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Review

Terpenoids in *Buddleja*: relevance to chemosystematics, chemical ecology and biological activity

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Dedicated to the memory of Professor Jeffrey B. Harborne

Abstract

The terpenoids reported from *Buddleja* species are described. The antifungal activity of chloroform extracts of *B. cordata* and *B. davidii* stembark against the soil fungi *Fusarium culmorum* and *Sordari fimicola* is reported, with buddledin A shown to be the major compound responsible. The terpenoids present support the view that the Buddlejaceae should be classified in a taxon with Scrophulariaceae rather than Loganiaceae. Ecological aspects of the terpenoids are considered in relation to insects and soil fungi and the role of terpenoids in the chemical basis of the use of *Buddleja* in traditional medicine is also discussed, especially with regard to their anti-inflammatory properties.

Keywords: *Buddleja*; Buddlejaceae; Terpenoids; Chemotaxonomy; Biological activity; Antifungal compounds; Biochemical ecology

Contents

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1. Introduction

The genus *Buddleja* has been the subject of a variety of investigations related to its chemistry in recent years. Taxonomically, it is placed either within the Loganiaceae or, as the major genus, within the Buddlejaceae, both of which are placed within the Tubiflorae. The genus is found in the temperate and drier subtropical regions of Asia, southern and eastern Africa and most of America south of the south-western states of the USA. Several species have been introduced as ornamental plants in parks and gardens in Europe and Australasia, because of their flowers and ability to attract butterflies, and one species, *B. davidii* Franch., has become extensively naturalised. There are about 100 species, most of which occur as bushes or small trees.

The relatively minor role of *Buddleja* species in traditional medicine has been reviewed (Houghton, 1984). These uses have prompted much, but not all, of the chemical investigations reported in recent years. Several types of chemical compound have been isolated, including flavonoids and other shikimate-derived compounds, such as the phenylethanoid glycosides typified by verbascoside. These, together with the monoterpene iridoids, are the compounds commonly associated with the Tubiflorae and could be predicted to be present. However, the genus has been found to produce a variety of less predictable terpenoids and their properties are the subject of this paper.

2. Terpenoids isolated from *Buddleja*

2.1. Monoterpenes

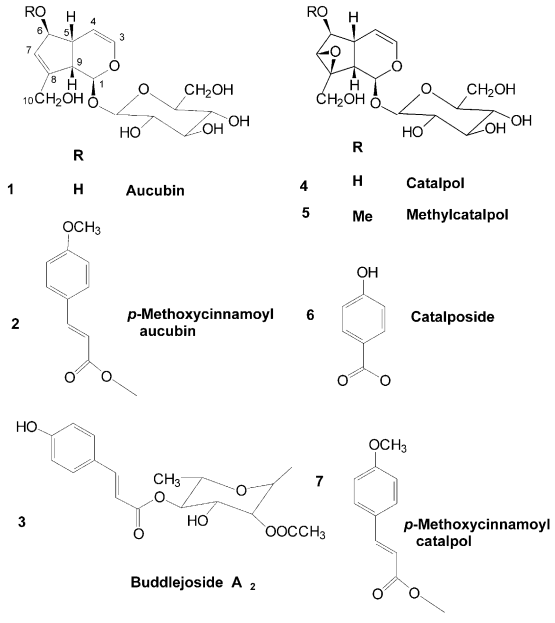
The major monoterpenes present, especially in the leaves and young stems of the plant, are iridoids consisting of a 9 carbon skeleton with an ester or glycosidal link at C-6. Aucubin derivatives reported include aucubin itself **1** (Trim and Hill, 1952) and conjugates with shikimate-derived moieties **2** (Houghton and Hikino, 1989) and **3** (Miyase et al., 1991). The largest group of iridoids reported contain catalpol **4** as the iridoid portion. Catalpol **4** itself, together with its methoxy, benzoyl and *p*-methoxycinnamoyl analogues **5**, **6**, **7** have been reported from *B. globosa* Lam. (Duff et al., 1965; Houghton and Hikino, 1989). The third type of iridoid compound contains the ajugol skeleton, where the C7–C8 bond is saturated and C8 is substituted with a methyl and hydroxyl group, and three such iridoids **8**–**10** have been reported, so far only from aerial parts of *B. japonica* Hemsl. (Miyase et al., 1991). From the same species a series of catalpol derivatives **11**–**24** has been isolated which consist of acylated rhamnose and glucose substituents at C-6. Congeners of ajugol and neolignans **25**–**27** have been reported from the roots of *B. davidii* Franch. (Yamamoto et al., 1993).

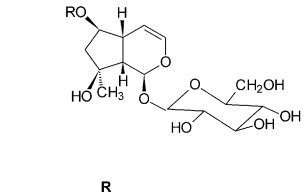
An extensive survey for iridoids on *Buddleja* species has not been carried out but aucubin **1** has been detected in several species, mainly in the aerial parts (Trim and Hill, 1952; Foucaud, 1954; Chaslot, 1955; Houghton et al., 1993).

The flowers of some species have a distinctive and quite strong odour and it is likely that this is due to volatile compounds which may well be non-glycosylated monoterpenes. However, no studies have been carried out on the chemical constitution of the flower volatiles, in spite of their possible insect attractant properties.

2.2. Sesquiterpenes

Sesquiterpenes have been reported from the roots and bark of some *Buddleja* species. The first reported were a





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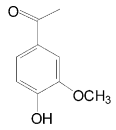
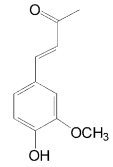
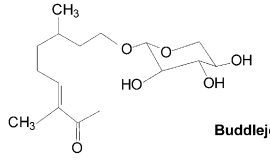


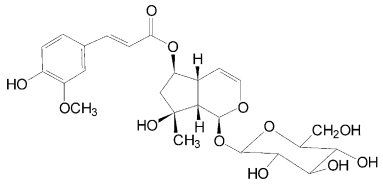
8 Vanillylajugol



9 Feruloylajugol



10 Buddlejoside A_1



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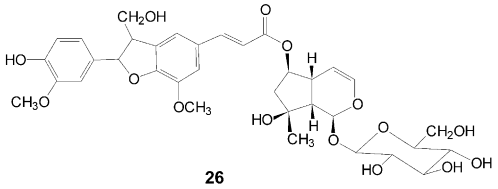

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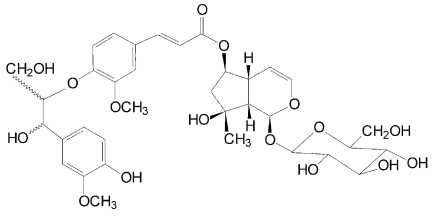
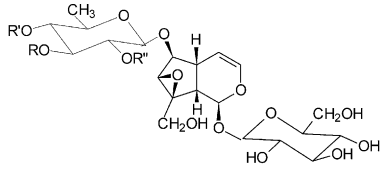


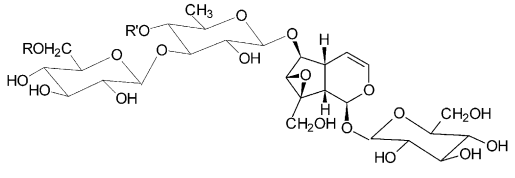
27

series of caryophyllane compounds known as the buddledins A–E **28**–**32** from the roots of *B. davidii* from Japan (Yoshida et al., 1978a,b). Buddledins A and B **28**, **29** have been reported from *B. globosa* (Mensah et al., 2000) and *B. madagascarensis*. Dehydrobuddledin A **33** was isolated from roots of *B. globosa,* in addition to three sesquiterpenes having a humulene skeleton. One of these was the known compound zerumbone **34**, but the other two were novel and were named buddledones A and B **35**, **36** (Liao et al., 1999).

A different sesquiterpene skeleton is found in two compounds **37**, **38** which were isolated from *B. cordata* H.B.K. and *B. sessiliflora* Kunth. (Devivar et al., 1995, 1996).

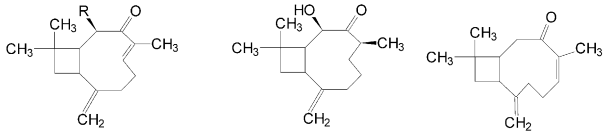


		R	R'	R"
11	Buddlejoside A_3	H	*t*-*p*-MeOCin	Ac
12	Buddlejoside A_4	Ac	*t*-*p*-MeOCin	H
13	Buddlejoside A_5	*t*-*p*-MeOCin	H	Ac
14	Buddlejoside A_6	H	*c*-*p*-MeOCin	Ac
15	Buddlejoside A_7	Ac	*c*-*p*-MeOCin	H
16	Buddlejoside A_8	H	*t*-diMeOCin	H
17	Buddlejoside A_9	H	*t*-diMeOCin	Ac
18	Buddlejoside A_{10}	Ac	*t*-diMeOCin	H
19	Buddlejoside A_{11}	Ac	*c*-diMeOCin	H
20	Buddlejoside A_{12}	Ac	*t*-Fer	H



		R	R'
21	Buddlejoside A_{13}	*t*-Caff	*t*-*p*-MeOCin
22	Buddlejoside A_{14}	*t*-Fer *	*t*-*p*-MeOCin*
23	Buddlejoside A_{15}	*t*- Fer*	*t*-*p*-Coum*
24	Buddlejoside A_{16}	*t*-Caff	*c*-*p*-MeOCin

*=Interchangeable.

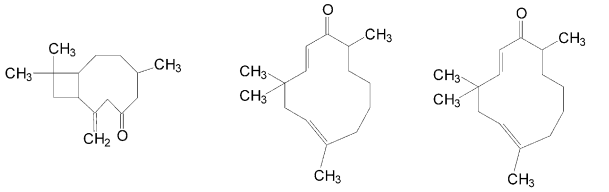


R

28 OH Buddledin A
29 H Buddledin B
30 $OOCCH_3$ Buddledin C

31 Dihydrobuddledin A

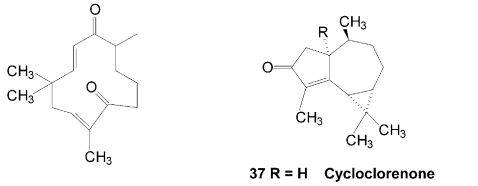
32 Buddledin D



33 Buddledin E

34 Zerumbone

35 Buddledone A

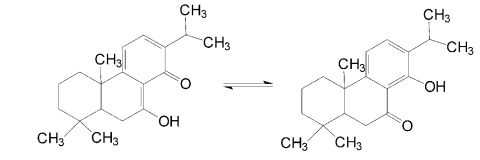


36 Buddledone B

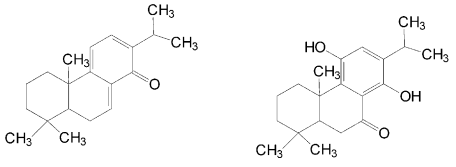
37 R = H Cyclocloronone
38 R = OH 1- Hydroxycyclocloronone

2.3. Diterpenes

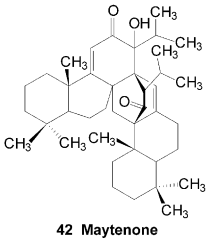
An abietane diterpene named buddlejone **39** was first detected in the rootbark of *B. albiflora* Hemsl. (Houghton et al., 1996). This was the first report of this type of compound in the genus and, indeed, in the Loganiaceae. It has since been isolated from the roots of *B. globosa* together with its deoxyanalogue **40** (Mensah et al., 2000) and 11,14-dihydroxy-8,11,13-abietatriene-7-one **41** from *B. yunanensis* bark (Liao et al., 1999). Maytenone **42**, which could be envisaged as a *bis* compound comprising two buddlejone-related moieties was also isolated from *B. globosa* roots and stembark (Mensah et al., 2000). The flowers of *B. officinalis* Maxim. have been shown to contain appreciable amounts of another type of diterpene, the non-cyclic crocetin-gentiobiose ester **43** (Liao et al., 1999). The diester has also been reported and is used as a yellow colourant in foods (Aoki et al., 2001). These esters, which are also found in the flowers of other species such as *Crocus* spp. are bright yellow and are presumably the major compounds responsible for the intense yellow colour found as a spot at the base of the inner surface of the corollar tube in the flowers of *Buddleja* species.



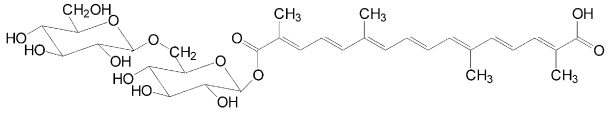
39 Buddlejone



40 Deoxybuddlejone **41** 11,14-Dihydroxy-8,11,13-abietatrien-7-one



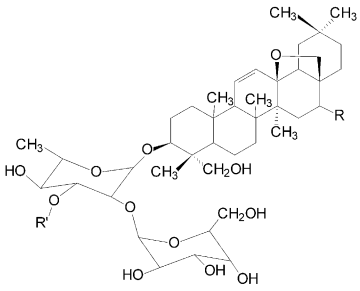
42 Maytenone



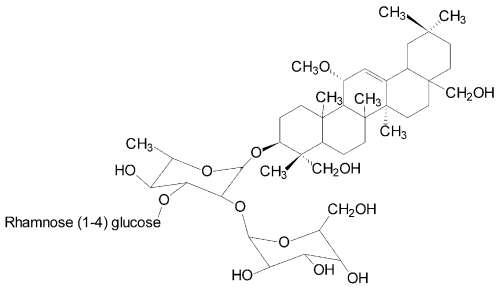
43 Crocetin monogentiobiose ester

2.4. Triterpenoids

The presence of saponins in the leaves of *Buddleja* species had been suspected for some time because of the use of the leaves for cleansing, washing and as fish poisons (Houghton, 1984). The first compounds were not isolated however until fairly recently when four compounds being glycosides of saikosaponin A **44**, were isolated from the aerial parts of *B. japonica* Hemsl. (Yamamoto et al., 1991). These compounds were named buddlejasaponins I–IV **45**–**48**. Buddlejasaponin I **45** has also been isolated from the leaves of *B. madagascariensis* Lam. (Emam et al., 1997). Two related compounds mimengoside A **49** and mimengoside B **50** were isolated from the flowers of *B. officinalis* Maxim., known as 'Mi Meng Hua' in Chinese Traditional Medicine (Ding et al., 1992).



	R	R'	
44	OH	H	Saikosaponin A
45	OH	Rhamnose (1- 4) glucose	Buddlejasaponin 1
46	OH	Xylose (1- 4) glucose	Buddlejasaponin 2
47	OH	Xylose	Buddlejasaponin 3
48	OH	Glucose	Buddlejasaponin 4
49	H	Rhamnose (1- 4) glucose	Mimengoside A

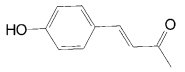
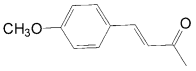
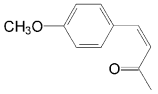
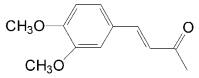
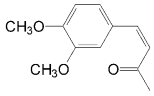
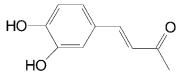
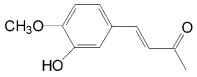


50 Mimengoside B

3. Results and discussion

3.1. Antifungal activity of Buddleja extracts against soil fungi

The results of the antifungal testing against the four fungi are shown in Table 1. Only the extracts of *B. davidii* and *B. cordata* showed appreciable activity and TLC examination revealed that only these two species gave a zone corresponding to reference buddledin A. The bioautography plate showed that this was the only zone that gave inhibition of fungal growth. Confirmation that this zone was, in fact, buddledin A **28**, was provided by the identical chromatographic and spectral data of the compound isolated by prep TLC with literature values (Yoshida et al., 1978a; Mensah et al., 2000) and the authentic sample. This result agrees with

Ac	
t-p-Coum	
t-p-MeOCin	
c-p-MeOCin	
t-diMeOCin	
c-diMeOCin	
t-Caff	
t-Fer	

earlier investigations which found buddledin A **28** to be the most active antifungal compound in *B. globosa* bark (Mensah et al., 2000).

3.2. Chemosystematic aspects of the terpenoids present

Buddleja is the major genus of the Buddlejaceae. This taxon is regarded as a separate family by most modern taxonomists although earlier classifications by Bentham and Hooker and Engler included it within the Loganiaceae (Brummit, 1992). Both of these authors recognised similarities which placed the family within the group containing Gentianaceae, an affinity also noted by Thorne and Young in their systems. Dahlgren, Takhtajan and Cronquist included *Buddleja* within the Scrophulariales whilst Melchior included the Buddlejaceae within the Solaninae which contained the Scrophulariaceae.

Differences in the morphology of the pollen and the trichomes has been previously noted as supporting evidence for the separation of *Buddleja* from the other tribes of the Loganiaceae (Bisset et al., 1980). The depth of chemical knowledge which now exists, particularly regarding the iridoids present, supports this distinction. Iridoids with the 9 carbon skeleton only have been isolated from *Buddleja* whereas the 10 carbon iridoid loganin is characteristic of the Loganiaceae. A common feature of the *Buddleja* iridoids is the degree of esterification with phenylpropanoid residues, either directly at C-6 of the iridoid or at positions on attached sugars. Such iridoids have not been widely reported from other genera and so appear to be a distinguishing feature of the genus *Buddleja*.

Another feature of the iridoids found in *Buddleja* is that three different structures co-exist i.e. those of aucubin **1**, catalpol **4** and ajugol. Catalpol **4** is very characteristic of some genera of the Bignoniaceae whilst ajugol derivatives are more often associated with the Lamiaceae. The latter affinity between *Buddleja* and the Lamiaceae is also reflected in the presence of the partially-aromatised and oxidised abietane diterpenes since these also occur in some Lamiaceous genera, notably *Salvia,* particularly *S. miltiorrhiza, Coleus* and *Plectranthus* (Hanson, 1991).

Less evidence of relationships with other families can be gained from the triterpenoids present. The mimengoside type has also been found in *Scrophularia* (Emam et al., 1997), and the Scrophulariaceae are also known as a source of aucubin iridoids, thus underlining some taxonomic affinity of *Buddleja* with this family, as noted by Dahlgren, Takhtajan, Cronquist and Melchior on morphological grounds.

The chemotaxonomic evidence therefore strongly supports the exclusion of *Buddleja* from the Loganiaceae, a position recently consolidated by studies involving nucleotide sequence data from plastids (Backlund et al., 2000). The evidence points to the Buddlejaceae being grouped in a taxon with Scrophulariaceae and Lamiaceae.

Table 1
Antifungal activities (MIC μg ml^{-1}) of chloroform extracts of stembark of four species of *Buddleja* and for isolated buddledin A **28**

Fungal species	Miconazole[a] 2.4 μg/ml (~5 μM)	Extract				Buddledin A **28**
		B. asiatica	*B. cordata*	*B. davidii*	*B. skutchii*	
Epidermophyton flocossum	–[b]	>1000	62.5	62.5	>1000	12.5
Trichyophton interdigitale	–	>1000	62.5	62.5	>1000	12.5
Fusarium culmorum	–	>1000	62.5	62.5	>1000	12.5
Sordari fimicola	–	>1000	62.5	62.5	>1000	12.5

[a] Positive control.
[b] – no growth observed.

3.3. The biological activity of the terpenoids

3.3.1. Iridoids

Little has been reported on the biological activity of iridoids isolated specifically from *Buddleja* species although aucubin **1** and catalpol **4**, isolated from other plant species, have been subject to some investigations. The hydrolysis products, formed in situ in the presence of glycosidases such as emulsin, have been shown to possess appreciable antibacterial activity, although the glycosides themselves are not active (Rombout and Links, 1956).

In vivo experiments using mice showed that 1 mg aucubin **1** applied to the ear of a mouse decreased by 80% the oedema induced by 12-*O*-tetradecanoylphorbol acetate (Recio et al., 1994). Catalpol **4** was less active, giving only a 20% reduction at the same dose. A study on the traditional use of *Buddleja* extracts for liver disease showed that aucubin **1** had no protective effect on challenged hepatocytes but its *p*-methoxycinnamoyl derivative **2** showed a weak effect, reducing the amount of glutamate-pyruvate transaminase released by 10%. Catalpol **4** and the corresponding *p*-methoxycinnamoyl derivative **7** both gave over 25% reduction at 0.1 mg ml^{-1} concentration (Houghton and Hikino, 1989). More recently aucubin **1** has been shown to confer a protective effect in mice challenged with carbon tetrachloride and α-amanitin, both of which induce hepatic damage (Chang, 1998). The same study showed that aucubin **1** also prevented a reduction in RNA biosynthesis induced by α-amanitin and suppressed hepatitis B viral DNA replication in vitro. The conflicting results for aucubin **1** activity between the in vitro and in vivo experiments might indicate some biotransformation of aucubin **1** to an active substance by enzyme systems in the body.

Catalposide **6** has recently been shown to inhibit inducible nitric oxide synthesis in macrophages but no other reports for similar activity on any other iridoids found in *Buddleja* have been published (Oh et al., 2002).

3.3.2. Sesquiterpenes

Buddledins A–E **28**–**30**, **32**, **33** have been shown to be piscicidal (Yoshida et al., 1978a,b) and, more recently, buddledin A **28** and buddledin B **29** have been shown to be selectively active against various dermatophytic fungal species (Mensah et al., 2000). **28** and **29** showed a minimum inhibitory concentration (MIC) of 51 μM (12 μg ml^{-1}) against *Epidermophyton floccosum, Trichophyton rubrum* and *Trichophyton interdigitale* but had no activity at 4250 μM (1 mg ml^{-1}) against the fungi *Aspergillus niger*, *Penicillium notatum*, *Scopulariopsis brevicaulis*, *Scytalidium dimidiatum* and the yeasts *Saccharomyces cerevisiae* and *Candida albicans*. Work described below shows that buddledin A **28** is active also against the soil fungi *Fusarium culmorum* and *Sordari fimicola*.

Investigation into the chemical basis for traditional uses of *Buddleja* species against conditions related to inflammation showed that buddledins A–C **28**–**30** displayed inhibitory effects on both cycloxygenase (COX) and 5-lipoxygenase (5-LOX) activity under in vitro conditions. Buddledin A **28** was the most active compound with IC_{50} of 13.7 μM against COX and 50.4 μM against 5-LOX (Liao et al., 1999). The dihydro analogue of buddledin A **31** showed no activity against either enzyme but buddledins D, E **32**, **33** were not tested.

3.3.3. Diterpenes

Buddlejone **39**, deoxybuddlejone **40** and maytenone **42** were also studied for their antifungal activity and displayed a similar profile of activity against dermatophytes although they were much less active than the sesquiterpenes (Mensah et al., 2000). The activities of **39** and **40** were identical with MIC of 2500 μM against the susceptible fungi whilst maytenone was slightly more active with a MIC of 625 μM against all three fungal species.

11,14-Dihydroxy-8,11,13-abietatriene-7-one **41** gave appreciable inhibition of both COX and 5-LOX ($50.0 \pm 15.1\%$ and $27.1 \pm 13.8\%$ respectively at 50 μg ml^{-1} respectively) but the crocetin derivative **44** showed some activity against COX, but not 5-LOX, giving 85% inhibition at 50 μg ml^{-1} (Liao et al., 1999).

3.3.4. Triterpenoids

The saponins reported from *Buddleja* are closely related to the saikosaponins from *Bupleurum* species, which have been shown to have anti-inflammatory activity (Chang and But, 1987). However the saponins from *Buddleja* have not been tested for this activity in any way. Buddlejasaponin 1 **45** has been shown to be molluscicidal against *Biomphalaria alexandrina,* giving 100% kill after 24 h at 10 μg ml^{-1} (Emam et al., 1997). The same compound had a reasonably strong activity against the protozoal species *Trichomonas vaginalis* and *Leishmania infantum* (lethal doses 20 μg ml^{-1} and 40 μg ml^{-1} respectively) and displayed a general antifungal activity with MIC 100 μg ml^{-1} against nine fungal species.

3.4. Aspects of biological activity related to the medicinal use of Buddleja species

The chemical basis of the traditional uses of *Buddleja* species has been discussed previously (Houghton, 1984; Houghton and Mensah, 1999). The major use of *Buddleja* aerial parts is as an applied compress to aid wound healing. Wound healing has a variety of aspects associated with it such as the stimulation of fibroblast growth, anti-inflammatory, antioxidant and anti-

microbial effects. The iridoids, notably aucubin **1**, have been shown to have anti-inflammatory properties and would be present in such a compress. Other anti-inflammatory compounds, especially flavonoids, are found in leaves of *Buddleja* species (Liao et al., 1999) so any effect is probably due to several types of compound and the terpenoids play only a relatively small part. Antioxidant effects have also been noted but these appear to be due to the phenolics rather than the terpenoids present (Mensah et al., 2001). There appears to be no traditional exploitation of the antifungal sesquiterpenes present in the roots and stembark. It might be thought that the use of Buddleja against skin conditions could include the eradication of dermatophytic fungi but only extracts from the leaves, which do not appear to contain the sesquiterpenes, are traditionally used and would not therefore be expected to display this activity.

Another aspect of anti-inflammatory activity is demonstrated in the Chinese drug 'Mi Meng Hua', the flowers of *B. officinalis*, which is used to treat sore eye conditions. The flowers contain appreciable amounts of the crocetin monogentiobiose ester **43** which has been shown to inhibit COX and thereby reduces the production of prostaglandins which are important in pain and inflammatory processes (Liao et al., 1999).

3.5. Ecological aspects of the terpenoids

In spite of the obvious attraction of the flowers of *B. davidii* for Lepidotera and of *B. globosa* for honeybees, there are no reports of the chemical basis for this. Several species of *Buddleja* emit a fairly strong odour, especially from the flowers, but the interaction with this and insect behaviour has not been investigated. The high levels of crocetin esters, visually apparent as a bright yellow spot, at the base of the floral tubes may well have a dimension of pollinator attraction but this hypothesis has not been tested.

The iridoids catalpol **4** and aucubin **1** are known to be feeding attractants and feeding stimulants for some Lepidotera and have been shown to be stored in the larvae and pupae of *Euphydras cynthia* feeding on *Plantago* species, possibly to act as a feeding deterrent for birds (Bowers and Puttick, 1986). No studies have been published on similar work as far as *Buddleja* is concerned. The sesquiterpenes present in the roots and stembark may have an ecological role. A fairly strong odour has been noted when the roots of *Buddleja* species are dug up, indicating the release of volatile substances into the air spaces in the soil (Houghton and Mensah, 1999). A similar release from aerial parts of plants is often associated with attraction or repellent effects on beneficial or hostile organisms respectively. The activity of some of the sesquiterpenes, notably buddledin A **28**, against the two species of soil fungi tested could indicate a role for these compounds in protecting roots, and stembark, against fungal infection. It should be noted that more work needs to be done to test the validity of this hypothesis. It can be seen, however, that there is some evidence that the lower molecular weight terpenoids play a role in interactions between the plants that produce them and fungi and insects.

4. Experimental

4.1. Plant material

Stem bark of *B. globosa* was obtained in May 1997 from a garden specimen in southwest London. The plant was authenticated by one of us (PJH) and a voucher specimen Bg 004 is deposited in the herbarium of the Department of Pharmacy, King's College, London. A sample of the bark is also deposited as sample Bud 2 1M1 in the museum of the Department of Pharmacy, King's College, London.

4.2. Antifungal testing on extracts and isolated buddledin A

Antifungal assay techniques were as described previously (Mensah et al., 2000). The soil fungi *F. culmorum* and *S. fimicola* cultures were obtained from the Biological Sciences Group, King's College London. The agar dilution method to determine MIC was chosen for preliminary testing against four fungi (*F. culmorum, S. fimicola, T. interdigitale* and *E. floccosum*) of the chloroform extracts of the stembark of four *Buddleja* species lodged in the museum of the Pharmacy Department, King College London, i.e. *B. asiatica* Lour. voucher number Bu1 3 M1, *B. cordata* H.B.K. voucher number Bu 1 1M1, *B. davidii* Franch. voucher number Bud 4 M1 and *B. skutchii* Morton voucher number Bu1 5 M1. The experiment was repeated three times and results are presented in Table 1. Agar overlay TLC (Silica gel/hexane: EtOAc 85:15 with applications of 10 μl of the chloroform extracts of the four barks and 10 μg buddledin A **28** as reference substance was carried out. Two identical plates were developed, one of which was subjected to bioautography using agar inoculated with the spores of *Fusarium fimicola*. Plates were incubated at 25° and examined for growth after 5 and 7 days.

The other TLC plate was visualised using anisaldehyde/sulphuric acid reagent and heating at 105° for 10 min. A compound showing an inhibitory zone in the extracts of *B. cordata* and *B. davidii* was isolated from these extracts by prep TLC (Silica gel PF_{254} 1 mm/hexane:

EtOAc 85:15) and mass spectra, ^{1}H NMR and ^{13}C NMR spectra obtained.

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