsible for LDH-X inactivation in neutral aqueous solution. These minor components could either be (a) Impurities contaminated in original gossypol sample or (b) The decomposition products or (c) Minor tautomeric forms of gossypol in neutral aqueous solution.

The irreversible interaction by gossypol could result from the covalent interaction between the active minor components in gossypol and the enzymes. Numerous hypotheses have been proposed regarding the specific expression of LDH-X in spermatogenic cells and its possible functional roles in the sperm. It is also been further shown that NADH was shown to partially protect the enzymes against the inactivation by the minor components of gossypol. There lactate dehydrogenase isoenzymes; malate dehydrogenase and glutathione S-transferase have also been inactivated by low concentration of gosyypol. It appeared that it didn't affect either the sex harmone levels or libido [59]. Gossypol did not inhibit ovulation in the female rat. In the case of female mouse it resulted in nonviable off spring, when administered during the days 1-13 of pregnancy [60]. Gossypol was also reported to possess fungitoxic [15], antiviral [61], antitumour [62-64], antiamebic [65] and anti-HIV [66] activities.

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The natural resistance of certain varieties of cotton plants to the insects of *Heliothis* complex is due to the presence of terpene aldehydes [67,68] found in the glands. The terpene aldehydes have been identified as hemigossypolone [34] (16), hemigossypolone-6-methyl ether[35] (17), heliocides H_1 [36] (31), H_2 [37] (32), H_3 [38] (33), H_4 [36] (34), B_1 [35] (35), B_2 [39] (36), B_3 [39] (37) and B_4 [35] (38), of which heliocides H_1 (31) and H_4 (34) were found to be most toxic. The cotton plant also synthesizes both myrcene (68) and trans-*β*-ocimene (69). The reaction of 69 with 16 would result in the formation of heliocides H_1 (31) and H_4 (34) (Scheme 1). Heliocides H_2 (32) and H_3 (33) can be regarded as resulting from the reaction of 16 and 68 and these were found to be less toxic than heliocided H_1 (31) and H_4 (34) and more toxic than quinines 16 and 17 [69-70]. Similarly, 68 and 69 on reaction with 17 will lead to the formation of heliocides B_2 (36) and B_3 (37), and B_1 (35) and B_4 (38), respectively. The reaction of 16 and 17 with myrcene (68) and trans-*β*-ocimene (69) *in vivo* is not region-specific since the isomers H_1 and H_4, B_1 and B_4, H_2 and H_3, B_2 and B_3 were found to be in a fixed ratio. Thus, a variety of cotton plants that could produce a larger quantity of trans-*β*-ocimene (69) would be desirable because this would increase the concentration of heliocides H_1 (31) and H_4 (34) and decrease the concentration of the quinones. Susceptible normally glanded varieties also contain heliocides H_1, H_2, H_3 and H_4, hemigossypolone and gossypol, but the concentrations of heliocides H_1 and H_4 were found to be three times lesser than the glanded resistant varieties. The glandless varieties did not contain the terpenoid aldehydes and they were found to be highly susceptible to *Heliothis* complex and other insects [71].

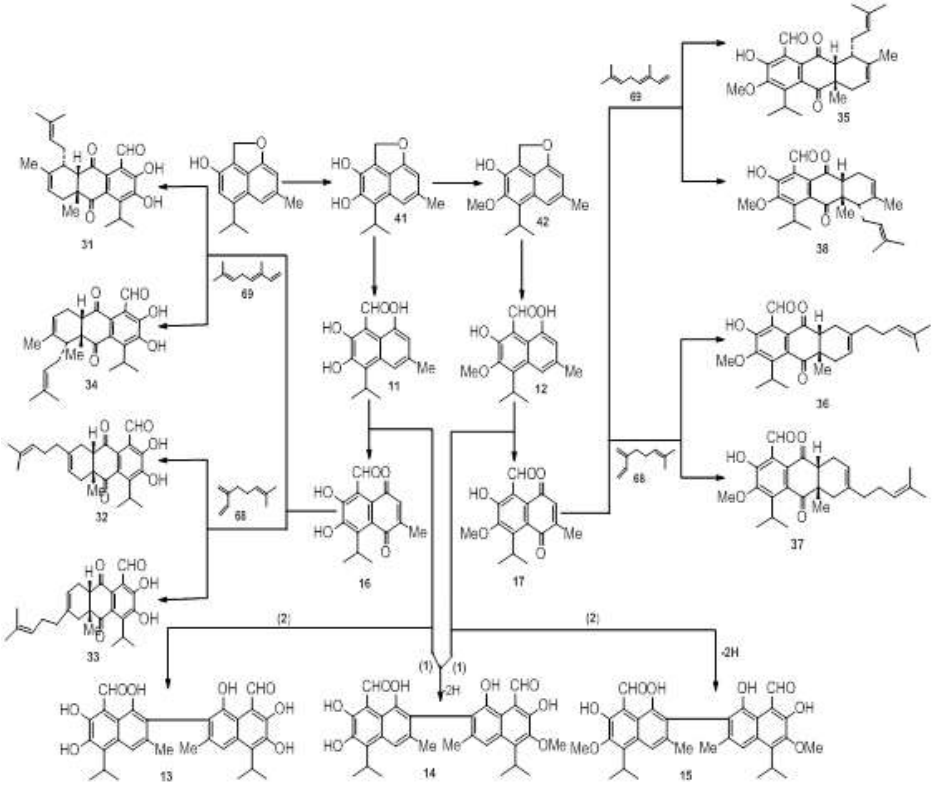
Lacinilene C 7-methyl ether (8) has been implicated as a causative of byssinosis [9]. The toxicity and hemodynamic and physiological effects of mansonones extracted from the bark of M. *altissima* was studies in rats and guinea pigs [72]. Mansonone C (48) and mansonone F (51) showed fungitoxic activity [73]. Mansonone C (48) was also found to be a powerful allergen [74].

Biosynthesis of cadalene derivatives

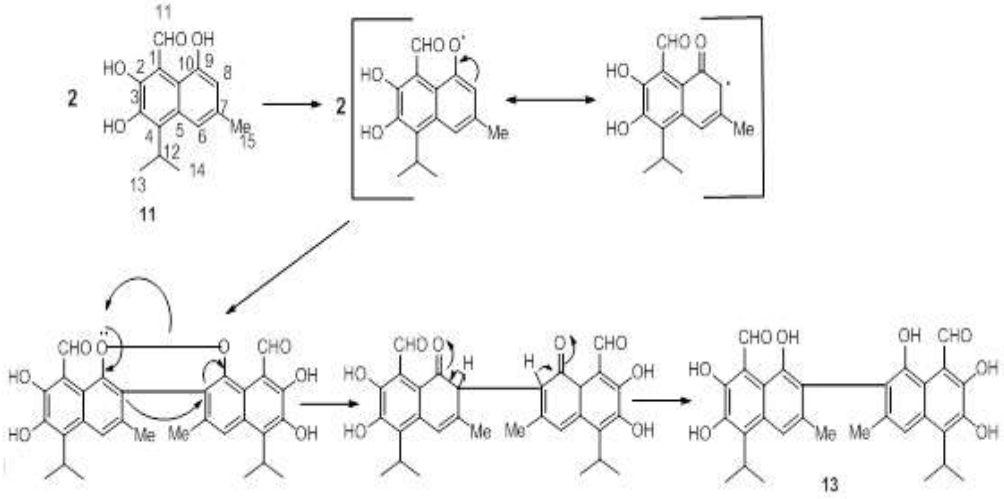
Probable pathways for the biosynthesis of cadalene derivatives have been proposed [75] and Heinstein et al., [76,77], have shown that gossypol is biosynthesized by the isoprenoid pathway. They isolated an enzyme system from the homogenates of cotton roots that stereo-specifically incorporated six molecules of mevalonate-2-^{14}C in each molecule of gossypol. The biosynthesis involved a specific cyclization of *cis*, *cis*-farnesyl pyrophosphate and is considered as a biosynthetic precursor to desoxyhemigossypol (41). Enzymatic reactions appear to be involved in the formation of desoxy-6-*O*-methylhemigossypol (42) and desoxyhemigossypol (41) and the oxidation of hemigossypol (11) or 6-O-methylhemigossypol (12) to hemigossypolone (16) or hemigossypolone-6-methyl ether (17), respectively. Desoxyhemigossypol (41) and desoxy-6-O-methylhemigossypol (42) spontaneously oxidize to hemigossypol (11) and 6-O-methylhemigossypol (12) in the presence of air. Veech et al. [42], showed that the enzyme horseradish peroxidase catalyses the coupling of hemigossypol to form gossypol. Myrcene (68) and trans-*β*-ocimene (69) react with hemigossypolone (16) and hemigossypolone-6-methyl ether (17) at room temperature without catalyst to form heliocides H_1, H_2, H_3, H_4, B_1, B_2, B_3 and B_4 (Scheme 1). Thus an enzyme may not be required for the formation of these latter compounds.

Akhila and Rani [78] have proposed a hypothetical scheme (Scheme 2) for the conversion of hemigossypol to gossypol by oxidative dimerization in the flowering tips of *T. populnea*. Two molecules of hemigossypol (11) have been shown to combine via free radical formation at C-8 or oxygen attached to C-9. Some tracer experiments were tried using [2-3H2] mevalonic acid which would label C-2, C-8 and C-14 of gossypol. Being involved in dimerization step, C-8 is crucial, but no conclusive evidence could be obtained because of the highly labile nature of the C-9 hydroxy proton.

It has been suggested that hibiscoquinones are derived from hibiscones C (60) and D (61), the two oxygen atoms which eventually appear in the quinine carbonyls being introduced at an early stage after (or before) the formation of carbon skeleton from farnesyl pyrophosphate. In principle, the mansonones in *H. tiliaceus* roots could be derived by a similar pathway. The mansonones generally co-occur with 7-hydroxycadalene (2) and other naphthols which could obviously be the quinine is not oxygenated unlike in the cotton terpenoids [52].



Scheme 1: Probable pathways for the biosynthesis of cadalene derivatives



Scheme 2: Hypothetical scheme for the conversion of hemigossypol to gossypol by oxidative dimerization

CONCLUSION

This review of literature including phytochemical, biological activity and biosynthetic path way investigations on naturally occurring compounds of cadalene type sesquiterpenoids from malvaceae family has covered 69 compounds. This review will help researchers and scientists in locating the detailed information and address the continuous development in the phytochemistry and the therapeutic applications.

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