REVIEW

Bioactive constituents form *Buddleja* species

Shafiullah Khan[1, 3*], Hamid Ullah[2] and Liqun Zhang[3]
[1]Institute of Chemical Sciences, Gomal University, Dera Ismail Khan, KPK, Pakistan
[2]Department of Chemistry, Faculty of Arts & Basic Sciences, BUITEMS, Quetta, Pakistan
[3]State Key Laboratory of Organic-Inorganic Composites, Beijing University of Chemical Technology, Beijing, PR China

Abstract: Present review discuss the reported work on structures, origins and the potent biologically active natural products isolated from Genus *Buddleja*, which is known for having many important pharmacologically active substances. The Genus *Buddleja* have more than 100 species, many of them are distributed in Mediterranean and Asian regions. A very small number of common species of the Genus in majority of fruiting plants have been investigated for their biological potential. So for, isolation of about 153 or more new/novel chemical substances have been reported. Purposes of the review is to discuss the structurally established and pharmacologically significant natural substances from wide variety of different species of this genus. Traditionally, species of the genus are reported to be used for healing, treatment of liver diseases, bronchial complaints, preventing several other diseases by exhibiting diuretic properties, sedative functions, analgesic potential, antirheumatic actions, antimicrobial activities, anti hyperglycemic functions and antioxidant properties. In this review we will describe recently established medicinal chemistry aspects and complete list of phytoconstituents as well as their sources and reference.

Keywords: *Buddleja,* Chemical constituents, structures, antimicrobial, antispasmodic, enzymeinhibitory and antioxidant activities.

INTRODUCTION

Genus *Buddleja* related to the family Scrophulariaceae that includes hundrade species, distributed worldwide from Southern USA to Chile, Africa and Asia but are lacking as natives from European countries. It represent only 04 species in Pakistan i.e., *B. asiatica Lour*, *B. crispa* Benth, *B. davidii* Franch and *B. lindleyana* (Abdullah 1974). Plants of Genus *Buddleja* are considered to be active against various diseases. The ethno-pharmacological studies of *Buddleja* species summarize main functions such as healing of wounds, against liver disfunctions, bronchial complaints, displaying diuretic actions, antioxidant properties, sedative, antirheumatic and in some cases analgesic functions (Ahmad *et al*., 2009; Houghton and Mensah, 1999). Various *Buddleja* species *have uses against* skin problems, ulcer, clustered nebulae, conjunctival congestion and other health problems. Plants of the genus have shown analgesic, anti-inflammatory, antimicrobial, anticataratic, antipyretic, antihepatotoxic, hypoglycaemic, neuroprotective, molluscicidal and amoebicidal activities (Hegnauer and Koolman, 1978; Ahmand *et al*., 1988: El-Domiaty *et al*., 2009). *Buddleja* species have also been used against cancers (Hu *et al*., 2001). Plant of *B. saligna* in whole is used to treat colds, and display purgatives functions (Hutchings A *et al*., 1996). The *B.* globosa leaves are used indigenously by *Mapuche* in wounds healing and ulcer (Murillo 1989). *B. globose* leaves are effective in wounds curing, thus offering antioxidant functions (Mensah *et al*., 2001). *B. officinalis'* flowers and flower buds have uses against Hepatitis (Lee S., *et al* 2008), as antispasmodic, and for treatment of cholagogue, and several ophthalmic problems (Duke and Ayensu, 1985). *B.madagascariensis'* leaves have traditional uses against asthma, curing coughs, bronchitis, and as substitute to soap (Houghton 1984). *B. asiatica* parts have been used as Chinese traditional medicines to cure fever, ache, diarrhea, and articular rheumatism (Jiangsu 1977). Some of their compounds display antiprliferative activity (Wu *et al*., 2012). *Buddleja* species comprises distinctive chemical features, bearing flowers with fused petals (Jiangsu 1977). Literature survey reveals that many constituents have been isolated from genus *Buddleja* that includes iridoids, lignin irdidoids. Also lignans, phenylethanoid, phenylpropanoid, terpenoids (sesquiterpen, di and tri terpens along with their glycosides), neolignans, flavonoids, steroids, aromatic esters, phenolic fattyacid esters and several saponins has been reported (Joshi 2012). Many of these substances display diverse biopotentials. In this review, we summaries all the compounds isolated from genus *Buddleja* reference to their biopotential published in last few years (table 1).

Compounds from buddleja species
Terpenoids
Monoterpenoids
Iridoids along with their glycosidic compounds bearing acubin, and catalpol skeletons as well as ajugol structure 1 to 32 are isolated from different Buddleja's species i.e. *B.*

**Corresponding author:* e-mail: s.khan@gu.edu.pk

globosa, B. japonica, B. asiatica, B. Japonica, and *B. Davidi* (Zhang *et al.*, 2010; Arciniegas *et al.*, 1997).

Sesquiterpenes

Composed 33-46 that have caryophyllane, humulene, benzofuran skeleton and others belongs to *sesquiterpenes* group are achieved from *B. davidii*, *B. globosa*, *B. sessiliflora*, *B. cordata*, *B. crispa* and *B. Lindleyana (*Yoshida *et al*., 1978; Yoshida *et al.*, 2011; Devivar *et al*., 1995; Ahmad *et al*., 2004; Lu *et al*., 2004; Houghton *et al*., 1996).

Diterpenes

Compound 47 (a abietane diterpene) has been isolated from *B. albiflora B. asiatica*, *B. globosa* and *B. yunanensis* bark (Mensah A *et al*., 2000; Yamamoto A *et al*., 1991) along with its deoxy analogues 48 and 49; (Yamamoto *et al*., 1993). Molecule 50 (Maytenone) bearing two buddlejone like moieties has also been isolated from *B. Globosa* (Yamamoto *et al*., 1991). *Lio et al* published compound 51 (a non-cyclic crocetin-gentiobiose ester) from the flowers of *B. officinalis* (Yamamoto *et al*., 1993) *maxim* and sesquiterpenes, buddlindeterpene C (52) has also been reported from *Buddleia lindleyana* (Houghton *et al*., 1996).

Triterpenes

From the leaves of *Buddleja* species, the presence of triterpene saponins had been assumed for some time since the leaves have been used for cleansing, washing purposes, and as fish poisons (Houghton 1984). Compound 53 (Saikosaponin A) and 04 oleanane kind of triterpenes 54-57 have been reported from *B. japonica* and *B. Madagascariensis* (Emam *et al*., 1997; Ding N *et al*., 1992). A range of saponines, mimangosides 58-64 and Songaroside A (66) had been isolated from flowers of *B. officinalis* Maxim including, known as "*Mi Meng Hua*" reported and use in Chinese medicine Traditionally (Guo *et al*., 2004; Liu *et al* 2008). Compounds 66-67, which are oleanane kind triterpenes, have also been published form *B. Asiatica* (Kapoor *et al*., 1982). Several analogues (68-72) of amyrin together with glutinol (73), Lupeol (74), and ursailc acid (75) have also been revealed from various *Buddleja* species (Abdullah 1974; Murillo 1989; Yamamoto *et al*., 1993; Devivar *et al*., 1995; Houghton 2003). Figs. 1- 6 show structure of the compounds 1-21, 22-29, 30-38, 39-58, 59-64, 65-84.

Flavonoids

The genus *Buddleja* contains many flavonoids and also glycosides. A set of Luteolin and its derived compounds 76-85 have been isolated from *B .officinalis, B. asiatica, B. globosa and B. Davidii* (Hu *et al*., 2001; Lee *et al*., 2009; Matsuda *et al*., 1995; Fan *et al*., 2008; Varma and Nobles 1968). Arciniegas *et al* (1997) have reported the flavonoids 86-88 from *B. Perviflora*, while 89, 90 and 91 were reported by Emam *et al* 39-40 form *B. madagascariensis*. Rutin also named as vitamin P or rutoside 92 which was isolated from the leaves of *B. Asiatica* (Raja *et al*., 2016) is well recognized for its nutraceutical effect (Ganeshpurkar *et al*., 2017).

Phenylethanoids

Many of the phenylethanoid compounds have also been reported from genus *Buddleja*. Compounds 94-99 were reported by *Lio and Houghton* form *B. Officinalis* (Yamamoto *et al*., 1993). Compound 100 (Angoroside) and compounds 102-110 have also been reported from roots of *B. Davidii* (Moussa and Balansard 1997; Ahmad and Sticher 1988), while 101 was reported from *B. Japonica* (Miyase *et al*., 1991). Recent reports revealed that the flowers of *B. Offficinalis* furnished compounds 111-113 Neobudofficide B (a phenylethanoid glycoside) has been isolated from *B. Officinalis* (Yamamoto *et al*., 1993; Li *et al.*, 1997). Acevedo and his collaborators, have characterized and identified mixture of 2[4'-hydroxyphenyl] derivatives of different fatty acid esters 114-123 by using extensive HPLC (Acevedo *et al*., 2000).

Phenylpropanoids

Liu et al isolated a range of phenylpropanoids asiatcide A-D (123-126) from *B. asiatica* (Gilani *et al*., 2009).

Lignans

lignans are also reported from *Buddleja* species, among which mostly are dimeric but some are trimeric congeners. *Houghton* isolated 127-132 (Buddlenol A-F) and compounds 133-134 from *B. davidii* stem (Liu *et al*., 2008; Houghton 1985).

Steroids

Glutinol 135 and Chondrillasterol 136 which are sterols have been isolated from *B. globosa* and *B. Asiatica* (Yamamoto *et al*., 1991) while the 137-140 sterols have been obtained repeatedly from genus *Buddleja* (Abdullah, 1974; Yamamoto *et al*., 1993; Hu *et al*., 2001; Ahmad *et al*., 2005). Among other substances, free sugar compounds, benzoic acids, fatty acid esters, several alkaloids and sphingolipids (141-154) are reported from the *Buddleja* species (Yamamoto *et al*., 1993; Yamamoto *et al*., 1991; Acevedo *et al*., 2000; Liu *et al*., 2008; Houghton, 1985; Ahmad *et al*., 2005; Ahmad *et al*., 2006; Ahmad *et al*., 2007; Bui *et al*., 2011). Figs. 7-9 show structure of the compounds 85-95, 96-102, 103-112 respectively.

Biological activity

Antimicrobial activities

The essential oil obtained from *B. asiatica* is known for potential antifungal actions against *Trichophyton rubrum*, *Trichoderma viride*, *Curvularia parasadii*, and *Aspargillus flavours* (Garg and Oswal 1981).

Table 1: Compounds isolated from the plants of the genus *Buddleja*.

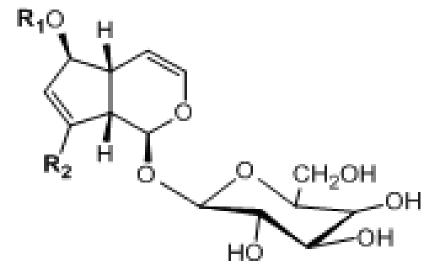
Compound	Name	Source
1	Acubin	*B. globosa*
2	*p*-methoxicinnamoyl acubine	*B. globosa*
3	Buddlejosid A_2	*B. japonica*
4	Buddlejosid A	*B. crispa*
5	Buddlejoside B	*B. crispa*
6	Buddlejoside C	*B. crispa*
7	Catalpol	*B. yunenesis*
8	Methyl-catalpol	*B. yunenesis*
9	Benzoyl Catalpol	*B.dividii*
10	*p*-Methoxycinnamoyl Catalpol	*B.dividii*
11	Dimethoxycinnamoyl Catalpol	*B.dividii*
12	Buddlejoside A_3	*B. japonica*
13	Buddlejoside A_4	*B. japonica*
14	Buddlejoside A_5	*B. japonica, B. crispa*
15	Buddlejoside A_6	*B. japonica*
16	Buddlejoside A_7	*B. japonica*
17	Buddlejoside A_8	*B. japonica*
18	Buddlejoside A_9	*B. japonica*
19	Buddlejoside A_{10}	*B. japonica*
20	Buddlejoside A_{11}	*B. japonica*
21	Buddlejoside A_{12}	*B. japonica*
22	Buddlejoside A_{13}	*B. japonica*
23	Buddlejoside A_{14}	*B. japonica*
24	Buddlejoside A_{15}	*B. japonica*
25	Buddlejoside A_{16}	*B. japonica*
26	6-vanillyajugol	*B. japonica*
27	6-feruloyl-ajugol	*B. japonica*
28	Buddlejoside A_1	*B. japonica*
29	Buddlin	*B. asiatica*
30	Neolignan 1	*B.devidi*
31	Neolignan 2	*B.devidi*
32	Neolignans 3	*B.devidi*
33	Buddledin A	*B. davidii*
34	Buddledin B	*B. davidii*
35	Buddledin C	*B. davidii*
36	Buddledin D	*B. davidii*
37	Buddledin E	*B. davidii*
38	Dihydroxybuddledin A	*B. globosa, B. asiatica*
39	Zerumbone	*B. globosa*
40	Buddledone A	*B. globosa*
41	Buddledone B	*B. globosa, B. asiatica*
42	Cycloclorinone	*B. cordata*
43	1-Hydroxycycloclorinone	*B. sessiliflora*
44	Buddlejone II	*B. crispa*
45	Buddlindeterpene A	*B. lindleyana*
46	Buddlindeterpene B	*B. lindleyana*
47	Buddlejone	*B. albiflora. B. globosa, B. asiatica*
48	Deoxy buddlejone	*B. globosa*
49	11,14-dihydroxy-8,11,13-abietatrien-7-one	*B. yunenesis*
50	Maytenone	*B. globosa*

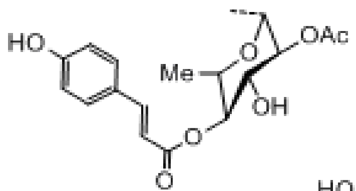
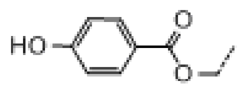
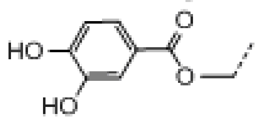
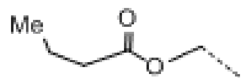
Continued…

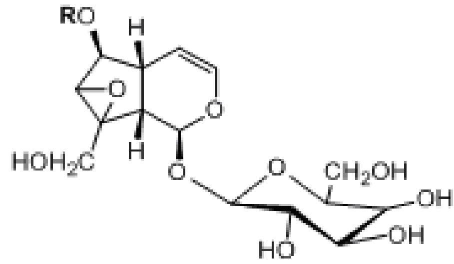
51	Crocetin-gentiobiose ester	*B. officinalis*
52	Buddlindeterpene C	*B. lindleyana*
53	saikosaponin A	*B. japonica*
54	Buddlejasaponin I	*B. japonica, B. madagascariensis*
55	Buddlejasaponin II	*B. japonica*
56	Buddlejasaponin III	*B. japonica*
57	Buddlejasaponin IV	*B. japonica*
58	Mimengoside A	*B. officinalis*
59	Mimengoside B	*B. officinalis*
60	Mimengoside C	*B. officinalis*
61	Mimengoside D	*B. officinalis*
62	Mimengoside E	*B. officinalis*
63	Mimengoside F	*B. officinalis*
64	Mimengoside G	*B. officinalis*
65	Songaroside A	*B. officinalis*
66	13,28-epoxy-23-dihydroxy-11-oleanene-3-one	*B. asiatica*
67	13,28-epoxy-21β,23-dihydroxy-11-oleanene-3-one	*B. asiatica*
68	11-Keto-β-amyrin	*B. madagascariensis*
69	α-Amyrin	*B. madagascariensis*
70	β-Amyrone	*B. officinalis*
71	β-Amyrin	*B. globosa*
72	β-Amyrin acetate	*B. globosa*
73	Glutinol	*B. globosa*
74	Lupeol	*B. globosa*
75	Ursalic acid	*B. asiatica*
76	Luteolin	*B. officinalis*
77	Luteolin glucopyranoside	*B. officinalis*
78	Apigenin	*B. officinalis*
79	Apigenin-7-*O*-glucoside	*B. globosa*
80	Acacetin	*B. officinalis*
81	Acacetin-7-*O*-rutenoside (Linarin)	*B. davidii. B. asiatica*
82	Quercitin	*B. davidii*
83	Diosmin	*B. asiatica*
84	Isorhoifolin	*B. officinalis*
85	6-Hydroxyluteolin	*B. globosa*
86	Eriodictyol	*B. perviflora*
87	Glucohesperetin	*B. perviflora*
88	Pyracanthoside	*B. perviflora*
89	Hesperetin	*B. madagascariensis*
90	Diosmetin	*B. madagascariensis*
91	Scutellarin 7-*O*-glucoside	*B. globosa, B. madagascariensis, B. asiatica*
92	Rutin	*B. asiatica*
93	Calceolarioside A	*B. officinalis*
94	Campneoside II	*B. officinalis*
95	Pliumoside	*B. officinalis*
96	Echinacoside	*B. officinalis*
97	Forsythoside B	*B. officinalis*
98	Angoroside A	*B. officinalis*
99	Angoroside C	*B. davidii*
100	Acetoside	*B. japonica, B. officinalis,*
101	Plantainoside C	*B. davidii*
102	Jionoside D	*B. davidii*
103	2-Acetylmartynoside	*B. davidii*

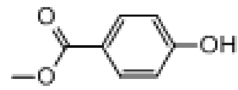
Continued…

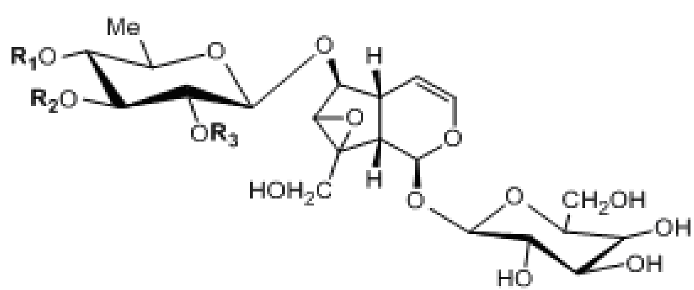
104	3-Acetylmartynoside	*B. davidii*
105	4-Acetylmartynoside	*B. davidii*
106	Martynoside	*B. davidii*
107	Isomartynoside	*B. davidii*
108	Leucosceptoside A	*B. davidii*
109	Leucosceptoside B	*B. davidii*
110	Phenylethyl glycoside	*B. officinalis*
111	Bioside	*B. officinalis*
112	Salidroside	*B. officinalis*
113	2[4′-hydroxyphenyl]-ethyl hexacosanoate	*B. cordata*
114	2[4′-hydroxyphenyl]-ethyl pentacosanoate	*B. cordata*
115	2[4′-hydroxyphenyl]-ethyl lignocerate	*B. cordata*
116	2[4′-hydroxyphenyl]-ethyl tricosanoate	*B. cordata*
117	2[4′-hydroxyphenyl]-ethyl behenate	*B. cordata*
118	2[4′-hydroxyphenyl]-ethyl arachidate	*B. cordata*
119	2[4′-hydroxyphenyl]-ethyl nonadecanoate	*B. cordata*
120	2[4′-hydroxyphenyl]-ethyl stearate	*B. cordata*
121	2[4′-hydroxyphenyl]-ethyl heptadecanoate	*B. cordata*
122	2[4′-hydroxyphenyl]-ethyl palmitate	*B. cordata*
123	Asiatiside A	*B. asiatica*
124	Asiatiside B	*B. asiatica*
125	Asiatiside C	*B. asiatica*
126	Asiatiside D	*B. asiatica*
127	Buddlenol A	*B. davidii*
128	Buddlenol B	*B. davidii*
129	Buddlenol C	*B. davidii*
130	Buddlenol D	*B. davidii*
131	Buddlenol E	*B. davidii*
132	Buddlenol F	*B. davidii*
133	Balanophonin	*B. davidii*
134	Syringaresinol	*B. davidii*
135	Glutinol	*B. globosa*
136	Chondrillasterol	*B. globosa*
137	β-Sitosterol	*B. yunenesis*
138	Stigmasterol	*B. madagascar*, *B. yunenesis*, *B. asiatica*
139	β-Sitosterol-*O*-glucoside	*B. asiatica*
140	(22*R*)-Stigmasta-7,9(11)-dien-22*α*-ol-3 *β*-*O*-*β*-D-galactopyranoside	*B. crispa*, *B. asiatcia*
141	Sucrose	*B. yunenesis*
142	Hexyl *p*-hydroxy-cinamate	*B. crispa*
143	Ferulic acid methyl ester	*B. globosa*
144	*p*-Coumeric acid methyl ester	*B. globosa*
145	3-(4-Acetoxy-phenyl)-acrylic acid 3-phenyl-propyl ester	*B. crispa*
146	Nonyl benzoate	*B. crispa*
147	Methyl β-orcinolcarboxylate	*B. cordata*
148	β-orcinolcarboxylate	*B. cordata*
149	Coniferaldehyde	*B. davidii*
150	Buddamin	*B. davidii*
151	Crispin A	*B. crispa*
152	Crispin B	*B. crispa*
153	BDL-H3 (Aryl ester)	*B. crispa*
154	Methylscutelloside	*B. officinalis*



	R_1	R_2
1	H	OH
2	*p*-MeOCin	CH_2OH
3		CH_2OH
4	H	
5	H	
6	H	



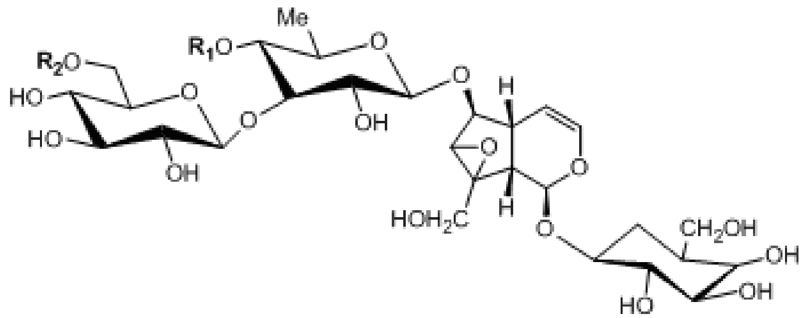
	R
7	H
8	CH_3
9	
10	*p*-MeOCin
11	Me2OCin

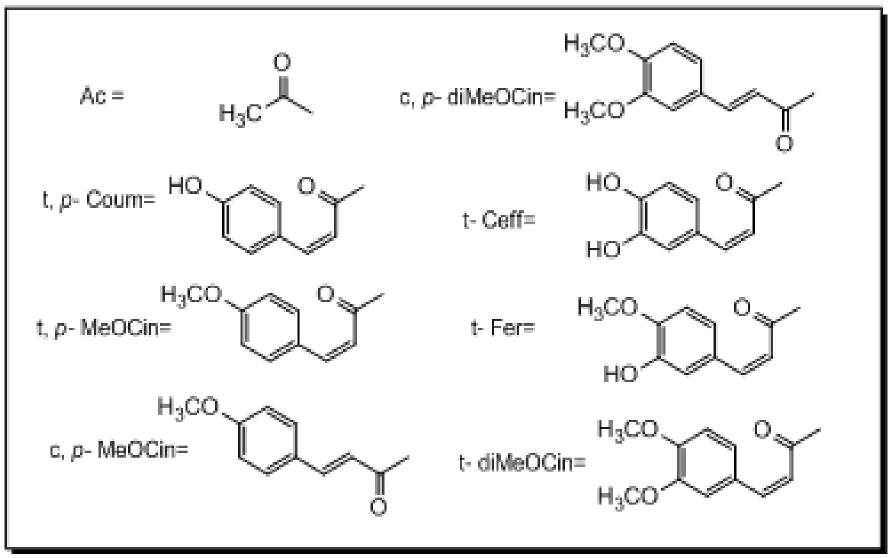


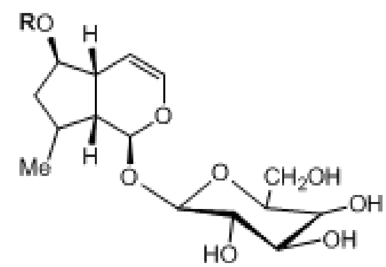
	R_1	R_2	R_3
12	H	*t-p*-MeOCin	Ac
13	Ac	*t-p*-MeOCin	H
14	*t-p*-MeOCin	H	Ac
15	H	*c-p*-MeOCin	Ac
16	Ac	*c-p*-MeOCin	H
17	H	*t-p*-MeOCin	H
18	H	*t-p*-MeOCin	Ac
19	Ac	*t-p*-MeOCin	H
20	Ac	*c-p*-MeOCin	H
21	Ac	OH	H

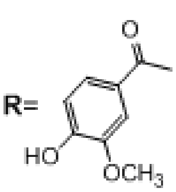
Fig. 1: Structure of the compounds 1-21

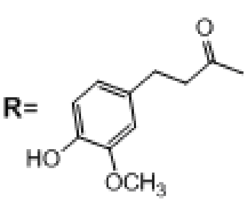
	R_1	R_2
22	*t*-*p*-MeOCin	*t*-Ceff
23	*t*-*p*-MeOCin	*t*-Fer
24	*t*-*p*-Coum	*t*-Fer
25	*c*-*p*-MeOCin	*t*-Ceff

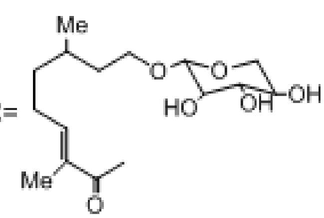


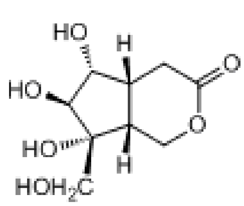




26 R= 

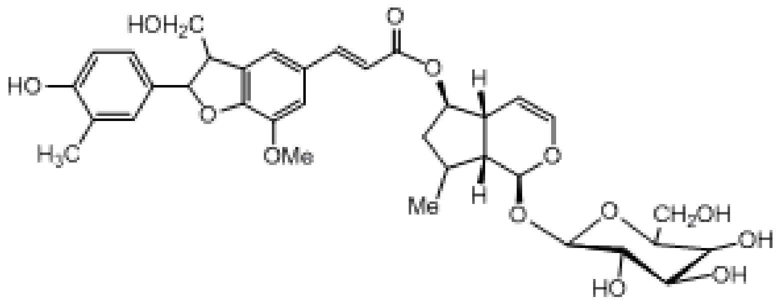
27 R= 

28 R= 

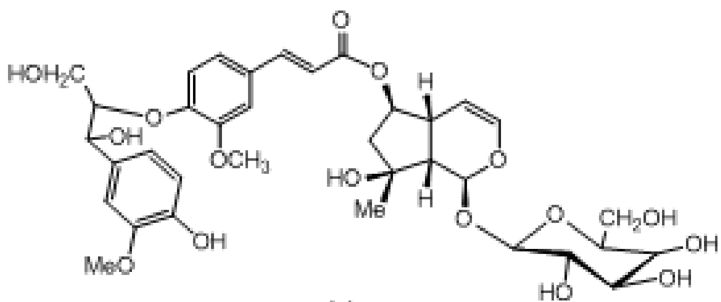


29

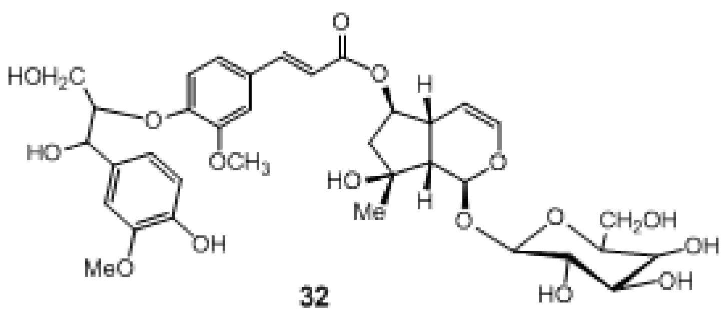
Fig. 2: Structure of the compounds 22-29



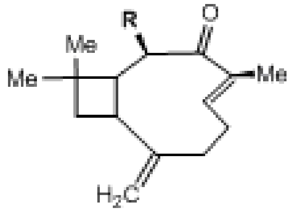
30



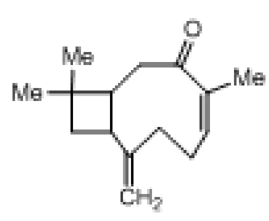
31



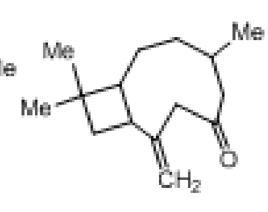
32



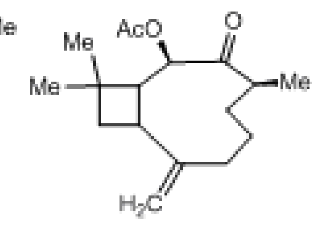
33 R= OAc
34 R=OH
35 R= H



36

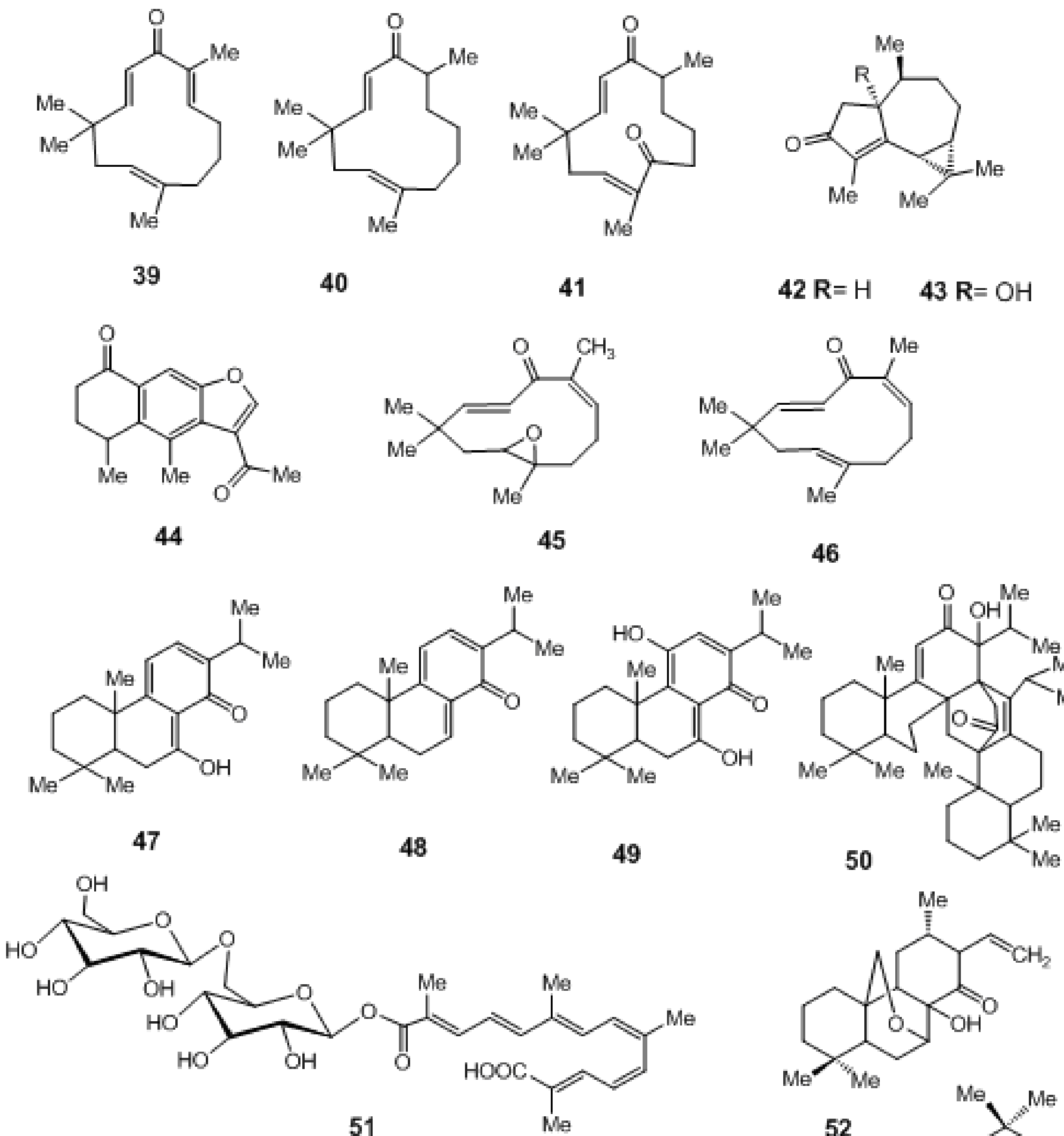


37



38

Fig. 3: Structure of the compounds 30-38



	R_1	R_2
53	OH	H
54	OH	Rhamnose(1-4)glucose)
55	OH	Xylose (1-4) glucose
56	OH	Xylose
57	OH	Glucose
58	H	Rhamnose(1-4)glucose)

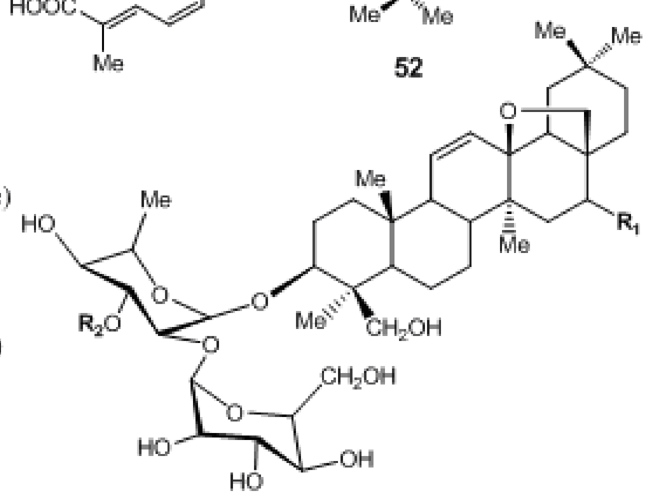
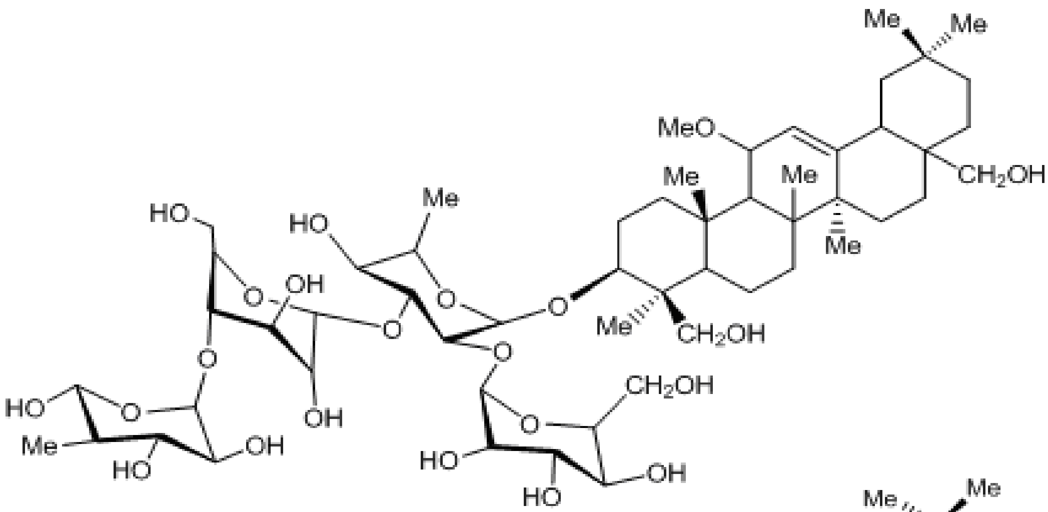
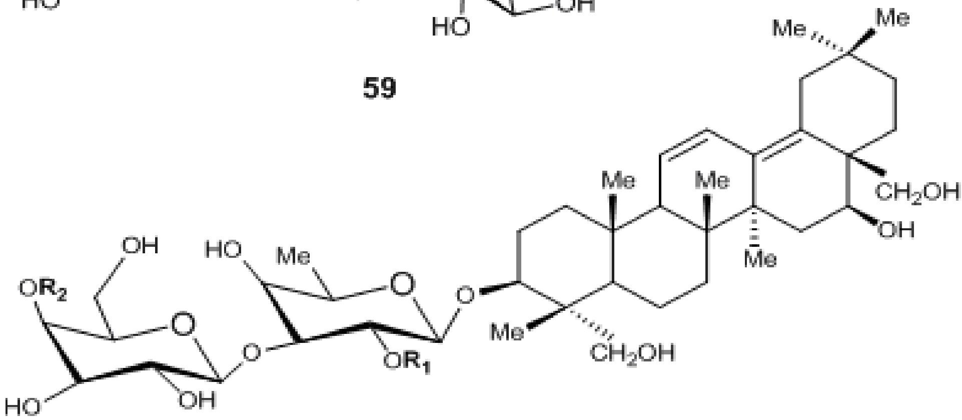


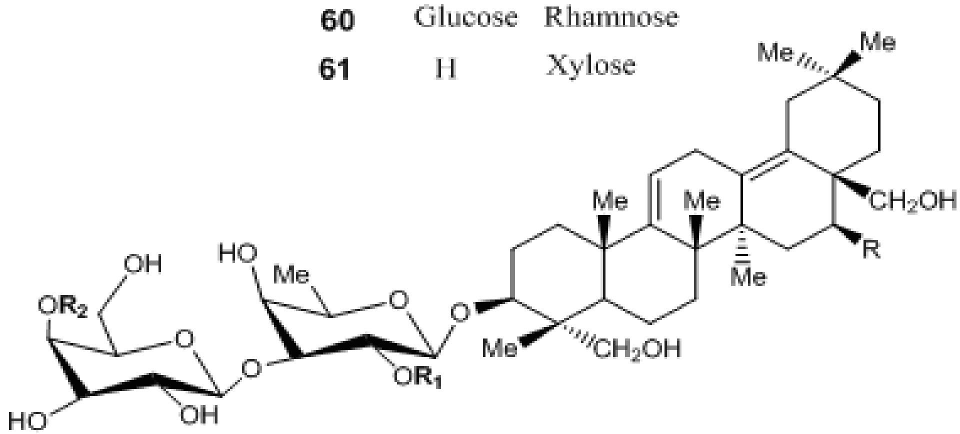
Fig. 4: Structure of the compounds 39-58



59

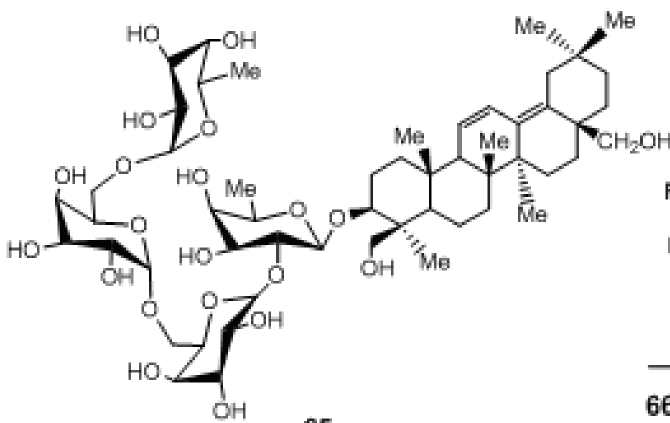


	R_1	R_2
60	Glucose	Rhamnose
61	H	Xylose

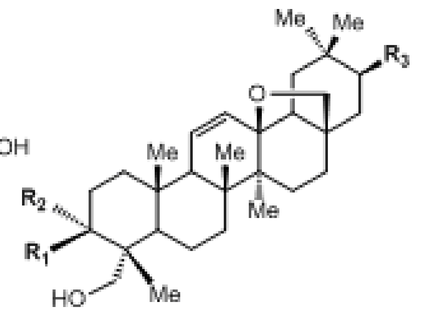


	R	R_1	R_2
62	OH	Glucose	Rhamnose
63	OH	H	Xylose
64	H	H	Xylose

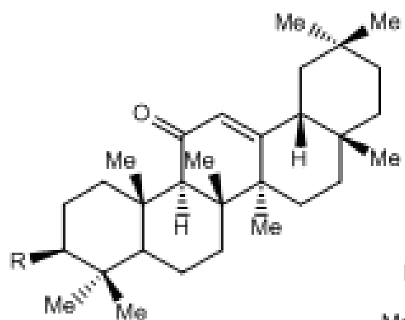
Fig. 5: Structure of the compounds 59-64



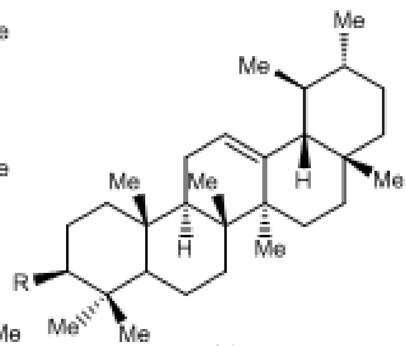
65



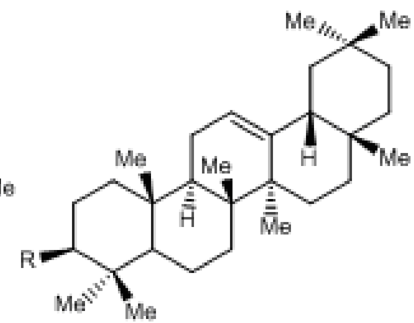
	R	R_1	R_2
66	O	O	H
67	O	O	OH



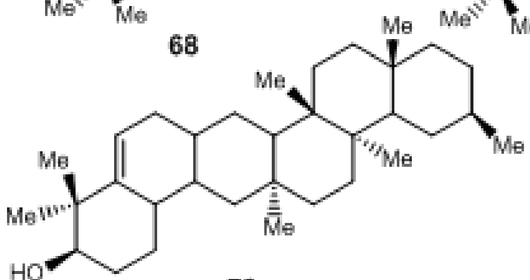
68



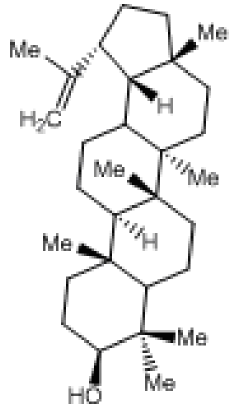
69



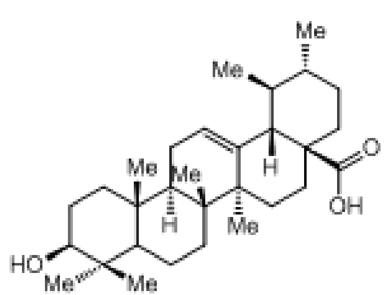
70 **R =** CO
71 **R =** OH
72 **R =** OAc



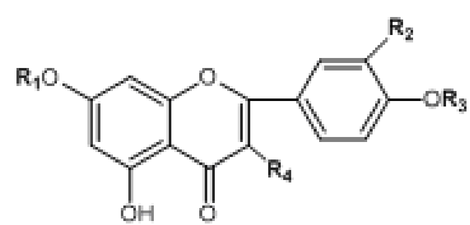
73



74

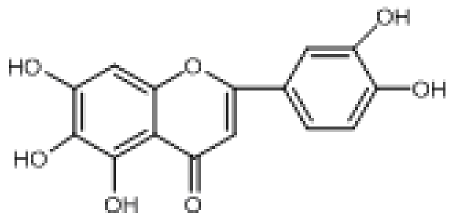


75

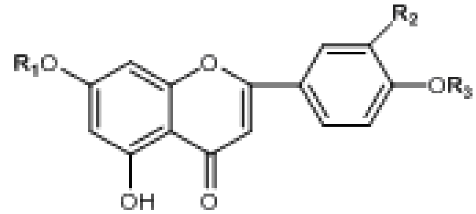


	R_1	R_2	R_3	R_4
76	H	OH	H	H
77	Glucose	OH	H	H
78	H	H	H	H
79	Glucose	H	H	H
80	H	H	Me	H
81	Rhutinose	H	Me	H
82	H	OH	H	O-rhamnose
83	Rhutinose	OH	Me	H
84	Rhutinose	H	H	H

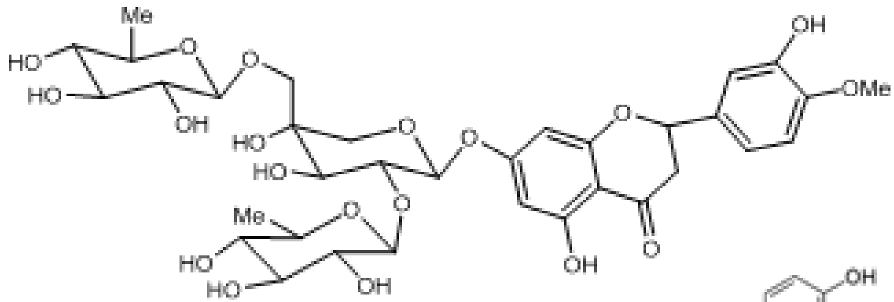
Fig. 6: Structure of the compounds 65-84



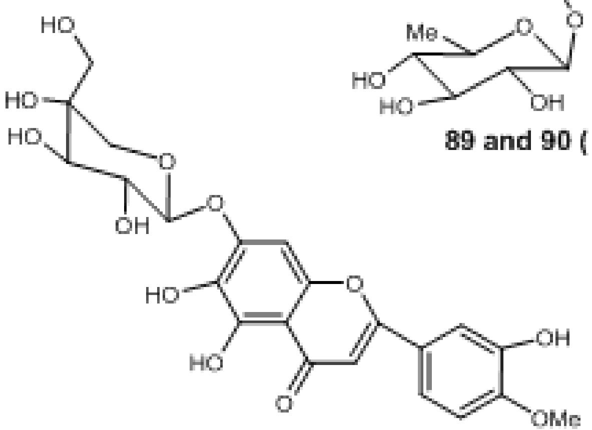
85



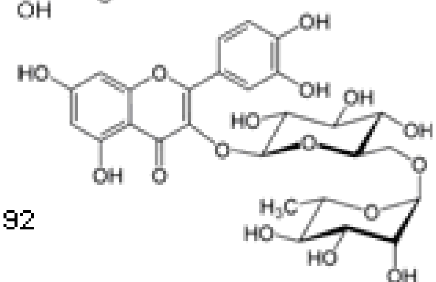
	R_1	R_2	R_3
86	H	OH	H
87	Glucose	OH	CH_3
88	Glucose	OH	H



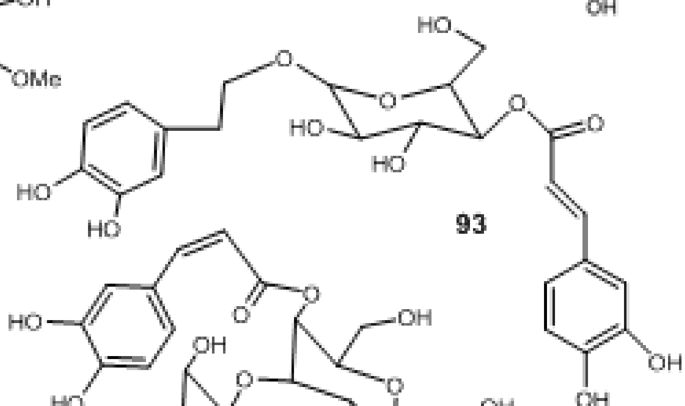
89 and 90 ($\Delta^{2,3}$)



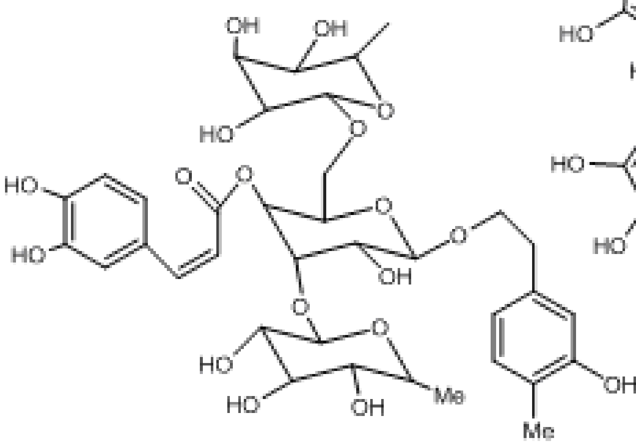
91



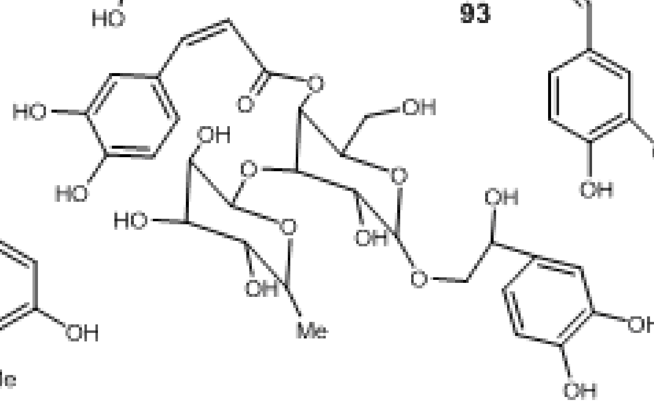
92



93

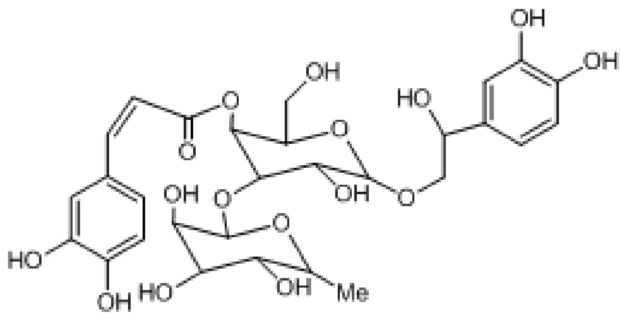


94

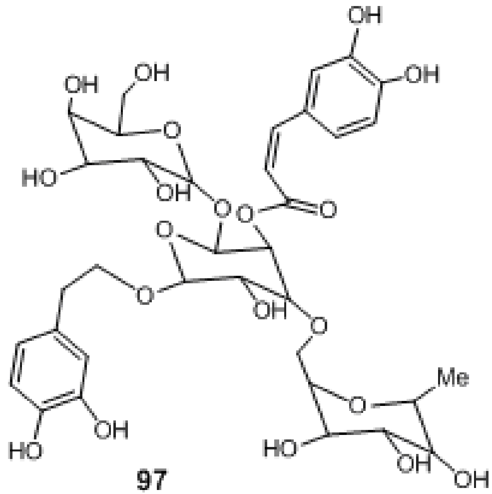


95

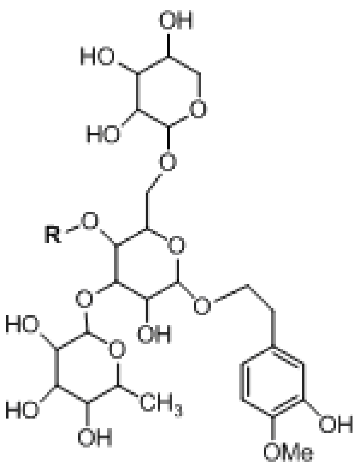
Fig. 7: Structure of the compounds 85-95



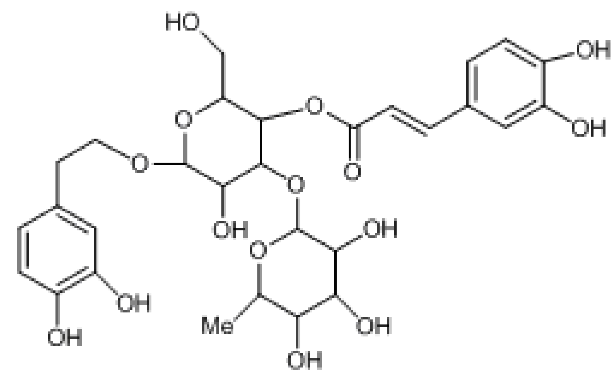
96



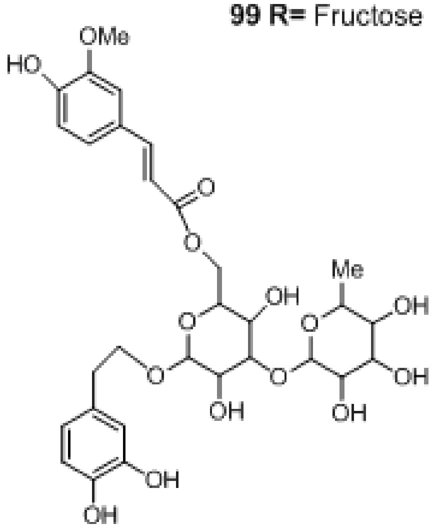
97



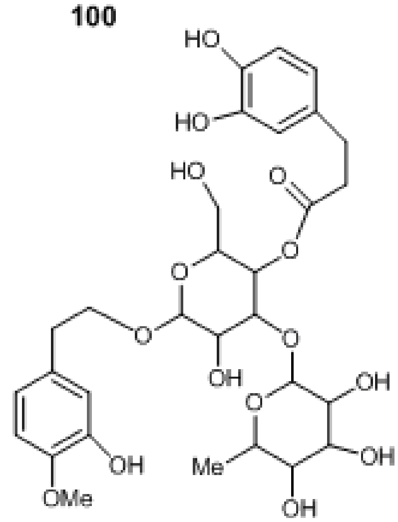
98 R= Caffoyl
99 R= Fructose



100



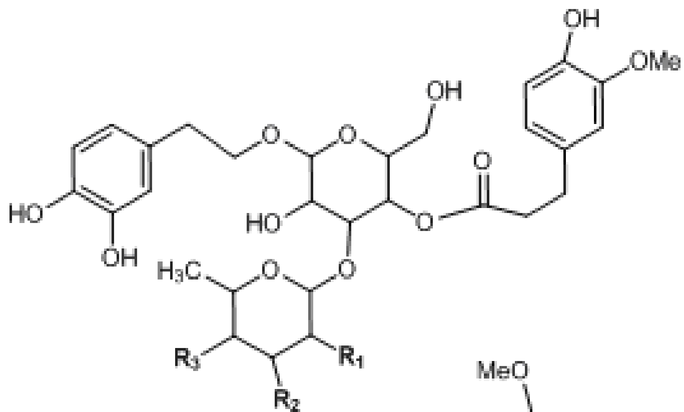
101

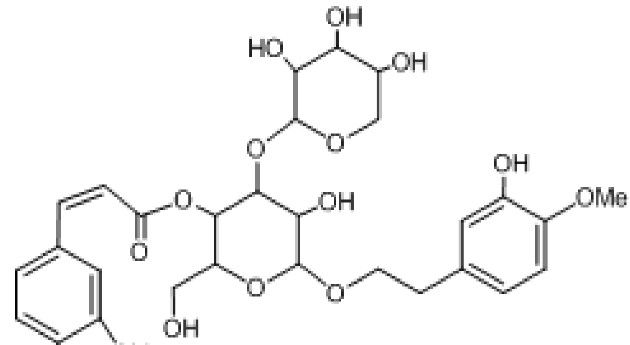


102

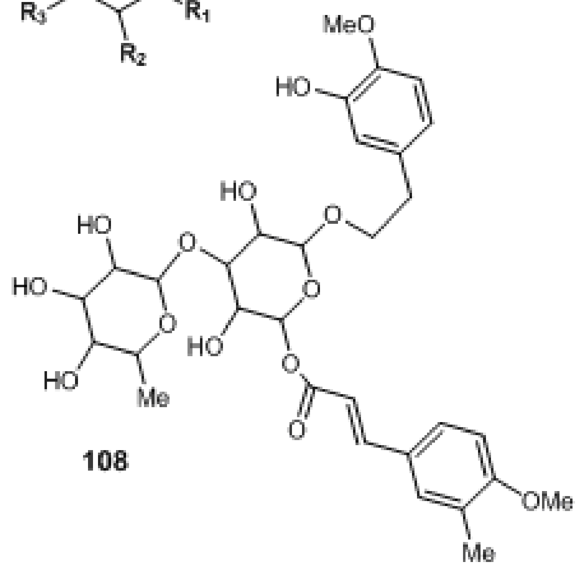
Fig. 8: Structure of the compounds 96-102

	R_1	R_2	R_3
103	OAc	OH	OH
104	OH	OAc	OH
105	OH	OH	OAc
106	OH	OH	OH

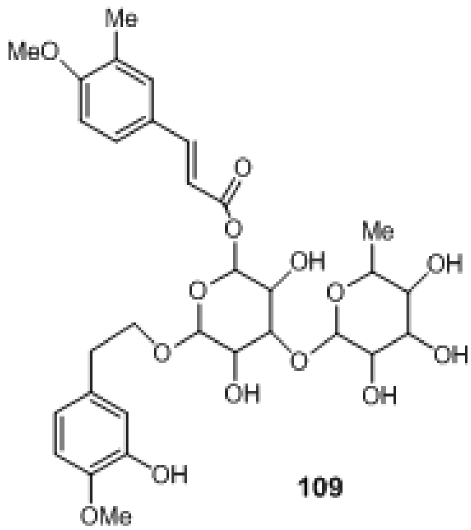




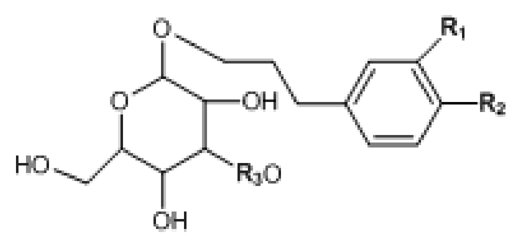
107



108

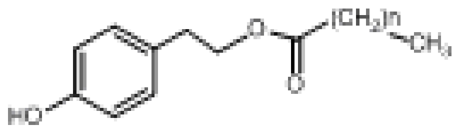


109

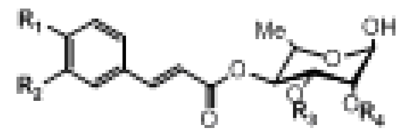


	R_1	R_2	R_3
110	H	H	H
111	OH	OH	Rhmnose
112	H	OH	H

Fig. 9: Structure of the compounds 103-112



113 n=24 **114** n=21
115 n=23 **116** n=18
117 n=15 **118** n=22
119 n=17 **120** n=20
121 n=14 **122** n=16



	R_1	R_2	R_3	R_4
123	MeO	Ac	H	H
124	OH	MeO	Ac	H
125	MeO	H	H	Ac
126	MeO	H	H	H

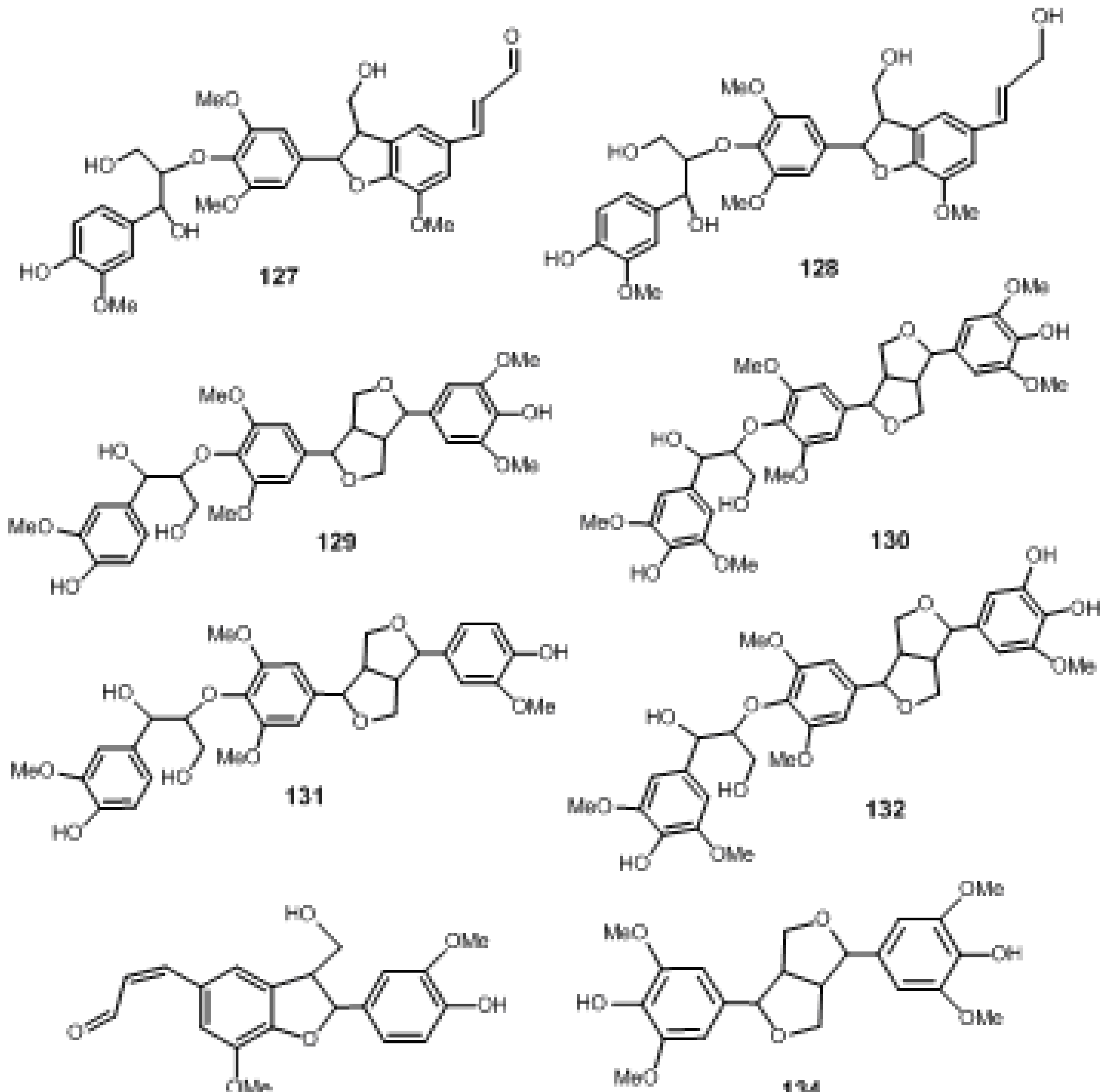
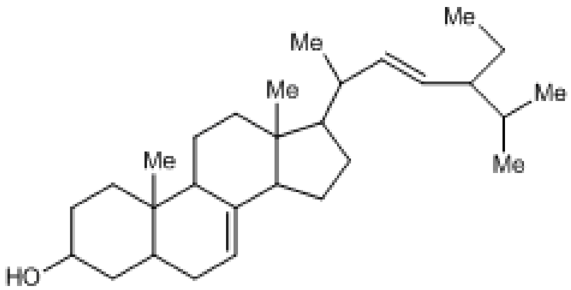
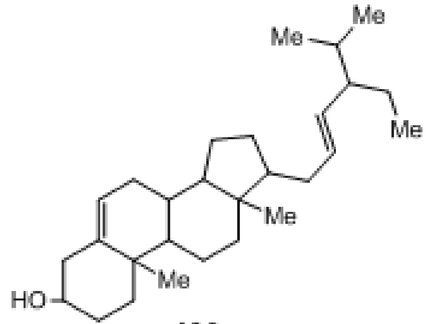


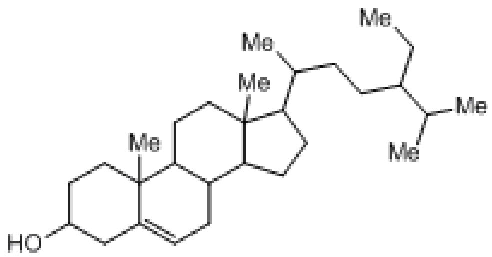
Fig. 10: Structure of the compounds 113-134



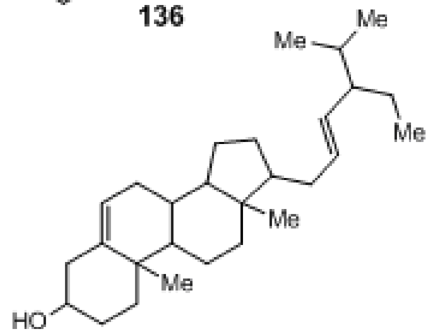
135



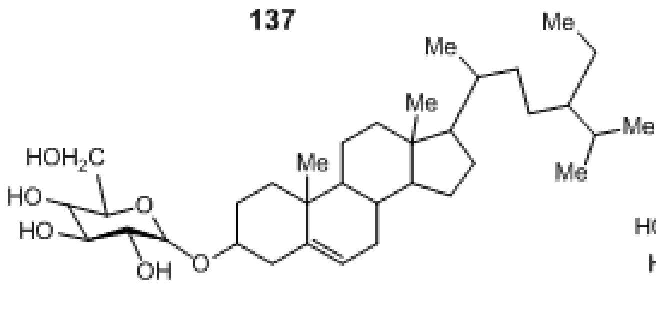
136



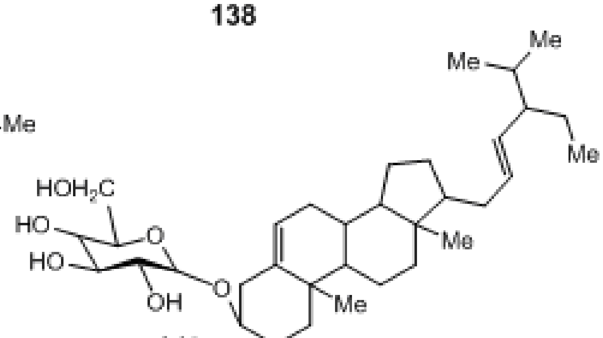
137



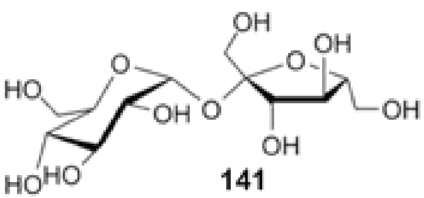
138



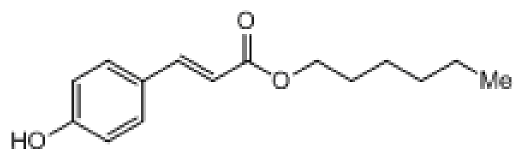
139



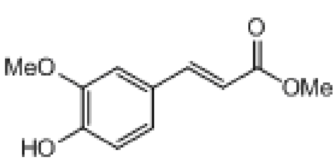
140



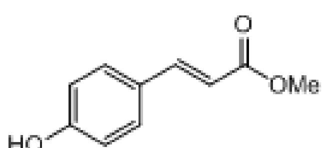
141



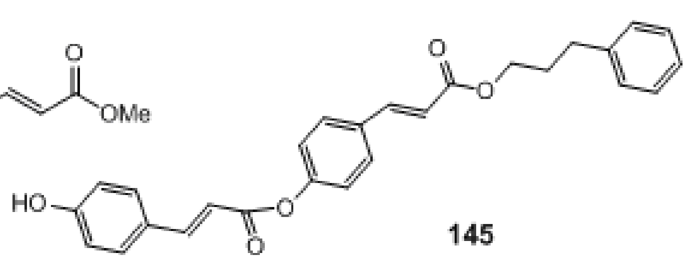
142



143

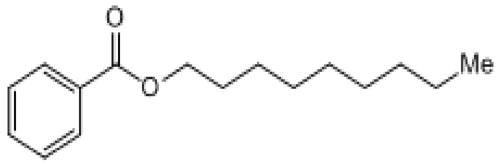


144

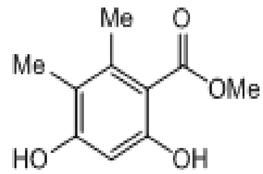


145

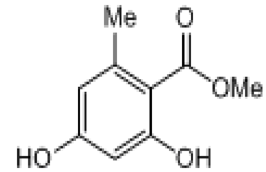
Fig. 11: Structure of the compounds 135-145



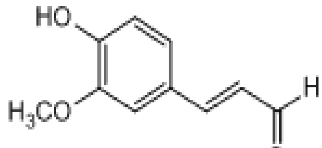
146



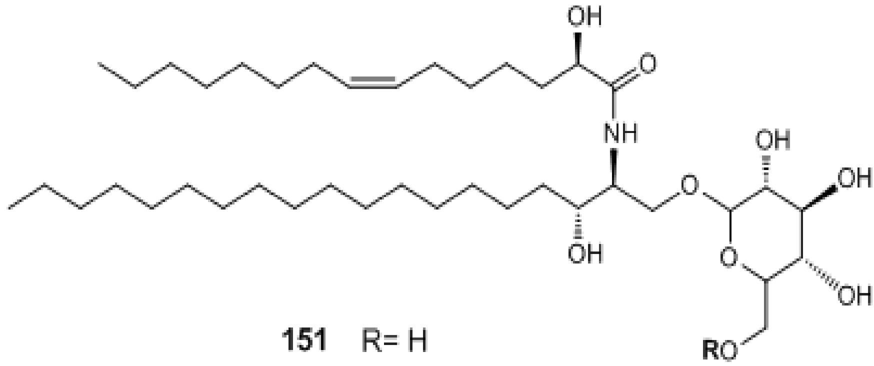
147



148

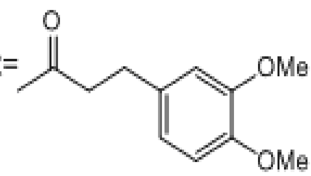


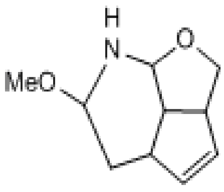
149



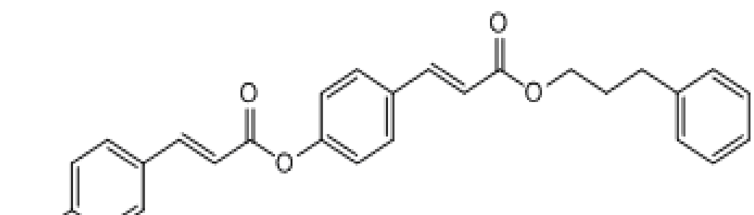
151 R= H

152 R=

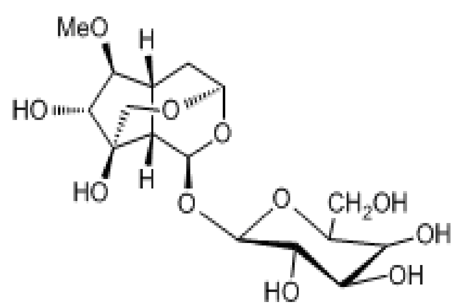




150



153



154

Fig. 12: Structure of the compounds 146-154

Literature also revealed that the essential oil display good to excellent inhibition potential against the tested bacteria of *Salmonella* sp i.e. *S. paratyphi* bacterial strains, *S. typhi* bacteria, *S. jlexneri* bacteria, *S. shiga* bacteria and *Vihrio cholera* Eltor. A profound inhibition potential of the oil has also been reported to resist tested fungi's growth (dermatophytes*) such as Aspergillus flavus*, *Trichoderma viride*and and others (A. fumigatus and Trychophyton ruhrum). Most of the reported bioactivity related result affirm the published uses of *B. asiatica's* leaves (in various forms) to encounter skin infections exists in Asian countries (Garg and Dengre 1992). Methanolic extract in crude form of *B. asiatica*, and its various ethyl acetate and *n*-butanol fractions are known for impressive antibacterial actions against Gram (-) strains e.g. *S. flexenari*, *S. boydi* and *E. coli* however the crude and its chloroform part exhibit profound antifungal activity against the function of *Fusarium solani* and *Microsporum canis* (Ali *et al*., 2011). Its stem bark's oleophilic extracts of *B. globosa* presented promising antifungal potential against functions of the three fungies i.e. *Trichophyton rubram*, *Tricophyton interdigitale*, and the *Epidermophyton floccosum* but no activity was observed for these against yeasts (Mensah *et al*., 2007). Buddledin A compound (33) and buddledin compound (34) sesquiterpenes previously obtained from *B. globosa* evident significant antifungal action against *T. rubrum*, *T. interdigitale*, and *E. floccosum*, showing MIC data 43μM and 51μM, respectively (Mensah *et al*., 2007). Some verbascosides has been repoted from *B. globosa* leaves which has proven antimicrobial effect (Pardo F *et al.*, 1993). Verbascoside 99 was obtained from *B. cordata* caused serious effect on *S. aureus* by disturbing protein synthesis and inhibiting leucine incorporation (Guillermo *et al*., 1999). Furthermore, the isolated compound 118 from stem bark extract of *B. cordata* revealed anti mycobacterial potential in a radio respirometric properties against *M. Tuberculosis* (Acevedo *et al* ., 2000).

Antioxidant properties

Different extracts (hexane, dichloromethane, methanol) of *B. globosa* exhibited antioxidant functions i.e. 1,1-diphenyl -2-picrylhydrazyl, DPPH, superoxid anion, lipid peroxidation property and xanthine oxidase inhibition, by using quercetin (*in vivo*) and allopurinol (*in vitro)* activity. Superoxide anion inhibition, lipo peroxidation, and DPPH bleaching action was found in MeOH serial and global extracts (Backhouse *et al*., 2008). Antioxidant potential has also been reported for the extracts of *B. officinalis* (Houghton *et al*., 2005). For all the isolated compounds, water and methanol extracts from *B. officinalis,* the antioxidant activities were examined by using total oxidant scavenging capacity (TOSC) assay against peroxynitrite. The obtained results showed that the phenylethanoid glycosides (a major class of compounds from flowers of *B. officinalis*), exhibited strong antioxidant activity. Among these, acteoside 100, echinacoside 96 and poliumoside 95 indicated 9.9, 9.8 and 9.5 times TOSC values respectively, compared to the positive control, Trolox (Tai *et al*., 2009). Structure of the Compounds 113-134, 135-145 and 146-154 are represented in fig. 10, 11 and 12 respectively.

Antispasmodic effects

The crude extracts from *B. crispa* and *B. asiatica* in ethanol responsible for concentration dependent (0.03 to 1.0mg/ml) relaxation of spontaneous and high potassium ion (80 mM) cause contraction displaying Ca^+ channel blocking (antispasmodic) functions in isolated rabbit's jejunum preparation (Gilani *et al*., 2009: Ali *et al*., 2011). *B. crispa* also showed anti hypertensive function, causes a dose dependent (3-10mg/kg) fall in mean arterial pressure in rat under anesthesia (Khan S, 2012). Compound 142 obtained from *B. crispa* proved to exhibit eight folds higher potential than Bc.Cr against the high K^+ than spontaneous contraction however the rest of the 02 molecules (140, 146) showed non active behavior (Gilani *et al*., 2009).

Enzyme Inhibitory Effects

The *B. davidii* leaves' extract in methanol exhibited inhibition potential of *acetylcholinesterase* (AChE) in a bioautographic TLC assay. Another isolated product from same plant was Linarin which showed the highest inhibition potential of AChE (Fan *et al*., 2008). Weak inhibitory effect of both AChE and Butyrylcholinestrase was observed by nonyl benzoate 146 and hexyl *p*-hydroxycinnamate 142 which were obtained from *B. crispa* (Ahmad *et al*., 2005). The two versatile sphingolipids (Crsipin A 151, Crispin B 152) obtained from *B. crispa* have shown significant inhibitory effect on α-chymotrypsin in concentrations dependent manner bearing IC_{50} data as 42.62 mm and 9.45 mm, respectively. Almost similar function as the positive control i.e. chymostatin was reported for compound 152 which had an IC_{50} value of 7.01mm (Ahmad *et al*., 2007). A significant inhibitory effect of Buddlejoside B 5 (isolated from *B. crispa*) was reported against lipoxygenase in concentrations dependent fashion with IC_{50} value of 39.7±0.02mM (*Miyase et al*., 1991). The roots of *B. globosa* provided Lipophilic extracts and Lipophilic extracts from the stem of *B. myriantha* have shown inhibitory effect in 5-LOX and COX enzyme assays, whereas those of *B. officinalis* flowers, *B. yunanesis*, and *B. asiatica* stems displayed inhibition potential only against COX. Experiments for inhibition of the eicosanoid synthesis by the isolated compounds revealed that buddledin A molecule (33), crocetin monogentibiosylester molecule (51), and acacetin (80) displayed inhibition properties on COX bearing IC_{50} values of 13.7μM, 28.2μM, and 77.5μM, respectively. On the other hand compound 33 have shown inhibitory action on 5-LOX bearing an IC50 value about 50.4μM (Liao *et al*., 1997). Crude extract of *B. officinalis* in methanol demonstrated *in vitro* aldose reductase inhibitory action. Flavonoids (compound 76-78 and 81) of *B. officinalis* have been reported as aldose reductase' inhibitors shown IC_{50} value of about 0.21, 0.28, 0.58 and 0.75 µM respectively (Matsuda *et al*., 1995).

Other activities

Ding *et al* reported that compounds 58-64 (Mimangosides) isolated from *B. officinalis* have shown profound inhibition potential against HL-60 leukemia cells (Ding *et al*., 1992). A substantial invitro anti-aldose-reductase activity was reported for Linarin 81 (Matsuda *et al*., 1995). It was also found to prevent H_2O_2 induced osteoblastic dysfunction of osteoblasts, employ antiresorptive action (at least in part) through RANKL reduction and by oxidative damage (Young *et al*., 2011). Compound 91 showed good antimicrobial activities (Ali *et al*., 2011). *B. officinalis* extracts were found to possess *neuroprotective* properties and microglial activating inhibition properties that possibly participate in brain ischemia (Lee *et al*., 2006). Compound 112 have shown selective inhibition of suppressed AP-1 activation due to its link to anti-inflammatory properties of *B. Officinalis* (Lee *et al*., 2005). The *B. asiatica* essential oil revealed for excellent anthelmintic effect against tapeworms (Garg and Dengre, 1992) while its petroether extract showed repellent actions against mosquitoes (Venkatachalam and Jebanesan 2001). Different extracts from many of the *Buddleja* species have been reported for possessing antihepatotropic properties (Houghton and Hikino, 1989). The *B. asiatica'* polar fractions have shown significant anti hapatotoxic properties compared to lignan silymarin (El-Domiatya *et al*., 2009). The iridoid 154 exert potential inhibition properties on PDGF-BB-induced proliferation in rat aortic VSMCs (Bui *et al*., 2011).

CONCLUSION

The pharmacological importance of genus *Buddleja*, its chemical constituents and their diverse biological potential is compiled in this review. The crude extracts, fractions and isolated compounds from different parts of various plants related to this genus have been proved as potent antimicrobial and anti-inflammatory. Main constituents include iridoid glycosides that are significantly bioactive. Flavonoids are primarily enzyme inhibitory while the lignans are potent cytotoxic. The great structural complexity and good biological potential found in compounds isolated from plants of this genus suggest that different species of the genus are needed to be further explored to investigate their biological activities and to establish structure function correlation.

ACKNOWLEDGMENT

We thank Dr. Abbas Hassan for critically reading the manuscript and for his many helpful suggestions.

REFERENCES

Abdullah P (1974). Flora of West Pakistan. Stewart Herbarium Garden College Rawalpindi and Department of Botany University of Karachi, **56**: 1-2.

Ali F, Iqbal M, Naz R, Malik A and Ali I (2011). Antimicrobial constituents from *Buddleja asiatica*. *J. Chem. Soc. Pak.,* **33**: 90-95.

Ahmad I, Afza N, Anis I, Malik A, Fatima I, Azhar-ul-Haq I and Tareen RB (2004). Iridoid Galactosides and a Benzofuran type sesquiterpene from *Buddleja crispa. Heterocycles.*, **63** : 1875-1882.

Arciniegas A, Avendano A, Perez-Castorena AL and De Vivar AR (1997). Flavonoids from *Buddleja parviflora. Biochem. Syst. Ecol.*, **25**: 185-186.

Ahmad M and Sticher O (1988). Isolation of acacetin-7-O-rutinoside and martynoside from *Buddleja davidii. J. Chem. Soc. Pak.*, **10**: 117-123.

Acevedo L, Martinez E, Castaneda P, Franblau S, Timmermann BN, Linares E, Bye R and Mata R (2000). New phenylethanoids from *Buddleja cordata* subsp. Cordata. *Planta Med*., **66**: 257-261.

Houghton P and Mensah A (1999). Phytochemicals in human health protection, nutrition and plant defense, Springer, pp.343-368.

Ahmad I, Afza N, Anis I, Malik A, Fatima I, Nawaz S, Tareen R and Choudhary M (2005). Enzymes Inhibitory Constituents from *Buddleja crispa*. *Z. Naturforsch B*., **60**: 41-346.

Ahmad I, Afza N, Malik A, Fatima I, Tareen R, Nawaz S and Choudhary M (2006). Iridoid glucoside and aryl ester from *Budleja crispa. Pol. J. Chem.*, **80**: 1483-1488.

Ahmad I, Anis I, Fatima I, Malik A, Khan S, Afza N, Tareen R, Lodhi M and Choudharya M (2007). Two New Protease-Inhibiting Glycosphingolipids from *Buddleja crispa. Chem. Biodivers.*, **4**: 917-924.

Ahmad I, Ahmad N and Wang F (2009). Antioxidant phenylpropanoid glycosides from *Buddleja davidii. Journal of Enzyme Inhibition and Medicinal Chemistry*. **24**: 993–997.

Ahmad M, Sticher O Apparent of Acetacin-7-O-Rutenoside and Martynoside from Buddleja davidii. (1988). *Proc Chem Soc Pak*., **10**:117–123.

Ali F, Ali I, Khan HU, Khan A and Gilani AH (2011). Studies on Buddleja asiatica antibacterial, antifungal, antispasmodic and Ca++ antagonist activities. *Afr. J. Biotechnol.,* **10**: 7679-7683.

Bui TH, Nguyen, NX, Tran QH, Nguyen NT, Yohan K, Jung LJ, Chang MS, Nguyen CM and Young KH (2011). A new iridoid and effect on the rat aortic vascular smooth muscle cell proliferation of isolated compounds from *Buddleja officinalis*. *Bioorg Med. chem. Lett.*, **1**: 3462-3466.

Backhouse N, Rosales L, Apablaza C, Goty L, Erazo S, Negrete R, Theodoluz C, Rodriguez J and Delporte C (2008). Analgesic, anti-inflammatory and antioxidant properties of *Buddleja globosa*, Buddlejaceae. *J. Ethnopharmacol.*, **116**: 263-269.

Chen H, Xu C, Liu Q, An Q and Tan X (2005). Buddlin, a new compound from *Buddleja asiatica*. *Fitoterapia*., **76**: 588-589.

Duke J and Ayensu E (1985). Medicinal Plants of China Reference Publications Inc. pp.315-328.

Devivar AR, Nieto DA, Gavino R and Perez L (1995). Isocapnell-9-en-8-one and 6α-hydroxyisocapnell-9-en-8-one, sesquiterpenes from *Buddleia* species. *Photo Chemistry*., **40** : 167-170.

Ding N, Yahara S and Nohara T (1992). Structure of mimengosides A and B, new triterpenoids glycosides from *Buddleja flos* produced in China. *Chem. Pharm. Bull.*, **40**: 780-782.

Emam AM, Diaz-Lanza AM, Matellano-Fernandez L, Faure R, Moussa AM and Balansard G (1997). Biological activities of Buddleja saponin isolated from *Buddleja madagascariensis* and *Scrophularia scorodonia*. *Pharmazie.*, **52**: 76-77.

El-Domiatya M, Winkb M, Abou-Hashem M and Abd-Allaa R (2009). Antihepatotoxic Activity and Chemical Constituents of *Buddleja asiatica* Lour. *Z. Naturforsch.*, **64**: 11-19.

Emam AM, Diaz-Lanza AM, Matellano-Fernandez L, Faure R, Moussa AM and Balansard G (1997). Biological activities of buddlejasaponin isolated from *Buddleja madagascariensis* and *Scrophularia scorodonia*. *Pharmazie.*, **52**: 76-77.

Emam A, Elias R, Moussa A, Faure R, Debrauwer L and Balansard G (1998). Two flavonoid triglycosides from Buddleja madagascariensis. *Phytochemistry*., **48**: 739-742.

Fan P, Hay A, Marston A and Hostettmann K (2008). Structure-activity relationships of related flavonoids and chemical investigation of *Buddleja nitida*. *Pharm. biol*., **46**: 596-601.

Guo H, Koike K, Li W, Satou T, Guo D and Nikaido T (2004). Saponins from the flower buds of *Buddleja officinalis. J. Nat. Prod.*, **67**: 10-13.

Garg S and Oswal V (1981). In vitro antifungal activity of the essential oil of *Buddleia asiatica Lour*. *Rivista Itlaiana, EPPOS ., 63*: 365-370.

Garg SC and Dengre SL (1992). Composition of the essential oil from the leaves of *Buddleia asiatica* lour. *Flavour Frag J.*, **7**: 125-127.

Guillermo Avila, J, de Liverant JG, Martinez A, Martinez G, Munoz J L, Arciniegas A and Romo de Vivar A (1999). Mode of action of *Buddleja cordata* verbascoside against *Staphylococcus aureus. J. Ethnopharmacol.*, **66**: 75-78.

Gilani A, Ishfaq A, Rafeeq A, Abdul J, Ahmad I and Malik A (2009). Presence of blood-pressure lowering and spasmolytic constituents in *Buddleja crispa. Phytother Res.*, **23**: 492-497.

Houghton P (1985). Lignans and neolignans from *Buddleja davidii. Phytochemistry*, **24**: 819-826.

Hu K, Dong A, Sun Q and Yao X (2001). Bioactivity of 247 traditional Chinese medicines against *Pyricularia oryzae. Pharm. Biol.*, **39**: 47-53.

Hutchings A, Scott H, Lewis S and Cunningham A (1996). *Zulu Medicinal Plants. An Inventory*, University of Natal Press, Pietermaritzburg, pp.195-196.

Houghton P and Manby J (1985). Medicinal plants of the Mapuche. *J. Ethnopharmacol.*, **13**: 89-103.

Houghton P (1984). Ethnopharmacology of some *Buddleja* species. *J Ethnopharmacol.*, **11**: 293-308.

Houghton P and Hikino H (1989). Anti-Hepatotoxic Activity of Extracts and Constituents of *Buddleja* Species. *Planta Med.*, **55**: 123-126.

Houghton P, Woldemariam T, Candau M, Barnardo A and Khen-Alafun O (1996). Buddlejone, a diterpene from *Buddleja albiflora*. *Phytochem.*, **42**: 485-488.

Houghton P (2003). *Boletín Latinoamericano y del Caribe de Plantas Medicinales Aromáticas* ., **2**: 36-41.

Houghton P, Hylands P, Mensah A, Hensel A and Deters A (2005). *In vitro* tests and ethnopharmacological investigations. *J. Ethnopharmacol*., **100**: 100-107.

Jiangsu (1977). New Medical College. A dictionary of Chinese traditional medicine, Shanghai Science and Technology, Press, Shanghai., 725.

Kapoor VK, Chawla A S, Gupta C, Passannanti S and Paternosro MP (1982). Constituents of *Buddleia* species leaves. *Fitoterapia* ., **52**: 235-237.

Khan S (2012). Concept of Natural Product Chemistry, *Lambert Academic Publishing, Saarbrücken,* Germany .,82-83.

Lee S, Xiao C and Pei S (2008). Ethnobotanical survey of medicinal plants at periodic markets of Honghe Prefecture in Yunnan Province, SW China. *J. Ethnopharmacol.*, **117**: 362-377.

Liao Y, Houghton P and Hoults J (1999) .Novel and known constituents from Buddleja species and their activity against leukocyte eicosanoidgeneration. *J. Nat. Prod.*, **62**: 1241-1245.

Lu J, Tu G, Zhao Y, Lv Y, Liu L and Wu Y (2004). Structural determination of novel terpenes from *Buddleja lindleyana. Magnetic Resonance in Chemistry.*, **42**: 893-897.

Lopez J, Sierra J, Vegazo M and Cortes M (1979). Chemical constituents of Buddleja globosa Lam. *Fitoterapia.*, **5:** 195-198.

Liu Y, Cai X, Du Z, Li W and Luo X (2008). Two New Oleanane-type Triterpenoids from *Buddleja asiatica*. *Z. Naturforsch B.*, **63**: 915-919.

Liu YP, Cai XH, Li WQ and Luo XD (2008). Phenylpropanoid Esters of Rhamnose from *Buddleja asiatica. Helvetica Chimica Acta.*, **91**: 1299-1304.

Liu Y, Cai X, Du Z, Li W and Luo X (2008). Two New Oleanane-type Triterpenoids from *Buddleja asiatica*. *Z. Naturforsch B.*, **63**: 915-919.

Lee DH, Ha N, Bu YM, Choi HI, Park YG, Kim YB, Kim MY and Kim H (2006). Neuroprotective Effect of

Buddleja officinalis Extract on TransientMiddle Cerebral Artery Occlusion in Rats. *Biol. Pharm. Bull.*, **29**: 1608-1612.

Lee JY, Woo ER and Kang KW (2005). Inhibition of lipopolysaccharide-inducible nitric oxide synthase expression by acteoside through blocking of AP-1 activation. *J. Ethnopharmacol.*, **97**: 561-566.

Murillo A (1989). Plantes Medicinales du Chilli. Exposition Universalle de Paris, Paris. 26-28.

Mensah AY, Sampson J, Houghton P, Hylands P. Westbrook J, Dunn M, Hughes M and Cherry G (2001). Effects of *Buddleja globosa* leaf and its constituents relevant to wound healing. *J. Ethnopharmacol*., **77**: 219-22.

Miyase T, Akahori C, Kohsaka H and Ueno A (1991). Acylated iridoid glycosides from *Buddleja japonica* Hemsl. *Chem. Pharm. Bull.*, **39**: 2944-2951.

Miyase T, Akahori C, Kohsaka H and Ueno A (1991). Acylated iridoid glycosides from *Buddleja japonica* Hemsl. *Chemical and Pharmaceutical Medicinal Chemistry.*, **23**: 140-143.

Mensah A, Houghton P, Bloomfield S, Vlietinck A and Berghe D (2000). Known and Novel Terpenes from *Buddleja globosa* Displaying SelectiveAntifungal Activity Against Dermatophytes. *J. Nat. Prod*., **63**: 1210-1213.

Matsuda H, Cai H, Kubo M, Tosa H and Iinuma M (1995). Effect of *Buddleja flos* on in vitro aldosreductase activity. *Biol. Pharm. bull.*, **18**: 463-466.

Mabberley DJ: The plant-book: A portable dictionary of the higher plants. Cambridge: Cambridge University Press; 1987:707

Trim A and Hill R (1952).The preparation and properties of aucubin, asperuloside and some related glycosides. *Biochem. J.*, **50**: 310-319.

Tai BH, Jung BY, Cuong NM, Linh PT, Tung NH, Nhiem NX, Huong TT, Anh NT, Kim JA, Kim SK and Kim YH. (2009). Total PeroxynitriteScavenging Capacity of Phenylethanoid and Flavonoid Glycosides from the Flowers of *Buddleja officinalis. Biol. Pharm. Bull*., **32**: 1952-1956.

Varma R and Nobles W (1968). Synthesis of beta-amino ketones. *J. Med. Chem.*, **11**: 195-195.

Venkatachalam M and Jebanesan A (2001). A Screening of repellent activity of certain plants of Tamil Nadu, India. *Convergence*., **3**: 39-43.

Yamamoto A, Nitta S, Miyase T and Ueno A (1993). Phenylethanoid and lignan-iridoid complex glycosides from roots of Buddleja davidii.*Phytochemistry*., **32**: 421-425.

Yoshida T, Nobuhara J, Uchida M and Okuda T (1978). Studies on the constituents of *Buddleja* species I. *Chem. Pharm. Bull.*, **26**: 2535-2542.

Yoshida T, Nobuhara J, Uchida M and Okuda T (1978). Studies on the constituents of *Buddleja* species II. *Chem. Pharm. Bull.*, **26**: 2543-2549.

Yamamoto A, Miyase T, Ueno A and Maeda T (1991). Four new oleanane-triterpene saponins from the arial parts of *Buddleja japonica* Hemsl. *Chem. Pharm. Bull*., **39**: 2764-2766.

Young KH, Young LS and Eun CM (2011). Linarin isolated from *Buddleja officinalis* prevents hydrogen peroxide-induced dysfunction in osteoblasticMC3T3-E1 cells. *Cell*. *Immunol.*, **268**: 112-116.

Joshi S, Mishra D, Bisht G and Khetwal KS (2012). Comparative study of essential oil composition of *Buddleja asiatica* and *buddleja davidii* aerial parts. *Int J. Green Pharm.*, **6**: 23-25.

Zhang HP and Tao L (2010). Studies on the chemical constituents of Buddleja albiflora (II). *Journal of Chinese medicinal materials*., **33**: 922-924.

Raja S and Ramya I (2016). A review on ethnopharmacology, phytochemistry and pharma cology of *B. asiatica*. *Int. J. Pharm. Sci. Res*., **7**: 4697-4709.

Ganeshpurkar A and Saluja AK (2017). The pharmacological potential of Rutin. *Saudi Pharm. J*., **25**: 149-164.

Hegnauer R, Kooiman P (1978). Apparent taxonomic significance of iridoids of Tubiflorae sensu Wettstein. *Proc Med.*, **33**: 1–33.

Li JS, Zhao YY and Ma LB (1997). A new phenylethanoid glucoside from *B. officinalis. J. chin. Pharm. Sci*., **6**: 178-181.

Pardo F, Perich F, Villarroel L and Torres R (1993). Isolation of verbascoside, an antimicrobial constituent of *Buddleja globosa* leaves. *J. Ethnopharmacology*., **39**: 221-222.

Wu J, Yi W, Jin L, Hu D and Song B (2012). Antiproliferative and cell apoptosis-inducing activities of compounds from Buddleja davidii in Mgc-803 cells. *Cell Division.*, 2012, **7:** 1-12.