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Phytochemical and pharmacological aspects of genus *haplophyllum* (Rutaceae): A review

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***Abstract*---**The genus *Haplophyllum* belongs to the large family of flowering plants, Rutaceae. The genus *Haplophyllum* comprises of about 133 species of low shrubs and perennial herbs in the subtropical and tropical regions of the northern hemisphere of the Old World, markedly in Iran, Turkey and Central Asia. Species from this genus contains a rich sources of secondary metabolites such as quinoline alkaloids, furoquinoline alkaloids, isoquinoline alkaloids, acridone alkaloids, amide alkaloids, quinolone alkaloids, lignans, arylnaphtalene lignans, lignan glycosides, flavonoids, coumarins, saponins, amides and sterols. Extracts and pure compounds isolated from *Haplophyllum* species have been experimentally shown to have various bioactivities such as antioxidant, anti-inflammatory, antimicrobial, insecticidal, antiprotozoal, molluscicidal, cytotoxic, anti-cancer and anti-HIV activities. This reviews compile the

phytochemical constituents, various pharmacological activities of the different plants of the *Haplophyllum* genus and the NMR value of different compounds of *Haplophyllum* genus.

Keywords---*Haplophyllum*, Phytochemicals, Alkaloids, Lignans, coumarins, flavonoids, saponins, sterols, amides, NMR, pharmacological activities.

1. Introduction

Rutaceae is a large family of flowering plants, commonly known as the rue or citrus family, of flowering plants, usually placed in the order Sapindales [1]. The rue family of flowering plants, comprises of 160 genera and about 2,070 species of woody shrubs and trees (and a few herbaceous perennials) and is distributed throughout the world. Which is found in most of the temperate and tropical regions of the world. The family contains a number of economically important fruit trees, genus and species [2]. The members of Rutaceae family have been used in perfumery, gastronomy, and traditional medicine. Phytochemical survey of this family reveals phytoconstituents such as alkaloids, coumarins, flavonoids, limonoids, and volatile oils [3] along with their different biological activities, for example, antimicrobial, [4] antidiarrhoeal, [5] anticholinesterasic, [6] antileishmanial, [7] antiprotozoal, [8] larvicidal, [9] and antioxidant activities [10]. *Haplophyllum* Jussieu is one of the richest genera in the Rutaceae family [11]**.** The genus *Haplophyllum* comprises over 133 species, out of which 73 are accepted species names [12]. The plants of genus *Haplophyllum* or its different parts are valued for its therapeutic and medicinal qualities[13]. The species of the genus are perennial herbs, sometimes low shrubs, which grow mainly on sandy, stony or rocky hills lopesinarid areas [14]. The genus is widely distributed in subtropical and tropical regions of the northern hemisphere of the Old World, notably in Iran, Turkey and Central Asia [11].*Haplophyllum* species contained alkaloids, lignans, coumarins, flavanoids, essential oil and volatile oil [15]**.** *Haplophyllum* species possessed many pharmacological activities included antioxidant, antimicrobial, insecticidal, antiprotozoal, molluscicidal, cytotoxic, cardiovascular, antiinflammatory and acetylcholinesterase inhibitory effects. The different parts of different species of this genus are used to treat various diseases including stomach-ache, nervous disorders, ulcer, hypnotic neurological, diabetes, liver disease, cardiac disease [16]. The aim of this paper is to accumulate information about the phytochemical constituents and also to compile various pharmacological studies of the different plants of the *Haplophyllum* genus.

2. Botanical Description

2.1. Habitat

Haplophyllum A. Juss, is a genus of Rutaceae, with 133 species [12] and reaches maximum species diversity in Turkey, Iran, and Central Asia (the latter region being bordered by the Caspian Sea in the west, China in the east, Iran and Afghanistan in the south, and Russia in the north). Many species of *Haplophyllum* exhibit an arrow geographic range (i.e.,“narrow endemics”), a feature that makes

them particularly vulnerable to extinction. Despite its importance for the characterization of the Irano-Turanian floristic region [17][18]. *Haplophyllum* species is distributed with different floristic regions: the Irano-Turanian, Mediterranean, Saharo-Arabian, and Sudano-Zambezian regions [17]. The main center of diversity of *Haplophyllum* is the Irano-Turanian region—in particular, Iran, Turkey, and Central Asia—which harbours 60% of the species diversity. Thirty species of *Haplophyllum* are present in Iran, fourteen of which are endemic to the country [19]. Fewer species occur in the other three floristic regions, most notably in the Mediterranean region, which contains 13% of the species diversity[14].

2.2. Toxonomic classification[20]

Kingdom:	Plantae
Phylum:	Tracheophyta
Class:	Magnoliopsida
Order:	Sapindales
Family:	Rutaceae
Genus:	*Haplophyllum*

2.3. Traditional uses

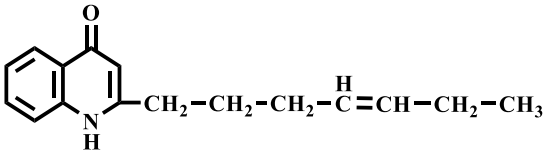
Haplophyllum species considered as a salve for wounds. In addition, the decoction also used as a cure in stomach-ache for children [21]. *Haplophyllum* species also have activity on central nervous system. The leaves of these plants are also given to children for the treatment of convulsion and other nervous disorders [22]. However, *Haplophyllum tuberculatum* is used in the treatment of various diseases including fever, liver disease, cardiac disease, diabetes, hypertension, rheumatism, otitis, constipation, diarrhea, flu, tonsillitis, menstrual pain, for injuries and ulcers, as calming, hypnotic neurological, as vermifuge, for obesity, colon, scorpion stings, vomiting, throat inflammation, cough, loss of appetite and also used as antiseptics [23]. In the north of Oman, the juice from the leaves was used as a remedy for headaches and arthritis. In Saudi Arabia, *Haplophyllum tuberculatum* are considered to be useful for easing headaches and arthritis, to treat skin discoloration, infections and parasitic diseases. In Sudan the herb was used as an antispasmodic, to treat allergic rhinitis, gynecological disorders, asthma and breathing difficulties [24-26].

3. Phytochemical Constituents

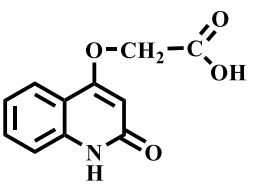
The phytochemical investigation on the different parts of different species of the *Haplophyllum* genus showed the presence of wide variety of chemical substances. A number of secondary metabolites such as alkaloids, lignans, coumarins, flavonoids, saponins, amides, sterols, essential oil and volatile oil have been isolated from different *Haplophyllum* species [15]. Among this the principal compounds found in *Haplophyllum* species are compiled in this paper.
Alkaloids isolated from the extracts of *Haplophyllum spp.* are compiled in Table 1.

Table 1: Alkaloids found in *Haplophyllum* species

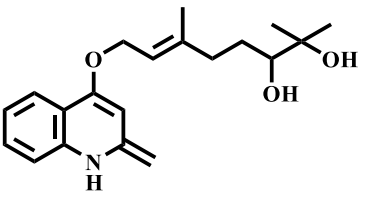
Compound	**References**
Acutine (1), Dictamnine (25), Leptomerine (38), N-Methyl-2-Phenylquinolin-4-One (43), 2-heptylquinoline-4-one (56),	[27]
Acutinine (2)	[102]
Bucharaine (3), Haplopine (9), 4-Hydroxyquinoline-2-one (27)	[30]
Daurine (45), Folimine (37), Robustinine (26), Robustine (11)	[28]
Dubinidine (4), Foliosine (28), Foliosidine (48)	[31]
Dubinine (5), Dubamine (44), Norgraveoline (29)	[29]
(+)-Dihydroperfamine (33)	[32]
Edulinine (51)	[86]
Evoxine (6), Flindersine (22), 3-(3,3-dimethylallyl)-4-(3,3-dimethylalloxy)-2-quinolone (54)	[45]
Glycohaplopine (50)	[33]
Heliparvifoline (8), Nkolbisine (40), Pteleine (10)	[34]
Haplophytin A (23, Haplophytin B (36),	[47]
Compound	**References**
Haplofoline (41), Malatyamine (59)	[35]
Haplophyllidine (34)	[36]
Haplamine (35)	[37]
Haplophylline (21), Kukusaginine (13),	[38]
Haplotubinone (39), Haplotubine (7)	[46]
Isoplatydesmine (42), Ribalinine (47), 4,8-dimethoxy-7-hydroxyfurol[2,3-b] quinoline (15)	[101]
Lunamarine (30), Ribalinidine (46)	[39]
(+)-Nigdenine (19), Vulcanine (53)	[40]
N-hydroxymethylflindersine (24), Skimmianine (12), γ-fagarine (14), 4,5,6-trimethoxyfuroquinoline (16), 4,5,7-trimethoxyfuroquinoline (17)	[43]
Perfamine (20)	[88]
Thehaplosine (49)	[41]
Tubacetine (31), Tubasenicine (32)	[48]
Glycoperine (50)	[104]
7-Hydroxy-9-methoxyflindersine (55)	[42]
Folipidine(57)	[44]
(+)-Tuberine (58), 7-Hydroxy-4-Methoxy-8-prenylfurol[2,3-b]quinoline (18)	[48]



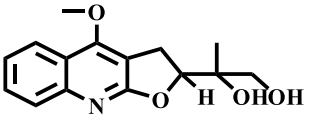
Acutine (1)



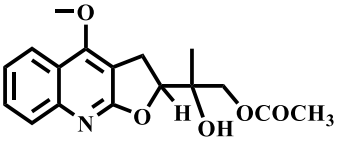
Acutinine (2)



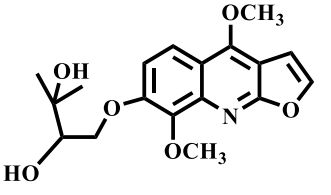
Bucharaine (3)



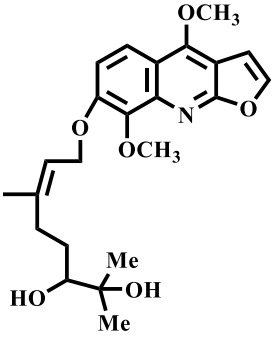
Dubinidine (4)



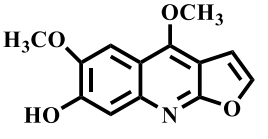
Dubinine (5)



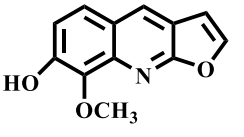
Evoxine (6)



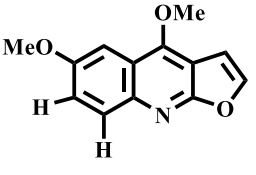
Haplotubine (7)



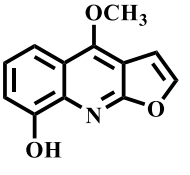
Heliparvifoline (8)



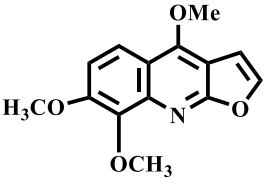
Haplopine (9)



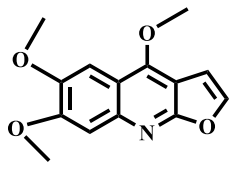
Pteleine (10)



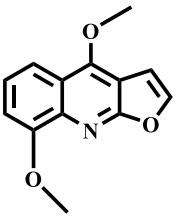
Robustine (11)



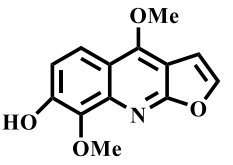
Skimmianine (12)



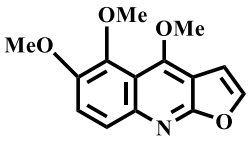
Kukusaginine (13)



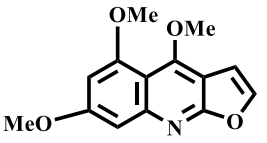
γ-fagarine (14)



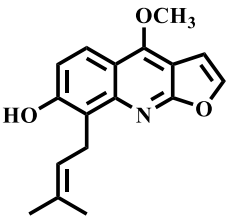
4,8-dimethoxy-7-hydroxyfurol [2,3-b] quinoline (15)



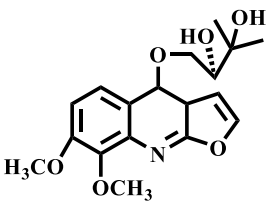
4,5,6-trimethoxyfuroquinoline (16)



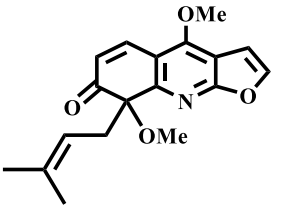
4,5,7-trimethoxyfuroquinoline (17)



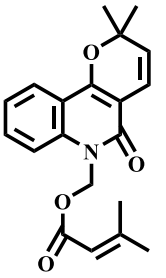
7-Hydroxy-4-Methoxy-8-prenylfurol[2,3-b]quinoline (18)



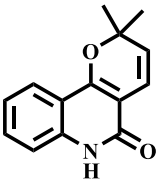
(+)-Nigdenine (19)



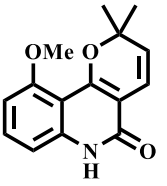
Perfamine (20)



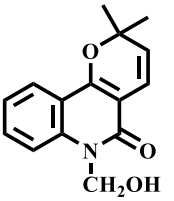
Haplophylline (21)



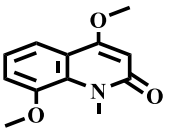
Flindersine (22)



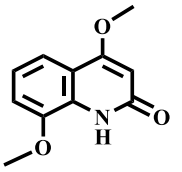
Haplophytin A (23)



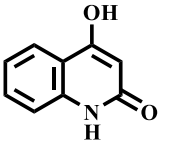
N-hydroxymethylflindersine (24)



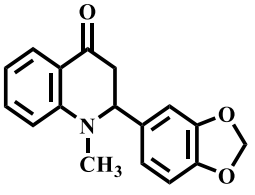
Dictamnine (25)



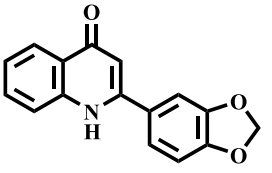
Robustinine (26)



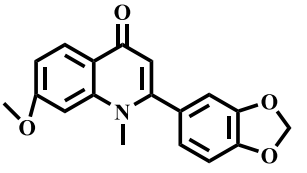
4-Hydroxyquinoline-2-one (27)



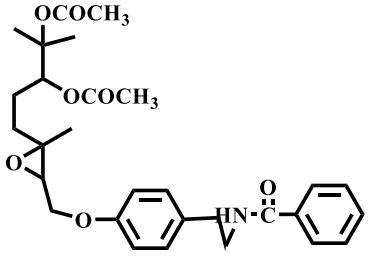
Foliosine (28)



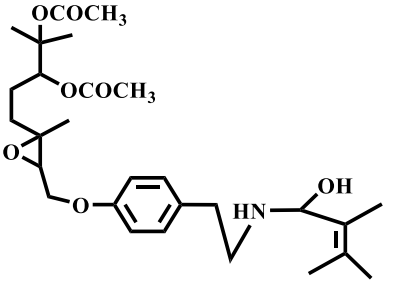
Norgraveoline (29)



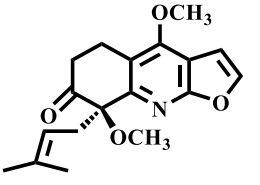
Lunamarine (30)



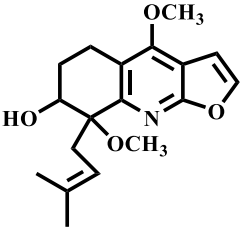
Tubacetine (31)



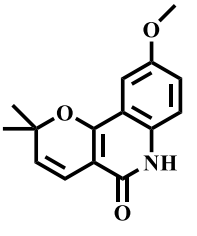
Tubasenicine (32)



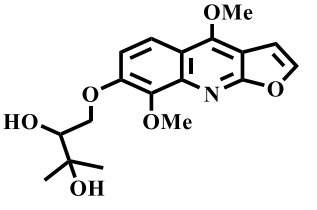
(+)-Dihydroperfamine (33)



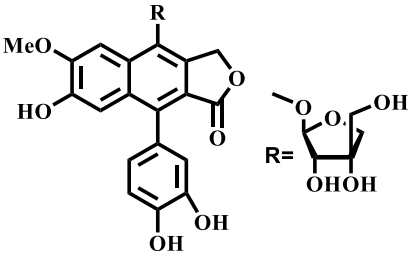
Haplophillidine (34)



Haplamine (35)



Haplophytin B (36)



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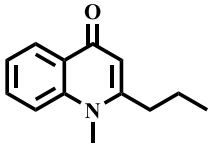
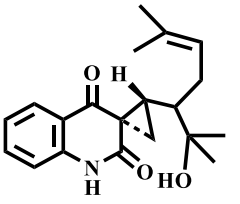
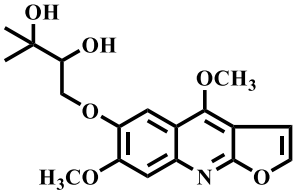


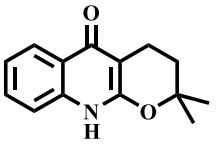
Leptomerine (38)



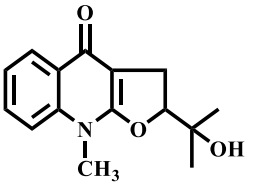
Haplotubinone (39)



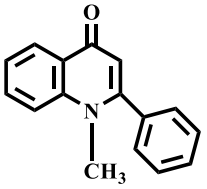
Nkolbisine (40)



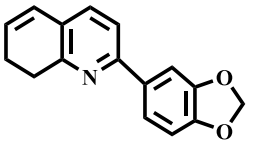
Haplofoline (41)



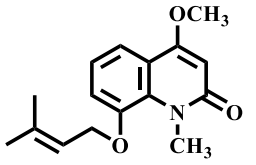
Isoplatydesmine (42)



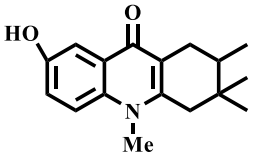
N-Methyl-2-Phenylquinolin-4-One (43)



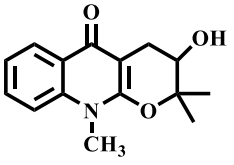
Dubamine (44)



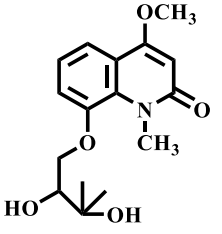
Daurine (45)



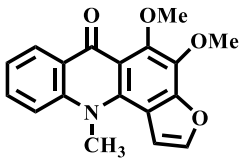
Ribalinidine (46)



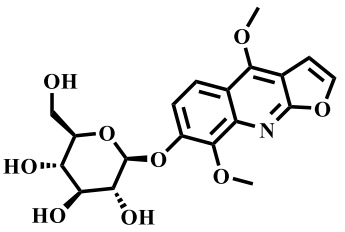
Ribalinine (47)



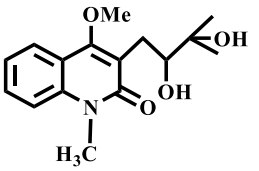
Foliosidine (48)



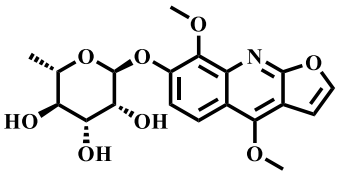
Thehaplosine (49)



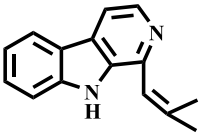
Glycohaplopine (50)



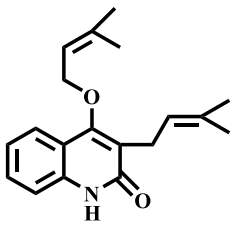
Edulinine (51)



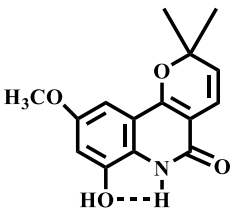
Glycoperine (52)



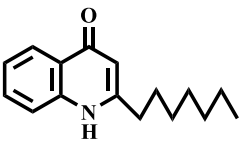
Vulcanine (53)



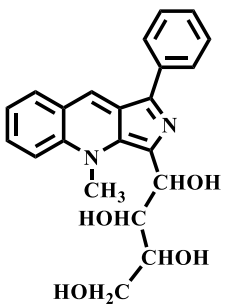
3-(3,3-dimethylallyl)-4-(3,3-dimethylalloxy)-2-quinolone (54)



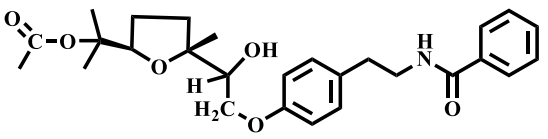
7-Hydroxy-9-methoxyflindersine (55)



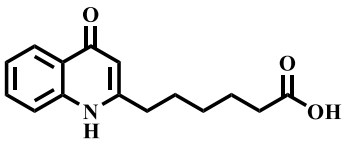
2-heptylquinoline-4-one (56)



Folipidine (57)



(+)-Tuberine (58)



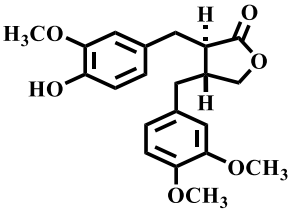
Malatyamine (59)

Figure 1: Chemical Structure Of Alkaloids Isolated From *Haplophyllum* Species

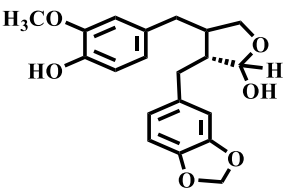
Lignans isolated from the extracts of *Haplophyllum spp.* are compiled in Table 2.

Table 2: Lignans found in *Haplophyllum* species

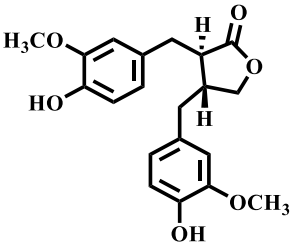
Compound	**References**
(-)- Arctigenin (60), Matairesinol (62)	[51]
Azizin (99),	[49]
Haplomyrtoside (90), Cappadocin (66), Taiwanin C (71), (-)-Cappadoside (67), (-)-Haplodoside (68)	[57]
Daurinol (81), Isodaurinol (83), 4-Deoxyisodiphyllin (70),	[56]
Daurinol mono-O-acetyl glucoside (82), Daurinol glucoside (108)	[52]
Diphyllin (86), Justicidin A (85), Diphyllidine (87), Diphyllidine monoacetate (91), Diphyllidine crotonate (92)	[55]
Furoguaiaoxidin (101)	[99]
Kusunokinin (96), (-)-Haplomyrfolol (69), (-)-Syringaresinol (80)	[58]
Nectandrin B (74), Tetrahydrofuroguaiacin B (77)	[90],[91],[92]
Patavine (93), Tuberculatin (100)	[87]
Justicidin B (84)	[43]
3,3-dimethoxy-4,4-dihydroxylignan-9-ol (97)	[98]
Eudesmin (78), Eudesmin A(79)	[105]
Dibenzobutyrolactone with isopentyl (63), Picropolygamine isomer (73), Matairesinol-4(6",7"-dihydroxygeraniol) (65)	[54]
Fragransin B2 (75), Fragransin B1 (76)	[89]
Compound	**References**
1-β-Polygamine (72)	[59]
Haplotonin (95)	[60]
Haplomarin (64), Haploborin (94)	[61]
4-acetyldiphyllin (88), Vanillic acid (98)	[42]
Haplomyrtine (89), (-)-Haplomyrfolin (69)	[50]
Cleistanthin (102), Qudsine (103), Arabelline (104), Majidine (107)	[53]
Diphyllin apioside (105), Diphyllin acetylapioside (106)	[87]
4-O-(3-methyl-2-butenyl)isodaurinol (109)	[103]



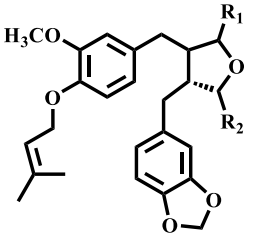
(-)- Arctigenin (60)



(-)-Haplomyrfolol (61)

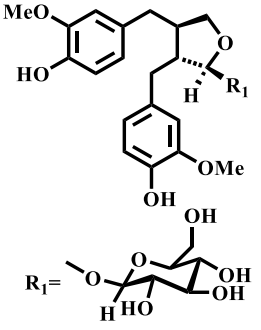


Matairesinol (62)

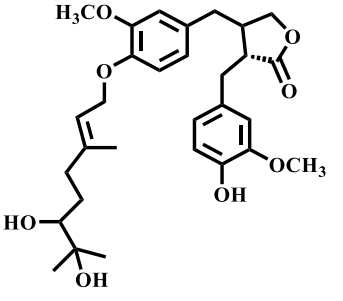


R_1=O, R_2= H
R_1=H, R_2= O

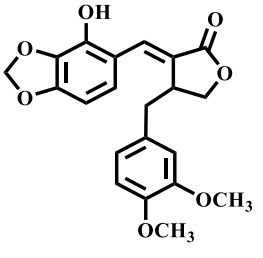
Dibenzobutyrolactone with isopentyl (63)



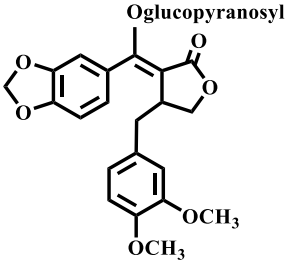
Haplomarin (64)



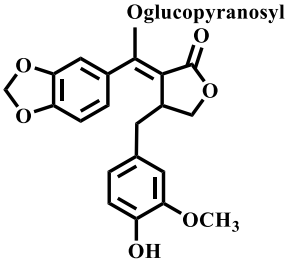
Matairesinol 4-(6",7" -dihydroxygeraniol) (65)



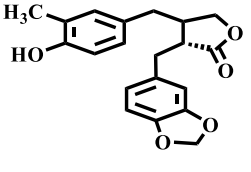
Cappadocin (66)



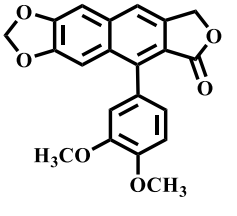
(-)-Cappadoside (67)



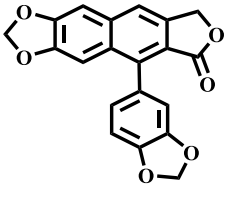
(-)-Haplodoside (68)



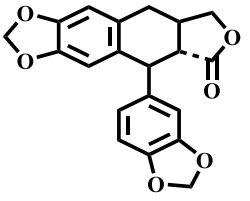
(-)-Haplomyrfolin (69)



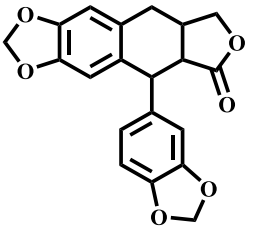
4- Deoxyisodiphyllin (70)



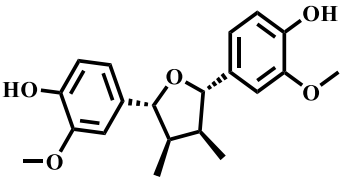
Taiwanin C (71)



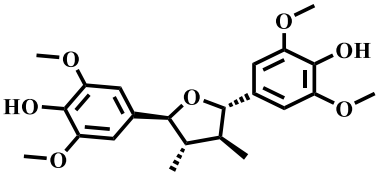
1–β–Polygamine (72)



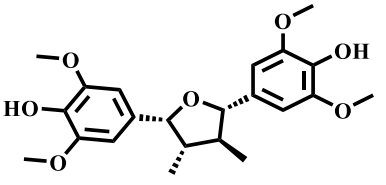
Picropolygamine isomer (73)



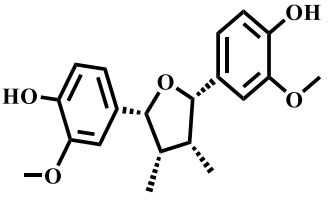
Nectandrin B (74)



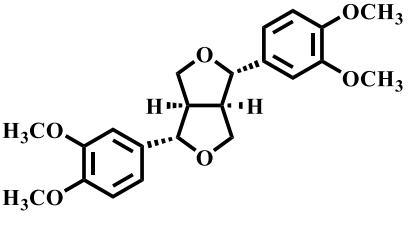
Fragransin B2 (75)



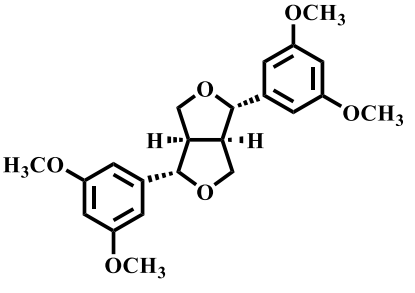
Fragransin B1 (76)



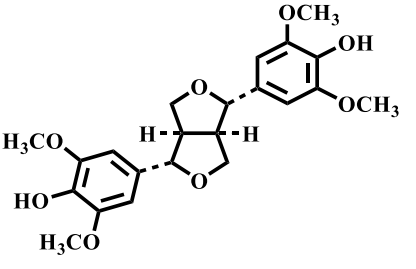
Tetrahydrofuroguaiacin B (77)



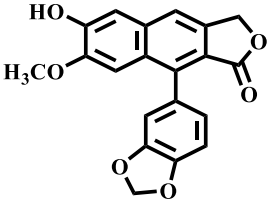
Eudesmin (78)



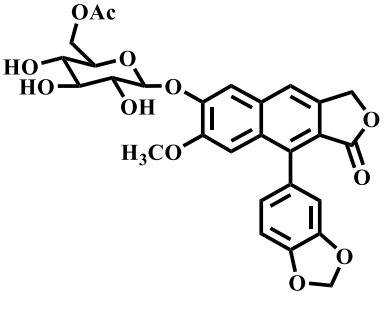
Eudesmin A (79)



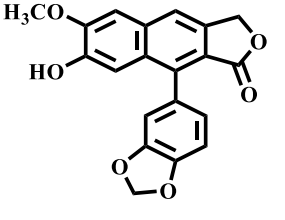
(-)-Syringaresinol (80)



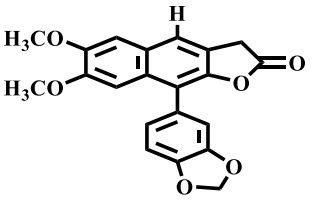
Daurinol (81)



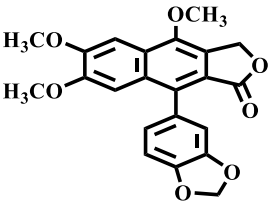
Daurinol mono-O-acetyl glucoside (82)



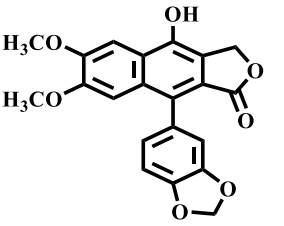
Isodaurinol (83)



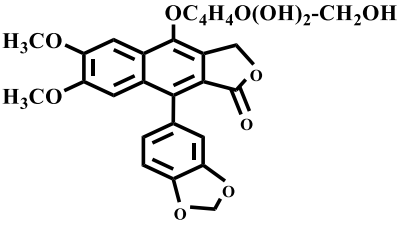
Justicidin B (84)



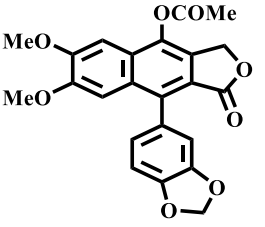
Justicidin A (85)



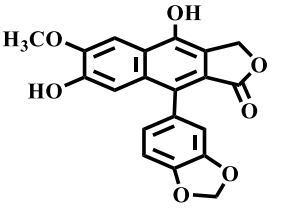
Diphyllin (86)



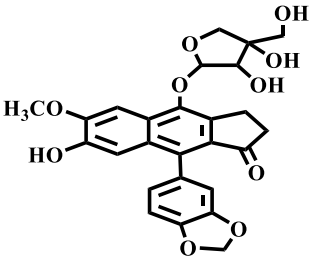
Diphyllidine (87)



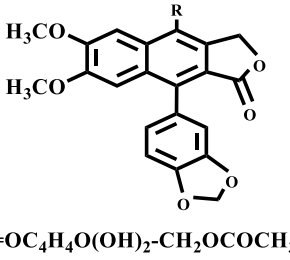
4-acetyldiphyllin (88)



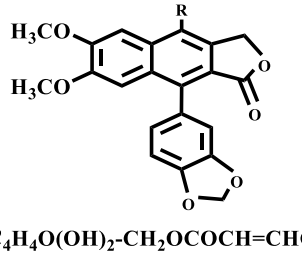
Haplomyrtine (89)



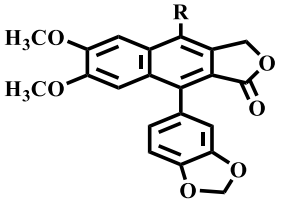
Haplomyrtoside (90)



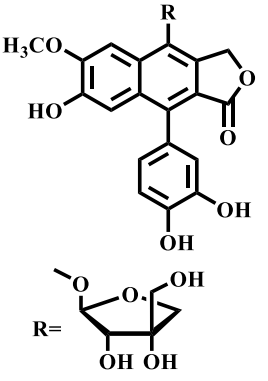
Diphyllidine monoacetate (91)



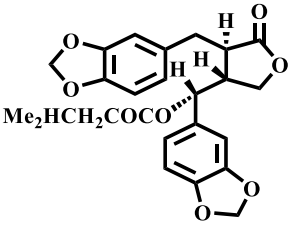
Diphyllidine crotonate (92)



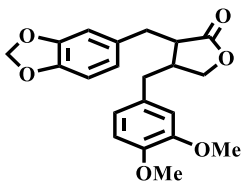
Patavine (93)



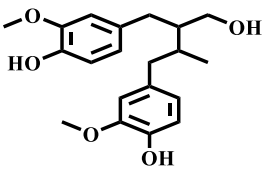
Haploborin (94)



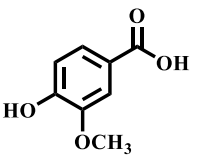
Haplotonin (95)



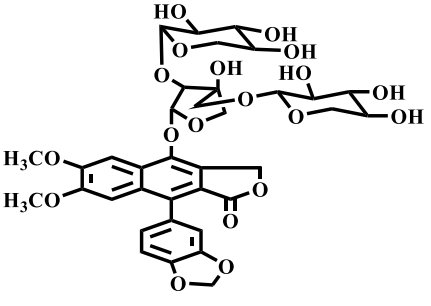
Kusunokinin (96)



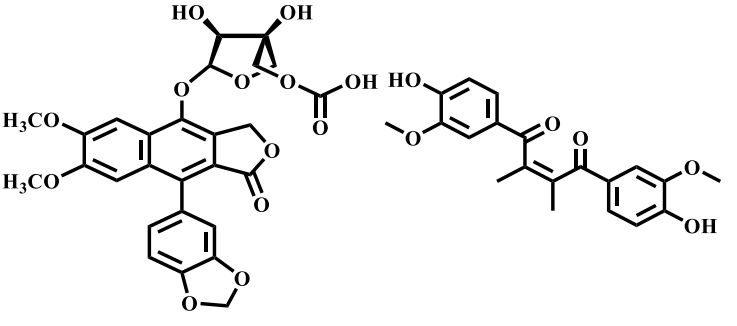
3,3-dimethoxy-4,4-dihydroxylignan-9-ol (97)



Vanillic acid (98)

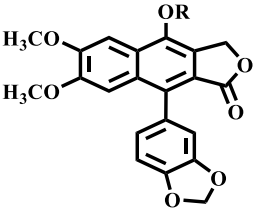


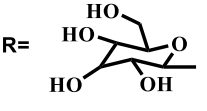
Azizin (99)



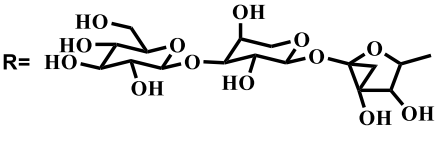
Tuberculatin (100)

Furoguaiaoxidin (101)

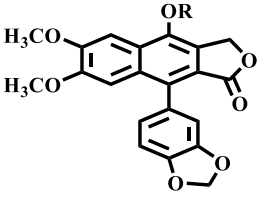


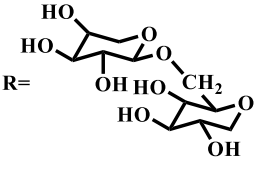


Cleistanthin (102)

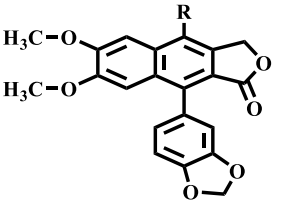


Qudsine (103)



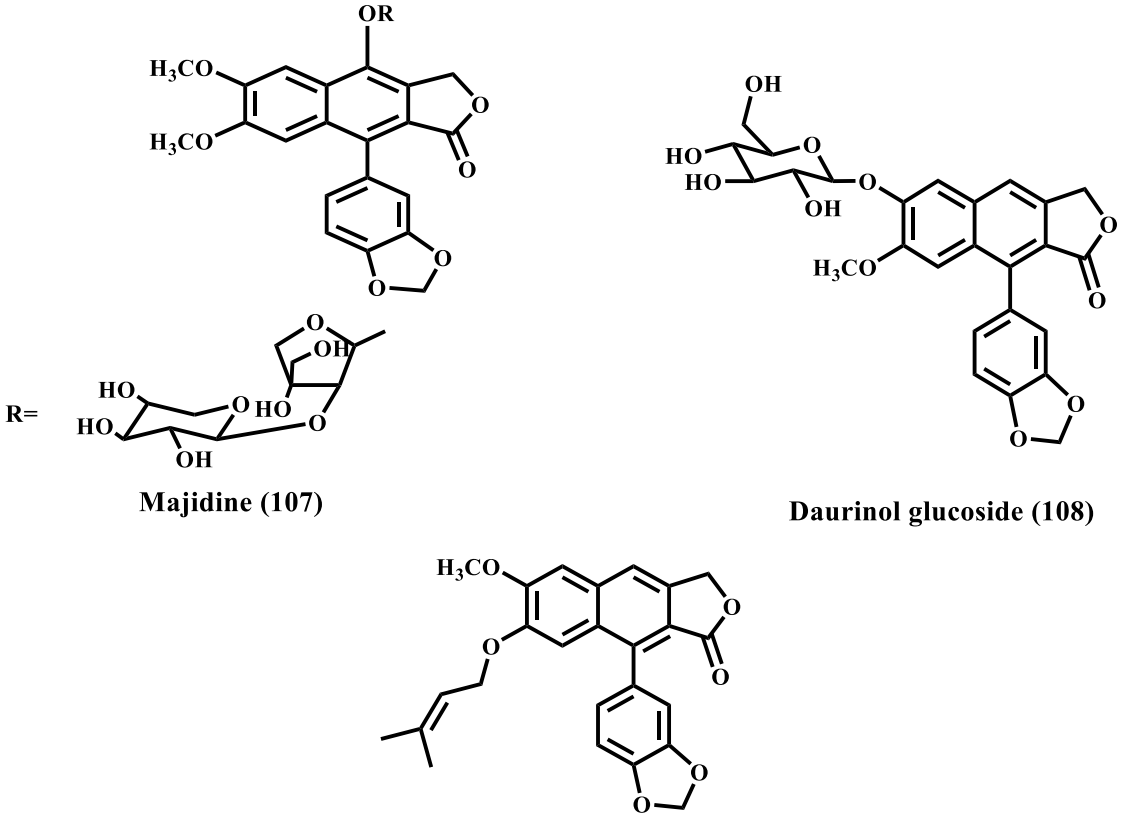


Arabelline (104)



R=O-apioside Diphyllin apioside (105)

R=O-5"-acetylapioside Diphyllin acetylapioside (106)



Majidine (107)

Daurinol glucoside (108)

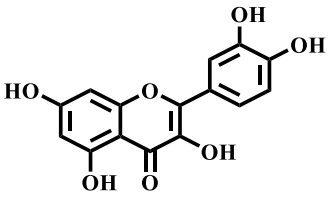
4-O-(3-methyl-2-butenyl) isodaurinol (109)

Figure 2: Chemical Structure Of Lignans Isolated From *Haplophyllum* Species

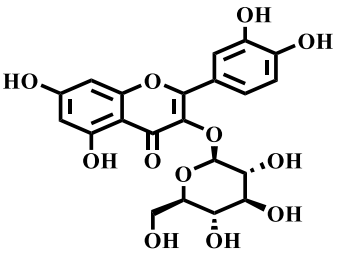
Flavonoids isolated from the extracts of *Haplophyllum spp*. are compiled in Table 3.

Table 3: Flavonoids found in *Haplophyllum* species

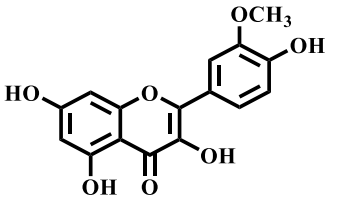
Compound	References
Quercetin (110), Quercetin 3-glucoside (111), Isorhamnetin (112), Isorhamnetin 3-glucoside (113), Isorhamnetin 3-rutinoside (114), Apigenin 7-glucoside (117)	[62]
Haploside D (115), Haploside B (116), Scopolin (118)	[63]



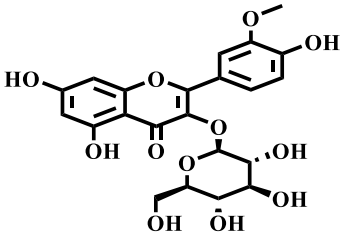
Quercetin (110)



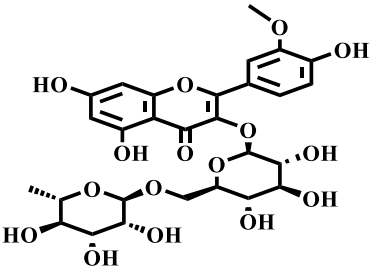
Quercetin 3-glucoside (111)



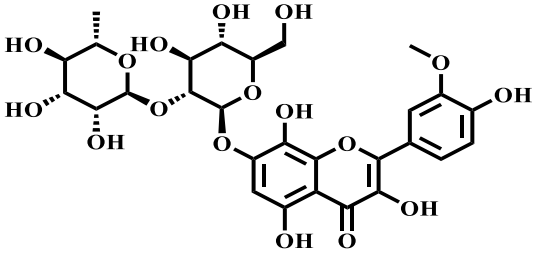
Isorhamnetin (112)



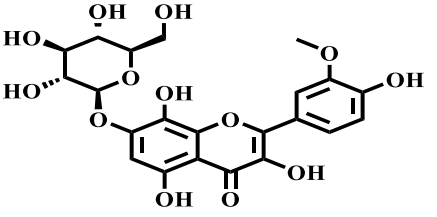
Isorhamnetin 3-glucoside (113)



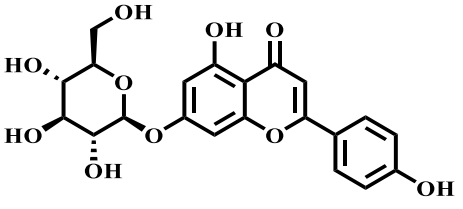
Isorhamnetin 3-rutinoside (114)



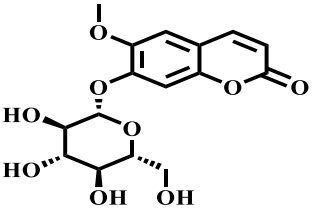
Haploside D (115)



Haploside B (116)



Apigenin 7-glucoside (117)



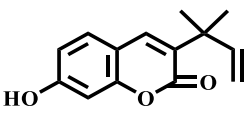
Scopolin (118)

Figure 3: Chemical Structure Of Flavonoids Isolated From *Haplophyllum* Species

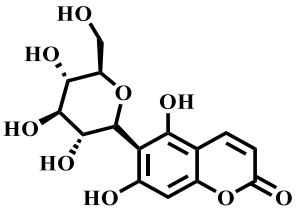
Coumarins isolated from the extracts of *Haplophyllum spp*. are compiled in Table 4.

Table 4: Coumarins found in *Haplophyllum* species

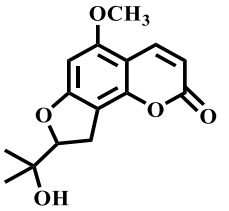
Compound	References
Angustifolin (119), Scaporon (124), Thesiolen (125), Seselin (126)	[34]
Dauroside D (120)	[66]
Ptilostol (121), Ptilostin (122)	[64]
Ptilin (123)	[51]
Umbelliferone (127), Scopoletin (128)	[58]
7-isoprenyloxycoumarin (129), Osthenol (130), Umbelliprenin (131), Columbianetin (132), Angelicin (133), Psoralen (134)	[65]
Xeroboside (135)	[61]



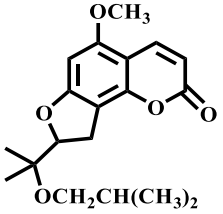
Angustifolin (119)



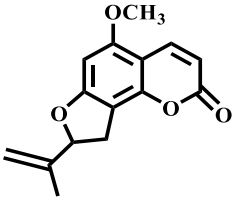
Dauroside D (120)



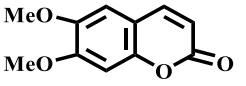
Ptilostol (121)



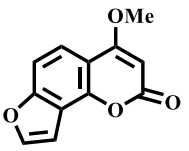
Ptilostin (122)



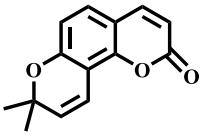
Ptilin (123)



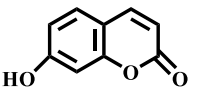
Scaporon (124)



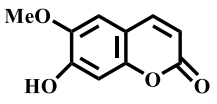
Thesiolen (125)



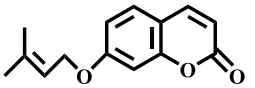
Seselin (126)



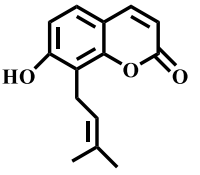
Umbelliferone (127)



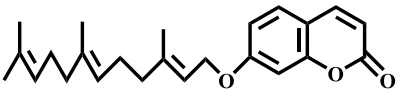
Scopoletin (128)



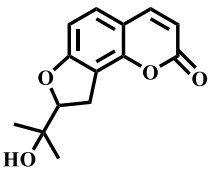
7-isoprenyloxycoumarin (129)



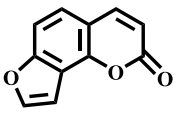
Osthenol (130)



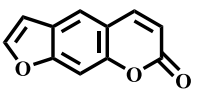
Umbelliprenin (131)



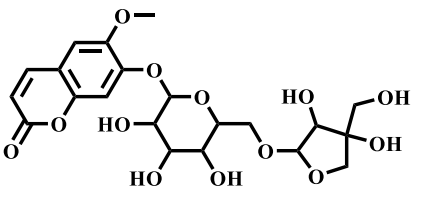
Columbianetin (132)



Angelicin (133)



Psoralen (134)



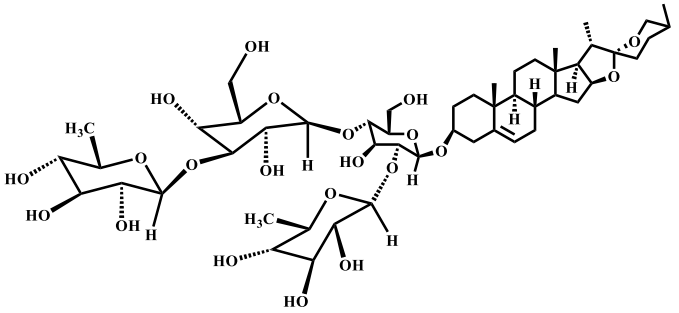
Xeroboside (135)

Figure 4: Chemical Structure Of Coumarins Isolated From *Haplophyllum* Species

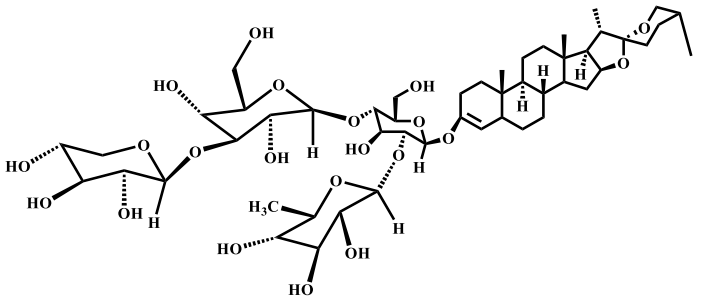
Saponins isolated from the extracts of *Haplophyllum spp.* are compiled in Table 5.

Table 5: Saponins found in *Haplophyllum* species

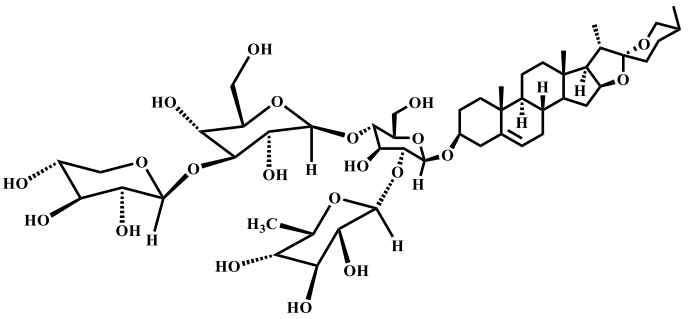
Compound	References
(3S,20S,22R,25S)-spirost-5-en-3-yl-(b-D-rhmnopyranosyl-(1®3)-b-D-glucopyranosyl-(1®4)[a-L-rhamnopyranosyl-(1®2)]-b-D-glucopyranoside (136)	[98]
(3S,20S,22R,25R)-spirost-5-en-3-yl-(b-D-xylopyranosyl-(1®3)-b-D-glucopyranosyl-(1®4)[a-L-rhamnopyranosyl-(1®2)]-b-D-glucopyranoside (137)	[97]
(3S,20S,22R,25S)-spirost-5-en-3-yl-(b-D-xylopyranosyl-(1®3)-b-D-glucopyranosyl-(1®4)[a-L-rhamnopyranosyl-(1®2)]-b-D-glucopyranoside (138)	[97]



(3S,20S,22R,25S)-spirost-5-en-3-yl-(b-D-rhmnopyranosyl-(1®3)-b-D-glucopyranosyl-(1®4)[a-L-rhamnopyranosyl-(1®2)]-b-D-glucopyranoside (136)



(3S,20S,22R,25R)-spirost-5-en-3-yl-(b-D-xylopyranosyl-(1®3)-b-D-glucopyranosyl-(1®4)[a-L-rhamnopyranosyl-(1®2)]-b-D-glucopyranoside (137)



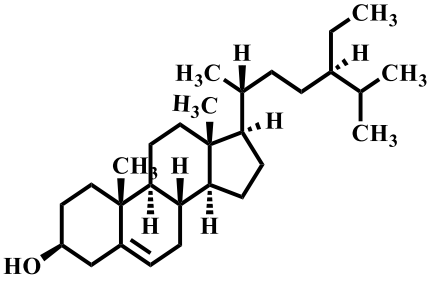
(3S,20S,22R,25S)-spirost-5-en-3-yl-(b-D-xylopyranosyl-(1®3)-b-D-glucopyranosyl-(1®4)[a-L-rhamnopyranosyl-(1®2)]-b-D-glucopyranoside (138)

Figure 5: Chemical Structure Of Saponins Isolated From *Haplophyllum* Species

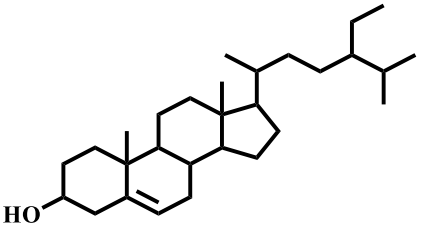
Sterols isolated from the extracts of *Haplophyllum spp.* are compiled in Table 6.

Table 6: Sterols found in *Haplophyllum* species

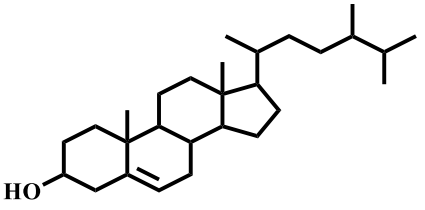
Compound	References
Beta-Sitosterol (139), Cholesterol (142)	[100]
Gamma-sitosterol (140), Campesterol (141)	[39]



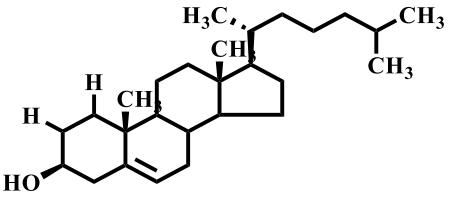
Beta-Sitosterol (139)



Gamma-sitosterol (140)



Campesterol (141)



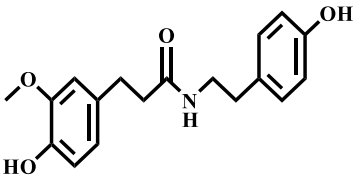
Cholesterol (142)

Figure 6: Chemical Structure Of Sterols Isolated From *Haplophyllum* Species

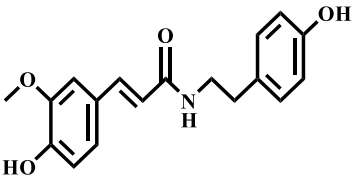
Amides isolated from the extracts of *Haplophyllum spp.* are compiled in Table 7.

Table 7: Amides found in *Haplophyllum* species

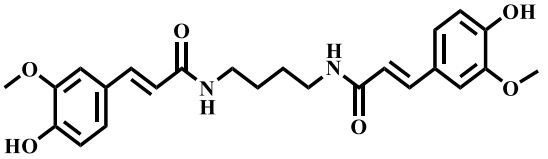
Compound	References
Dihydro-feruloyltyramine (143)	[93]
(E)-N-feruloyltyramine (144)	[94]
N,N'-diferuloylputrescine (145)	[95]
7'-ethoxy-feruloyltyramine (146)	[96]



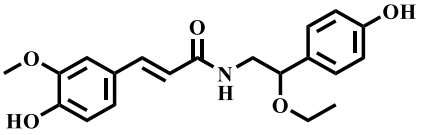
Dihydro-feruloyltyramine (143)



(E)-N-feruloyltyramine (144)



N,N'-diferuloylputrescine (145)



7'-ethoxy-feruloyltyramine (146)

Figure 7: Chemical Structure Of Amides Isolated From *Haplophyllum* Species

4. NMR

Acutinine; ^{1}H NMR ($CDCl_3$): δ 7.83 (1H, *J* = 8.1 and 1.4 Hz, H-5), 7.30 (1H, *J* = 8.1 and 1.1 Hz, H-8), 7.19 (*J* = 7.2, 1.1 Hz, H-6), 7.53 (*J* = 7.2, 1.4 Hz, H-7). A 1H singlet for H-3 was located at δ 5.81 ppm.
2-heptylquinolin-4-one; ^{1}H NMR (400 MHz, $CDC1_3$): δ 0.72 (3H, t, *J* = 7.02, CH_3), 1.14 (8H, m, 4 × CH_2), 1.72 (2H, m, CH_2), 2.90 (2H, t, *J* = 7.78, Ar-CH_2), 6.74 (1H, s, H-3), 7.43 and 7.64 (1H each, m, H-6, 7), 8.25 (1H, d, *J* = 9.63, H-8), 8.33 (1H, dd, *J* = 8.28, *J*=1.50, H-5).
γ-fagarine; ^{1}H NMR (400 MHz, $CD2C1_3$): δ 4.02 (3H, s, OCH_3), 4.39 (3H, s, OCH_3), 6.88 (1H, dd, *J* = 7.68, *J*=1.16, H-7), 7.02 (1H, d, *J* = 2.84, H-3), 7.30 (lH, dd, *J* = 8.63, *J* = 7.68, H-6), 7.58 (1H, d, *J* = 2.84, H-2), 7.78 (1H, dd, *J* = 8.63, *J* = 1.16, H-5).
Dictamnine; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.41 (3H, s, CH_3O-4), 7.45 (1H, d, *J* = 3.75, H-3), 7.46 and 7.64 (1H each, ddd, *J* = 8.48, *J* = 6.74, *J*=1.50, H-6, 7), 7.84 (1H, dm, *J* = 8.48, H-8), 8.01 (1H, d, *J* = 3.75, H-2), 8.18 (1H, ddd, *J* = 8.48, *J* = 1.50, *J* = 0.62, H-5).
Thehaplosin; ^{1}H NMR: δ 8.27 (lH, dd, *J*=1.5 and 8 Hz, H-7), 7.35 (lH, dt, *J*=1.5, 8, 8 Hz, H-8), 7.42 (lH, dt; *J*=1.5, 8, 8 Hz, H-9), 7.60 (lH, br d, *J*=8.2 Hz, H-10),

7.57 (1H, d, *J* =2 Hz, H-2), 7.04 (1H, d, *J*=2 Hz, H-1), 4.30 (3H, s, NMe) and 4.00 (6H, s, 2×OMe).

Leptomerine; ^{1}H NMR (100 MHz, $CDCl_3$) : δ 8.34 (q, IH, J_{ortho} = 9 Hz, J_{meta} = 3 Hz; H_5), 7.42 (m, 3H, $H_{6,\ 7,\ 8}$), 6.11 (s, 1H), 3.62 (s, 3H), 2.59 (t, 2H, *J* = 7.5 Hz, Ar-CH_2), 1.63 (m, 2H, CH_2), and 0.99 (t, 3H, *J* = 7.5 Hz, CH_3).

Norgraveoline; ^{1}H NMR (100 MHz, CF_3COOH) : δ 2.00 (H_5, doublet), 2.42 ($H_{6,7}$, doublet), 2.64 (H_8, multiplet), 3.13 (H_3, singlet), 2.95-3.05 and 3.30-3.50 (3 H, $H_{2'}$, $_{5'}$, $_{6'}$), 4.31 (-CH_2O_2, singlet).

7-hydroxy-9-methoxyfiindersine ; ^{1}H NMR ($CDCl_3$) : δ 6.72 (lH, d, *J*= 10 Hz, H-4), 5.55 (lH, d, *J*= 10 Hz, H-3) 1.54(6H, s, C-2 Me groups), 7.28 (lH, d, *J*= 2 Hz) and 7.13 (lH, d, *J*= 2 Hz) indicated the two aromatic protons at either C-8 and C-10 or at C-7 and C-9, 3.89 (3H, s), 9.82 (lH, br s) C-7. δ 11.75 showed the amide proton. 3.89 (OMe) enhanced the signals at 7.13 and 7.28 (H-8 and H-10).

Azizin; ^{1}H NMR $(CD_3)_2SO$: δ 3.08-3.18 (3 H, m), 3.47 (1 H, d, *J* = 11.4 Hz), 3.57 (1 H, d, *J* = 11.4 Hz), 3.67 (1 H,m), 3.78 (1 H, d, *J* = 9.4 Hz, C-H"a), 4.22 (1 H),7.60 (s, C-5H), 6.99 (s, C-8H), 6.90 (d, *J* = 1.7 Hz, C-2'H), 7.04 (d, *J* = 8.0 Hz, C-5'H), 6.78 (dd, *J* = 7.9 Hz, 1.7 Hz), 3.97 (3 H, s, C6-OCH_3), 3.66 (3 H, s, C7-OCH_3), 5.46 (2 H, s, C3a-2H), 6.12 (2 H, C3',4'-OCH_2O), 5.54 (1 H, d, *J* = 3.3 Hz,C1"-H), 4.47 (1 H, d, *J* = 7.6 Hz, C1"' H), 4.23 (1 H, d, *J* = 7.4 Hz, H-1"").

Taiwanin C; ^{1}H NMR $(CD_3)_2SO$: δ 3.63 (3 H, s, C-7 OCH_3), 3.93 (3 H, s, C-6 OCH_3), 2H, s, C-3a 2 H), 6.54 (1 H, dd, *J* = 8.0, 2.1 Hz, C-6' H), 6.67 (1 H, d, *J* = 2.1 Hz, C-2'H), 6.82 (1 H, d, *J* = 8.0 Hz, C-5'H), 7.02 (1 H, s, C-8 H), 7.64 (1 H, s, C-5 H).

Haplomyrtoside; ^{1}H NMR (MeOH-d_4): δ 3.67 (1H, d, *J* = ll.4 Hz, H-5"), 3.71 (1H, d, *J* = ll.4 Hz, H-5"), 3.93 (1H, d, *J*= 9.6 Hz, H-4"α), 4.05 (3H, s, OCH_3), 4.34 (1H, d, *J* =9.6 Hz, H-4"β), 4.51 (1H, d, *J*= 3.6 Hz, H-2"), 5.48, 5.49 (1H, d, *J*= 14.7 Hz, H-10), 5.52 (1H, d, *J* =3.6 Hz, H-l"), 5.55, 5.56 (1H, d, *J* = 14.7 Hz, H-10), 6.03 (2H, s, 3',4'-OCH_2O), 6.73, 6.74 (1H, dd, *J* = 7.9, 1.6 Hz, H-6'), 6.76, 6.77 (1H, d, *J* = 1.6 Hz, H-2'), 6.94 (1H, d, *J* = 7.8 Hz, H-5'), 7.05 (1H, s, H-8), 7.70 (1H, s, H-5).

Haplotonin; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.72 (1H, d, *J*= 8.1 Hz, H-5 or H-5'), 6.70 (1H, d, *J* =8.4 Hz, H-5 or H-5'), 6.69-6.52 (4H, m, H-2, H-2', H-6, H-6'), 5.94 (4H, m, 2xOCH_2O), 5.72 (1H, d, *J*= 6.5 Hz, H-7), 3.99 (1H, dd, *J*=10.0 and 7.8 Hz, H_b-9), 3.92 (1H, dd, *J*=10 and 6.0 Hz,H_a-9), 2.90(2H, m, CH_2-7'), 2.80(1H, m, H-8'), 2.72(1H, m, H-8), 2.24 (2H, d, *J*=7.0Hz, $COCH_2CHMe_2$), 2.09 (1H, m, $COCH_2CHMe_2$), 0.94 (3H, d, *J*= 6.5Hz, $COCH_2CHMe$), 0.92 (3H, d, *J*=6.5 Hz, $COCH_2CHMe$)

Polygamine; ^{1}H NMR ($CDCl_3$): δ 2.49 (1H, dd, *J*= 13.5, ll.0 Hz, H-2), 2.60 (1H, m, H-3), 2.89 (1H, dd, *J*= 15.4, 10.9 Hz, H-4α), 2.98 (1H, dd, *J*=15.3, 5.0 Hz, H-4β), 3.98 (1H, dd, *J*=10.4, 8.6 Hz, H-10β), 4.05 (1H, d, *J*= 10.9 Hz, H-1), 4.52 (1H, dd, *J*=8.6, 6.4 Hz, H-10α), 5.88, 5.89 (2H, 2d, *J*= 1.5 Hz, 6,7-OCH_2O), 5.94, 5.95 (2H, 2d, *J*= 1.5 Hz, 3',4'-OCH_2O), 6.33 (1H, s, H-8), 6.59 (2H, s,H-2', H-5), 6.76 (1H, dd, *J*= 8.0, 1.3 Hz, H-6'), 6.79 (1H, d, *J*= 8.0 Hz, H-5').

Matairesinol; ^{1}H NMR(300 MHz, $CDCl_3$): δ 2.42-2.65 (4H, m, H-7, H-8, H-8'), 2.87 (1H, dd, *J*=6.7, 14.0, H-7'a), 2.95 (IH, dd, *J*=5.3, 14.0, H-7'b), 3.80(3H, s, 3'-OMe), 3.81 (3H, s, 3-OMe), 3.88 (IH, dd, *J*=7.0, 9.1, H-9a), 4.15 (1H, dd, *J* =7.0. 9.1, H-9b), 6.41 (1H, d, *J*= 1.9. H-2'), 6.50 (lH, dd, *J*= 1.9, 8.0, H-6'), 6.60(1H, dd, *J*=1.9,8.0, H-6), 6.61 (lH, d, *J*=1.8, H-2), 6.79 (lH, d, *J*=8.0, H-5'), 6.81 (lH, d, *J*=8.0, H-5).

4-Acetyldiphyllin; ^{1}H NMR ($CDCl_3$) : δ 7.56 (lH, s, H- 5), 7.02 (lH, s, H-8), 6.91 (lH, d, *J*=8 Hz, H-5'), 6.75 (lH, dd, *J*=2 Hz and 8 Hz, H-6'), 6.80 (lH, d, *J*=2 Hz, H-

2') , 6.07 (lH, d, *J*= 1 Hz) and 6.02 (lH, d, *J*= 1 Hz) (O-CH_2-O), 5.45 (2H, br s, C-11 H_2), 4.05 (3H, s, C- 6 OMe), 3.77 (3H, s, C-7 OMe), 2.27 (3H, s, OAc).
Haploside D; ^{1}H NMR (100 MHz, C_5 D_5 N): δ 1.63 (3H, d, *J* = 6.0, CH_3), 1.91 (3H, s, $OCOCH_3$), 3.66 (3H, s, OCH_3), 3.72-4.75 (sugar protons), 5.55 (1H, d, *J* = 6.5, H-1"), 6.96 (1H, s, H-6), 7.05 (1H, d, *J* = 9.0, H-5′), 8.10 (1H, dd, *J* = 2.5 and *J* = 9.0, H-6′), 8.16 (1H, br.s, H-2′), 12.42 (1H, br.s, 5-OH).
Haploside B; ^{1}H NMR (100 MHz, C_5D_5N): δ 3.72 (3H, s, OCH_3), 3.79-4.30 (glucose protons), 5.62 (1H, d, *J* = 7.5, H-1″), 6.95 (1H, s, H-6), 7.09 (1H, d, *J* = 8.5, H-5′), 8.22 (1H, dd, *J* = 2.5 and *J* = 8.5, H-6′), 8.23 (1H, br.s, H-2′).
Scopolin; ^{1}H NMR (100 MHz, C_5D_5N): δ 3.62 (3H, s, OCH_3), 4.00-4.42 (m, sugar protons), 5.65 (1H, m,H-1), 6.20 (1H, d, *J* = 10.0, H-3), 6.92 (1H, s, H-8), 7.37 (1H, s, H-5), 7.59 (1H, d, *J* = 10.0, H-4).
Angustifolin; ^{1}H NMR ($CDCl_3$): δ 7.53 (s, H, β-coumarin proton), aromatic protons H-5, H-8 and H-6 at 7.30 (d, H, *J* = 7 Hz), 6.94 (d, H, *J* = 2 Hz) and 6.80 (dd, H, *J* = 7, *J*′ = 2 Hz), 1.47 (s, 6H, gem-dimethyl), 6.15 (dd, H, *J* = 17.4, *J*′ = 10.5 Hz), 5.09 (dd, H, *J*′ = 10.5, *J*″ = 0.9) and 5.08 (dd, H, *J* = 17.4, *J*" = 0.9 Hz).
Thesiolen; ^{1}H NMR: δ 7.57 (1H,d, *J*=2.5 Hz, H-l'), 7.05(lH, d, *J*=2.5 Hz, H-2'), 7.10(1H, d, *J*=8.5 Hz, H-5), 6.80 (1H, d, *J*=8.5 Hz, H-6), 6.35 (lH, s, H-3), 3.96 (3H, s, OMe).

5. Pharmacological Activities

Table 8: Reported pharmacological activity of *Haplophyllum* genus

Stated biological activity	Plant Extracts/Constituents	Effect	References
Anti-inflammatory activity	Two aryl naphthalide lignans: diphyllin acetyl apioside and tuberculation methanol extract Essential oils	Showed anti inflammatory activity against acute TPA edema with ID50 of 0.27 mumol/ear. Possessed a 50% reduction of the ear edema when administerd topically. Demonstrated potent topical anti-inflammatory action with no obvious toxicity when applied twice daily (15 µL, 1 mg/ml) to the left ears of Swiss mice. exhibited a significant acute anti-inflammatory activity against carrageenan induced oedema in rats.	[67], [68], [69],[114]
Antioxidant activity	Polyphenols and alkaloids Ethanol extract leaves extract	Exhibited good antioxidant activity with the β-carotene bleaching test and the reducing power test When compared to Vitamin E, showed significance anti-oxidant activity (98%) Possessed a significant antioxidant activity	[70], [71] ,[72]

Stated biological activity	Plant Extracts/Constituents	Effect	References
Antimicrobial activity	Ethanol extract	with (MIC 0.49, 0.12 and 1.95 µg/ml), it showed effective antifungal activity against Aspergillus fumigates, Geotricum candidum and Syncephalastrum racemosum.	[71], [74] ,[70] ,[73]
	(+)-tuberine	Showed significant antibacterial potency against Staphylococcus aureus and Escherichia coli witj (MIC 1.95 and 15.63 µg/ml).	
	polyphenols and alkaloid extracts	At 1µg/ml, it showed high antimicrobial activity against Staphylococcus aureus, Bacillus subtilis and Saccharomyces cerevisiae. Escherichia coli slightly inhibited by it. With MICs ranging from 0.625 mg/ml to 10 mg/ml for alkaloids and from 5 mg/ml to 20 mg/ml for polyphenols, it showed moderate activity on a few bacterial strains (Bacillus subtilis, Staphylococcus aureus , and Pseudomonas aerginosa)	
Insecticidal, antiprotozoal and molluscicidal activity	Essential oils	At concentration as low as 0.074 mg/cm2, exhibited insecticidal and repellent activity against Aedes aegypti. Using the cloth patch assay the oil was found to repelle the yellow fever mosquito Aedes aegypti,	[77], [75] ,[69] ,[76]
	diphyllin apioside and diphyllin acetylapioside		
	methanolic extract	In axenic cultures, it was assessed against epimastigotes of T. cruzi.	
	chloroform extract	When applied continuosly, it possessed a severe topical toxicity, that induces skin necrosis.	
		With snail treatment demonstrated palliation in egg laying capacity, a decrease in phenol oxidase enzyme, a disruption in steroid sex hormones and a significant change in the histopathological picture of snails tissue.	
Cytotoxic activity	Oil	With IC50% value of 4.7 µg/ml and 4.1 µg/ml demonstrated antitumor activities against liver carcinoma cell line (HEPG2) and lung carcinoma cell line (H1299).	[71], [78], [69]
	Diphyllin		

	Extract of *H. linifolium* Arylnaphtalene lignans	At a concentration of 0.05 µg/ml exhibited stronger specific cytostatic activity than 6–mercaptopurine with mutability more than 95%, exhibited cytotoxicities when assessed on elicited peritoneal leukocytes from rats. At a concentration of just over 40 µM, showed cytotoxicity	
Anticancer activity	Extract of *H. tuberculatum*	with the highest IC50 values of 31.64 µg/mL showed toxicity against cancer cell line Hep-G2. A change in the mitochondrial membrane potential triggered apoptosis in CCRF-CEM cells.	[79]
Anti-HIV activity	methanolic extract buchapine quinoline 2,4-diol	With the value of (EC50 0.94 µM, IC5029.0 µM and EC50 1.64 µM, IC50 26.9 µM), demonstrated anti-HIV activity against HIV-1 in cultured human lymphoblastoid CEM-SS cells. Tested against CEM-GFP (human CD4+ T cell line), for anti-HIV activity. Examined for anti-HIV potential in human CD4+ T cell line CEM-GFP 45 alkylated derivatives of a base chemical. Thirteen of these compounds show more than 60% inhibition, all active compounds have higher than CC50 values.	[80] ,[81], [82] ,[83], [84] ,[85]

Conclusion

The genus *Haplophyllum* (Rutaceae) is a rich source of structurally various secondary metabolites with promising pharmacological activities. The present review compiled the chemical constituents, pharmacological activities and NMR value of compounds of *Haplophyllum* genus. The main categories of phytochemicals present in *Haplophyllum* spp. include alkaloids, lignans, coumarins and flavonoid; which are responsible for the pharmacological actions. The isolated phytochemicals shows potential pharmacological activity including antioxidant, anti-inflammatory, antimicrobial, insecticidal, antiprotozoal, molluscicidal, cytotoxic, anti-cancer and anti-HIV activities. The NMR value also included in this review which may help the researchers to identify isolated compounds. So, the review concludes that there is a great potential for researchers to search new drug lead secondary metabolites from the genus *Haplophyllum.*

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