

Alkaloids, Coumarins and Lignans from *Haplophyllum* Species

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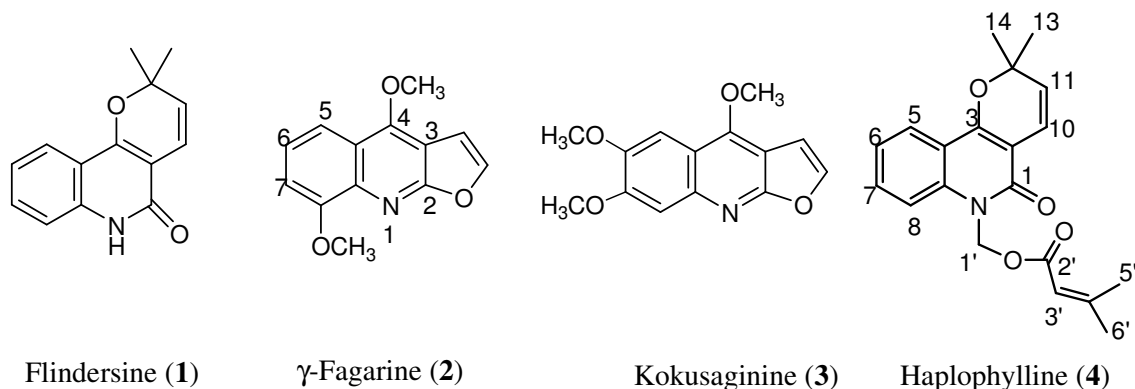
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Abstract: Although there are a number of *Haplophyllum* species in the world, *H. acutifolium* (DC.) G. Don., *H. buxbaumii* (Poiret) G. Don., *H. buxbaumii* (Poiret) G. Don. subsp. *Buxbaumii*, *H. cappadocium* Spach, *H. glabrinum*, *H. hispanicum* Sprach, *H. myrtifolium* Boiss., *H. patavinum* (L.) G. D. ON. fil., *H. perforatum* (M.B.) Vved., *H. pilostylum* Spach, *H. suaveolens* (DC.) G. Don., *H. telephioides* Boiss., *H. thesioides* (Fisch ex DC.) G. Don., *H. tuberculatum* (Forssk.) A. Juss. and *H. vulcanicum* Boiss. & Heldr. were most studied and various compounds isolated. Only alkaloids, coumarins and lignans of these species are mentioned in this article. In addition some volatile components of *H. tuberculatum* were also given.

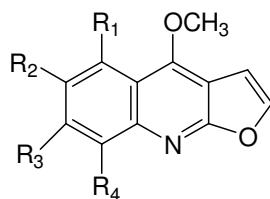
Keywords: *Haplophyllum* species; alkaloids; coumarins; lignans

There are about seventy (70) *Haplophyllum* species naturally grown in the world, mostly located around the Mediterranean section of Europa and in western Asia up to Siberia. In Turkey there are 14 species 7 of them being endemic. The genus contains alkaloids, lignans, coumarins and flavanoids as secondary metabolites. Our group has studied 5 of these species [1], the rest were investigated by Gözler's group. Four alkaloids flindersine (1), γ -fagarine (2), kokusaginine (3) and haplophylline (4) have been isolated from *H. suaveolens* (DC.) G. Don [2].

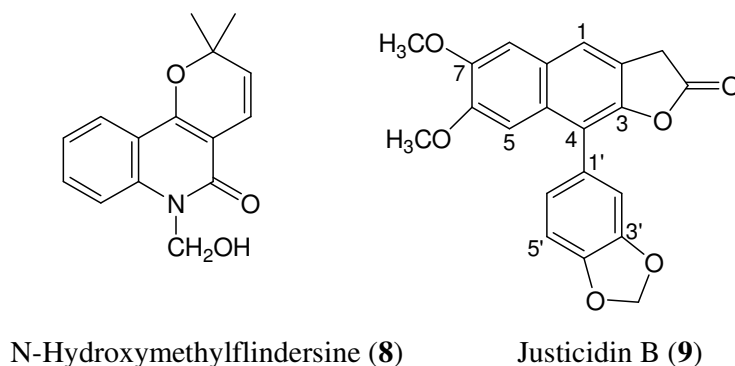
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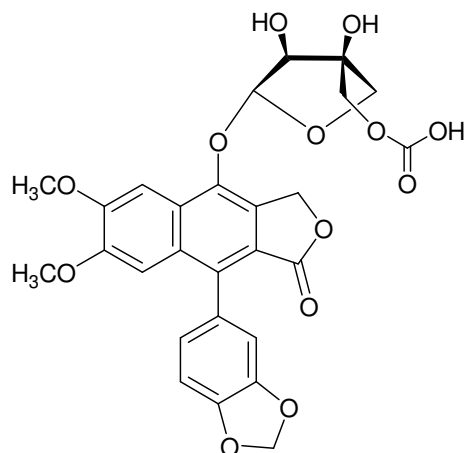
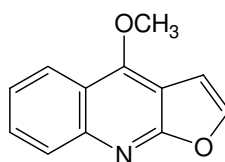
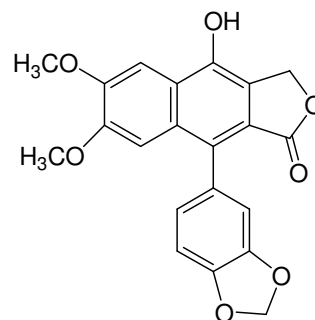
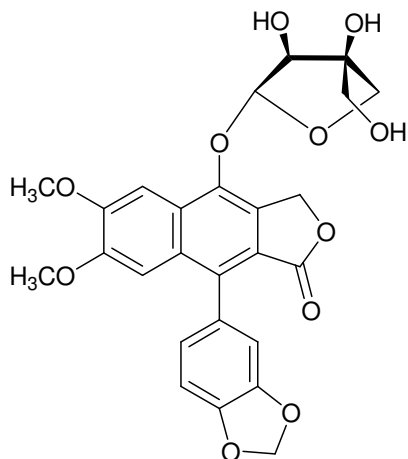
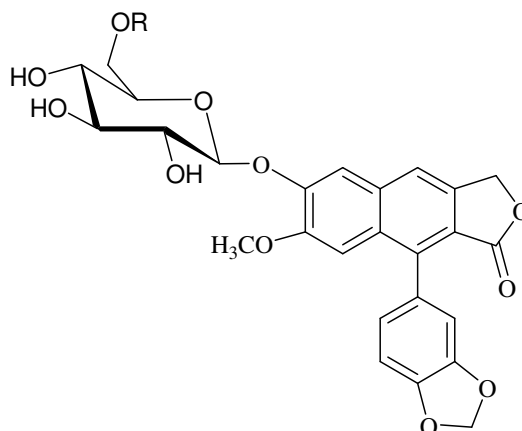
H. buxbaumii subsp. *buxbaumii* [3] has yielded furoquinoline type five compounds γ -fagarine (2), kokusagine (3), skimmianine (5), and 4,5,6-trimethoxyfuroquinoline (6), 4,5,7-trimethoxyfuroquinoline (7) and an angular pyranoquinoline type alkaloid N-hydroxymethylflindersine (8). Only one lignan justicidin B (9) was isolated from the plant in this study.



Skimmianine (5) $R_1=R_2=H$; $R_3=R_4=OCH_3$
 4,5,6-Trimethoxyfuroquinoline (6) $R_1=R_2=OCH_3$; $R_3=R_4=H$
 4,5,7-Trimethoxyfuroquinoline (7) $R_1=R_3=OCH_3$; $R_2=R_4=H$

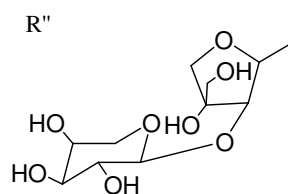
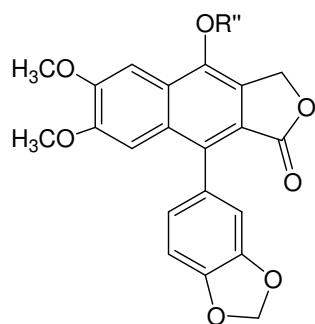
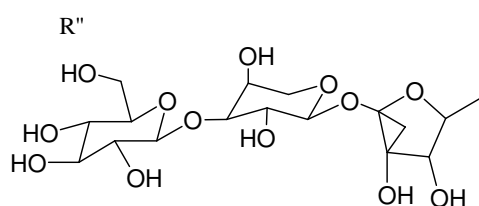
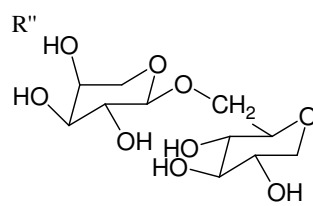
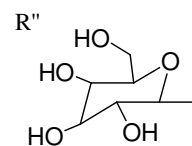
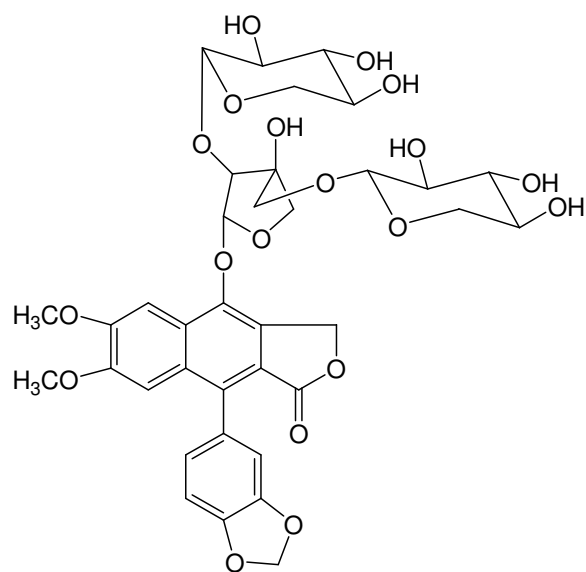


In another study with the same plant, in Jordan [4] a lignan glycoside, monoacetyldiphyllin apioside (10) has been isolated together with previously known compounds dictamnine (11), γ -fagarine (2), justicidin B (9), diphyllin (12), and (-)-tuberculatol (13).

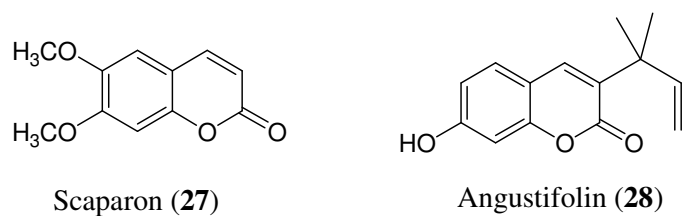
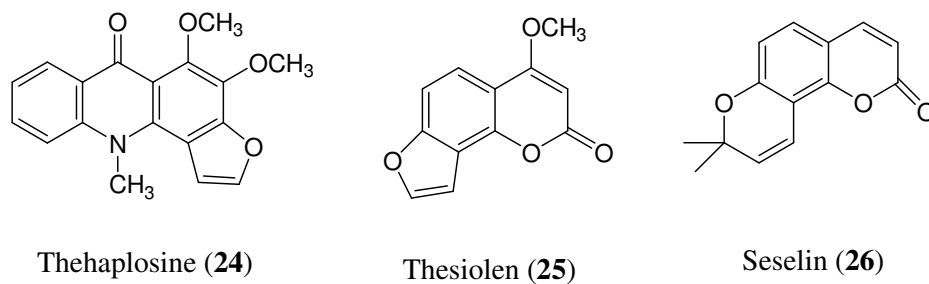
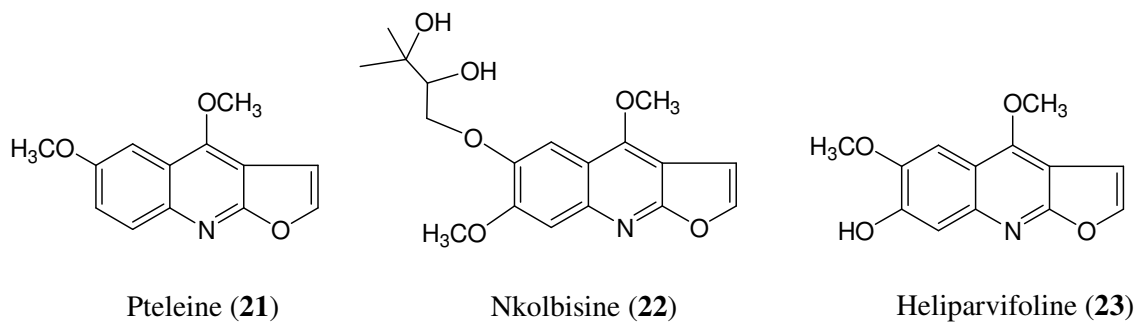
Monoacetyldiphilline apioside (**10**)Dictamnine (**11**)Diphyllin (**12**)(-)-Tuberculatin (**13**)R=H Daurinol glucoside (**14**)R=Ac Daurinol mono-*O*-acetyl glucoside (**15**)

Still another study with the same plant [5] two aryl lignans, daurinol glucoside (**14**) and mono-*O*-acetyl daurinol glucoside (**15**) were isolated.

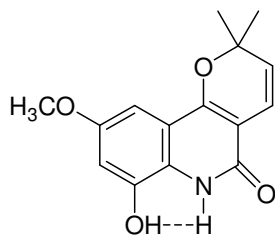
The same group, in continuation of the studies with *H. buxbaumii*, obtained three type A lignan glycosides [6], majidine (**16**), qudsine (**17**), arabelline (**18**) as well as cleistanthin B (**19**). In a recent study [7] a diphyllin glycoside 4-*O*-[bis- α -L-xylopyranosyl (1 \rightarrow 2, 1 \rightarrow 5) β -D-apiofuranosyloxy] - 6,7-dimethoxy 1-(3,4-methylenedioxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic acid lactone (azidin) (**20**) was isolated from *H. buxbaumii*.

Majidine (**16**)Qudsine (**17**)Arabelline (**18**)Cleistanthin (**19**)Azidin (**20**)

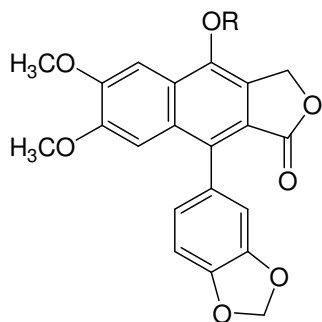
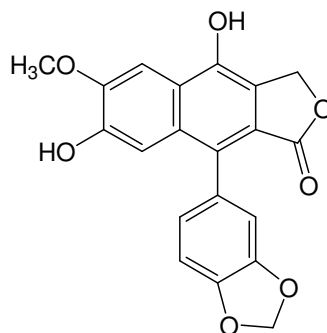
Six previously known alkaloids flindersine (**1**), kokosaginine (**3**), skimmianine (**5**), pteleine (**21**), nkolbisine (**22**), heliparvifoline (**23**) and an acridone type alkaloid theaplosine (**24**) were isolated from *H. thesioides* (Fisch et DC.) G. Don [8] together with a coumarin thesiolen (**25**) and previously known coumarins seselin (**26**), scaparon (**27**) and angustifolin (**28**).



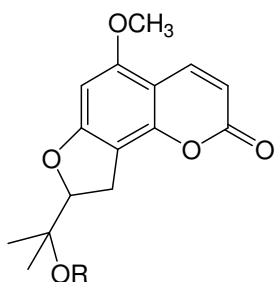
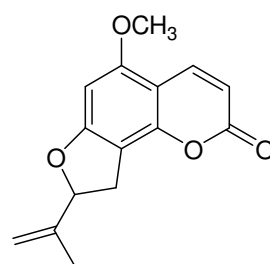
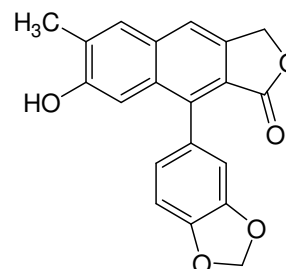
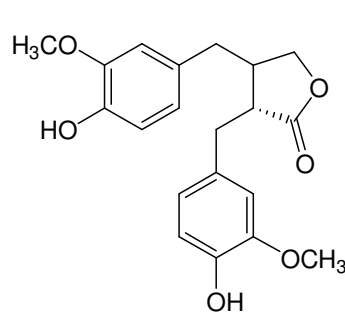
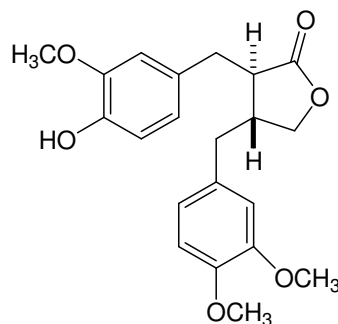
H. telephioides Boiss [9] has yielded an alkaloid 7-hydroxy-9-methoxyflindersine (29) and a lignan 4-acetyldiphyllin (30) in addition to previously known lignans diphyllin (12) [10] and haplomyrtine (31) [11]



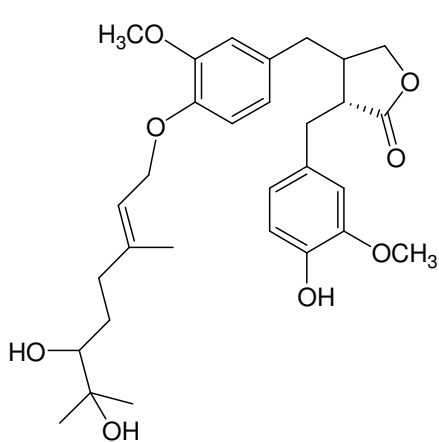
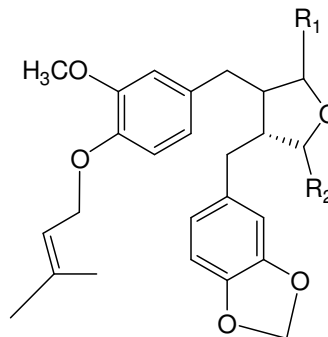
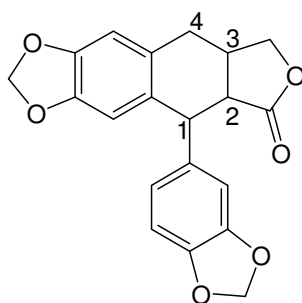
7-Hydroxy-9-methoxyflindersine (29)

R=H Diphylline (**12**)R= COCH₃ 4-Acetyldiphylline (**30**)Haplomyrtin (**31**)

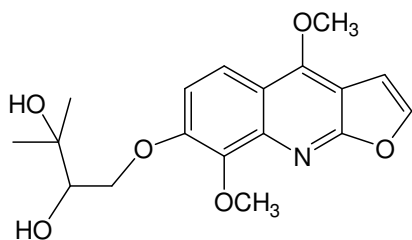
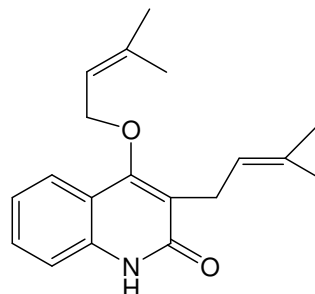
From *Haplophyllum ptilostylum* Spach coumarins ptilostin (**32**), ptilostol (**33**) [12] and ptilin (**34**) [13] together with previously known lignans justicidin B (**9**), isodaurinol (**35**), matairesinol (**36**) and arctigenin (**37**) were obtained. No alkaloid was found in this species [13].

R=CH₂-CH(CH₃)₂ : Ptilostin (**32**)R=H : Ptilostol (**33**)Ptilin (**34**)Isodaurinol (**35**)(-)-Matairesinol (**36**)(-)-Arctigenin (**37**)

An aryltetraline lignan an isomer of picropolygamain (**41**) together with three prenylated arylbutyrolactone lignans (**38-40**) were isolated from *H. pilostylum*. The latter compound showed a moderate activity ($IC_{50}=11.7 \mu\text{g ml}^{-1}$) in HIV-1 reverse transcriptase (p66/p51) assay [14].

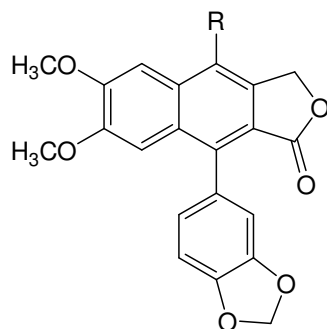
Matairesinol 4-(6'',7''-dihydroxygeraniol) (**38**)Mixture of Dibenzobutyrolactone with Isopentyl at C-4 ; $R_1=O$, $R_2=H$ (**39**)
 $R_1=H$, $R_2=O$ (**40**)Picropolygamain isomer (**41**)

Flindersine (**1**) was obtained from *H. tuberculatum* [15] collected from Iraq, together with other alkaloids γ -fagarine (**2**), skimmianine (**5**), evoxine (**42**) and 3-(3,3-dimethylallyl)-4-(3,3-dimethylalloxy)-2-quinolone (**43**).

Evoxine (**42**)3-(3,3-dimethylallyl)-4-(3,3-dimethylalloxy)-2-quinolone (**43**)

Four lignans also isolated from *H. tuberculatum* [16], diphyllin (**12**), justicidin A (**44**), justicidin B (**9**), and tuberculatin (**13**). From the same plant an alkaloid (+)-tuberine (**45**) was isolated [17, 18].

Tuberine (**45**) exhibited strong antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* in 0.1- 1.0 $\mu\text{g/ml}$ doses.

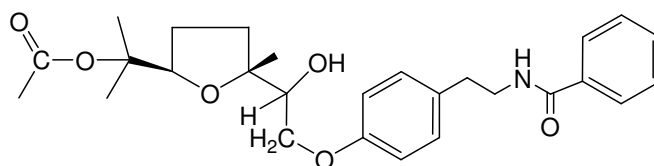


R=OH Diphylline (**12**)

R=OCH₃ Justicidin A (**44**)

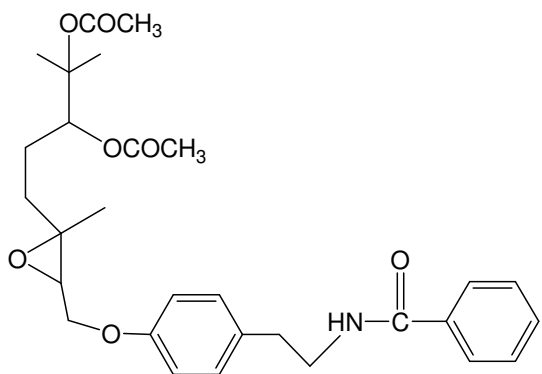
R=H Justicidin B (**9**)

R= β -D-Apiofurosyl=Tuberculatol (**13**)

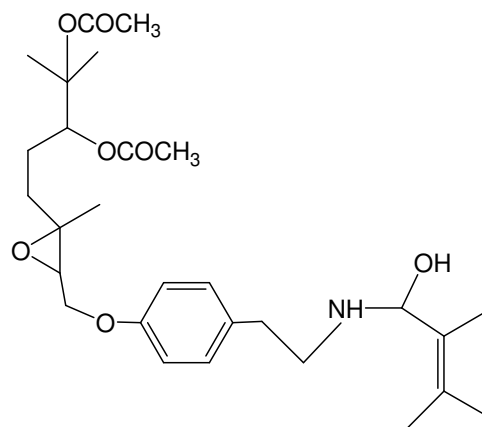


(+)-Tuberine (**45**)

A further study with *H. tuberculatum* naturally growing in Saudi Arabia [19] showed the presence of amide alkaloids and they are tuberine (**45**), tubacetine (**46**), tubasenicine (**47**) and 7-Hydroxy-4-Methoxy-8-prenylfuro[2,3-b]quinoline (**48**) the only tyramine derivative alkaloids.

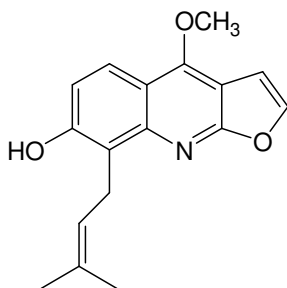


Tubacetine (**46**)

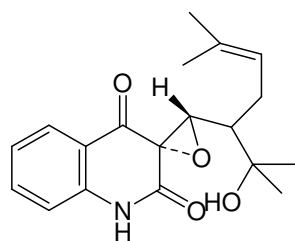


Tubasenicine (**47**)

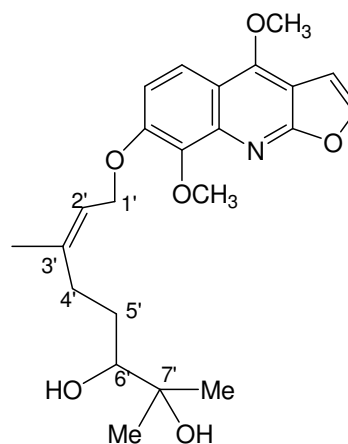
The plant is used against rheumatoid arthritis, malaria and in the cure of some gynecological problems [19]. In a recent study with the same plant [20] in addition to known alkaloids and lignans, two alkaloids haplotubinone (**49**) and haplotubine (**50**) were obtained.



7-Hydroxy-4-Methoxy-8-prenylfuro[2,3-b]quinoline (**48**)



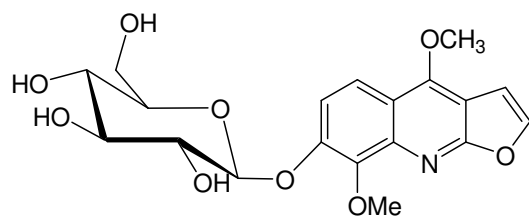
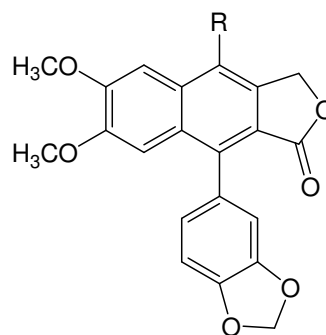
Haplotubinone (**49**)



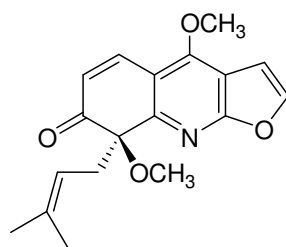
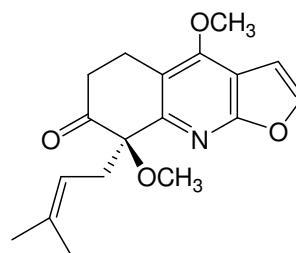
Haplotubine (**50**)

In a new study, the essential oil of the fresh twigs and flowers of *H. tuberculatum* [21] was subjected GS-MS and β -phellandrene (23.3 %) was found to be the main part of the oil, other components were β -myrcene (11.3 %), α -phellandrene (10.9%), (*Z*)- β -ocimene (12.3 %), limonene (12.6 %), and β -caryophelene (11.6 %). Most of the remaining 23 compounds were less than 1 %. The antibacterial and antifungal activity of the oil was tested against standard bacteria, only moderate activity was found. From *H. perforatum* [22] a group of known furanoisoquinoline type alkaloids were isolated only one alkaloid glycohaplopine (**51**) was found in the plant [23].

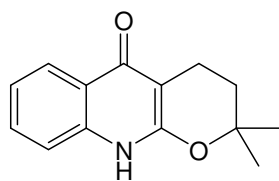
A Spanish group has studied the lignans of *H. hispanicum* Sprach. [24]. In addition to diphyllin (**12**) diphyllin derivatives such as diphyllinine (**52**), diphyllidine monoacetate (**53**), diphyllidin crotonate (**54**) and diphyllin methoxy derivative (justicidin A) (**44**) were obtained and when tested *in vitro*, diphyllin showed cytostatic activity in 0.05 $\mu\text{g/ml}$ doses, although the other compounds were also active but not as high as the standard compound 6-mercaptopurine.

Glycohaplopine (**51**)R=OH Diphyllin (**12**)R=OC₄H₄O(OH)₂-CH₂OH Diphyllidine (**52**)R=OC₄H₄O(OH)₂-CH₂OCOCH₃ Diphyllidine monoacetate (**53**)R=OC₄H₄O(OH)₂-CH₂OCOCH=CHCH₃ Diphyllidine crotonate (**54**)R=OCH₃ Justicidin A (**44**)

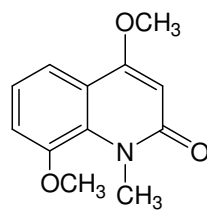
From *H. glabrinum* an alkaloid was isolated [25]. The alkaloid was quite similar to perfamine (**55**) and named as dihydroperfamine (**56**).

Perfamine (**55**)(+)-Dihydroperfamine (**56**)

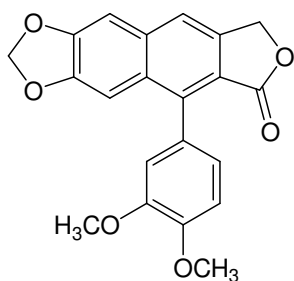
Studies with *H. cappadocium* [26] a plant native to eastern Turkey, alkaloids dictamine (**11**), haplofoline (**57**), folimine (**58**) and malatyamine (**59**) together with an arylnaphtalene lignan 4-deoxyisodiphyllin (chinensin) (**60**) and previously known compounds isodaurinol (**35**), daurinol (**61**), justicidin A (**44**), justicidin B (**9**) and diphyllin (**12**), (-)-matairesinol (**36**). Three furoquinolone alkaloids were also obtained robustine (**62**), haplopine (**63**) and skimmianine (**5**) [27]. In another study with the same plant [28] two lignan glycosides (-)-cappadoside (**64**) and (-)-haplodoside (**65**) and a benzylidene benzylbutyrolactone lignan (-)-cappadocin (**66**) were obtained. Minor lignans were also found in this endemic species haplomyrtoside (**67**), haplomyrtin (**31**), majidine (**16**), Taiwanin C (**68**).



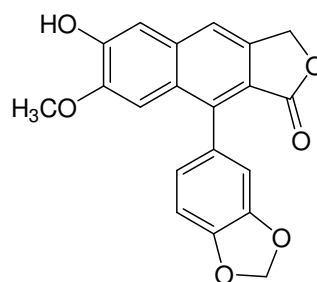
Haplofoline (57)



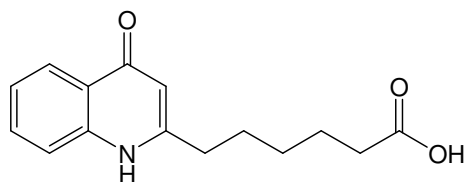
Folimine (58)



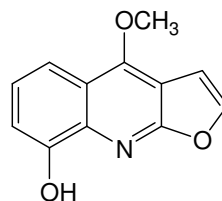
4-Deoxyisodiphyllin (60)



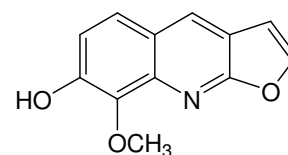
Daurinol (61)



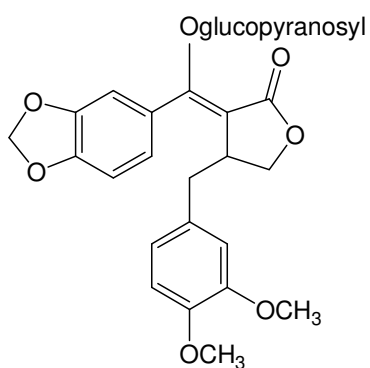
Malatyamine (59)



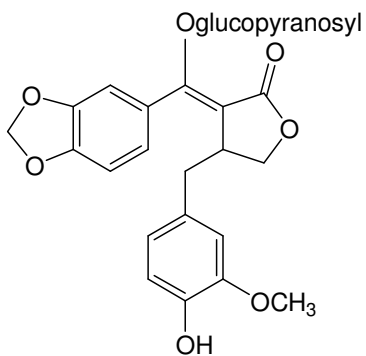
Robustine (62)



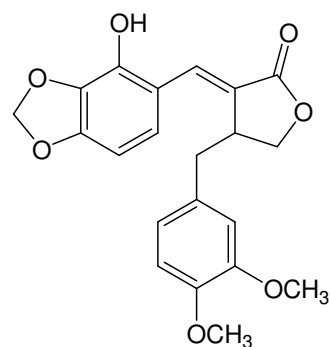
Haplopine (63)



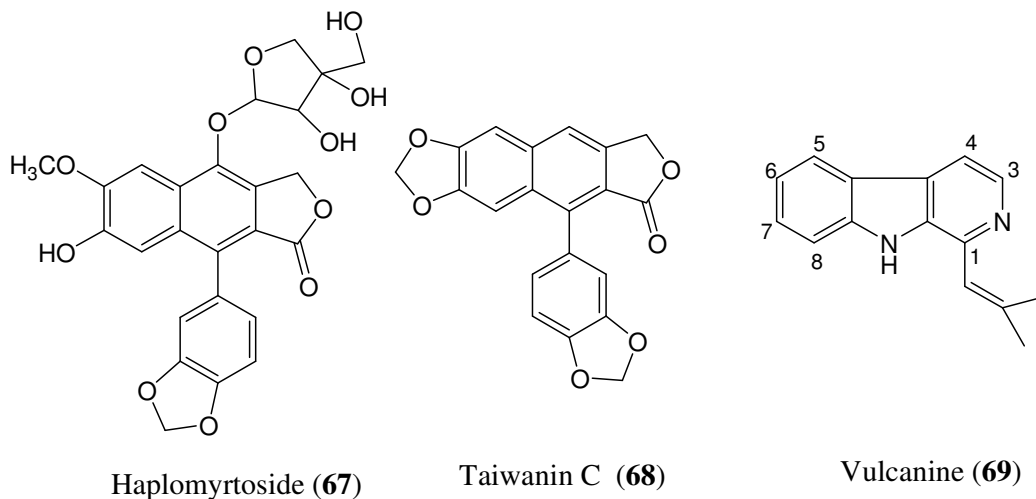
(-)-Cappadoside (64)



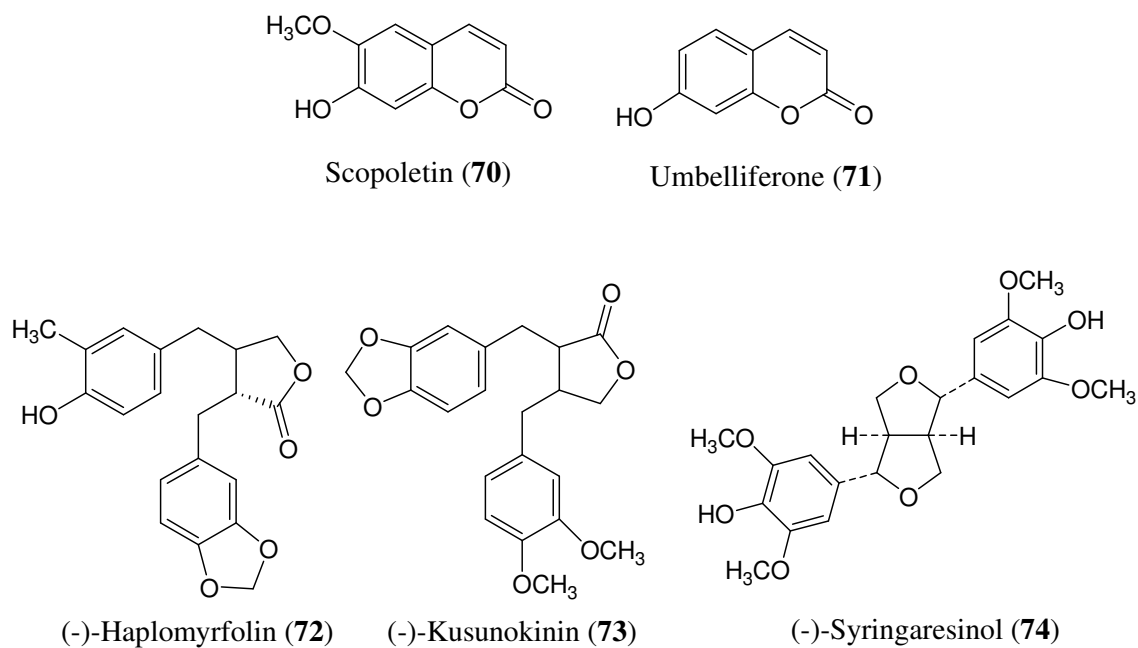
(-)-Haplodoside (65)

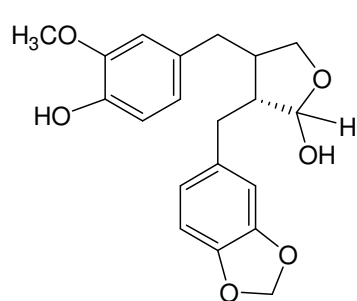
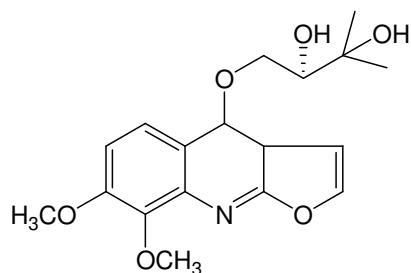


Cappadocin (66)

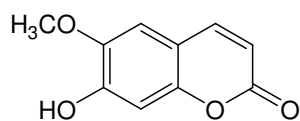
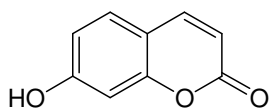
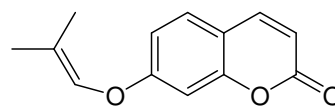
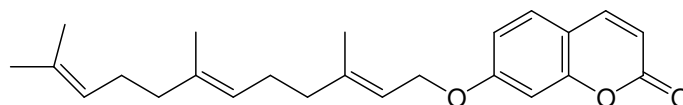
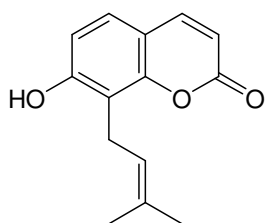
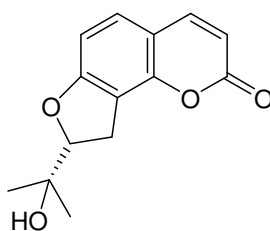
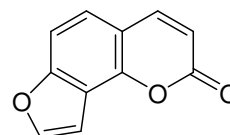


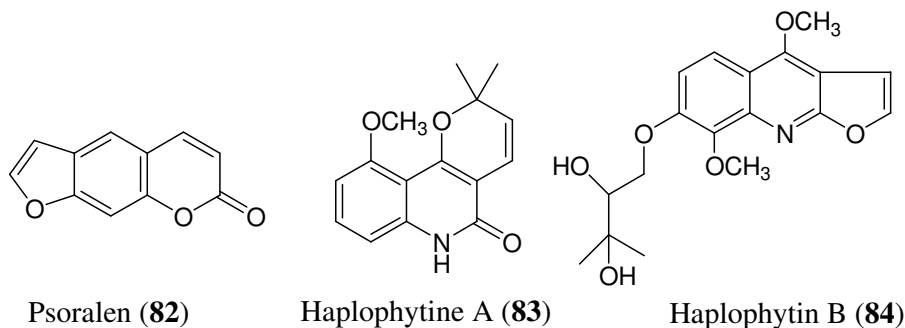
H. vulcanicum [29] is an endemic plant in central Turkey, has yielded a β -carboline alkaloid vulcanine 1-(2-methyl-1-propenyl)- β -carboline (69). In a previous study with the same plant [30] the same group obtained alkaloids, coumarins and lignans, that those are dictamnine (11), γ -fagarine (2), robustine (62), haplopinine (63), and skimmianine (5) together with two coumarins scopoletin (70), umbelliferone (71), and the lignans (-)-haplomyrfolin (72), (-)-kusunokinin (73), (+)-syringaresinol (74), haplomyr-folol (75), diphyllin (12) and tuberculatin (13). (+)-Nigdenine (76) an alkaloid was also obtained together with other alkaloids [28, 29].



(-)-Haplomyrfolol (**75**)(+) -Nigdenine (**76**)

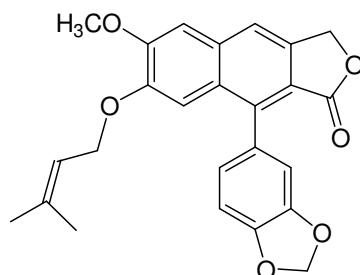
From the native plant of *H. patavinum* and from its *calli* and *suspension cultures* [31] a number of coumarins were obtained, these were scopoletin (**70**), umbelliferone (**71**), 7-isoprenyloxycoumarin (**77**), umbelliprenin (**78**), ostenol (**79**), columbianetin (**80**), angelicin (**81**) and psoralen (**82**). The plant is used in folk medicine as antimicrobial, antimalarial, insecticidal agent.

Scopoletin (**70**)Umbelliferone (**71**)7-Isoprenyloxycoumarin (**77**)Umbelliprenin (**78**)Ostenol (**79**)Columbianetin (**80**)Angelicin (**81**)



In addition to a known alkaloid flindersine (1), and a lignan kusunokinin (73) two alkaloids haplophytin A (5-methoxy flindersine) (83) and haplophytin B (Evoxine=Haploperine) (84) were isolated from *H. acutifolium* [32].

A prenylated arylnaphtalene lignan 4-O-(3-methyl-2-butenyl) isodaurinol (85) was obtained from *H. myrtifolium* [33], in this study, in addition to the lignan Taiwanin C (68) furoquinoline alkaloids dictamnine (11), robustine (62), γ -fagarine (2) and skimmianine (5) were also isolated.



4-O-(3-methyl-2-butenyl) isodaurinol (85)

There are some more studies with other *Haplophyllum* species, which were not covered here.

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