An Update on Secondary Metabolites from *Haloxylon* Species

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Summary: Secondary metabolites have been isolated from the various species of the genus *Haloxylon* (Chenopodiaceae) including *H. ammodendron, H. aphyllum, H. articulatum, H. griffithii, H. persicum, H. recurvum, H. salicornicum, H. schmittianum* Pomel and *H. scoparium*. These compounds belong to the classes, fatty acids and their esters, triglycerides, alcohols, steroids and their glycosides, phenol derivatives, coumarins, alkaloids of different classes, monocyclic naphthene derivatives, terpenes and flavonoids, and their glycosides. This present review will discuss the secondary metabolites **1-107** of different classes isolated from *Haloxylon* species with biological activities up to 2010.

Key Words: *Haloxylon ammodendron, Haloxylon aphyllum, Haloxylon articulatum, Haloxylon griffithii, Haloxylon persicum, Haloxylon recurvum, Haloxylon salicornicum, Haloxylon schmittianum* Pomel*, Haloxylon scoparium*

Introduction

Since the ancient times, plants have been used as a primary source of medicine. Documentary evidences show that, herbal medicines have been used for at least, 7000 years in China [1]. In Europe, there is a rich history of the use of herbal medicines such as Culpeper's and Gerard's *Materia Medica* [2]. The emerging neutraceutical industry based on medicinal plants has great potential as a component of preventative and curative treatments throughout the world. Recently herbal supplements have created multimillion-dollar industries [1].

Haloxylon belongs to the family Chenopodiaceae, which consists of 100 genera and 1200 species [3]. Most of its members are weedy and grow in waste and unfertile soil. The genus *Haloxylon* comprises 13 species growing in the arid zones of the North-African and Arabian deserts, and South-West Asia. The members of the genus *Haloxylon* are shrubs or small trees. The genus is said to be poisonous [4]. There are about 5 species found in Pakistan out of 6 species in Central Asia [5].

Haloxylon recurvum in the form of ash is used for internal ulcers. The plant is traditionally applied externally on insect stings, and is used for neural disorders treatment [6, 7]. Ethylacetate fraction of *H. recurvum* showed the significant *in vitro* lipoxygenase inhibitory activity [8]. Aqueous, butanol, ethylacetate, chloroform and n-hexane soluble fractions were obtained form methanolic extract of the *Haloxylon recurvum*, and they were investigated for *in vivo* toxic potential using Lorke's method and inverted screen test by determining their acute neurotoxicity and acute toxicity in mice [8]. Aqueous fraction (TD_{50}1264mg/kg) was only found to produce neurotoxicity at non-lethal doses in mice, and this fraction did not produce any mortality even at the highest tested dose (5000 mg/kg). All remaining fractions showed a narrow margin of safety in mice [8]. Ethanol extract of *H. salicornicum* showed antidiabetic [9] and anticoagulant activities in experimental animal [10]. *Haloxylon salicornicum* extracts have exhibited persistent hypoglycaemic activity in normal, fasting and alloxanized rats [11].

Phytochemical studies of the genus *Haloxylon* revealed the presence of compounds **1-107** isolated from the aerial parts of *Haloxylon ammodendron, H. aphyllum, H. articulatum, H. griffithii, H. persicum, H. recurvum, H. salicornicum, H. schmittianum* Pomel and *H. scoparium* up to 2010. These compounds belong to the classes, fatty acids and their esters **1-8**, triglyceride **9**, alcohol **10**, steroids **11-27**, steroidal glycosides **28-32**, phenol derivatives **33-37** and coumarins **38-45**. Alkaloids of different classes, tetrahydroisoquinoline alkaloids **46-48**, indole alkaloids **49** and **50**, isoquinoline alkaloids **51-53**, isoquinolone alkaloid **54**, β-carboline alkaloids **55-58**, piperidine alkaloids **59-69**, pyridine alkaloids **70-72**, aliphatic quaternary alkaloids **73** and **74**, phenylethylamine alkaloids **75-80**, and N-

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containing compounds **81-83** are also isolated. Monocyclic naphthene derivatives **84** and **85**, terpenes **86-95**, flavonoid **96,** flavonoid glycosides **97-102** and some other compounds **103-107** are also reported.

This review deals with the various classes of secondary metabolites isolated from different *Haloxylon* species, reported up to 2010. Chemical structures of compounds **1-107** are represented in Fig. 1, and their detail is also mentioned in table-1.

Fatty Acids and their Esters

Ahmed and co-workers in 2004 isolated first time octadecanoic acid (**1**), octacosonic acid (**2**) and triacontanoic acid (**3**) from chloroform soluble fraction of *H. recurvum*. These compounds, **1-3** were screened for phytotoxicity but non of these were found to be active [12]. Triacontanoic acid (**3**) was also isolated first time from methanolic extract of *H. salicornicum* [13]. Ahmed and co-workers in 2007 isolated an unsaturated fatty acid, (E)-20-nonacosenoic acid (**4**) and an ester of saturated fatty acid, methyl triacontanaote (**5**) from chloroform soluble fraction of *H. recurvum*. Both compounds **4** and **5** exhibited significant chymotrypsin inhibitory activity in a conc. dependent fashion, IC_{50} = 81.78±0.071 and 80.01±0.0061, respectively [14]. The diethyl ether extract of *H. ammodendron* yielded 0.85% oil. The glyceride consisted of 10% palmitic acid (**6**), 40% oleic acid (**7**) and 40% linoleic acid (**8**) [15]. Oleic acid (**7**) and linoleic acid (**8**) were unsaturated fatty acids.

Triglycerides

A triglyceride, haloxylase (**9**) was isolated from chloroform fraction of *Haloxylon recurvum* [14], which showed significant chymotrypsin inhibiting activity (IC_{50} = 90.16±0.013) in a conc. dependent fashion.

Alcohols

Ahmed and co-workers in 2004 isolated first time 1-triacontanol (**10**) from chloroform soluble fraction of *H. recurvum*. This compound **10** was screened for phytotoxicity but it was found to be inactive [12]. 1-Triacontanol (**10**) was also isolated from *H. salicornicum* [13].

Steroids

Ahmed and co-workers in 2004 isolated first time β-sitosterol (**11**) from chloroform soluble fraction of *H. recurvum*. This compound **11** was screened for phytotoxicity but it was found to be inactive [12]. β-Sitosterol (**11**) was also reported from *H. salicornicum* [16].

Dawidar and Amer in 1976 isolated an sterol named fucosterol (**12**) form *H. salicornicum* [17]. Hussain and co-workers in 2006 isolated two new sterols, halosterol A (**13**) and halosterol B (**14**) from chloroform soluble fraction of *H. recurvum*. Both compounds **13** and **14** showed significant chymotrypsin inhibitory activity with IC_{50} = 47.11± 1.62 and 21.57± 1.02, respectively whereas chymostatin is used as positive control (IC_{50} = 8.01 ±0.11) [18].

Ahmed and co-workers in 2006 isolated C-24 alkylated sterols, haloxysterol A (**15**), haloxysterol B (**16**), haloxysterol C (**17**), haloxysterol D (**18**), 5α,8α-epidioxy-(24S)-ethyl-cholesta-6,9(11),22(E)-triene-3β-ol (**19**), (24S)-ethyl-cholesta-7,9(11),22(E)-triene-3β-ol (**20**), lawsaritol (**21**), (24R)-ethyl-5α-cholest-7-ene-3β,5,6β-triol (**22**) and 24-ethyl-cholest-6-ene-3,5-diol (**23**) from the $CHCl_3$ fraction of *H. recurvum* [19]. These compounds **15-23** inhibited acetylcholinesterase (AChE; EC 3.1.1.7) and butyrylcholenesterase (BChE; EC 3.1.1.8) enzymes in a concentration-dependent manner with *K*i values ranging between 0.85-25.5 and 1.0-19.0 μM against both enzymes, respectively. Lineweaver-Burk, Dixon plots and their secondary replots indicated that these compounds **15-23** are non-competitive inhibitors of both AChE and BChE enzymes [19].

Ferheen and co-workers in 2005 isolated ergosterol peroxide (**24**) from methanolic extract of *H. salicornicum* [13]. 24-Ethyl cholesta-3,5-diene (**25**) was also isolated first time from chloroform soluble *fraction* of *H. salicornicum* [16]. This compound **25** was screened for phytotoxicity but it was found to be inactive.

Table-1: Secondary metabolites from *Haloxylon* species.

S. No.	Name of Compound	Class of Compound	*Haloxylon* Species	Reference
1	Octadecanoic acid (1)	Fatty acid	*H. recurvum*	12
2	Octacosonic acid (2)	Fatty acid	*H. recurvum*	12
3	Triacontanoic acid (3)	Fatty acid	*H. recurvum* *H. salicornicum*	12,13
4	(E)-20-Nonacosenoic acid (4)	Fatty acid	*H. recurvum*	14
5	Methyl triacontanaote (5)	Ester of fatty acid	*H. recurvum*	14
6	Palmitic acid (6)	Fatty acid	*H. ammodendron*	15
7	Oleic acid (7)	Fatty acid	*H. ammodendron*	15
8	Linoleic acid (8)	Fatty acid	*H. ammodendron*	15
9	Haloxylase (9)	Triglyceride	*H. recurvum*	14
10	1-Triacontanol (10)	Alcohol	*H. recurvum* *H. salicornicum*	12,13
11	β-Sitosterol (11)	Steroid	*H. recurvum* *H. salicornicum*	12,16
12	Fucosterol (12)	Steroid	*H. salicornicum*	17
13	Halosterol A (13)	Steroid	*H. recurvum*	18
14	Halosterol B (14)	Steroid	*H. recurvum*	18
15	Haloxysterol A (15)	Steroid	*H. recurvum*	19
16	Haloxysterol B (16)	Steroid	*H. recurvum*	19
17	Haloxysterol C (17)	Steroid	*H. recurvum*	19
18	Haloxysterol D (18)	Steroid	*H. recurvum*	19
19	5α,8α-Epidioxy-(24S)-ethyl-cholesta-6,9(11),22(E)-triene-3β-ol (19)	Steroid	*H. recurvum*	19
20	(24S)-Ethyl-cholesta-7,9(11),22(E)-triene-3β-ol (20)	Steroid	*H. recurvum*	19
21	Lawsaritol (21)	Steroid	*H. recurvum*	19
22	(24R)-Ethyl-5α-cholest-7-ene-3β,5,6β-triol (22)	Steroid	*H. recurvum*	19
23	24-Ethyl-cholest-6-ene-3,5-diol (23)	Steroid	*H. recurvum*	19
24	Ergosterol peroxide (24)	Steroid	*H. salicornicum*	13
25	24-Ethyl cholesta-3,5-diene (25)	Steroid	*H. salicornicum*	16
26	Recursterol A (26)	Steroid	*H. recurvum*	20
27	Recursterol B (27)	Steroid	*H. recurvum*	20
28	β-Sitosterol 3-O-β-D-glucopyranoside (28)	Steroidal glycoside	*H. recurvum* *H. salicornicum*	12,16
29	Recurvoside A (29)	Steroidal glycoside	*H. recurvum*	21
30	Recurvoside B (30)	Steroidal glycoside	*H. recurvum*	21
31	24β(24S)-ethyl-cholesta-4,22-E-diene-3-*O*-β-D-glucoside (31)	Steroidal glycoside	*H. salicornicum*	13
32	24β(24S)-ethyl-cholesta-4,22-E-diene-3-*O*-α-L-rhamnoside (32)	Steroidal glycoside	*H. salicornicum*	13
33	Ferulic acid (33)	Phenol derivative	*H. griffithii*	22
34	2,6-Dimethoxy-4-hydroxy acetophenone (34)	Phenol derivative	*H. griffithii*	22
35	p-Hydroxy acetophenone (35)	Phenol derivative	*H. griffithii*	22
36	Methyl 3,4-dihydroxy cinnamate (36)	Phenol derivative	*H. griffithii*	22
37	Methyl 4-hydroxy-3-methoxy cinnamate (37)	Phenol derivative	*H. griffithii*	22
38	Herniarin (38)	Coumarin	*H. griffithii*	22
39	Dihydroisocoumarin (39)	Coumarin	*H. scoparium*	23
40	Scopoletin (40)	Coumarin	*H. salicornicum*	24
41	Scopolin (41)	Coumarin	*H. salicornicum*	24
42	Umbelliferone (42)	Coumarin	*H. salicornicum*	24
43	Xanthotoxol (43)	Coumarin	*H. salicornicum*	24
44	Isooxyimperatorin (44)	Coumarin	*H. salicornicum*	24
45	Esculetin (45)	Coumarin	*H. salicornicum*	24
46	Salsolidine (46)	Tetrahydroisoquinoline alkaloid	*H. articulatum*	25
47	*N*-Methyl isosalsoline (47)	Tetrahydroisoquinoline alkaloid	*H. articulatum*	25
48	Carnegine (48)	Tetrahydroisoquinoline alkaloid	*H. articulatum*	25
49	Tryptamine (49)	Indole alkaloid	*H. articulatum*	26
50	Dipterine (50)	Indole alkaloid	*H. articulatum*	26
51	Isosalsoline (51)	Isoquinoline alkaloid	*H. articulatum*	26
52	Dehydrosalsolidine (52)	Isoquinoline alkaloid	*H. articulatum*	26
53	Isosalsolidine (53)	Isoquinoline alkaloid	*H. articulatum*	26
54	*N*-methylcorydaldine (54)	Isoquinolone alkaloid	*H. articulatum*	26
55	Tetrahydroharman (55)	β-Carboline alkaloid	*H. articulatum*	26
56	Laptocladine (56)	β-Carboline alkaloid	*H. articulatum*	27
57	3-Methyl-1,2,3,4- tetrahydro-β-carboline (57)	β-Carboline alkaloid	*H. articulatum*	27
58	2-Methyl-1,2,3,4-tetrahydro-β-carboline (58)	β-Carboline alkaloid	*H. articulatum*	25
59	*N*-Acetylpiperidine (59)	Piperidine alkaloid	*H. salicornicum*	28
60	Piperidine (60)	Piperidine alkaloid	*H. salicornicum*	28,31,32
61	Aldotripiperidiene (61)	Piperidine alkaloid	*H. salicornicum*	28,31
62	Haloxine (62)	Piperidine alkaloid	*H. salicornicum*	28,31
63	Halosaline (63)	Piperidine alkaloid	*H. salicornicum*	28,31
64	Simpine (64)	Piperidine alkaloid	*H. salicornicum*	28
65	*N*-(2-Hydroxy ethyl) piperidine (65)	Piperidine alkaloid	*H. salicornicum*	28
66	3,4-Dihydro-5-(2-piperidinyl)-1(2H)pyridine carboxaldehyde (66)	Piperidine alkaloid	*H. salicornicum*	28
67	Anabasine (67)	Piperidine alkaloid	*H. salicornicum* *H. persicum*	28,29,30

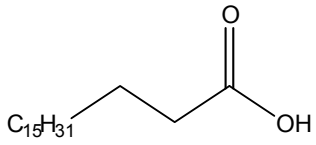
Table-1: Contine

68	**Haloxyline A (68)**	**Piperidine alkaloid**	***H. salicornicum***	**33**
69	**Haloxyline B (69)**	**Piperidine alkaloid**	***H. salicornicum***	**33**
70	**Nicotine (70)**	**Pyridine alkaloid**	***H. persicum***	**29,30**
71	**Cotinine (71)**	**Pyridine alkaloid**	***H. persicum***	**30**
72	**Methyl nicotinate (72)**	**Pyridine alkaloid**	***H. salicornicum***	**28**
73	**Betaine (73)**	**Aliphatic quaternary alkaloid**	***H. salicornicum***	**31**
74	**Betaine chloride (74)**	**Aliphatic quaternary alkaloid**	***H. persicum***	**34**
75	**Tyramine (75)**	**Phenylethylamine alkaloid**	***H. salicornicum***	**35**
76	***N*-Methyltyramine (76)**	**Phenylethylamine alkaloid**	***H. salicornicum***	**28,35**
77	**Phenethylamine (77)**	**Phenylethylamine alkaloid**	***H. salicornicum***	**28**
78	***N*-Methylphenethylamine (78)**	**Phenylethylamine alkaloid**	***H. salicornicum***	**28**
79	**Hordenine (79)**	**Phenylethylamine alkaloid**	***H. salicornicum***	**28**
80	**Oxedrine (80)**	**Phenylethylamine alkaloid**	***H. salicornicum***	**31**
81	**Norephedrine (81)**	**N-Containing compound**	***H. salicornicum***	**28**
82	**Ammodendrine (82)**	**N-Containing compound**	***H. salicornicum***	**28**
83	**Haloxynine (83)**	**N-Containing compound**	***H. salicornicum***	**28**
84	**Cyclohexanedocosanol (84)**	**Monocyclic naphthene derivative**	***H. salicornicum***	**13**
85	**Cyclohexanetetracosanol (85)**	**Monocyclic naphthene derivative**	***H. salicornicum***	**13**
86	**Ursolic acid (86)**	**Terpene**	***H. salicornicum*** ***H. recurvum***	**12, 16**
87	**24-Nor-12-ursene (87)**	**Terpene**	***H. salicornicum***	**16**
88	**β-Amyrin (88)**	**Terpene**	***H. salicornicum***	**16**
89	**Lupeol (89)**	**Terpene**	***H. salicornicum***	**13**
90	**α-Pinene (90)**	**Terpene**	***H. schmittianum*** **Pomel**	**36**
91	**Camphene (91).**	**Terpene**	***H. schmittianum*** **Pomel**	**36**
92	**Caryophyllene (92)**	**Terpene**	***H. schmittianum*** **Pomel**	**36**
93	**Longifolene (93)**	**Terpene**	***H. schmittianum*** **Pomel**	**36**
94	**Germacrene D (94)**	**Terpene**	***H. schmittianum*** **Pomel**	**36**
95	**β-Fernesene (95)**	**Terpene**	***H. schmittianum*** **Pomel**	**36**
96	**Quercetin (96)**	**Flavonoid**	***H. salicornicum***	**35**
97	**Quercetin-7-O-rhamnoside (97)**	**Flavonoid glycoside**	***H. salicornicum***	**35**
98	**Isorhamnetin-3-O-β-D-xylopyranosyl-(1‴→3‴)-α-L-rhamnopyranosyl-(1‴→6″)-β-D-galactopyranoside (98)**	**Flavonoid glycoside**	***H. articulatum***	**37**
99	**Isorhamnetin-3-O-β-D- apiofuranosyl-(1‴→2″)|α-L-rhamnopyranosyl-(1‴→6″)|-β-D-galactopyranoside (99)**	**Flavonoid glycoside**	***H. articulatum***	**37**
100	**Isorhamnetin-3-O-α-L-rhamnopyranosyl-(1‴→2″)|α-L-rhamnopyranosyl-(1‴→6″)|-β-D-galactopyranoside (100)**	**Flavonoid glycoside**	***H. articulatum***	**37**
101	**Isorhamnetin-3-O-β-D-robinobioside (101)**	**Flavonoid glycoside**	***H. articulatum***	**26**
102	**Rutin (102)**	**Flavonoid glycoside**	***H. aphyllum***	**38**
103	**7-Hydroxy-4-triacontanone (103)**	**Other compound**	***H. salicornicum***	**16**
104	**24-Hydroxy-4-octacosanone (104)**	**Other compound**	***H. salicornicum***	**16**
105	**5-Hydroxy-3-methoxy-4H-pyran-4-one (105)**	**Other compound**	***H. salicornicum***	**39**
106	**Oxalic acid (106)**	**Other compound**	***H. aphyllum*** ***H. persicum***	**40**
107	**Citric acid (107)**	**Other compound**	***H. aphyllum*** ***H. persicum***	**40,41**

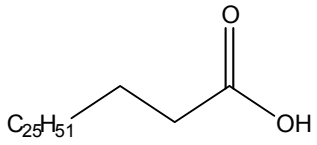
Hussain and co-workers in 2006 isolated new C-24 alkylated sterols, recursterol A (**26**) and recursterol B (**27**) from the chloroform fraction of *Haloxylon recurvum* [20]. Both compounds **26** and **27** showed promising inhibitory potential against the enzyme chymotrypsin with IC_{50} = 11.4±0.02 and 25.6±0.1, respectively whereas chymostatin is used as an standard (IC_{50} = 7.01±0.1).

Steroidal Glycosides

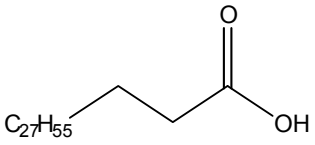
Ahmed and co-workers in 2004 isolated β-sitosterol 3-O-β-D-glucopyranoside (**28**) from chloroform soluble fraction of *H. recurvum* [12]. The compound **28** was screened for phytotoxicity but it was found to be inactive [12]. This compound **28** was also isolated from chloroform soluble fraction of *H. salicornicum* [16].



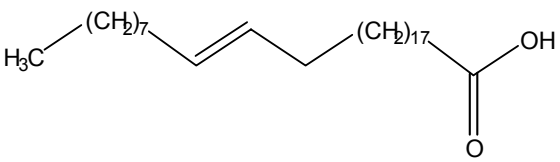
Octadecanoic acid (**1**)



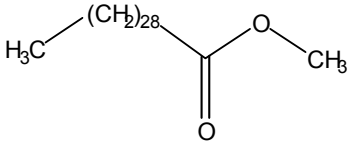
Octacosonic acid (**2**)



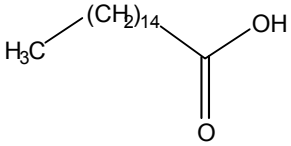
Triacontanoic acid (**3**)



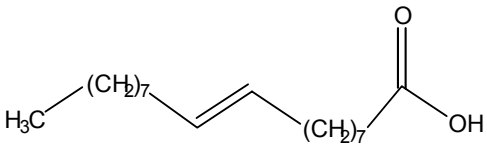
(E)-20-Nonacosenoic acid (**4**)



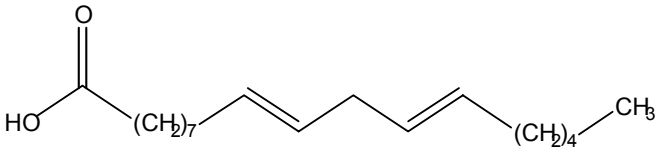
Methyl triacontanoate (**5**)



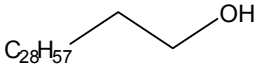
Palmitic acid (**6**)



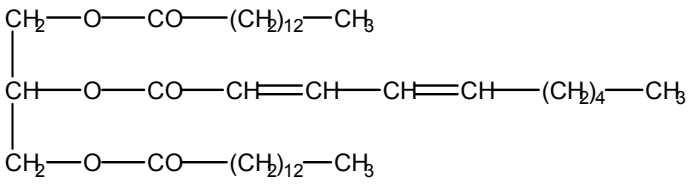
Oleic acid (**7**)



Linoleic acid (**8**)

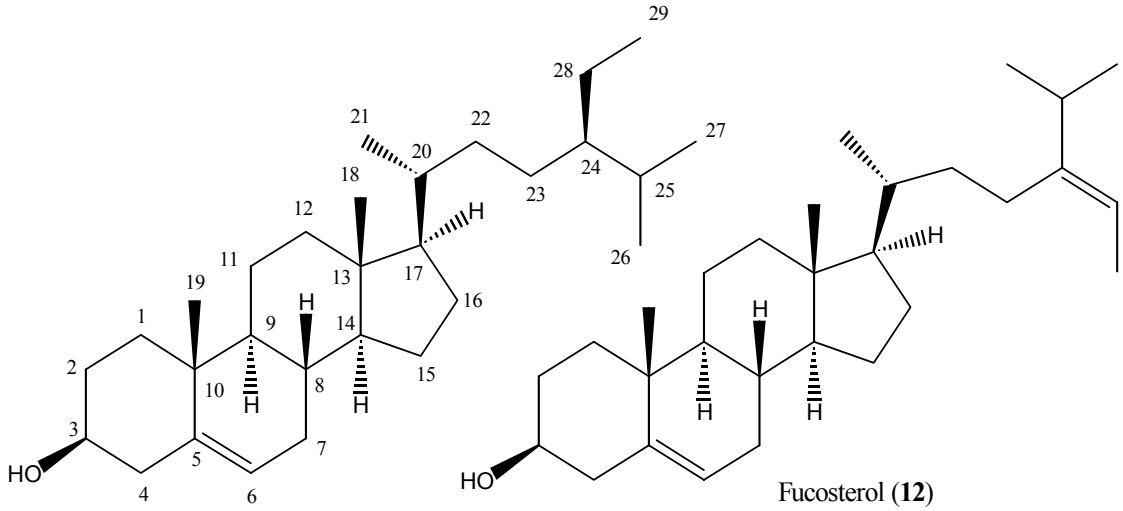


1-Triacontanol (**10**)



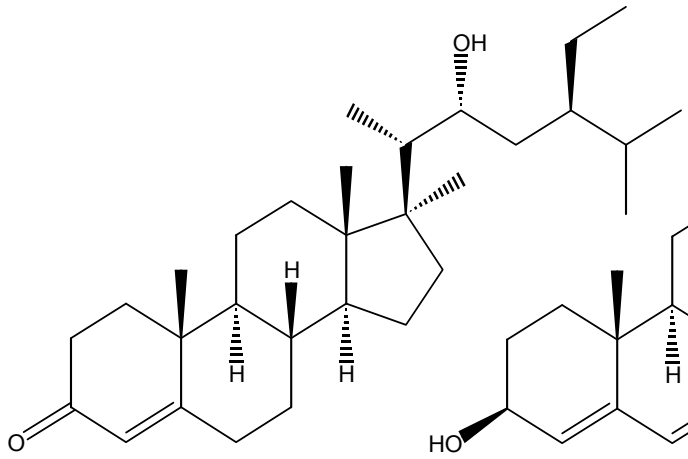
Haloxylase (**9**)

Fig. 1 Continue

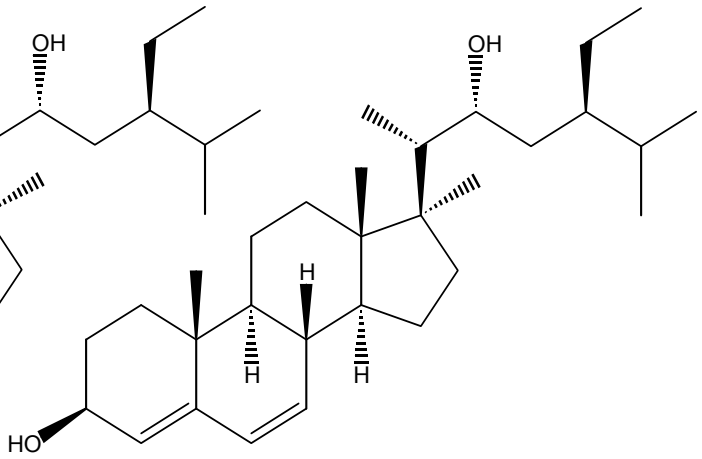


β-Sitosterol (**11**)

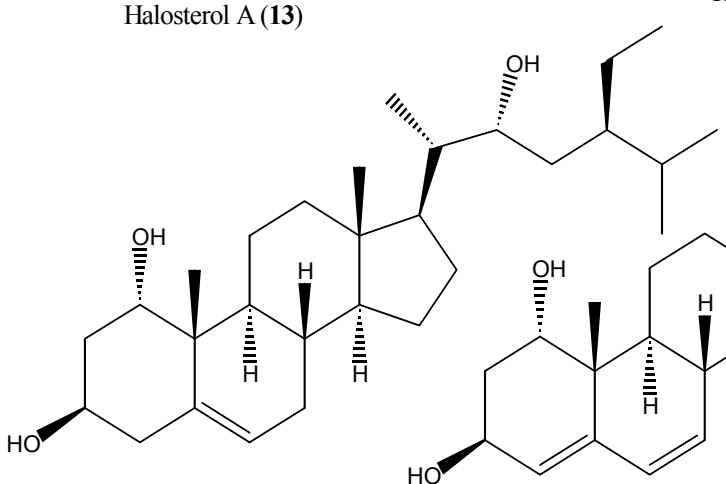
Fucosterol (**12**)



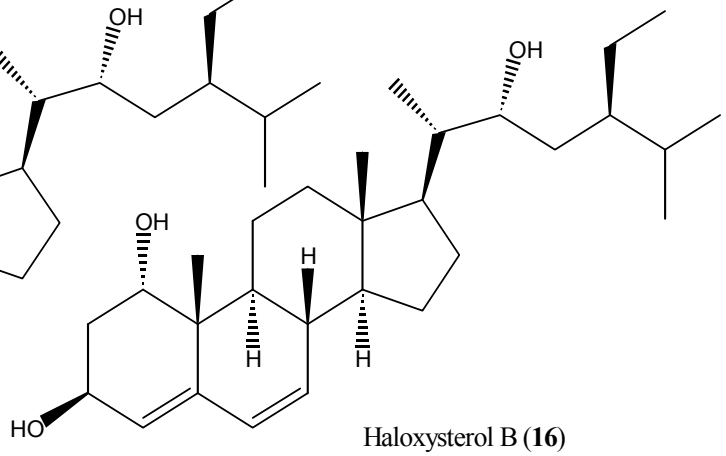
Halosterol A (**13**)



Halosterol B (**14**)

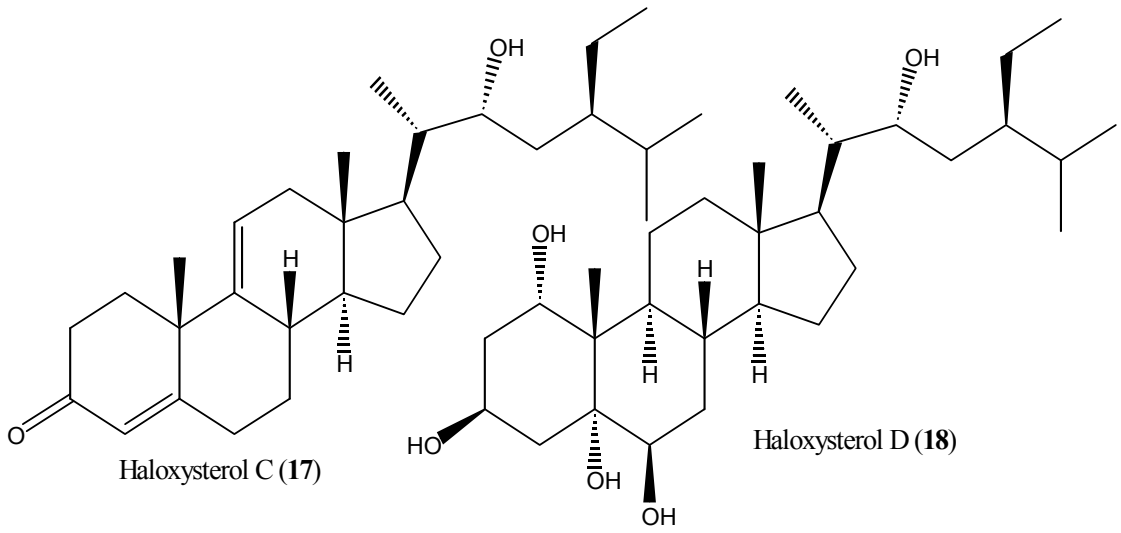


Haloxysterol A (**15**)



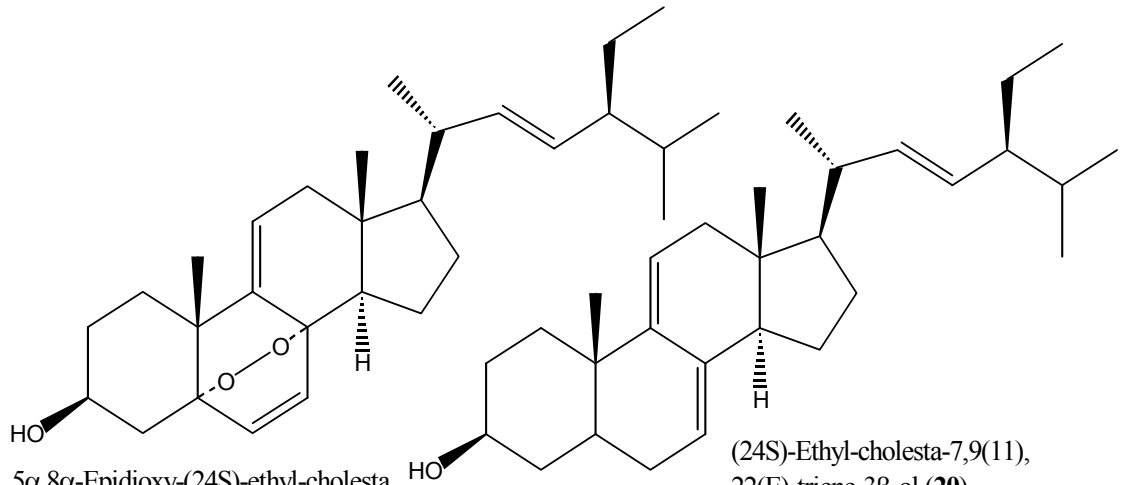
Haloxysterol B (**16**)

Fig. 1: Continue



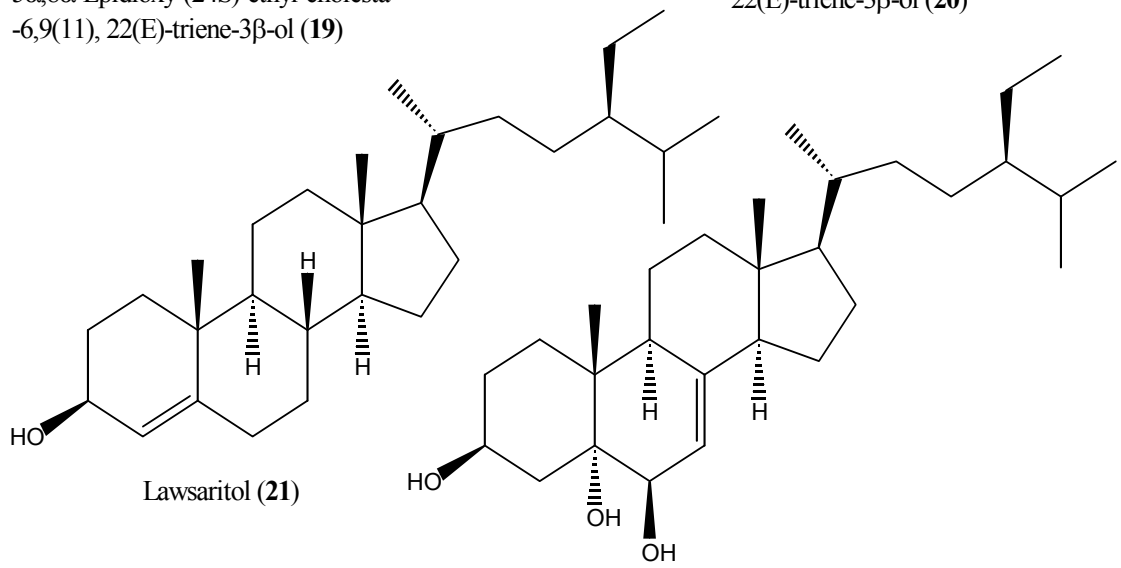
Haloxysterol C (**17**)

Haloxysterol D (**18**)



5α,8α-Epidioxy-(24S)-ethyl-cholesta -6,9(11), 22(E)-triene-3β-ol (**19**)

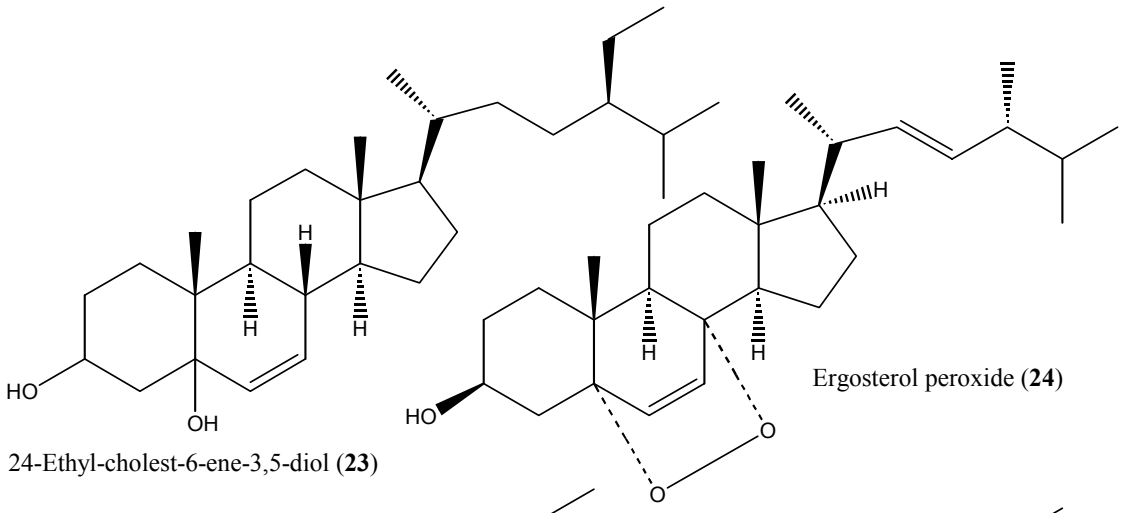
(24S)-Ethyl-cholesta-7,9(11), 22(E)-triene-3β-ol (**20**)



Lawsaritol (**21**)

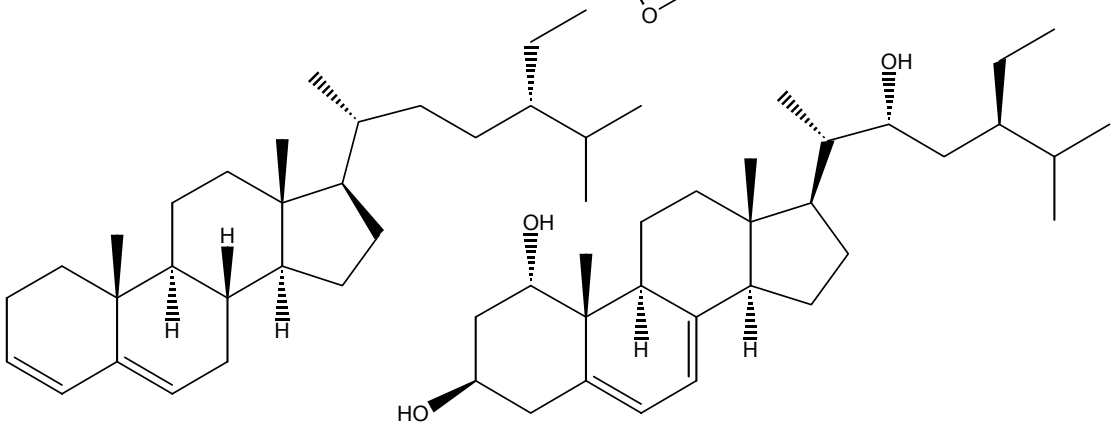
(24R)-Ethyl-5α-cholest-7-ene-3β,5,6β-triol (**22**)

Fig. 1: Continue



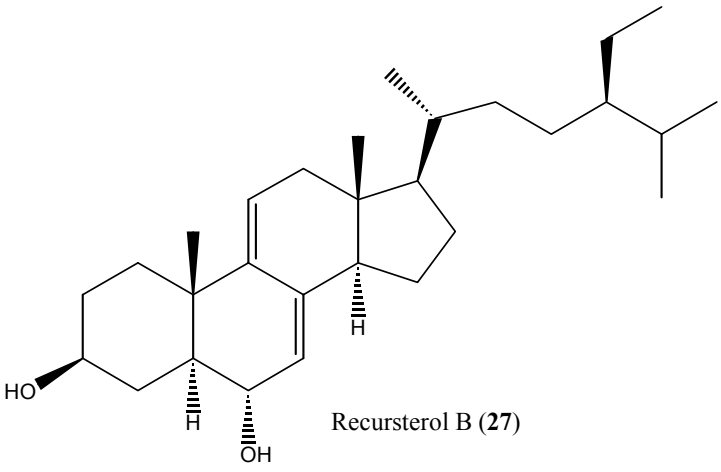
24-Ethyl-cholest-6-ene-3,5-diol (**23**)

Ergosterol peroxide (**24**)



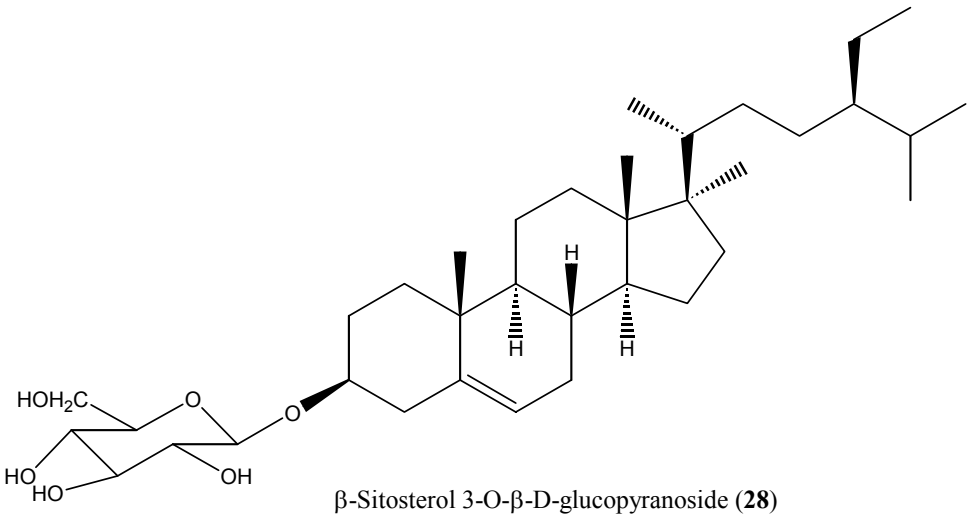
24-Ethyl cholesta-3,5-diene (**25**)

Recursterol A (**26**)

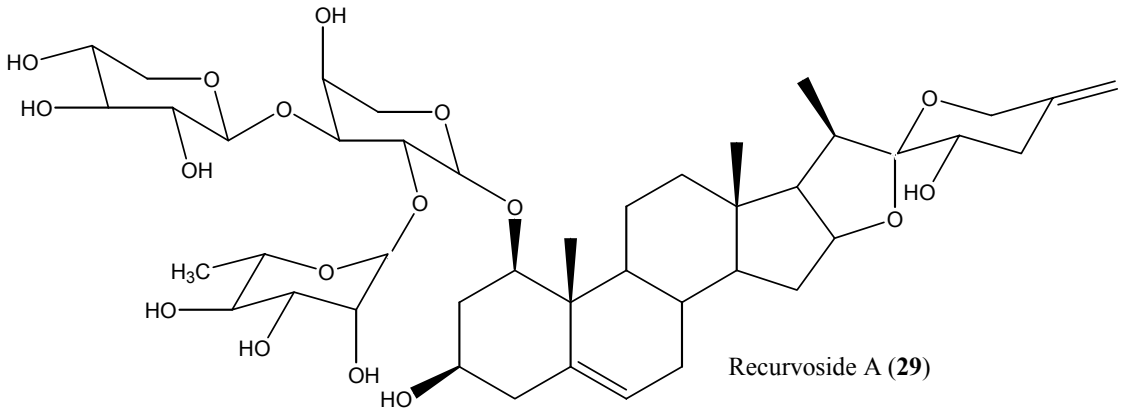


Recursterol B (**27**)

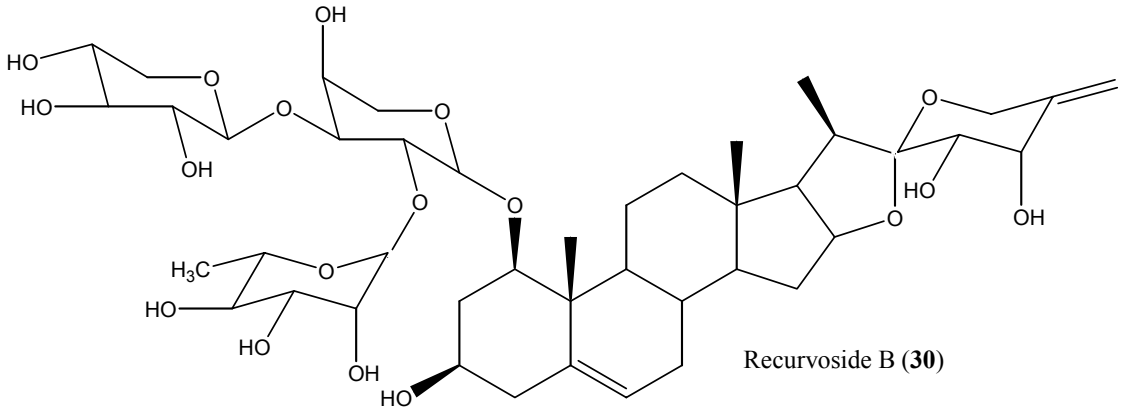
Fig. 1: Continue



β-Sitosterol 3-O-β-D-glucopyranoside (**28**)

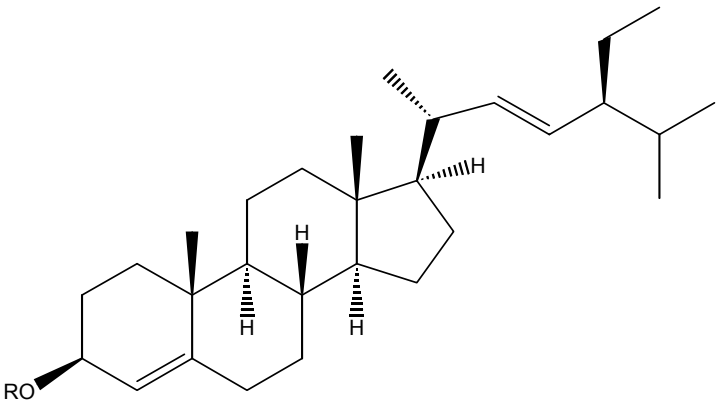


Recurvoside A (**29**)



Recurvoside B (**30**)

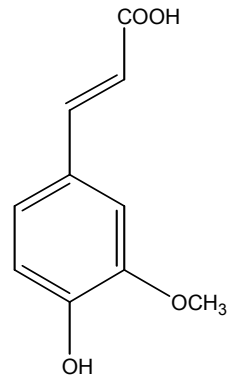
Fig. 1: Continue



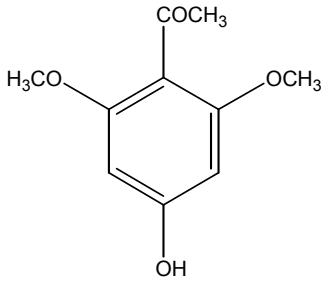
24β(24S)-Ethyl-cholesta-4,22-E-diene-3-O-β-D-glucoside (**31**)

24β(24S)-Ethyl-cholesta-4,22-E-diene-3-O-α-L-rhamnoside (**32**)

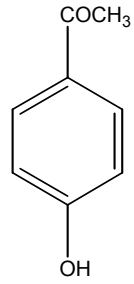
R = 3–O–β-D-Glucose or α-L-rhamonose



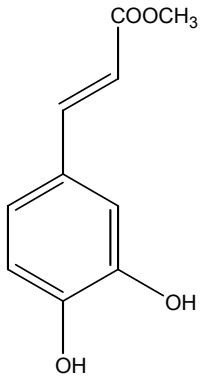
Ferulic acid (**33**)



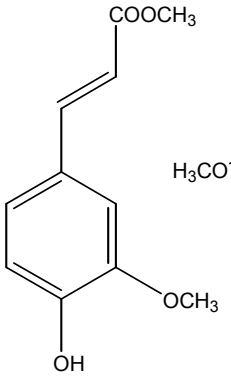
2,6-Dimethoxy-4-hydroxy acetophenone (**34**)



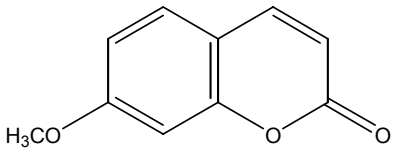
p-Hydroxy acetophenone (**35**)



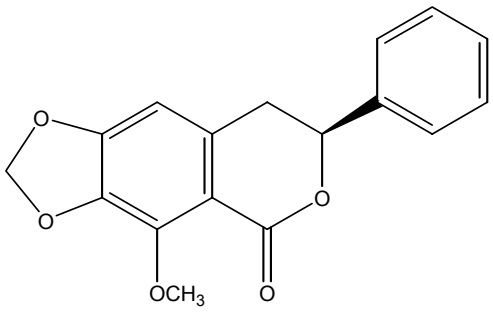
Methyl 3,4-dihydroxy cinnamate (**36**)



Methyl 4-hydroxy-3-methoxy cinnamate (**37**)

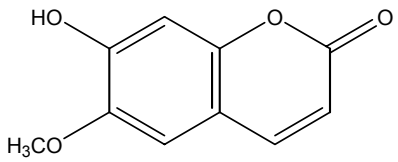


Herniarin (**38**)

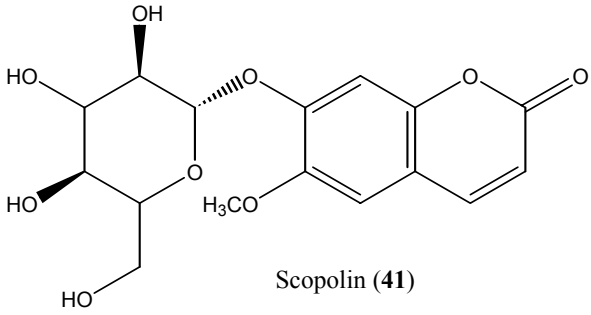


Dihydroisocoumarin (**39**)

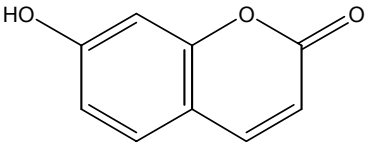
Fig. 1: Continue



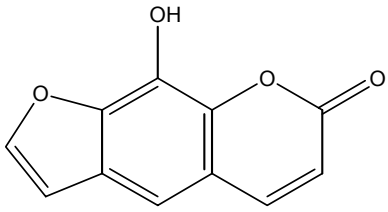
Scopoletin (**40**)



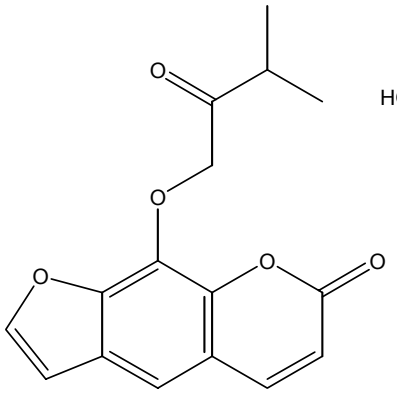
Scopolin (**41**)



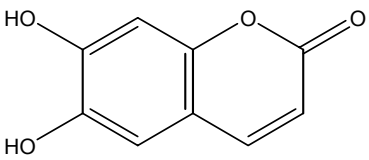
Umbelliferone (**42**)



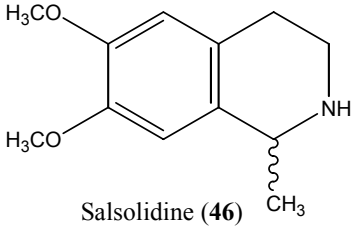
Xanthotoxol (**43**)



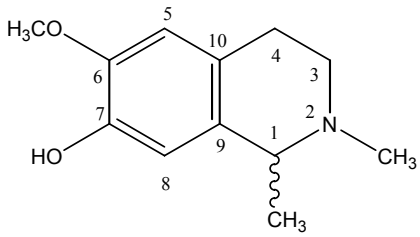
Isooxyimperatorin (**44**)



Esculetin (**45**)

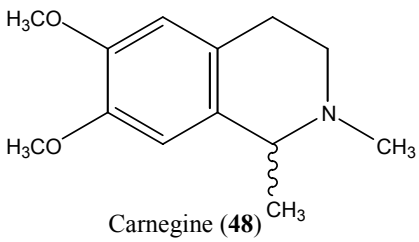


Salsolidine (**46**)

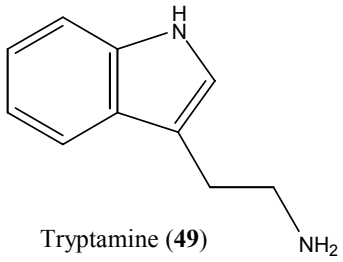


N-Methyl isosalsoline (**47**)

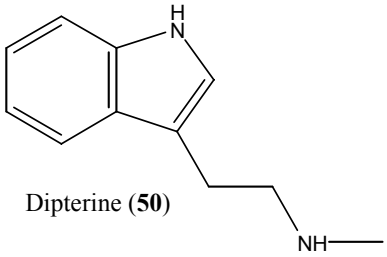
Fig. 1: Continue



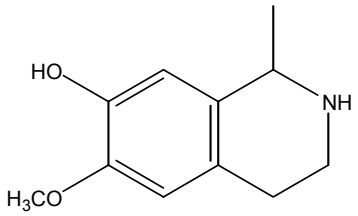
Carnegine (**48**)



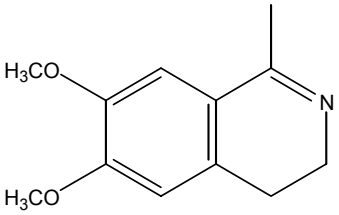
Tryptamine (**49**)



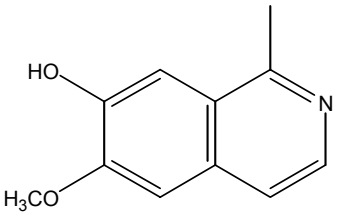
Dipterine (**50**)



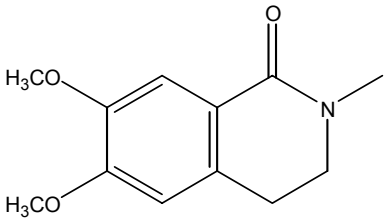
Isosalsoline (**51**)



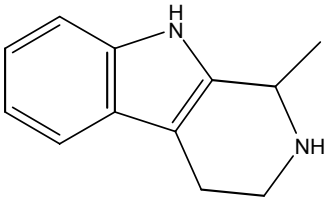
Dehydrosalsolidine (**52**)



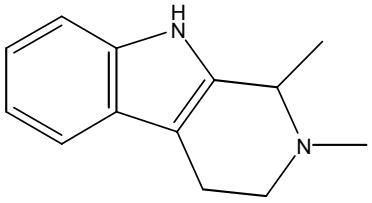
Isosalsolidine (**53**)



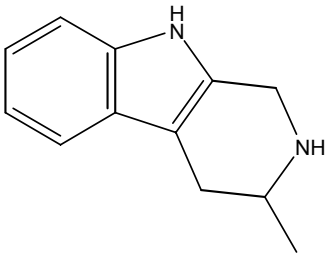
N-Methylcorydaldine (**54**)



Tetrahydroharman (**55**)

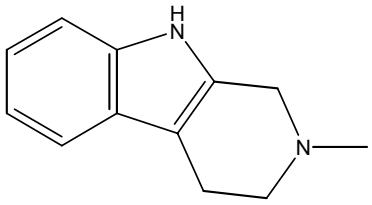


Laptocladine (**56**)

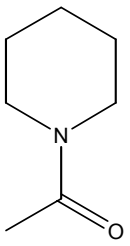


3-Methyl-1,2,3,4-tetrahydro-β-carboline (**57**)

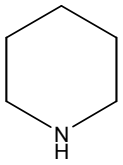
Fig. 1: Continue



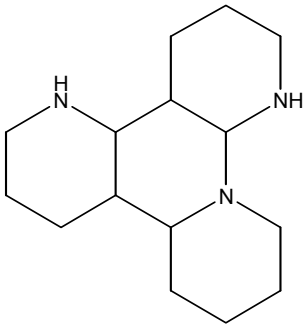
2-Methyl-1,2,3,4-tetrahydro-β-carboline (**58**)



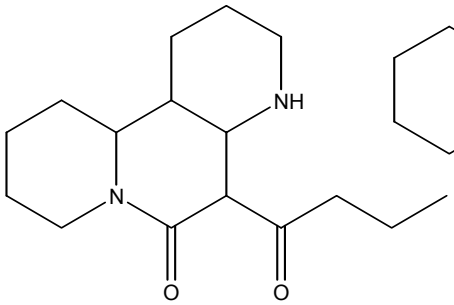
N-Acetylpiperidine (**59**)



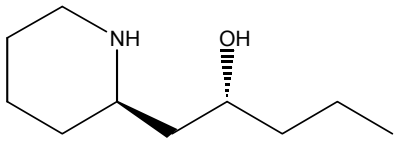
Piperidine (**60**)



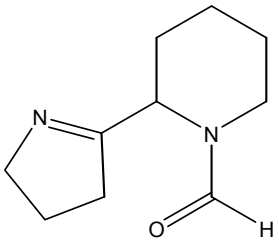
Aldotripiperidiene (**61**)



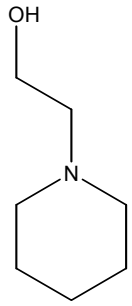
Haloxine (**62**)



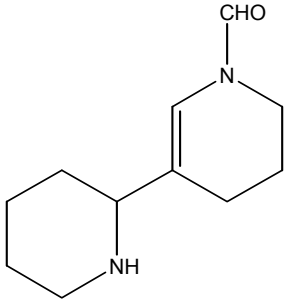
Halosaline (**63**)



Simpine (**64**)

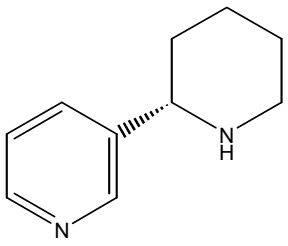


N-(2-Hydroxyethyl)piperidine (**65**)

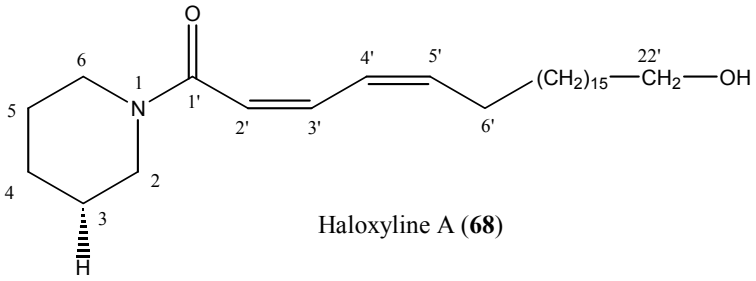


3,4-Dihydro-5-(2-piperidinyl)-1(2H) pyridinecarboxaldehyde (**66**)

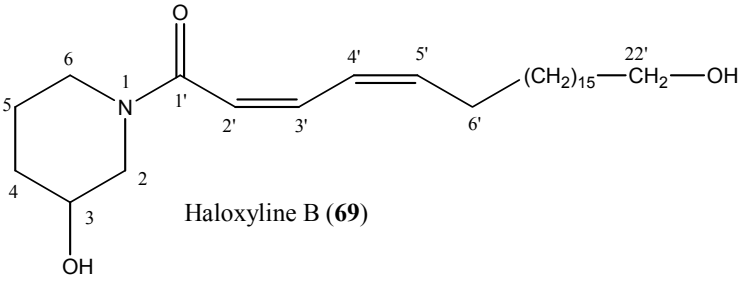
Fig. 1: Continue



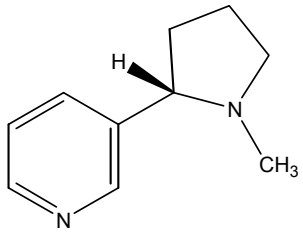
Anabasine (**67**)



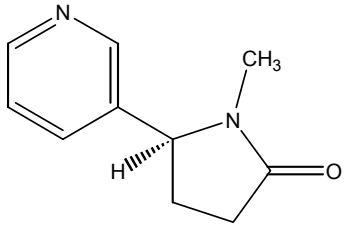
Haloxyline A (**68**)



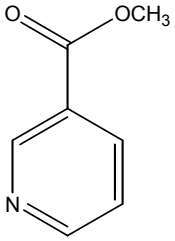
Haloxyline B (**69**)



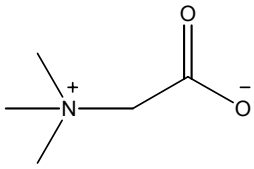
Nicotine (**70**)



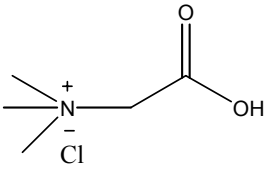
Cotinine (**71**)



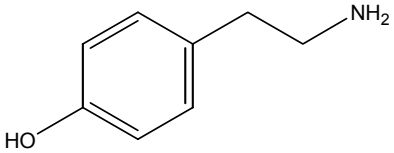
Methylnicotinate (**72**)



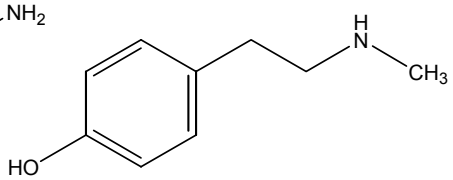
Betaine (**73**)



Betaine chloride (**74**)

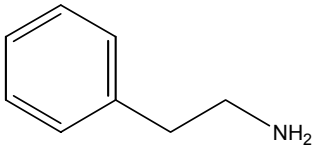


Tyramine (**75**)

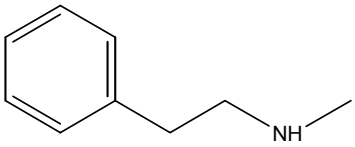


N-Methyl tyramine (**76**)

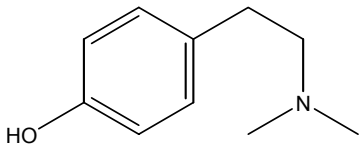
Fig. 1: Continue



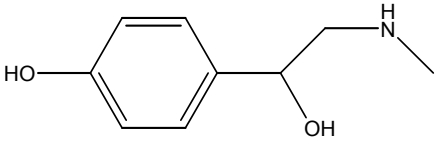
Phenethylamine (**77**)



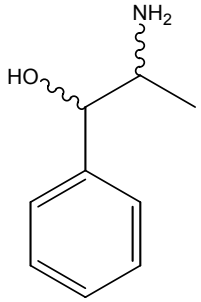
N-Methylphenethylamine (**78**)



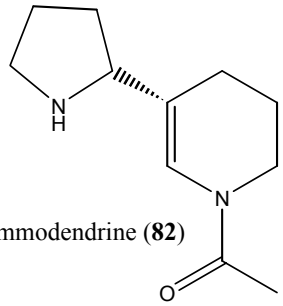
Hordenine (**79**)



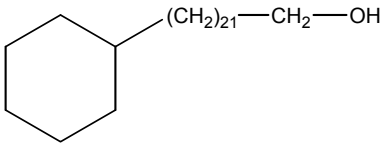
Oxedrine (**80**)



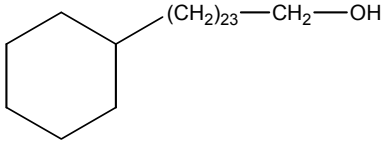
Norephedrine (**81**)



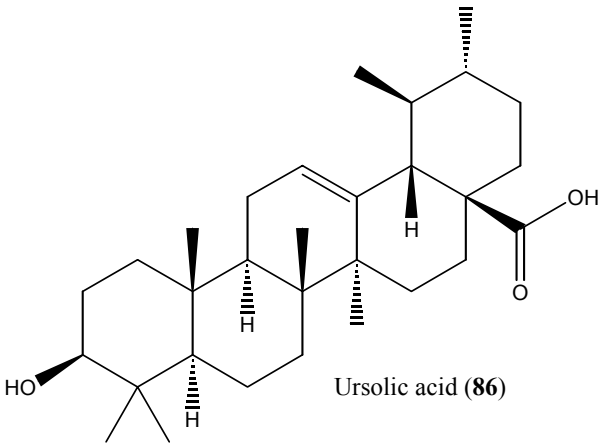
Ammodendrine (**82**)



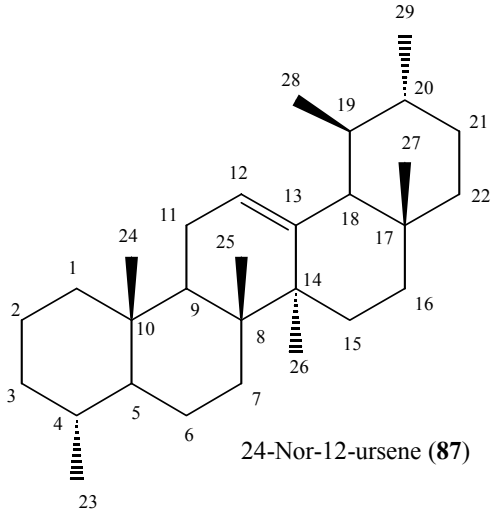
Cyclohexanedocosanol (**84**)



Cyclohexanetetracosanol (**85**)

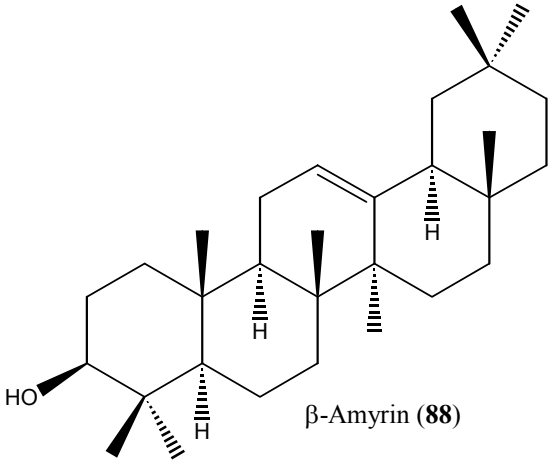


Ursolic acid (**86**)

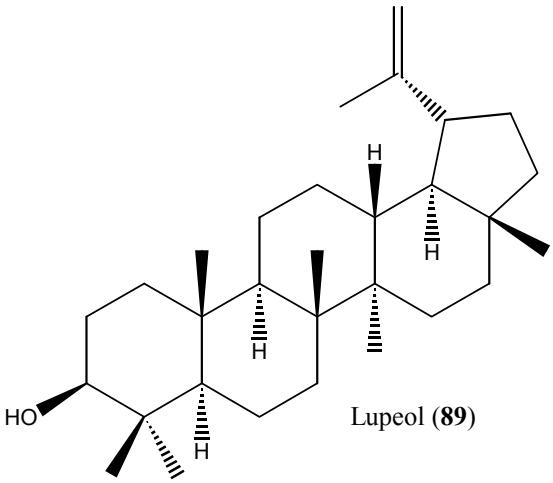


24-Nor-12-ursene (**87**)

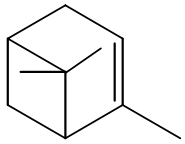
Fig. 1: Continue



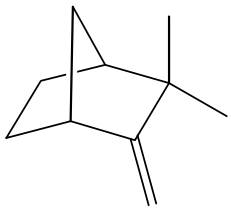
β-Amyrin (**88**)



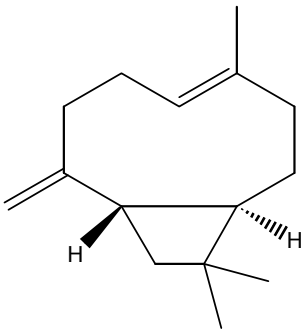
Lupeol (**89**)



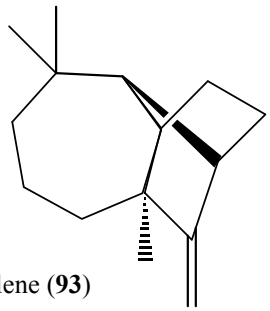
α-Pinene (**90**)



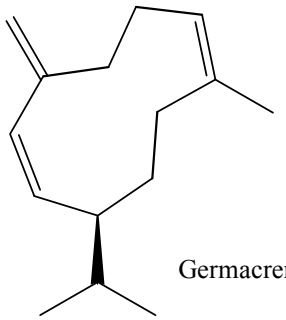
Camphene (**91**)



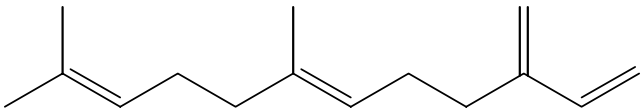
Caryophyllene (**92**)



Longifolene (**93**)

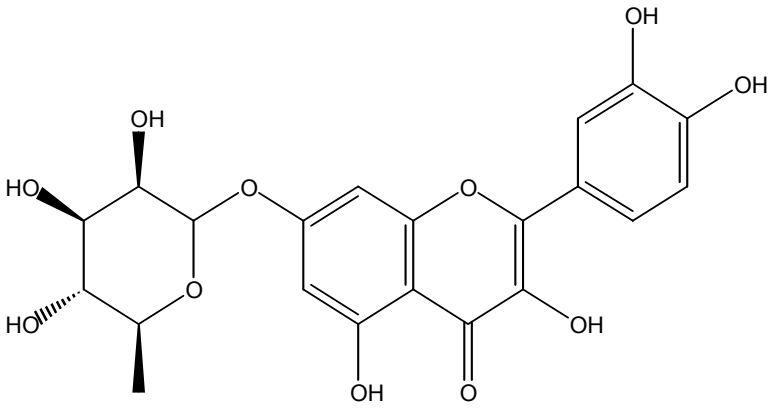


Germacrene D (**94**)

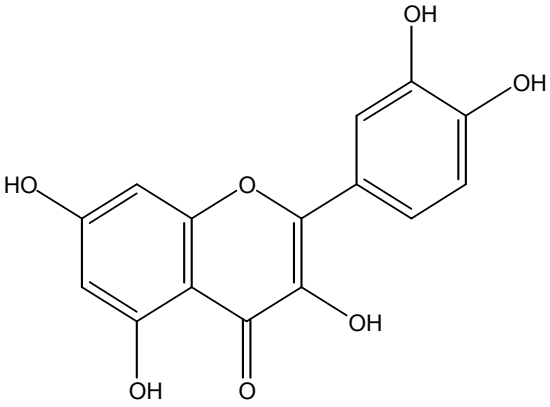


β-Fernesene (**95**)

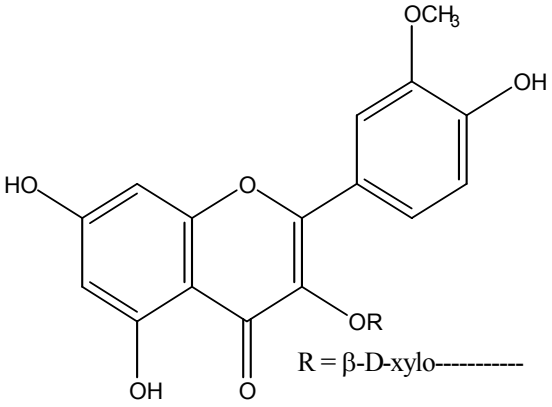
Fig. 1: Continue



Quercetin-7-O-rhamnoside (**97**)

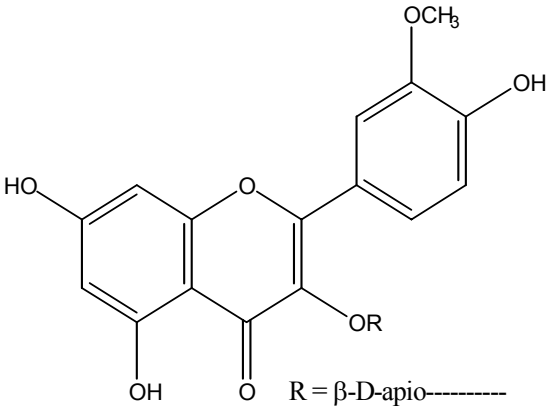


Quercetin (**96**)



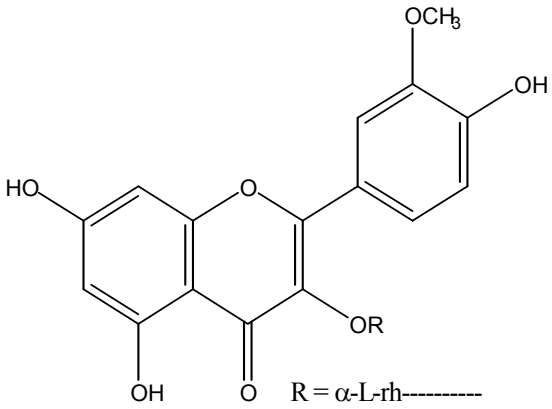
R = β-D-xylo----------

Isorhamnetin-3-O-β-D-xylopyranosyl-(1'''---3''')-α-L-rhamnopyranosyl -(1'''---6'')-β-D-galactopyranoside (**98**)



R = β-D-apio----------

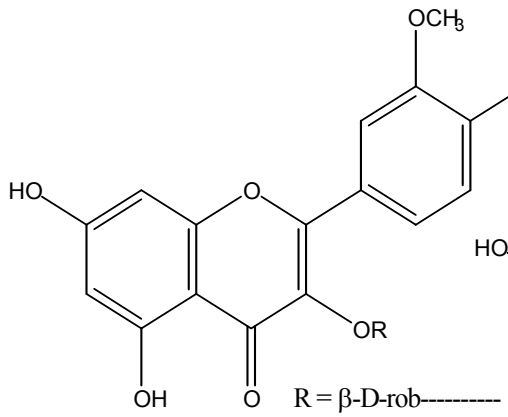
Isorhamnetin-3-O-β-D-apiofuranosyl-(1'''----2'') [α-L-rhamnopyranosyl-(1'''---6'')]-β-D-galactopyranoside (**99**)



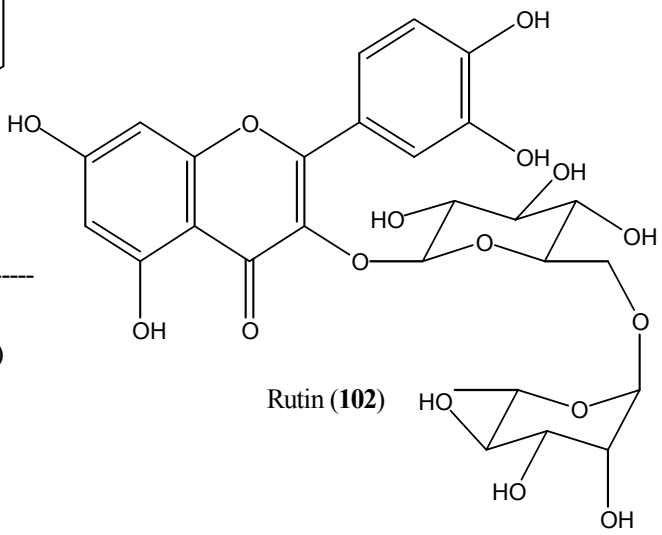
R = α-L-rh----------

Isorhamnetin-3-O-α-L-rhamnopyranosyl -(1'''----2'')[α-L-rhamnopyranosyl-(1'''---6'')]-β -D-galactopyranoside (**100**)

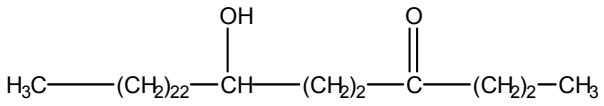
Fig. 1: Continue



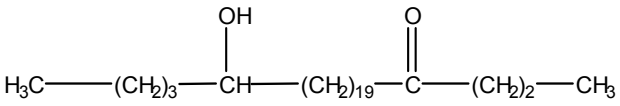
Isorhamnetin-3-O-β-D-robinobioside (**101**)



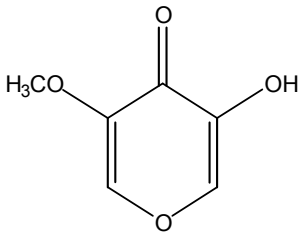
Rutin (**102**)



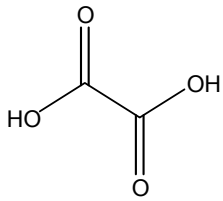
7-Hydroxy-4-triacontanone (**103**)



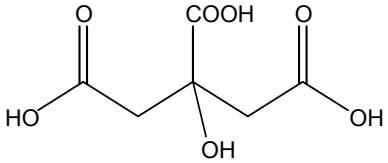
24-Hydroxy-4-octacosanone (**104**)



5-Hydrox-3-methoxy-4H-pyran-4-one (**105**)



Oxalic acid (**106**)



Citric acid (**107**)

Fig. 1: Structures of secondary metabolites isolated from *Haloxylon* species.

Sharif and co-workers in 2006 isolated two novel steroidal glucosides, recurvoside A (**29**) and recurvoside B (**30**) from ethyl acetate fraction of *H. recurvum* [21]. Both compounds **29** and **30** were screened against *Aspergillus flavus*, *Candida albicans*, *Candida glabrata* and *Fusarium solani,* and exhibited potent antifungal activity.

Ferheen and co-workers in 2005 isolated two allostigmasterol glycosides, 24β(24S)-ethyl-cholesta-4,22-E-diene-3-*O*-β-D-glucoside (**31**) and 24β(24S)-ethyl-cholesta-4,22-E-diene-3-*O*-α-L-rhamnoside (**32**) from methanolic extract of *H. salicornicum*. Both compounds **31** and **32** showed moderate lipoxygenase inhibitory activity with IC_{50} = 70.5±0.08 and 81.0±0.1, respectively. Baicalein was used as positive control (IC_{50} = 22.0±0.05) [13].

Phenol Derivatives

Choudhary and co-workers isolated ferulic acid (**33**), 2,6-dimethoxy-4-hydroxy acetophenone (**34**), p-hydroxy acetophenone (**35**), methyl 3,4-dihydroxy cinnamate (**36**) and methyl 4-hydroxy-3-methoxy cinnamate (**37**) from chloroform soluble fraction of *Haloxylon griffithii* [22]. These compounds **33**-**37** were screened against lipoxygenase enzyme. Methyl 3,4-dihydroxy cinnamate (**36**) was found moderate active (IC_{50} = 86.10±2.80) whereas others did not show any lipoxygenase inhibitory activity. These compounds **33**-**37** were also submitted for respiratory burst inhibition in human neutrophils. Methyl 3,4-dihydroxy cinnamate (**36**) showed again the most potent respiratory burst inhibitory activity in human neutrophils (IC_{50} = 150.26 ± 1.14) among all the compounds. 2,6-Dimethoxy-4-hydroxy acetophenone (**34**) also showed significant activity (IC_{50} = 655.71 ± 2.56) whereas methyl 4-hydroxy-3-methoxy cinnamate (**37**) showed moderate respiratory burst inhibitory activity (IC_{50} = 1449.42 ± 2.56). All others were found inactive against respiratory burst in human neutrophils [22].

Coumarins

Choudhary and co-workers in 2006 isolated herniarin (**38**) from chloroform soluble fraction of *H. griffithii*, which was screened for respiratory burst and lipoxygenase inhibitory activities. It showed moderate respiratory burst inhibitory activity in human neutrophils (IC_{50} = 1991.70 ± 0.21) and did not show any lipoxygenase inhibitory activity [22].

Li and co-workers in 2010 isolated dihydroisocoumarin (**39**) from dichloromethane fraction of *H. scoparium* with the aid of a functional assay with Xenopus oocytes transiently expressing GABAA receptors of defined subunit compn. (α1β2γ2S) [23]. Dihydroisocoumarin (**39**) induced a maximum potentiation of the chloride currents by 144.6 ± 35.3% with an EC_{50} of 140.2 ± 51.2 μM. Various coumarins, scopoletin (**40**), scopolin (**41**), umbelliferone (**42**), xanthotoxol (**43**), isooxyimperatorin (**44**) and esculetin (**45**) were isolated from *H. salicornicum* [24].

Alkaloids

(i) Tetrahydroisoquinoline Alkaloids

El-Shazly and Wink in 2003 isolated salsolidine (**46**), N-methyl isosalsoline (**47**) and carnegine (**48**) from *H. Articulatum* [25].

(ii) Indole Alkaloids

Benkrief and co-workers in 1990 isolated indole alkaloids including tryptamine (**49**) and dipterine (**50**) from *Haloxylon articulatum* [26].

(iii) Isoquinoline Alkaloids

Benkrief and co-workers in 1990 also isolated isosalsoline (**51**), dehydrosalsolidine (**52**) and isosalsolidine (**53**) from *H. articulatum* [26].

(iv) Isoquinolone Alkaloids

Benkrief and co-workers in 1990 also isolated N-methylcorydaldine (**54**) from *H. articulatum* [26].

(v) β-Carboline Alkaloids

Benkrief and co-workers in 1990 also isolated tetrahydroharman (**55**) from *H. articulatum* [26]. Orzakuliev and co-workers in 1964 isolated laptocladine (**56**) and 3-methyl-1,2,3,4-tetrahydro-β-carboline (**57**) from *H. articulatum* [27] whereas El-Shazly and Wink in 2003 isolated 2-methyl-1,2,3,4-tetrahydro-β-carboline (**58**) from *H. articulatum* [25].

(vi) Piperidine Alkaloids

El-Shazly and co-workers in 2005 isolated N-acetylpiperidine (**59**), piperidine (**60**), aldotripiperidiene (**61**), haloxine (**62**), halosaline (**63**), simpine (**64**), N-(2-hydroxy ethyl) piperidine (**65**), 3,4-dihydro-5-(2-piperidinyl)-1(2H)pyridine carboxaldehyde (**66**) and anabasine (**67**) from *H. salicornicum* [28]. Anabasine (**67**) was also isolated

from *H. persicum* [29, 30]. Michel and Sandberg in 1967 also isolated piperidine (**60**), aldotripiperidiene (**61**), haloxine (**62**) and halosaline (**63**) from *H. salicornicum* [31]. The crystal structure of haloxine (**60**) was also reported [32].

Ferheen and co-workers in 2005 isolated haloxyline A (**68**) and haloxyline B (**69**) from *H. salicornicum* [33]. Both compounds **68** and **69** displayed significant to moderate antifungal activities against *Candida albicans, Microsporum canis, Trichophyton longifusus, Aspergillus flavus, Fusarium solani and Candida glabrata.* The haloxyline B (**69**) was slightly more potent. Both compounds **68** and **69** also displayed moderate cholinesterase (AChE and BChE) inhibitory potential. Haloxyline B (**69**) was again slightly more potent. IC_{50} Values of haloxline A (**68**) and B (**69**) against acetylcholinesterase (AChE) were 25.3±0.02 and 20.2±0.01, respectively, whereas against butyrylcholinesterase (BChE) were 19.0±0.03 and 14.7±0.02, respectively [33].

(vii) Pyridine Alkaloids

Habib and co-workers in 1974 isolated nicotine (**70**) from *H. persicum* [29]. Muhtadi and Hussain in 1981 reported the presence of nicotine (**70**) and cotinine (**71**) in *H. persicum* as minor alkaloids [30]. El-Shazly and co-workers in 2005 isolated methylnicotinate (**72**) from *H. salicornicum* [28].

(viii) Aliphatic Quatneray Alkaloids

Michel and Sandberg in 1967 isolated betaine (**73**) from *H. salicornicum* [31]. Habib and co-workers in 1974 isolated betaine chloride (**74**), a quaternary base from *H. persicum* [3].

(ix) Phenylethylamine Alkaloids

Michel and Sandberg in 1968 isolated tyramine (**75**) and N-methyltyramine (**76**) from *H. salicornicum* [35]. El-Shazly and co-workers in 2005 also isolated N-methyltyramine (**76**), phenethylamine (**77**), N-methylphenethylamine (**78**) and hordenine (**79**) from *H. salicornicum* [28]. Michel and Sandberg in 1967 isolated oxedrine (**80**) from *H. salicornicum* [31].

(x) N-Containing Compounds

El-Shazly and co-workers in 2005 isolated norephedrine (**81**), ammodendrine (**82**) and haloxynine (**83**) from *H. salicornicum* [28]. Haloxynine (**83**) is a piperidyl alkaloid, whose structure was not found. Michel and Sandberg in 1967 isolated base 3, base 5, and base 7 from *H. salicornicum*, whose molecular formula were $C_{15}H_{27}N_3O$ and $C_{17}H_{27}N_3O$, respectively and molecular formula of base 7 was not found [31]. Their structrues were also not found.

Monocyclic Naphthene Derivatives

Ferheen and co-workers in 2005 isolated cyclohexanedocosanol (**84**) and cyclohexan-etetracosanol (**85**) from methanolic extract of *H. salicornicum*. They showed moderate lipoxygenase inhibitory activity [13].

Terpenes

Ferheen and co-workers in 2005 isolated first time ursolic acid (**86**), 24-nor-12-ursene (**87**) and β-amyrin (**88**) from chloroform soluble fraction of *H. salicornicum* [16]. These compounds **86-88** were screened for phytotoxicity but were found to be inactive [16]. Ahmed and co-workers in 2004 isolated ursolic acid (**86**) from *H. recurvum* [12]. Lupeol (**89**) was also isolated from methanolic extract of *H. salicornicum* [13].

Furthermore, Aboutabl and co-workers in 1997 also analyzed the volatile oil of *H. schmittianum* Pomel and revealed the presence of monoterpenes including α-pinene (**90**) and camphene (**91**). Sesquiterpenes, caryophyllene (**92**), longifolene (**93**), germacrene D (**94**) and β-fernesene (**95**) were also identified [36]. This volatile oil of *H. schmittianum* Pomel exhibited antimicrobial activity against *Bacillus subtilis, Staphycoccus aureus, Escherichia coli* and *Saccheromyces cerevisiae* [36].

Flavonoids

Michel and Sandberg in 1968 isolated a well known compound, quercetin (**96**) from *H. salicornicum* [35].

Flavonoid Glycosides

Michel and Sandberg in 1968 isolated quercetin-7-*O*-rhamnoside (**97**) from *H. salicornicum* [35]. Salah and co-workers in 2002 isolated isorhamnetin-3-*O*-β-D-xylopyranosyl-(1‴→3‴)-α-L-rhamnopyranosyl-(1‴→6″)-β-D-galactopyranoside (**98**), isorhamnetin-3-*O*-β-D-apiofuranosyl-(1‴→2″)[α-L-rhamnopyranosyl-(1‴→6″)]-β-D-galactopyranoside (**99**) and isorhamnetin-3-*O*-α-L-rhamnopyranosyl-(1‴→2″)[α-L-rhamnopyranosyl-

(1‴→6″)]-β-D-galactopyranoside (**100**) from *Haloxylon articulatum* [37].

Benkrief and co-workers in 1990 isolated isorhamnetin-3-*O*-β-D-robinobioside (**101**) from *H. articulatum* [26]. Rutin (**102**) was also identified in higher amount in *H. aphyllum* [38].

Other Compounds

Ferheen and co-workers in 2005 isolated 7-hydroxy-4-triacontanone (**103**) and 24-hydroxy-4-octacosanone (**104**) from chloroform soluble fraction of *H. salicornicum* [16]. Simon and co-workers in 2000 isolated 5-hydroxy-3-methoxy-4H-pyran-4-one (**105**) from *H. salicornicum* [39]. The presence of oxalic acid (**106**) and citric acid (**107**) were reported in *H. aphyllum* and *H. persicum* [40,41].

Conclusions

Since the last decade, there has been considerable attention towards the phytochemical studies of the plants of genus *Haloxylon*. This review aimed to highlight the isolated secondary metabolites, **1**-**107** from various species of the genus *Haloxylon.* Regarding this detailed survey, it is assumed that no more phytochemical and pharmacological investigation has ever been carried out on *Haloxylon* species as well as biological activities of whole plants and their isolated secondary metabolites.

Acknowledgement

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