CHAPTER II

HISTORICAL

1. Botanical aspect of Labiatae

The Labiatae (Lamiaceae) contains 200 genera and about 3,000 species (Heywood, 1978), which are distributed chiefly in North temperate regions.

The Labiatae is a family of herbs, rarely shrubs, usually loaded with oil-glands. *Stem* usually 4-gonous. *Leaves* opposite or whorled, stipules 0. *Flowers* irregular, solitary 2-nate or fascicled and axillary, or in centrifugal spicate cymes which by their union in pairs form false whorls. *Calyx* persistent irregular, 4-5-cleft or 2-lipped. *Corolla* sympetalous, hypogynous; limb 4-5-lobed or 2-lipped, lobes imbricate in bud. *Stamens* inserted in the corolla-tube, 4 didynamous, or the 2 upper imperfect. Anther-cells connate or separate or confluent. Disc prominent. *Ovary* free, 2 of 2-celled carpels; style simple, inserted between the lobes, stigma usually bifid; ovules one in each cell, erect, anatropous. *Fruit* of 4 dry or rarely fleshy 1-seeded lobes (nutlets) at the base of the calyx. *Seeds* small, erect, albumen sparing or ,radicle inferior. (Hooker, 1953)

The genus *Coleus* belongs to subfamily Ocimoideae and subtribe Euocimeae of this family (Hooker, 1953). According to Smitinand (1980), there are 5 species of *Coleus* in Thailand. These are as follows:

1. *Coleus amboinicus* Lour.

   C. aromaticus Benth.

   C. carnosus , Hassk.

   [Huu suea (หูเสือ) , Niam huu suea (เนียมหูเสือ) (Central) ; Hom duan luang (หอมด่วนหลวง) , Hom duan huu suea (หอมด่วนหูเสือ) (Northern) ; Indian borage ; Country borage ; Oregano]

2. *Coleus atropurpureus* Benth.

   [Ruesee phasom laeo (ฤาษีผสมแล้ว) (Central)]

3. *Coleus blumei* Benth.

   [Waan lueat haeng (ว่านเลือดแห้ง) (Chiang Mai)]

   Coleus blumei var. *verschaffeltii* , Lem.

   [Ruesee phasom laeo (ฤาษีผสมแล้ว) (Central)]

4. *Coleus parvifolius* Benth.

   C. tuberosus Benth.

   [Man khee nuu (มันขี้หนู), Man nuu (มันหนู) (Peninsular) ; U-bee ka-ling (อุบีกะลิง) (Malay-Narathiwat)]

2. Classification of *Coleus* terpenoids

A number of terpenoids with great potential in drug development were reported as constituents of *Coleus forskohlii* Brig. (syn. *C. barbatus*). A preliminary biological screening of root extract of this plant indicated hypotensive and spasmolytic activities (Dubey *et al.*, 1981). The steam distillate of its roots has been reported to contain mono and sesquiterpenes (Mathela, Kharkwal and Mathela, 1986). Benzene extract of its roots also afforded labdane diterpenoids including coleonol (forskolin) (Tandon *et al.*, 1977), a major component which is a potential drug for treatment of glaucoma, cardiomyopathy and asthma (Valdes, Mislankar and Paul, 1987; Bhat, 1993) because of its unique adenylate cyclase stimulant activity (Seamon, 1983; de Souza, 1993). Several species of *Coleus* are used in traditional Ayurvedic healing. Chemical studies of plants in the genus *Coleus* led to isolation of a large number of terpenoids. Currently, there are about 116 terpenoids of 16 structural types reported from 11 species of *Coleus*. These terpenoids can be classified into 4 major groups as shown in Table 2.

Table 2 Terpenoids from *Coleus* species

Compound type	Compounds	Sources	References
1. Monoterpenes			
1.1 Acyclic	Myrcene (1)	*Coleus amboinicus*	Malik *et al*., 1985
		Coleus barbatus	Mathela *et al*., 1986; Maia *et al*., 1988
1.2 *p*-Menthanes	*p*-Cymene (2)	*Coleus amboinicus*	Bos, Hendriks and van Os, 1983; Malik *et al*., 1985; Haque, 1988
		Coleus barbatus	Mathela *et al*., 1986; Maia *et al*., 1988
	Thymol (3)	*Coleus amboinicus*	Baslas and Kumar, 1981; Bos *et al*., 1983; Malik *et al*., 1985; Haque, 1988
	Carvacrol (4)	*Coleus amboinicus*	Baslas and Kumar, 1981; Bos *et al*., 1983; Malik *et al*., 1985; Morton, 1992
		Coleus barbatus	Maia *et al*., 1988
	Limonene (5)	*Coleus amboinicus*	Malik *et al*., 1985; Morton, 1992
	α–Terpinene (6)	*Coleus barbatus*	Maia *et al*., 1988

Table 2 Terpenoids from *Coleus* species (Continued)

Compound type	Compounds	Sources	References
	α–Terpinolene (7)	*Coleus amboinicus*	Baslas and Kumar, 1981
		Coleus barbatus	Maia *et al*., 1988
	γ-Terpinene (8)	*Coleus amboinicus*	Malik *et al*., 1985
		Coleus barbatus	Maia *et al*., 1988
	α-Phellandrene (9)	*Coleus barbatus*	Maia *et al*., 1988
	β-Phellandrene (10)	*Coleus amboinicus*	Baslas and Kumar, 1981
		Coleus barbatus	Mathela *et al*., 1986
	Terpinen-4-ol (11)	*Coleus amboinicus*	Haque, 1988
		Coleus barbatus	Maia *et al*., 1988
	α–Terpineol (12)	*Coleus barbatus*	Maia *et al*., 1988
	Piperitone (13)	*Coleus barbatus*	Maia *et al*., 1988
1.3 Bicyclic			
- Camphanes	Borneol (14)	*Coleus barbatus*	Maia *et al*., 1988

Table 2 Terpenoids from *Coleus* species (Continued)

Compound type	Compounds	Sources	References
	Camphor (15)	*Coleus amboinicus*	Morton, 1992
		Coleus barbatus	Maia *et al*., 1988
- Pinanes	α-Pinene (16)	*Coleus amboinicus*	Baslas and Kumar, 1981; Malik *et al*., 1985
		Coleus barbatus	Mathela *et al*., 1986; Maia *et al*., 1988
	β-Pinene (17)	*Coleus amboinicus*	Baslas and Kumar, 1981; Malik *et al*., 1985
		Coleus barbatus	Mathela *et al*., 1986; Maia *et al*., 1988
	Verbenone (18)	*Coleus amboinicus*	Haque, 1988
- Carane	3- Carene (19)	*Coleus barbatus*	Maia *et al*., 1988
- Thujane	α–Thujene (20)	*Coleus barbatus*	Mathela *et al*., 1986
2. Sesquiterpenoids			
2.1 Bisabolanes	α–Curcumene (21)	*Coleus barbatus*	Mathela *et al*., 1986
	β–Bisabolene (22)	*Coleus barbatus*	Mathela *et al*., 1986
2.2 Elemane	β–Elemene (23)	*Coleus barbatus*	Mathela *et al*., 1986

Table 2 Terpenoids from *Coleus* species (Continued)

Compound type	Compounds	Sources	References
2.3 Humulane	α–Humulene (24)	*Coleus barbatus*	Maia *et al.*, 1988
2.4 Caryophyllanes	β–Caryophyllene (25)	*Coleus amboinicus*	Baslas and Kumar, 1981; Bos *et al.*, 1983
		Coleus barbatus	Maia *et al.*, 1988
2.5 Cuparane	Cuparene (26)	*Coleus barbatus*	Mathela *et al.*, 1986
2.6 Eudesmane	β–Selinene (27)	*Coleus amboinicus*	Malik *et al.*, 1985
2.7 Cadinane	δ-Cadinene (28)	*Coleus barbatus*	Maia *et al.*, 1988
2.8 Copaane	α–Copaene (29)	*Coleus barbatus*	Mathela *et al.*, 1986; Maia *et al.*, 1988
3. Diterpines			
3.1 Labdanes	Coleonol E (30)	*Coleus barbatus*	Painuly, Katti and Tandon, 1979
	Coleonol D (31)	*Coleus barbatus*	Katti, Jauhari and Tandon, 1979
	Coleonol F (32)	*Coleus barbatus*	Painuly *et al.*,1979
	1α, 6β, 7α-Triacetylcoleonol B (33)	*Coleus barbatus*	Jin, Xie and Mu, 1990; Gan, Zheng and Shen, 1993

Table 2 Terpenoids from *Coleus* species (Continued)

Compound type	Compounds	Sources	References
	8, 13-Epoxy-labd-14-en-11-one (34)	*Coleus barbatus*	Gabetta, Zini and Daneli, 1989
	6β, 7α-Diacetoxy-8, 13-epoxy- labd-14-en-11-one (35)	*Coleus barbatus*	Gabetta *et al.*, 1989
	Coleol (36)	*Coleus barbatus*	Katti *et al*, 1979
	6β-Hydroxy-8, 13-epoxy-labd-14-en-11-one (37)	*Coleus barbatus*	Gabetta *et al.*, 1989
	Coleosol (38)	*Coleus barbatus*	Jauhari *et al.*, 1978
	1-Acetoxycoleosol (39)	*Coleus barbatus*	Roy *et al.*, 1993
	6β, 7β-Dihydroxy-8, 13-epoxy- labd-14-en-11-one (40)	*Coleus barbatus*	Gabetta *et al.*, 1989
	6β, 7β, 9α-Trihydroxy-8, 13-epoxy-labd-14-en-11-one (41)	*Coleus barbatus*	Gabetta *et al.*, 1989

Table 2 Terpenoids from *Coleus* species (Continued)

Compound type	Compounds	Sources	References
	1α, 6β, 7β, 9α-Tetrahydroxy-8, 13-epoxy-labd-14-en-11-one (42)	*Coleus barbatus*	Tandon *et al*., 1977
	1,9-Dideoxyforskolin (43)	*Coleus barbatus*	Gabetta *et al*., 1989; Khandelwal *et al*., 1989; Roy *et al*., 1993
	9-Dideoxyforskolin (44)	*Coleus barbatus*	Gabetta *et al*., 1989; Tandon *et al*., 1992
	1-Dideoxyforskolin (45)	*Coleus barbatus*	Khandelwal *et al*., 1989
	Forskolin (Coleonol, Colforsin, USAN) (46)	*Coleus barbatus*	Tandon *et al*., 1977, 1984, 1992; Singh and Tandon, 1982; Viswanathan and Gawad, 1985; Valdes *et al*., 1987; Gabetta *et al*., 1989
	6β- Acetoxy -7β- hydroxy-8, 13-epoxy-labd-14-en-11-one (47)	*Coleus barbatus*	Painuly *et al*.,1979
	Coleonol B (48)	*Coleus barbatus*	Tandon *et al*., 1978, 1984; Jin *et al*., 1990; Gan *et al*., 1993

Table 2 Terpenoids from *Coleus* species (Continued)

Compound type	Compounds	Sources	References
	Coleonol C (49)	*Coleus barbatus*	Tandon *et al.*, 1978
	Coleonone (50)	*Coleus barbatus*	Katti *et al.*, 1979
3.2 Abietanes			
- Abietanes	20-Deoxocarnosol (51)	*Coleus barbatus*	Kelecom, 1984
	6α-Hydroxycarnosol (52)	*Coleus barbatus*	Kelecom and Medeiros, 1987
	Esquirolin D (53)	*Coleus esquirolii*	Li *et al.*, 1991b, 1992
	6β-Hydroxycarnosol (54)	*Coleus barbatus*	Kelecom, 1983a
	Carnosolone (55)	*Coleus amboinicus*	Yoshizaki, Ruedi and Eugster, 1979
	Royleanone (56)	*Coleus amboinicus*	Yoshizaki, *et al.*, 1979
	7α-Hydroxyroyleanone (Horminone) (57)	*Coleus amboinicus*	Yoshizaki, *et al.*, 1979
	7α-Acetoxyroyleanone (58)	*Coleus amboinicus*	Yoshizaki, *et al.*, 1979
	6β-Hydroxyroyleanone (59)	*Coleus amboinicus*	Yoshizaki, *et al.*, 1979

Table 2 Terpenoids from *Coleus* species (Continued)

Compound type	Compounds	Sources	References
	6β, 7α-Dihydroxyroyleanone (60)	*Coleus amboinicus*	Yoshizaki, *et al*., 1979
	7α-Acetoxy-6β-hydroxyroyleanone (61)	*Coleus amboinicus*	Yoshizaki, *et al*., 1979
		Coleus zeylanicus	Mehrotra *et al*., 1989
	7α-Acetoxy-6β-20-dihydroxyroyleanone (62)	*Coleus amboinicus*	Yoshizaki, *et al*., 1979
	6β, 7β-Dihydroxyroyleanone (63)	*Coleus zeylanicus*	Mehrotra *et al*., 1989
	7β-Acetoxy-6β-hydroxyroyleanone (64)	*Coleus zeylanicus*	Mehrotra *et al*., 1989
	6, 7-Dehydroroyleanone (65)	*Coleus amboinicus*	Yoshizaki, *et al*., 1979
	Coleon U (66)	*Coleus amboinicus*	Yoshizaki, *et al*., 1979
		Coleus xanthanthus	Li *et al*., 1991a, 1991b

Table 2 Terpenoids from *Coleus* species (Continued)

Compound type	Compounds	Sources	References
	Coleon C (67)	*Coleus barbatus*	Yoshizaki, *et al*., 1979
	Coleon H (68)	*Coleus somaliensis*	Matloubi-Moghadam, Ruedi and Eugster, 1984
	Coleon L (69)	*Coleus somaliensis*	Ruedi and Eugster, 1977; Matloubi-Moghadam *et al*., 1984
	Sugiol (70)	*Coleus xanthanthus*	Li *et al*., 1991a, 1991b
	Coleon V (71)	*Coleus amboinicus*	Yoshizaki, *et al*., 1979
	Coleon D (72)	*Coleus barbatus*	Yoshizaki, *et al*., 1979
	Coleon I (73)	*Coleus somaliensis*	Matloubi-Moghadam *et al*., 1984
	Coleon K (74)	*Coleus somaliensis*	Matloubi-Moghadam *et al*., 1984
	6,11-Epoxy-6,12-dihydroxy-6,7-seco-8,11,13-abietatrien-7-al (75)	*Coleus barbatus*	Kelecom, 1983b
	Cariocal (76)	*Coleus barbatus*	Kelecom and Dos Santos, 1985

Table 2 Terpenoids from *Coleus* species (Continued)

Compound type	Compounds	Sources	References
	Coleon A (77)	*Coleus igniarius*	Eugster *et al*, 1963
	Edulone A (78)	*Coleus edulis*	Kunzle *et al.*, 1986
	Coleon B (79)	*Coleus igniarius*	Eugster *et al*, 1963
- 13, 16-Cycloabietanes	Barbatusin (80)	*Coleus barbatus*	Wang *et al.*, 1973; Zelnik *et al.*, 1977
	3β-Hydroxy-3-deoxybarbatusin (81)	*Coleus barbatus*	Zelnik *et al.*, 1977
	Coleon J (82)	*Coleus somaliensis*	Ruedi and Eugster, 1973
	Coleon G (83)	*Coleus somaliensis*	Matloubi-Moghadam *et al.*, 1984
	Coleon O (84)	*Coleus barbatus*	Devriese, Buffel and Geuns, 1988
		Coleus blumei	Devriesee *et al.*, 1988
		Coleus coerulescens	Grob *et al.*, 1978
		Coleus somaliensis	Arihara, Ruedi and Eugster, 1975; Matloubi-Moghadam *et al.*, 1984

Table 2 Terpenoids from *Coleus* species (Continued)

Compound type	Compounds	Sources	References
	12-o-Deacetyl-18-acetoxycoleon Q (85)	*Coleus somaliensis*	Matloubi-Moghadam *et al*., 1984
	12-o-Deacetyl-7- o-acetyl-19-hydroxycoleon Q (86)	*Coleus somaliensis*	Matloubi-Moghadam *et al*., 1984
	12-o-Deacetylcoleon R (87)	*Coleus coerulescens*	Grob *et al*., 1978
	6,12-o-bis-Deacetylcoleon R (88)	*Coleus coerulescens*	Grob *et al*., 1978
	Coleon Y (89)	*Coleus coerulescens*	Grob *et al*., 1978
		Coleus somaliensis	Matloubi-Moghadam *et al*., 1984
	3-o-Deacetyl-3-o-formylcoleon Y (90)	*Coleus coerulescens*	Grob *et al*., 1978
		Coleus somaliensis	Matloubi-Moghadam *et al*., 1984
	Cyclobutatusin (91)	*Coleus barbatus*	Zelnik *et al*., 1977
	Fredericone A (92)	*Coleus fredericii*	Zhu *et al*., 1988

Table 2 Terpenoids from *Coleus* species (Continued)

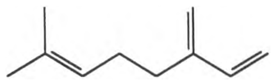
Compound type	Compounds	Sources	References
- 19(4$\rightarrow$3)-*abeo*-abietanes	19(4β$\rightarrow$3β)-*abeo*-6,11-Epoxy-6,12-dihydroxy-6,7-*seco*-4(18),8,11,13-abietatetraen-7-al (93)	*Coleus barbatus*	Kelecom, 1983b
	Coleon E (94)	*Coleus barbatus*	Ruedi and Eugster, 1973; Ruedi, 1986
	Coleon E (94)	*Coleus kilimandschari*	Ruedi and Eugster, 1973
	Coleon F (95)	*Coleus barbatus*	Ruedi, 1986
	Coleon F (95)	*Coleus kilimandschari*	Ruedi and Eugster, 1973
	Fredericone C (106)	*Coleus fredericii*	Zhu *et al*., 1988
	Fredericone D (107)	*Coleus fredericii*	Zhu *et al*., 1988
- 9(10$\rightarrow$20)-*abeo*-abietanes	Barbatusol (96)	*Coleus barbatus*	Kelecom, 1983b
	11-Hydroxypisifcranol (97)	*Coleus barbatus*	Kelecom, 1983b
- 17(15$\rightarrow$16)-*abeo*-abietanes	Xanthathusin A (98)	*Coleus xanthanthus*	Li *et al*., 1991b

Table 2 Terpenoids from *Coleus* species (Continued)

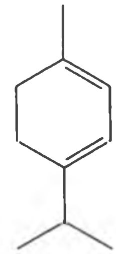
Compound type	Compounds	Sources	References
	17(15→16)-*abeo*-3α,18-Diacetoxy-6β,7α,16-trihydroxyroyleanone (99)	*Coleus coerulescens*	Grob *et al.*, 1978
	Fredericone B (102)	*Coleus fredericii*	Zhu *et al.*, 1988
	Esquirolin A (103)	*Coleus esquirolii*	Li *et al.*, 1991a
	Esquirolin B (104)	*Coleus esquirolii*	Li *et al.*, 1991b, 1992
	Esquirolin C (105)	*Coleus esquirolii*	Li *et al.*, 1991b, 1992
- 17(15→16),19(4→3)-Bis-*abeo*-abietanes	17(15→16),19(4→3)-Bis (*abeo*)-6β,7α,16 -trihydroxyroyleanone (3α)-form (100)	*Coleus coerulescens*	Grob *et al.*, 1978
	17(15→16),19(4→3)-Bis (*abeo*)-6β,7α,16 -trihydroxyroyleanone (3β)-form (101)	*Coleus coerulescens*	Grob *et al.*, 1978

Table 2 Terpenoids from *Coleus* species (Continued)

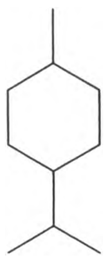
Compound type	Compounds	Sources	References
4. Triterpenes			
4.1 Oleananes	Maslinic acid (108)	*Coleus amboinicus*	Brieskorn and Riedel, 1977b
	Oleanolic acid (109)	*Coleus amboinicus*	Brieskorn and Riedel, 1977b
		Coleus esquirolii	Li *et al.*, 1991b
4.2 Taraxerane	Taraxerol (110)	*Coleus esquirolii*	Li *et al.*, 1991b, 1992
4.3 Ursanes	Ursolic acid (111)	*Coleus amboinicus*	Brieskorn and Riedel, 1977b
	Mirianthic acid (112)	*Coleus amboinicus*	Higuchi *et al.*, 1982
	Euscaphic acid (113)	*Coleus amboinicus*	Brieskorn and Riedel, 1977b
	Tormentic acid (114)	*Coleus amboinicus*	Brieskorn and Riedel, 1977b
		Coleus spicatus	Painuly and Tandon, 1983
	α–Amyrin (115)	*Coleus spicatus*	Painuly and Tandon, 1983
	Hyptadienic acid (Coleonolic acid) (116)	*Coleus barbatus*	Roy *et al.*, 1990



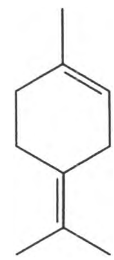
(1) Myrcene



(6) α - Terpinene



(2) p-Cymene



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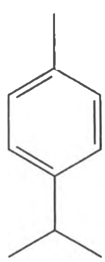

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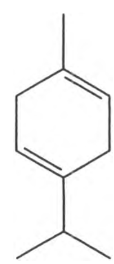
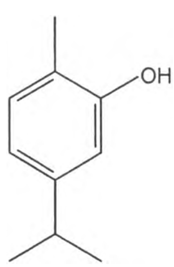


(8) γ - Terpinene



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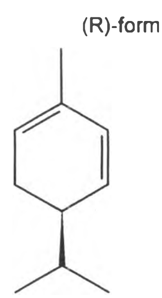
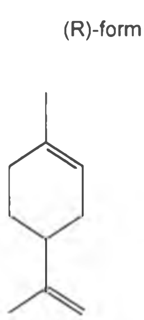


(9) α - Phellandrene



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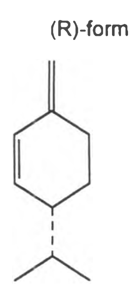
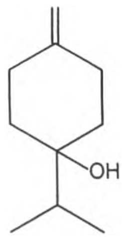
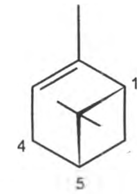


(10) β - Phellandrene

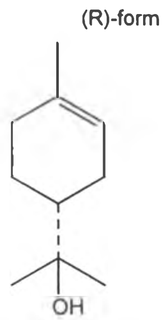
Figure 2. Monoterpenoids from *Coleus* species



(11) Terpinen-4-ol



(16) α - Pinene



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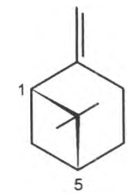

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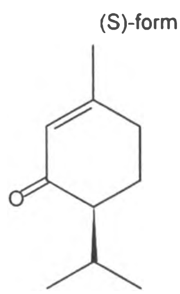
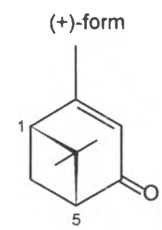
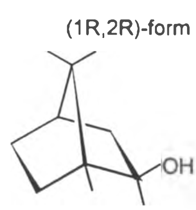


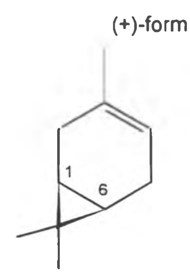
(13) Piperitone



(18) Verbenone

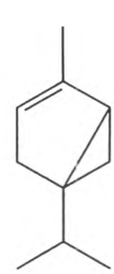


(14) Borneol



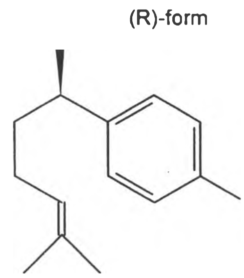
(19) 3 - Carene

(15) Camphor

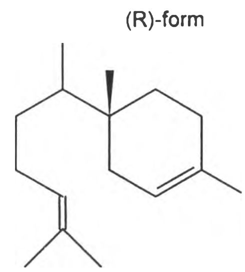


(20) α - Thujene

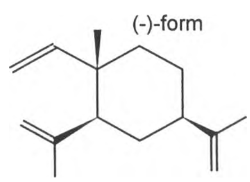
Figure 2. Monoterpenoids from *Coleus* species (Continued)



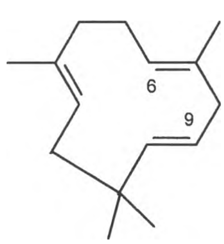
(21) α - Curcumene



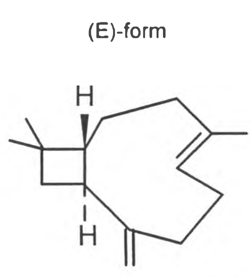
(22) β - Bisabolene



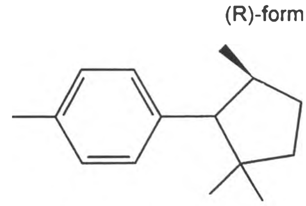
(23) β - Elemene



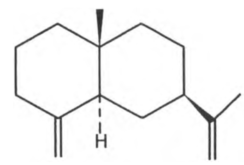
(24) α - Humulene



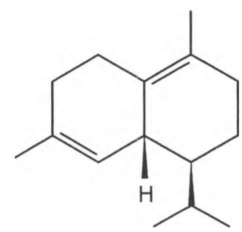
(25) β - Caryophyllane



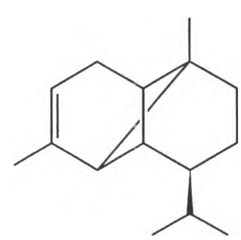
(26) Cuparene



(27) β - Selinene

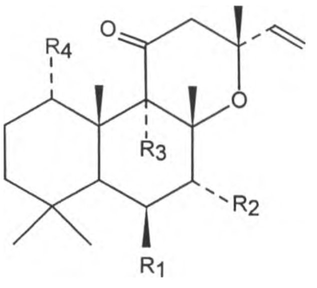


(28) δ - Cadinene

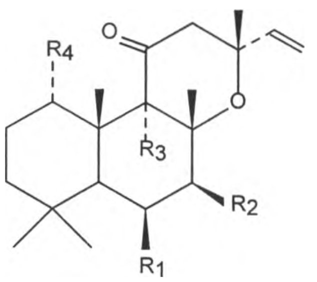


(29) α - Copaene

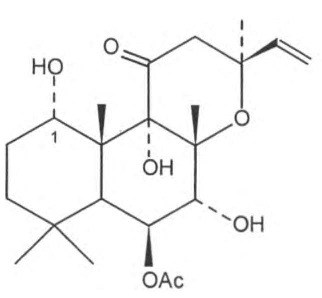
Figure 3. Sesquiterpenoids from *Coleus* species



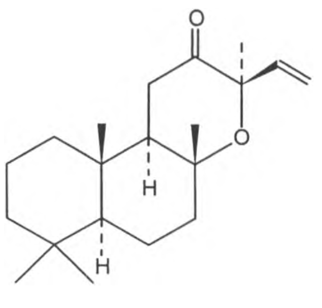
	R_1	R_2	R_3	R_4
(30)	OH	OAc	H	H
(31)	OH	OAc	OH	H
(32)	OAc	OH	OH	H
(33)	OAc	OAc	OH	OAc
(34)	OAc	OAc	OH	H



	R_1	R_2	R_3	R_4
(35)	H	H	H	H
(36)	H	H	OH	H
(37)	OH	H	H	H
(38)	OH	H	OH	H
(39)	OH	H	OH	OAc
(40)	OH	OH	H	H
(41)	OH	OH	OH	H
(42)	OH	OH	OH	OH
(43)	OH	OAc	H	H
(44)	OH	OAc	H	OH
(45)	OH	OAc	OH	H
(46)	OH	OAc	OH	OH
(47)	OAc	OH	H	H
(48)	OAc	OH	OH	OH

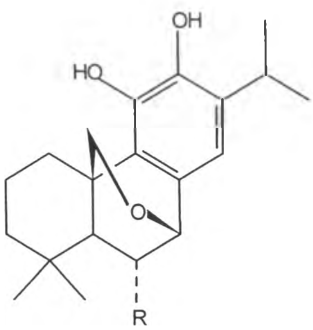


(49) Coleonol C

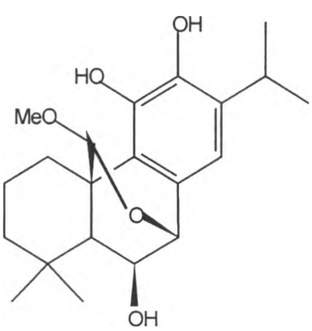


(50) Coleonone

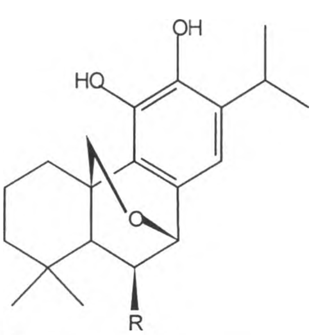
Figure 4. Diterpenoids from *Coleus* species



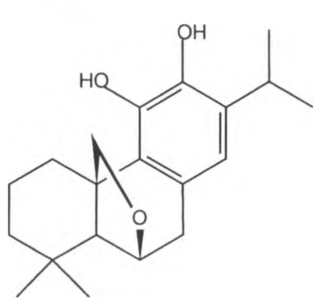
(51) R = H
(52) R = OH



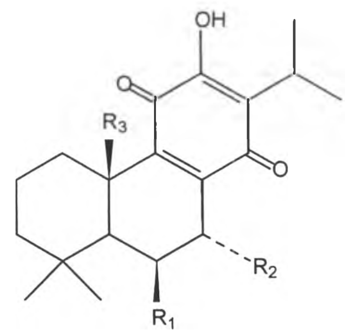
(53) Esquirolin D



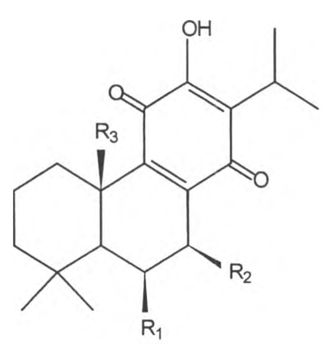
(54) R = OH



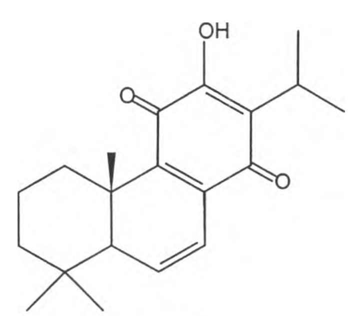
(55) Carnosolone



	R_1	R_2	R_3
(56)	H	H	H
(57)	H	OH	H
(58)	H	OAc	H
(59)	OH	H	H
(60)	OH	OH	H
(61)	OH	OAc	H
(62)	OH	OAc	OH

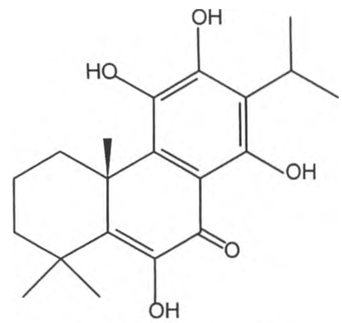


	R_1	R_2	R_3
(63)	OH	OH	H
(64)	OH	OAc	H

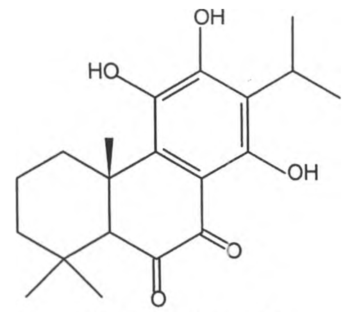


(65)

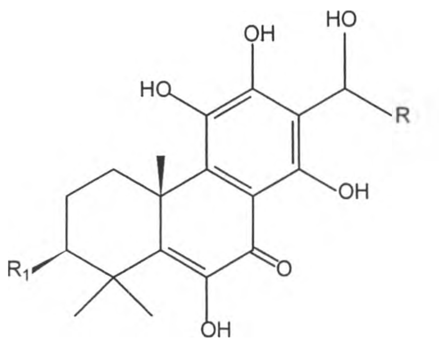
Figure 4. Diterpenoids from *Coleus* species (Continued)



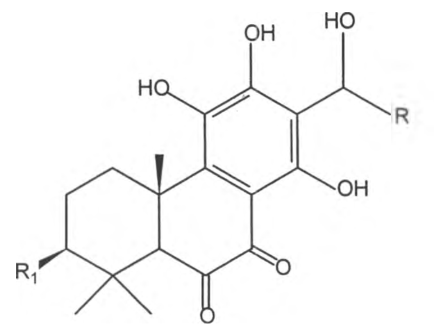
(66) Coleon U



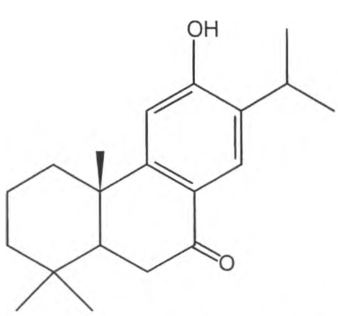
(71) Coleon V



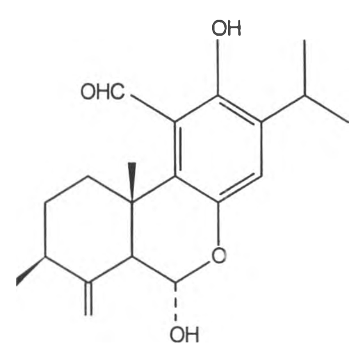
		R	R_1
(67)	Coleon C	H	H
(68)	Coleon H	H	OAc
(69)	Coleon L	OAc	OAc



		R	R_1
(72)	Coleon D	H	H
(73)	Coleon I	H	OAc
(74)	Coleon K	OAc	OAc

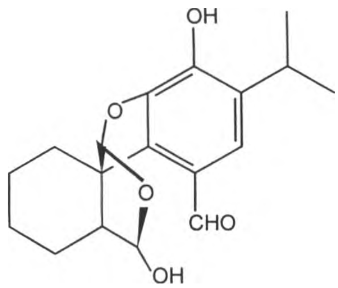


(70) Sugiol

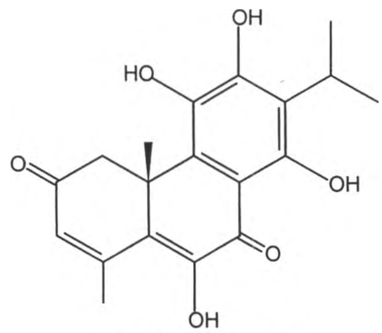


(75)

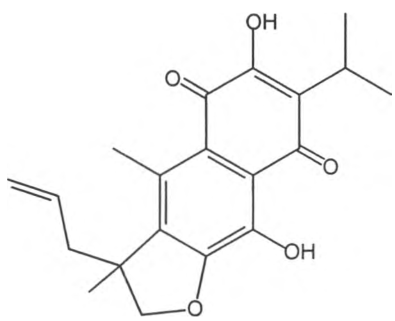
Figure 4. Diterpenoids from *Coleus* species (Continued)



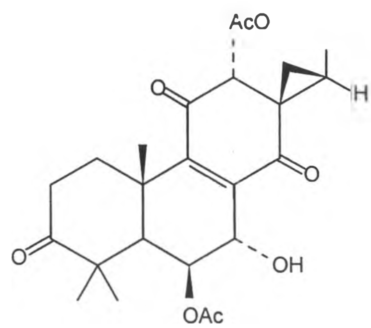
(76) Cariocal



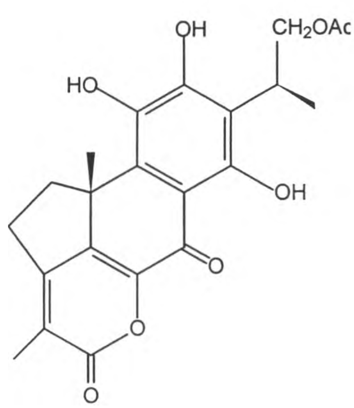
(79) Coleon B



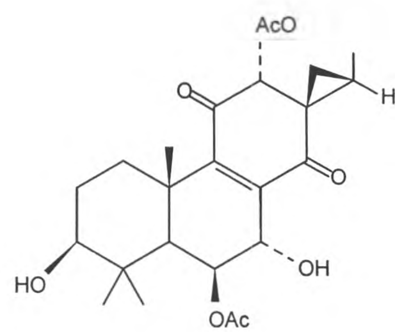
(77) Coleon A



(80) Barbatusin

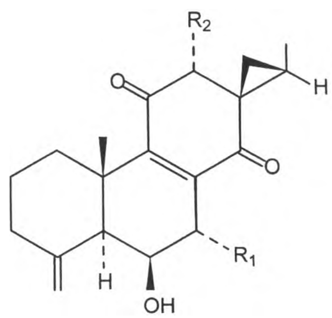


(78) Edulone A

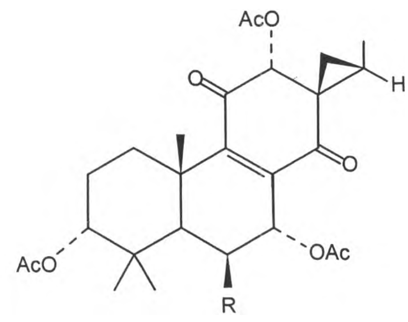


(81)

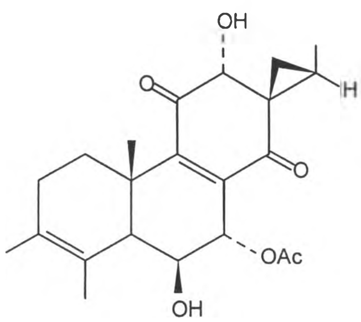
Figure 4. Diterpenoids from *Coleus* species (Continued)



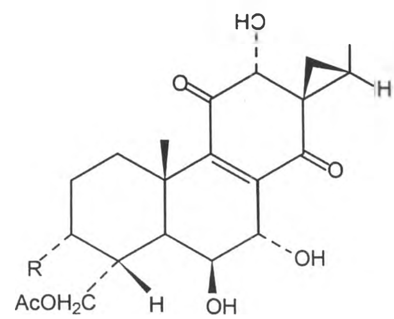
		R_1	R_2
(82)	Coleon J	OH	OH
(83)	Coleon G	OAc	OH



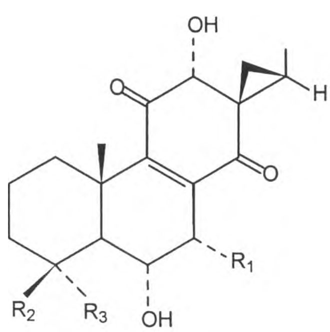
(87) R = OH
(88) R = Oac



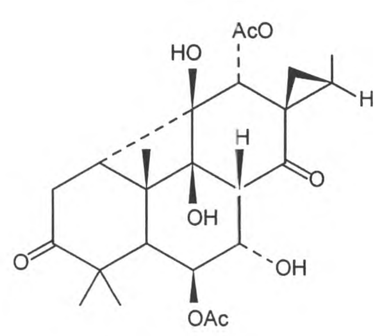
(84) Coleon O



(89) Coleon Y R = OAc
(90) R = formyl

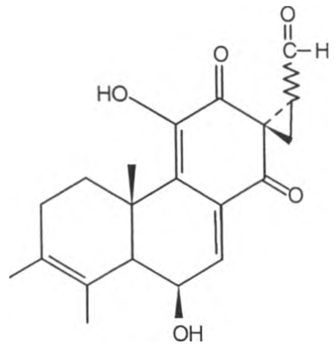


	R_1	R_2	R_3
(85)	OH	H	OAc
(86)	OAc	OH	H

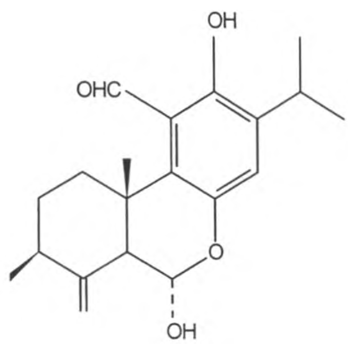


(91) Cyclobutatusin

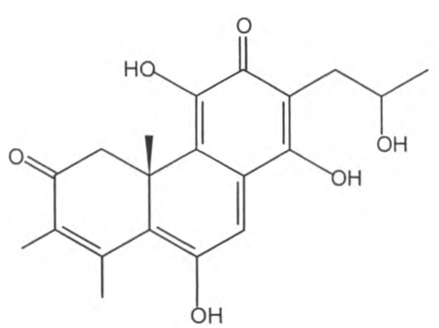
Figure 4. Diterpenoids from *Coleus* species (Continued)



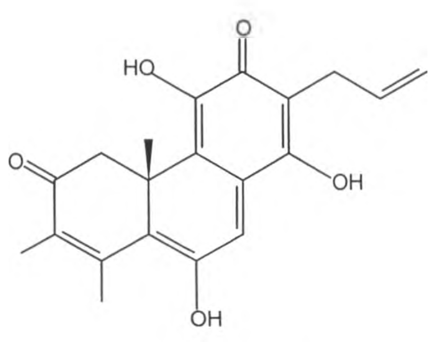
(92) Fredericone A



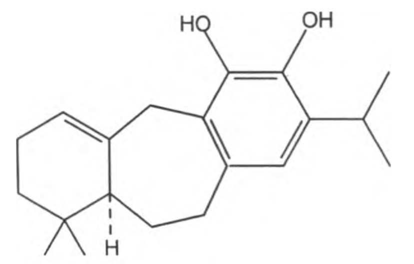
(93)



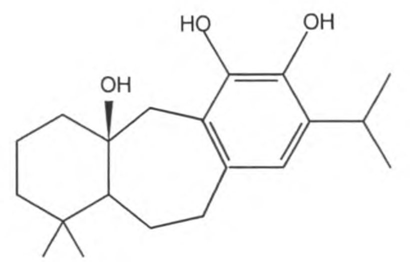
(94) Coleon E



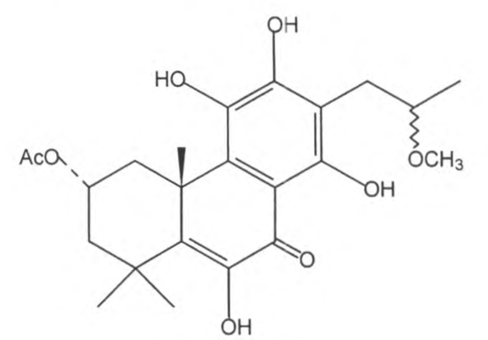
(95) Coleon F



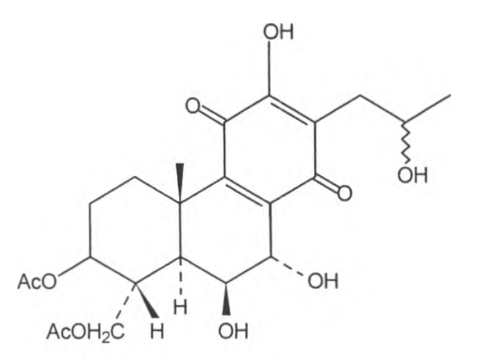
(96) Barbatusol



(97) 11-Hydroxypisiferanol

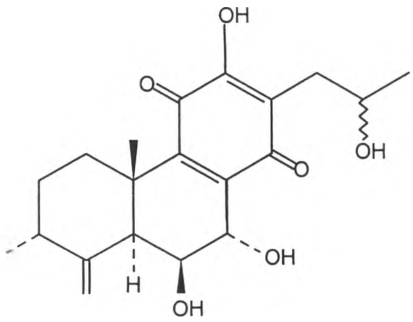


(98) Xanthanthusin A

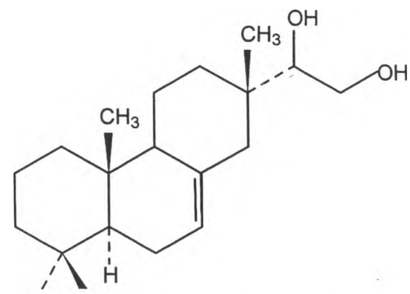


(99)

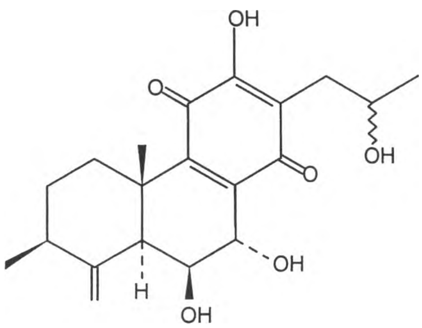
Figure 4. Diterpenoids from *Coleus* species (Continued)



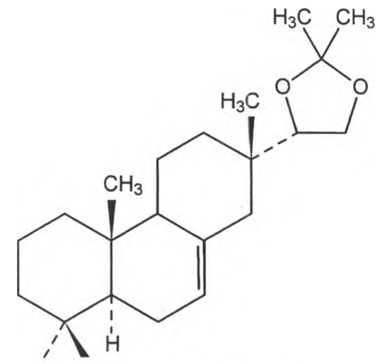
(100)



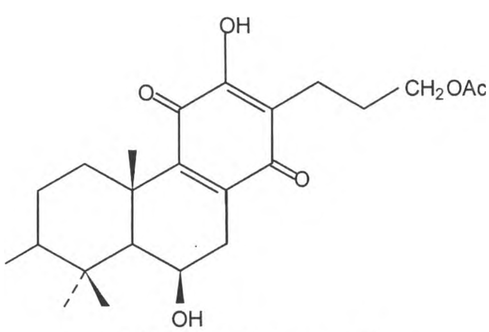
(104) Esquirolin B



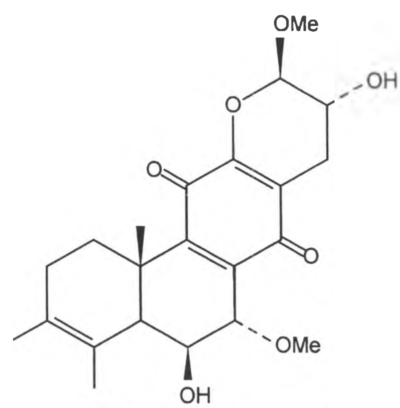
(101)



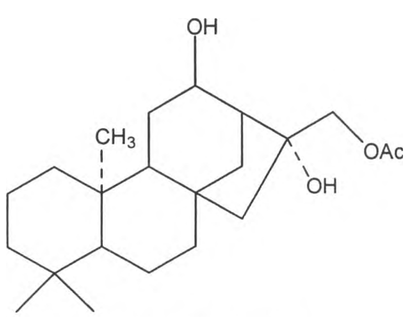
(105) Esquirolin C



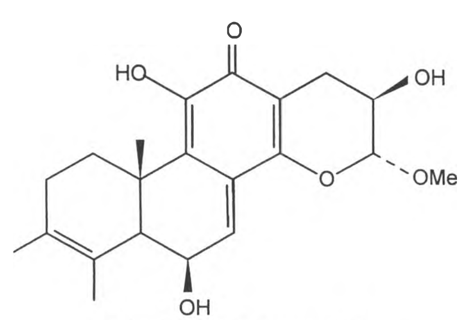
(102) Fredericone B



(106) Fredericone C

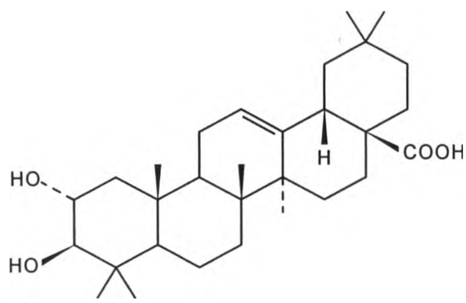


(103) Esquirolin A

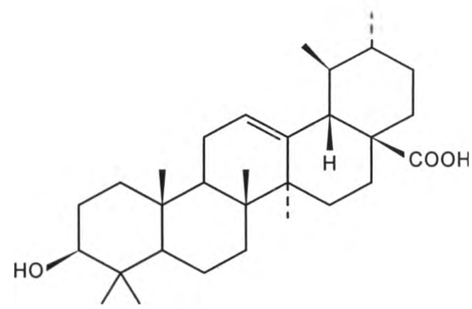


(107) Fredericone D

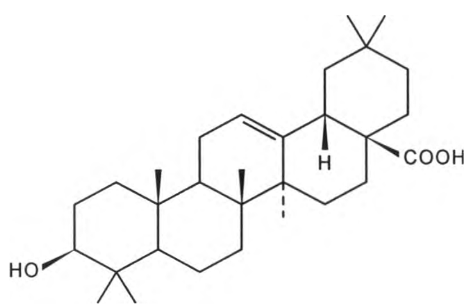
Figure 4. Diterpenoids from *Coleus* species (Continued)



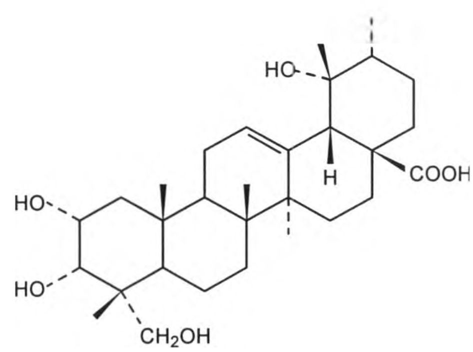
(108) Maslinic acid



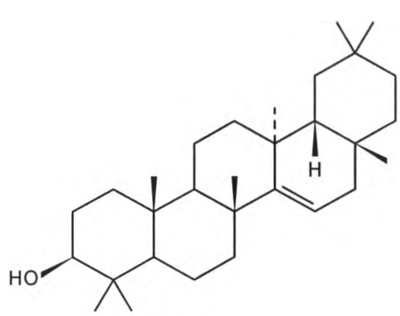
(111) Ursolic acid



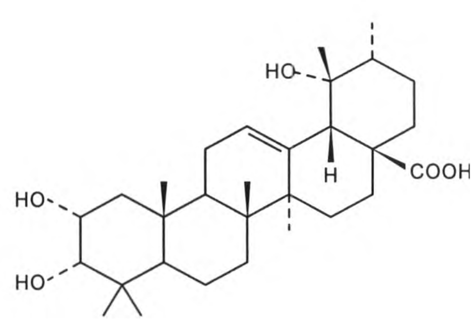
(109) Oleanolic acid



(112) Mirianthic acid

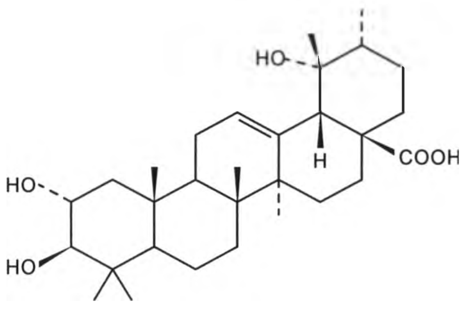


(110) Taraxerol

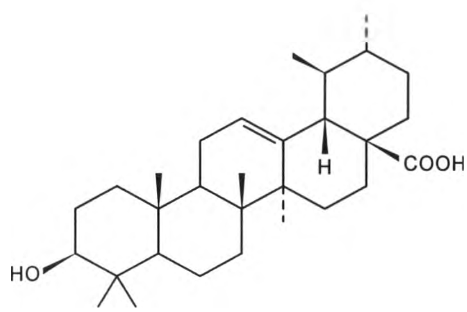


(113) Euscaphic acid

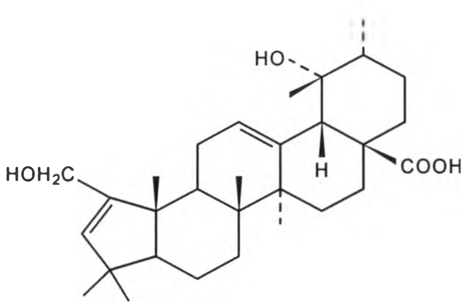
Figure 5. Triterpenoids from *Coleus* species



(114) Tormentic acid



(115) α–Amyrin



(116) Hyptadienic acid

Figure 5. Triterpenoids from *Coleus* species (Continued)

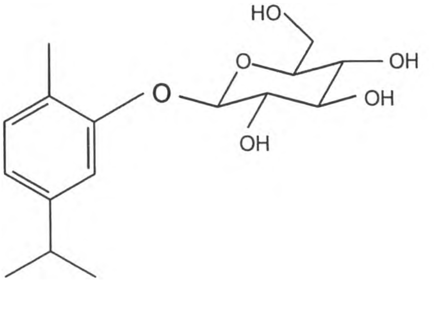
3. *p*-Menthane monoterpene glycosides in plants

Monoterpene glycosides are widely distributed in nature and comprise a great variety of different structures due to the individual aglycones or carbohydrates. An immense number of papers have been published in the last few years describing the isolation and characterization of monoterpene glycosides. This report covers *p*-menthane monoterpene glycosides found in plants during the period 1976-1996.

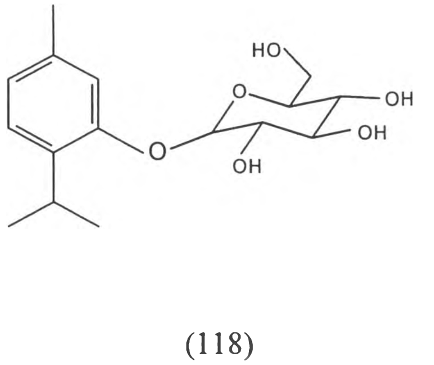
Carvacrol-β-D-glucopyranoside (117) and thymol-β-D-glucopyranoside (118) have been isolated from *Thymus vulgaris* (Skopp and Horster, 1976), and the latter was also found in the aerial parts of *Jasonia montana* (Ahmed and Jakupovic, 1990). Their structures were elucidated by NMR techniques. Thymoquinol-β-D-glucopyra noside (1,4-dihydroxy-2-*iso*-propyl-5-methylphenyl-1-0-β-D-glucopyranoside) (119), identified as 2-isopropyl-5-methylhydroquinone, has been isolated from *Geum japonicum* which are used in Japan as a diuretic (Shigenaga, Kouno and Kawano, 1985) and later was first isolated as a natural product from *Pteridium aquilinum* var. *caudatum* (L. Kuhn), one of the five most widely distributed organisms of the plant kingdom (Castillo *et al.*, 1995).

Coleus forskohlii (*C. barbatus*) has yielded a number of interesting terpenoids, some with therapeutic potential. Further examination of the polar fraction of the root extract of this plant has furnished a new monoterpene glycoside named coleoside (120) and characterized as cuminyl-0-β-D-glucopyranosyl(1→2)-β-D-galactopyra noside (Ahmed and Vishwakarma, 1988).

Phenol glucoside gallates, querglanin (121) and isoquerglanin (122), were isolated from the leaves of *Quercus glauca* (Sheu, Hsu and Lin, 1992). Finally, a non-aromatic *p*-menthane derivative, 6-O-β-D-glucopyranosyloxy-3-hydroxy-*p*-menth-1-ene (123), was reported from the butanolic extract of *Eupatorium tinifolium* H.B.K. (D'Agostino *et al.*, 1990) growing in the highlands of Colombia.

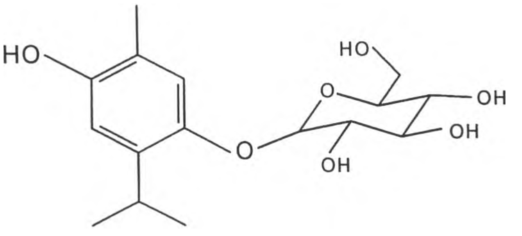


(117)

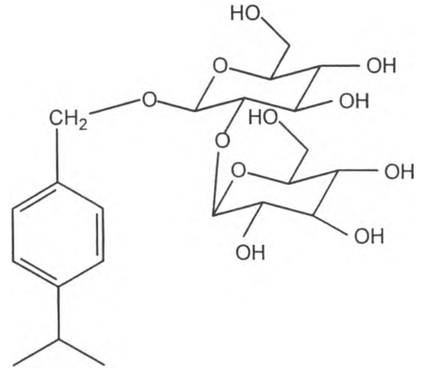


(118)

Figure 6. *p*-Menthane monoterpene glycosides in plants

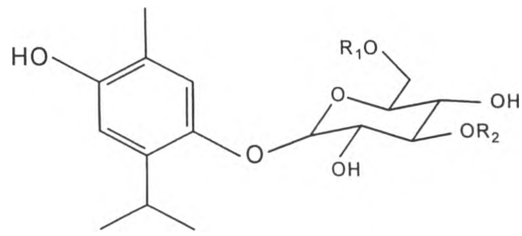


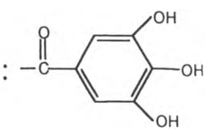
(119)



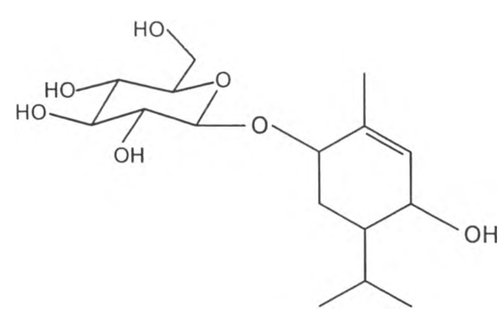
(120)

Figure 6. *p*-Menthane monoterpene glycosides in plants (Continued)



galloyl : 

	R_1	R_2
(121)	galloyl	H
(122)	H	galloyl



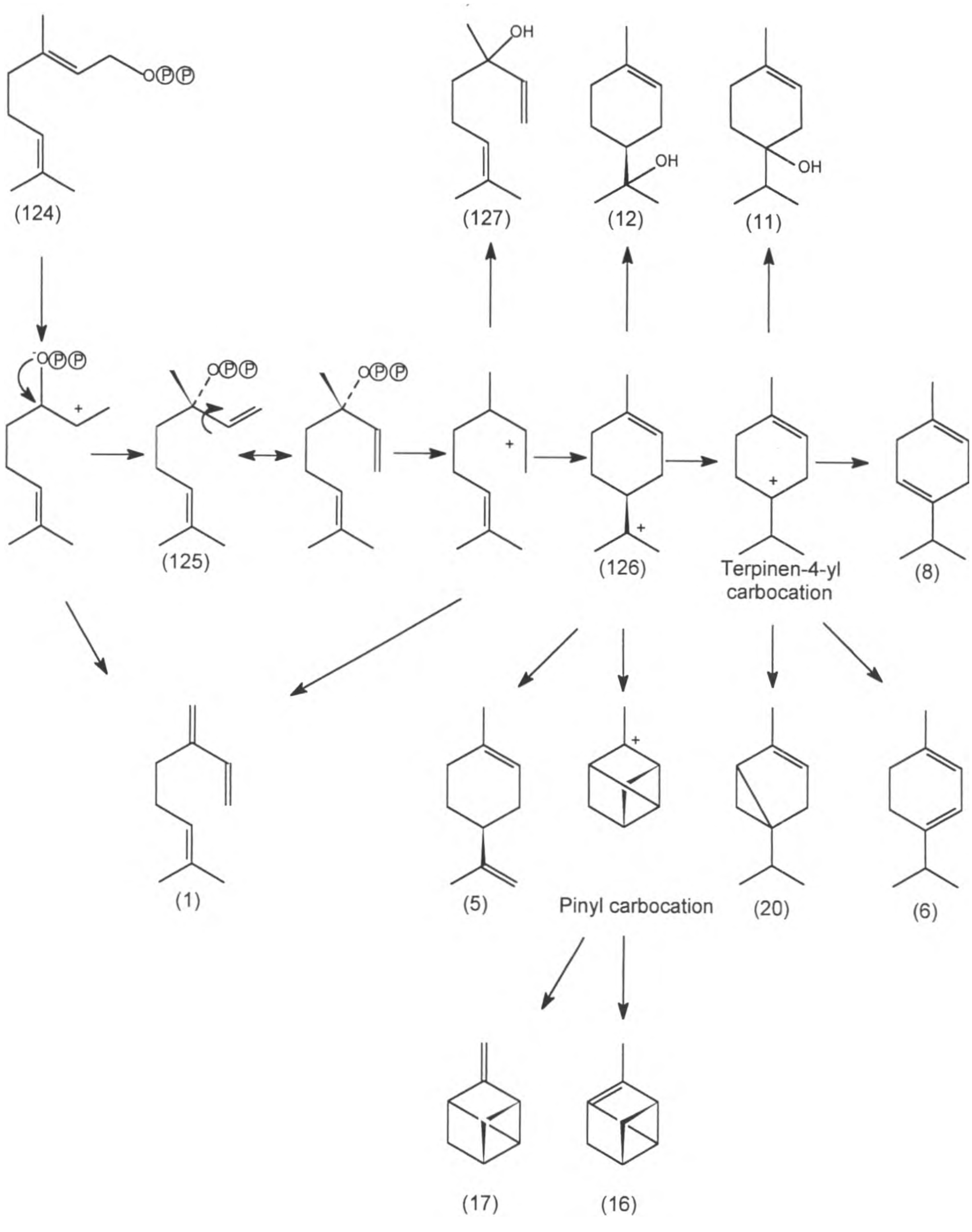
(123)

Figure 6. *p*-Menthane monoterpene glycosides in plants (Continued)

4. Biosynthesis of Monoterpenoids

The enzymic transformation of geranyl diphosphate (GPP) into simple cyclic monoterpenes, e.g. (-)-(4S)-limonene (5) is now firmly established. Initial isomerization of GPP (124) to (+)-(3S)-linalyl diphosphate (LPP) (125) allows cyclization to the (4S)-α-terpinyl cation (126), which loses a proton to give limonene (Scheme 1). (4S)-Limonene synthase enzymes have been isolated from glandular trichomes of both peppermint (*Mentha x piperita*) and spearmint (*M. spicata*) and the enzymes have been purified and characterized (Alonso *et al.*, 1992). Both enzymes were monomeric, had almost identical properties, and transformed GPP principally into limonene (exclusively with the 4S configuration) plus trace amounts of the other cyclic monoterpenes myrcene (1), α-pinene (16), and β-pinene (17). General properties of the enzyme resembled those of other terpene cyclases in that a divalent metal ion was required, Mn^{2+} being preferred over Mg^{2+} ,and that a single enzyme catalyzed both the isomerization of GPP and the subsequent cyclization step. Neryl diphosphate (NPP) was a less acceptable substrate than GPP, with both enantiomers of LPP being better than GPP. Inhibitor of the enzyme provided evidence for carbocationic intermediates. The substrate GPP in the presence of Mn^{2+} afforded protection against inhibition, as did the sulfonium analogue of the linalyl cation in the presence of diphosphate and Mn^{2+}.

A monoterpene cyclase from the leaves of thyme (*Thymus valgaris)* that converts GPP into γ-terpinene (8) has also been purified and studied (Alonso and Croteau, 1991). This enzyme was a very hydrophobic homodimer with a marked preference for Mg^{2+} over Mn^{2+} as cofactor. It also possessed the ability to cyclize GPP to small amounts of α-thujene (20), myrcene (1), α-terpinene (6), limonene (5), linalool (127), terpinen-4-ol (11), and α-terpineol (12), all derivable from intermediates in the reaction sequence (Scheme 1).

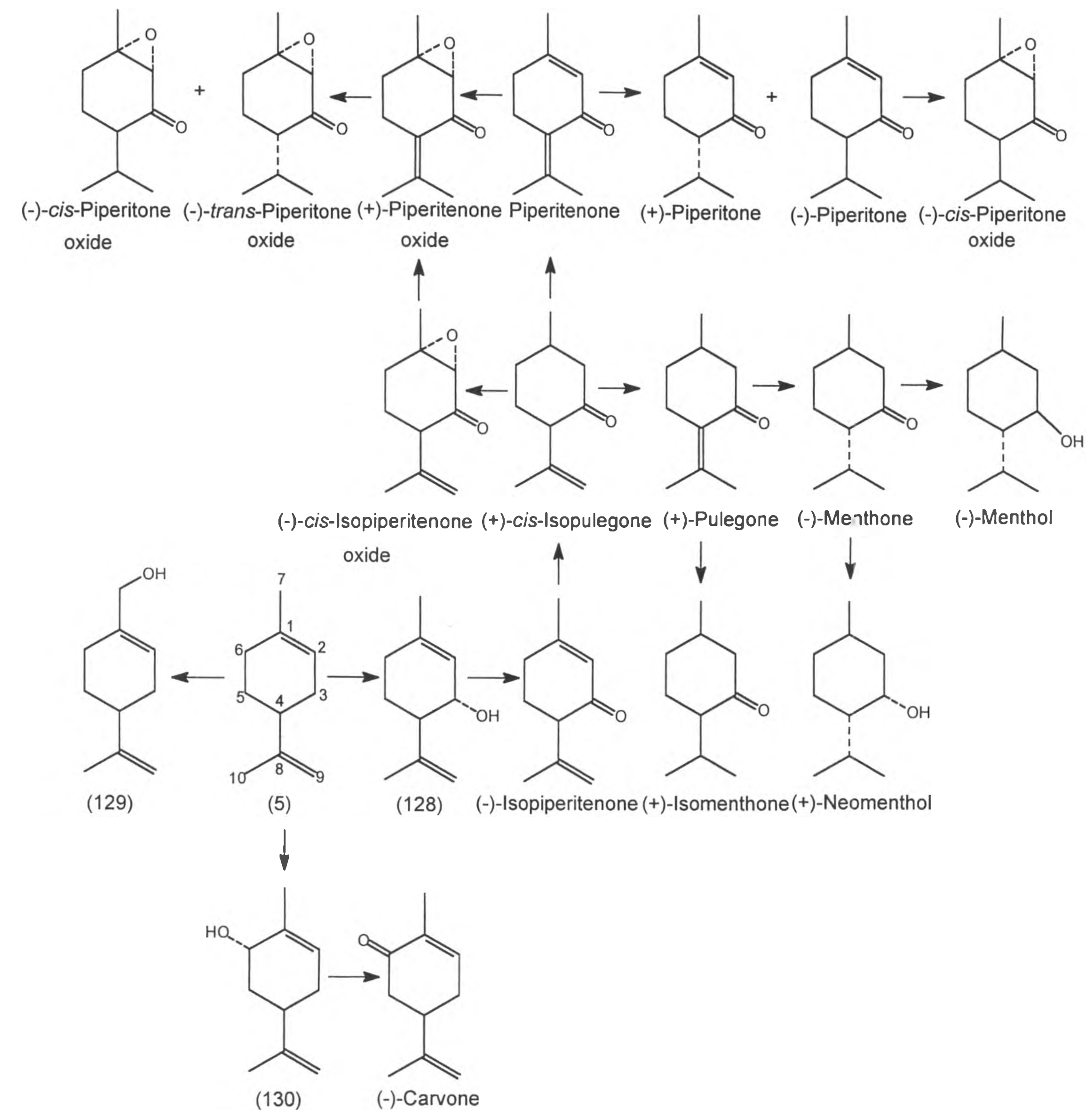


Scheme 1. Biosynthesis of monoterpenoids I

The biosynthesis of limonene, along with DMAPP, GPP, and FPP, could be demonstrated when isolated chromoplasts from *Citrus sinensis* fruits were incubated with IPP (Perez *et al*., 1990). Monoterpene biosynthesis required Mg^{2+} or Mn^{2+} , but was not dependent on an allylic diphosphate . The role of the metal cofactor in monoterpene biosynthesis is to facilitate elimination of the diphosphate group by chelation, thus leading to cyclization. Limonene was the only hydrocarbon product formed from exogenous GPP, NPP, LPP, and terpinyl PP, suggesting the presence of a single cyclase activity that could use all four precursors, probably via the terpinyl carbocation intermediate.

The allylic hydroxylation of (-)-limonene (5) may occur at positions 3, 6 or 7 according to the specificity of the cytochrome P-450-dependent monooxygenases produced by individual plant species (Karp *et al*., 1990). Thus, microsomal preparations from epidermal oil glands of peppermint (*Mentha piperita)* hydroxylate (-)-limonene at C-3 to produce (-)-*trans*-isopiperitenol (128), those from spearmint (*Mentha spicata*) hydroxylate at C-6 to give (-)-*trans*-carveol (130), and enzyme preparations from perilla (*Perilla frutescens*) hydroxylate the side-chain to produce (-)-perillylalcohol (129) (Scheme 2). The reactions required NADPH and O_2 , were completely regiospecific, and were highly specific for limonene as substrate.

Results from a study of the oil produced by a radiation induced mutant of Scotch spearmint (*Mentha x gracilis*), containing mostly 3-oxygenated *p*-menthane derivatives, and the *in vitro* measurement of enzyme activities present have allowed a detailed biosynthetic pathway (Scheme 2) inter-relating the *Mentha* monoterpenes to be proposed (Croteau *et al*., 1991). Enzyme assays showed that all of the enzymes responsible for the production of both the 3- and 6-oxygenated families from the common precursor (-)-limonene were present in the wild-type plant and also in the mutant strain, except for the microsomal cytochrome P-450-dependent (-)-limonene



Scheme 2. Biosynthesis of monoterpenoids II

hydroxylase. The 6-hydroxylase which transforms (-)-limonene into (-)-*trans*-carveol (130) in the wild-type plant was absent but a new 3-hydroxylase activity which transformed (-)-limonene into (-)-*trans*-isopiperitenol (128) was detectable in the mutant. Therefore, mutation had disabled the 6-hydroxylation system and somehow replaced it with a 3-hydroxylation system. Although other enzyme activities functioning the 3-oxygenated pathway (which typically leads to menthol isomers) were shown to be present in the wild-type plant, the lack of the key 3-oxygenated intermediate (-)-*trans*-isopiperitenol (128) means such products are not elaborated. A further observation was that the mutant strain, but not the wild-type, was able to carry out a cytochrome P-450-dependent epoxidation of the α,β-unsaturated bond of 3-ketones formed by the new 3-hydroxylation route. These epoxidase and 3-hydroxylase activities appeared to have some properties in common, and it is possible that a single modified oxygenase is actually responsible for both reactions. The results clarify the origins of the 3- and 6-hydroxylation patterns, and also allow the correction of a number of earlier biogenetic proposals for monoterpene biosynthesis.

5. Biological activities of extracts of *Coleus* species

The biological activities of extracts of *Coleus* species are listed in Table 3.

Table 3. Biological activities of extracts of *Coleus* species

Plant Names	Part uses	Activities	References
Coleus barbatus	Aerial Parts	Antispasmodic	Bhakuni *et al.*, 1971
	Entire Plant	Antihypertensive	Dubey *et al.*, 1981
	Flower	Molluscicidal	Kloos *et al.*, 1987
	Leaf	Antitumor	Zelnik *et al.*, 1977
	Root	Hypotensive	Tandon *et al.*, 1977; de Souza, Dohadwalla and Reden, 1983
		Antiamebic	Varma *et al.*, 1990
		Passive Cutaneous Anaphylaxis Inhibition	Gupta, Srimal and Tandon, 1993
Coleus blumei	Entire Plant	Glutamate-Pyruvate- Transaminase Inhibition	Yanfg *et al.*, 1987
	Leaf	Antibacterial	Garcia *et al.*, 1973
		Antimycobacterial	Garcia *et al.*, 1973
		Cytotoxic	Garcia *et al.*, 1973
Coleus caninus	Entire Plant	Antitumor	Aswal *et al.*, 1984
		Diuretic	Aswal *et al.*, 1984

Table 3. Biological activities of extracts of *Coleus* species (Continued)

Plant Names	Part uses	Activities	References
Coleus kilimandschari	Root and Stem	Antibacterial	Boily and Van Puyvelde, 1986
		Antimycobacterial	Boily and Van Puyvelde, 1986
		Antiyeast	Boily and Van Puyvelde, 1986
Coleus spicatus	Aerial Parts	Antitumor	Painuly and Tandon, 1983
		Cytotoxic	Painuly and Tandon, 1983
		Diuretic	Painuly and Tandon, 1983