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Review Article

Phytochemical and Pharmacological Properties of the Genus Melodinus – A Review

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Abstract

Melodinus is an important genus comprising of approximately 53 species of medicinal plants (Apocynaceae). Some species have been used in Chinese folk medicine for the treatment of meningitis in children, rheumatic heart diseases, and diuresis, as well as a decongestive against migraine and sinusitis. This paper is a review of the literature up to May 2015 and describes 263 compounds from 69 articles, and includes chemical constituents isolated from Melodinus, mainly indole alkaloids, quinoline alkaloids, dimeric alkaloids, terpenoids and other compounds. It is also hoped that an overview of their cytotoxic characteristics will further the development of new anti-cancer agents.

Keywords: *Melodinus, Indole alkaloids, Dimeric alkaloids, Cytotoxicity, Medicinal plants*

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INTRODUCTION

Melodinus is a genus of *ca.* 53 species in the family Apocynaceae, mainly distributed in tropical and subtropical Asia and from Oceania to the Pacific coast. Among them, *ca.* 11 species occur in South China, Southwest China and Taiwan [1]. Some species, such as *M. suaveolens* and *M. henyri* have been used in Chinese folk medicine for the treatment of meningitis in children, rheumatic heart diseases, diuresis, bone fracture and so on [2,3]. *M. scandens* is used as a decongestive, against migraines, sinusitis and otitis [4]. In Australia, an aq extract of *M. australis*, when injected into a dog, produced a sharp drop in blood pressure, accompanied by an increase in the depth of respiration and decrease in rate [5]. Current crude alkaloid mixtures and purified alkaloids from some *Melodinus* species have demonstrated antitumor and antibacterial activities [6,7]. Many characteristic melodinus alkaloids, such as meloscine, epimeloscine, scandine and vincadifformine, had for a long time attracted great interest of synthetic organic chemists as challenging targets due to their marked diversity and complicated architectures [8,9,10] And more than twenty alkaloids were reviewed from the genus *Melodinus* by Sevenet *et al* [11]. About 14 alkaloids can be classified into the melodan skeleton and its rearranged version and derived from 18, 19-didehydrotabersonine as parent compound in the plant family Apocynaceae [12]
Recently, much attention has been paid to *Melodinus* plants to search active melodinus alkaloids. Extensive studies of the *Melodinus* genus have led to the identification of several novel alkaloids. Only 22 species of the genus have been chemically investigated and provided an array of structurally interesting indole

alkaloids, quinoline alkaloids, dimeric indole alkaloids, diterpenoids, triterpenes and others compounds over the past few decades. Some compounds show cytotoxic and anti-inflammatory activities. In this paper, we summarize phytochemistry and pharmacological activities of the *Melodinus* species so as to collate the existent information on this plant.

PHYTOCHEMICAL CONSTITUENTS

By the deadline of MAY 2015, phytochemical studies on this genus led to the isolation of 263 compounds. Their structures are shown below and their names, the corresponding plant sources are collected. As can be seen, indole alkaloids are the dominant constituents within this genus.

Alkaloids

Plants of the genus *Melodinus* (Apocynaceae) have been proven to be good sources of alkaloids. This genus has been regarded as a rich source of monoterpenoid indole alkaloids, which originated from the condensation of tryptophan with secologanin. We now list 252 alkaloids which were obtained from the genus *Melodinus*. The structural characters and relationships of the major *Melodinus* alkaloid groups are discussed.

Monoterpenoid indole alkaloids

Kopsinine-type

In this paper, indole alkaloids could be classified into ten groups from some *Melodinus* plants. This first type included nineteen alkaloids (**1-19**) (Table 1, Figure 1) [13-35]. The common characteristic compounds, venalstonine (**3**) and venalstonine (**7**) were produced by more than fifteen *Melodinus* species. Three aspidofractinine oxo-derivatives (9-11) were obtained from *M. reticulates* and *M. guillauminii* [13,14]. Melodinine L (**12**) was new alkaloid identified as venalstonine-N (4)-oxide from *M. tenuicaudatus* and *M. yunnanensis* [27,34]. Methoxyl substitution at C (**15**), a rare phenomenon, were present in pyrifoline (**13**) and refractidine (**14**) obtained from *M. australis* [33]. Melodinine Q (**17**) was venalstonine derivative with a CH_3−CO−CH−unit [29]. 14, 15-Seco-3-oxo-kopsinal (**16**) originated a further oxidation of bond C (14)-C (**15**) of venalstonine was identified by comparison of their spectral and physical properties from *M. guillauminii* [14]. 10, 22 - Dioxokopsane was a known alkaloids but was isolated obtained from this genus for the first time [35].

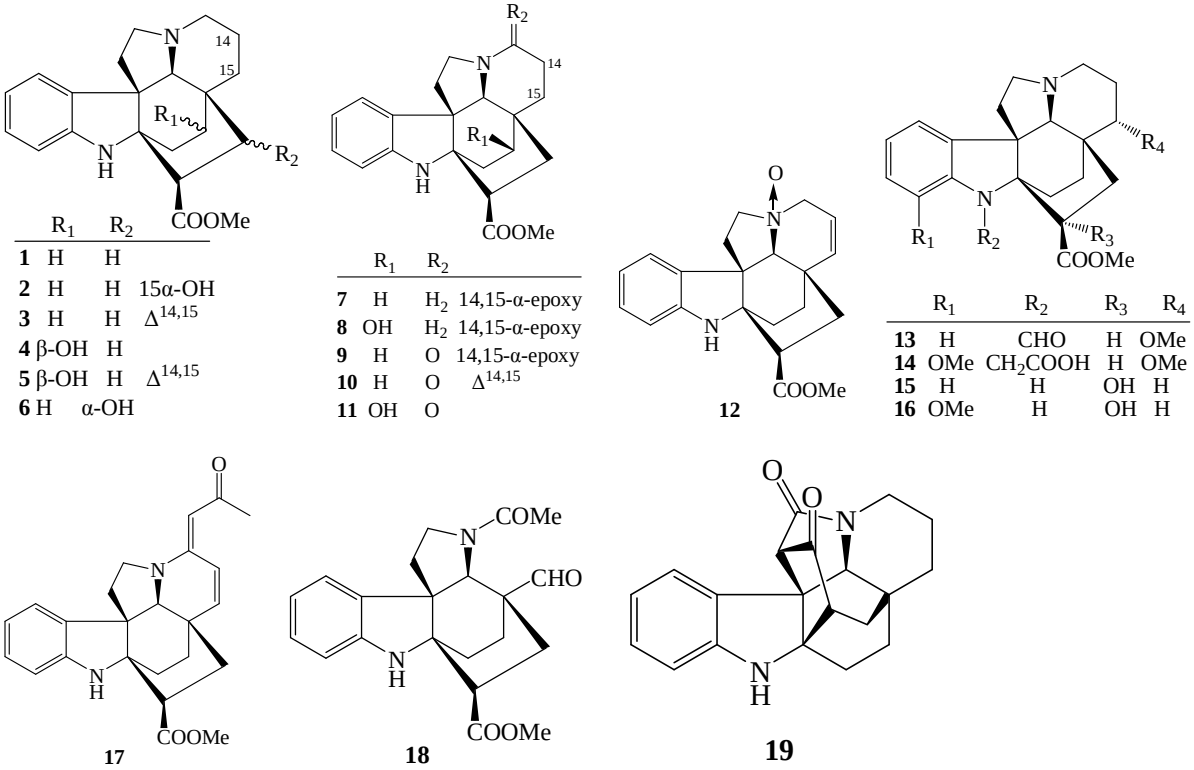

Figure 1: Structures of kopsinine-type alkaloids from *Melodinus* spps

Nomenclature:

A= aerial parts
B= stem bark
F= fruit
L= leaves
N= not mentioned
R= root
S= stems
T= twigs
Tr= trunk

Table 1: Kopsinine-type alkaloids from genus *Melodinus*

No.	Compound name	Species	Ref.
1	Kopsinine	*M. fusiformis*(R & S),*M. guillauminii*(A & B),*M. morsei*(N),*M. reticulatus*(L & S)	[13-16]
2	15*α*-Hydroxykopsinine	*M. fusiformis*(R & S),*M. guillauminii*(A & B),*M. hemsleyanus*(R), *M. morsei*(N)	[14-17]
3	Venalstonine= Δ^6-Kopsinine	*M. australis*(N),*M. balansae*(L),*M. fusiformis* (L, R & S),*M. guillauminii*(A & B),*M. hemsleyanus*(A),*M. insulae-pinorum*(A & B), *M. oblongus*(L), *M. polyadenus*(L& S), *M. phylliraeoides*(L),*M. reticulatus*(L & S), *M. scandens* (N), *M. suaveolens*(N), *M. tenuicaudatus*(N)	[13-15,18-29]
4	19*β*-Hydroxykopsinine	*M. insulae-pinorum*(A & B)	[24]
5	19*β*-Hydroxyvenalstonine	*M. guillauminii*(A & B),*M. oblongus*(S),*M. reticulatus*(S & L)	[13,14,30
6	17*α*-Hydroxyvenalstonine	*M. tenuicaudatus*(N)	[27]
7	Venalstonidine= 6,7*ξ*-Epoxy-kopsinine	*M. australis*(N),*M. balansae*(L),*M. celastroides*(A),*M. fusiformis*(L & S),*M. guillauminii*(A & B),*M. hemsleyanus*(A),*M. insulae-pinorum*(A & B),*M. morsei*(L & S),*M. polyadenus*(L& S),*M. phylliraeoides*(L),*M. reticulatus*(L & S),*M. scandens*(N),*M. yunnanensis*(L & T)	[13,14,18-25,28,31, 32]
8	19-*β*-Hydroxyvenalstonidine	*M. insulae-pinorum*(A & B),*M. reticulatus*(L & S)	[13,24]
9	3-Oxovenalstonidine	*M. reticulatus*(L & S)	[13]
10	3-Oxovenalstonine	*M. guillauminii*(A & B),*M. reticulatus*(L & S)	[13,14]
11	3-Oxohydroxykopsinine	*M. guillauminii*(A & B)	[14]
12	Melodinine L	*M. tenuicaudatus*(N),*M. yunnanensis*	[27,32]
13	Refractidine	*M. australis*(N)	[33]
14	Pyrifoline	*M. australis*(N)	[33]
15	Kopsinine B	*M. henryi*(L & S)	[34]
16	12-Methoxykopsinaline	*M. henryi*(L & S)	[34]
17	Melodinine Q	*M. suaveolens*(N)	[29]
18	14,15-Seco-3-oxokopsinal	*M. guillauminii*(A & B)	[14]
19	10,22-Dioxokopsane	*M. henryi*(L)	[35]

Tabersonine-group

This stereochemical series was more commonly encountered in the tabersonine group, as indicated in structures 20-55 (Table 2, Figure 2), respectively. The simple tabersonine derivatives (**20-47**) were identified from sixteen Melodinus species. Compounds 30- 36, in which C (14)-C (**15**) were epoxidized, were also isolated from *M. aeneus, M. fusiformis, M. hemsleyanus, M. henryi, M. morsei, M. oblongus, M. suaveolens* and *M. tenuicaudatus* [15,25-29,37,38,42,43]. Continuation of study on the genus *Melodinus* had led to the isolation of six new monoterpenoid indole alkaloids, melodinines M- S (**47-52**, resp.), as well as seven known tabersonine derivatives (**25, 26, 29, 31, 45, 53**) from *M. suaveolens* by Liu *et al*. The structure difference of 11-hydroxytabersonine and melodinine A (**47**), melodinine A was that the benzene ring A was oxidized to a dienone system. Alkaloids (**51 - 53**) were identified as an acetonyl derivative of tabersonine by the NMR from *M. tenuicaudatus* [29]. And melotenine A (**55**), an unprecedented skeleton with a 6/5/5/6/7 pentacyclic rearranged

ring system, which have been derived from tabersonine, was also isolated [41].

Vindolinine-type

This type was a small group with eleven alkaloids, **56-66** (Table 3, Fig 3), which contained a C (2)-C (**19**) bond in an aspidospermine ring from *Melodinus* spps. All of them expect compound **66** belong to the five pair of epimers and their names, the corresponding plant sources and the reference are collected in Table 3.

Aspidospermidine-type

Aspidospermidine alkaloids, **67-73** (Fig 4), may be derived from vincadifformine by deformylation. Eburenine (1,2-dehydroaspidospermidine) (**67**) and (-)-aspidospermidine (**68**) were isolated from air-dried leaves, twigs and aerial parts of *M. morsei* (L & T), *M. henryi* and air-dried leaves of *M. celastroides* [28,44,48,49]. Previous pharmacological investigations on leaves of *M. celastroides*, epi-20, 21(+)-aspidospermidine (**69**), Nb-oxyepi-20, 21(+)-aspidospermidine (**70**), melocelinine (**71**) and meloceline (**72**) were

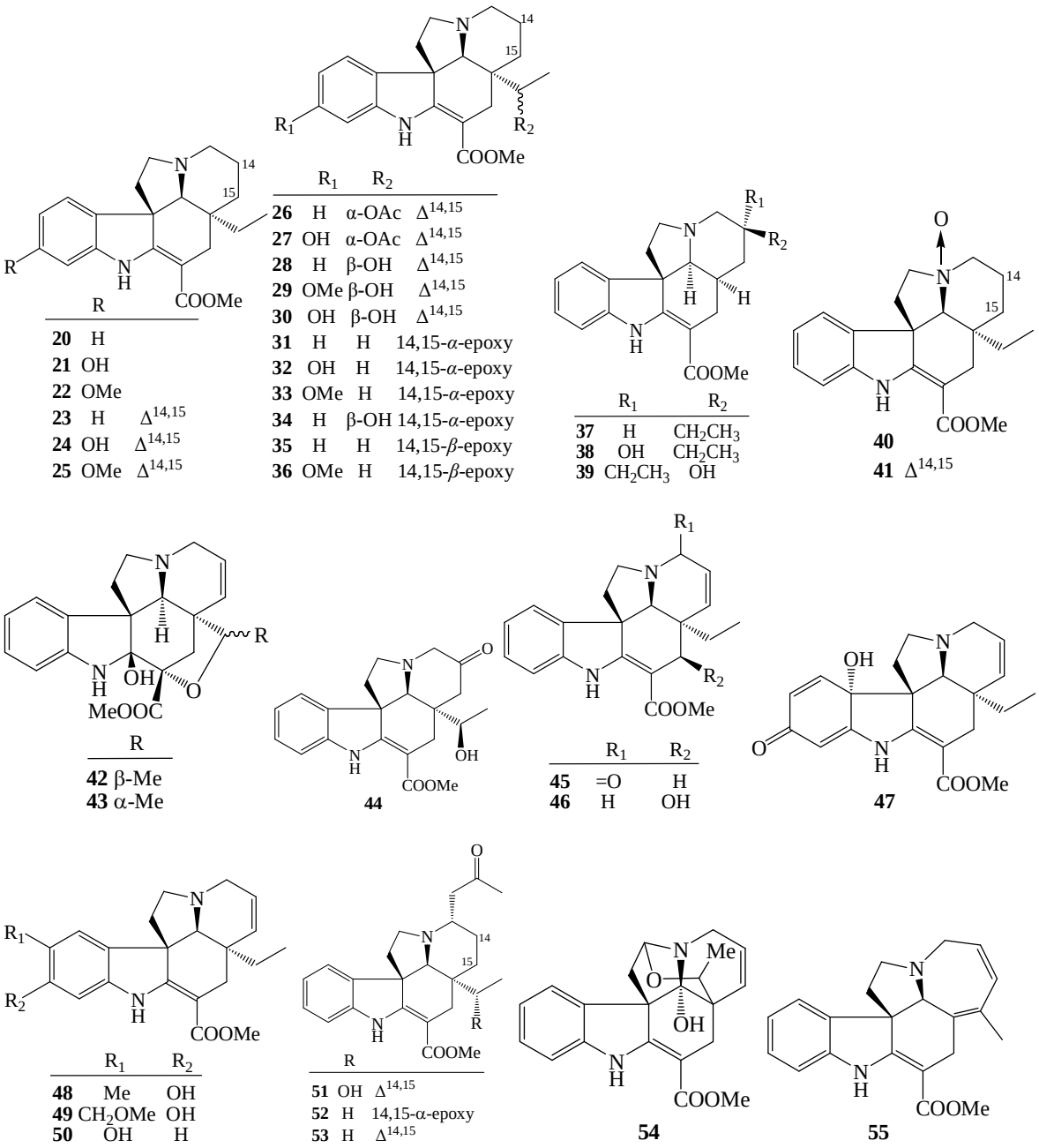

Figure 2: Structures of tabersonine-group alkaloids from *Melodinus* spps

Table 2: Tabersonine-group alkaloids from genus *Melodinus*

No.	Compound name	Species	Ref.
20	Vincadifformine	*M. aeneus*(L),*M. morsei*(L & S)),*M. polyadenus*(L & S),*M. scandens*(N), *M. suaveolens*(Tr)	[16,19,22,28,36-38]
21	11-Hydroxyvincadifformine	*M. hemsleyanus*(A),*M. morsei*(L & S)	[25,28]
22	11-Methoxyvincadifformine	*M. suaveolens*(Tr)	[37]
23	Tabersonine	*M.aeneus*(L), *M. balansae*(L), *M. elastroides* (L),*M. fusiformis*(L, R & S), *M. hemsleyanus*(A),*M. henryi*(F & R), *M. morsei*(L & S),*M. oblongus*(S),*M. polyadenus*(L & S),*M. reticulatus*(F),*M. scandens*(N), *M. suaveolens*(Tr), *M. tenuicaudatus*(N),*M. yunnanensis*(L & T)	[13,15,19,20,22,25,28-32,37-42]
24	11-Hydroxytabersonine	*M. axillaris*(R),*M. balansae*(L),*M. fusiformis*(R & S),*M. guillauminii*(A & B), *M. hemsleyanus*(A & R),*M. morsei*(L & S),*M. oblongus*(L),*M. tenuicaudatus*(B), *M. suaveolens*(Tr, L & T)	[14,15,17,20,25-29,37,43-46]
25	11-Methoxytabersonine	*M. aeneus*(L),*M. fusiformis*(R & S),*M. guillauminii*(A & B),*M. hemsleyanus*(A), *M. henryi*(F & R), *M. polyadenus*(L & S), *M. reticulatus*(F),*M. suaveolens*(Tr),*M. tenuicaudatus*(B),*M. yunnanensis*(L & T)	[13-15,22,25,27,29,32,37,38,42,43]
26	19-Acetyltabersonine	*M. morsei*(L & S),*M. suaveolens*(N)	[28,29]
27	11-Hydroxy-19-acetyltabersonine	*M. tenuicaudatus*(N),*M. morsei*(L & S)	[27,28]
28	19*R*-Hydroxytabersonine	*M. suaveolens*(Tr)	[37]
29	11-Methoxy-19*R*-hydroxytabersonine	*M. suaveolens*(Tr)	[29,37]
30	11,19*R*-Dihydroxytabersonine	*M. fusiformis*(R & S),*M. hemsleyanus*(A), *M. suaveolens*(Tr)	[15,25,37]
31	Lochnericine	*M. aeneus*(L),*M. morsei*(L & S),*M. suaveolens*(N),*M. yunnanensis*(L & T)	[28,29,32,38]
32	11-Hydroxy-14,15*α*-Epoxytabersonine	*M. fusiformis*(R & S),*M. hemsleyanus*(A), *M. morsei*(L & S),*M. tenuicaudatus*(N)	[15,25,27,28]
33	Hazuntine	*M. suaveolens*(Tr),*M. tenuicaudatus*(B)	[37,43]
34	Cathovalinine	*M. suaveolens*(Tr)	[37]
35	*β*-Epoxytaberonine	*M. oblongus*(L)	[26]
36	Lochnerinine	*M. aeneus*(L),*M. henryi*(F & R)	[38,42]
37	(+)-20-*R*-Pseudovincadifformine	*M. polyadenus*(L & S)	[22]
38	(+)-20-*R*-Pandoline	*M. polyadenus*(L & S)	[22]
39	(+)-20-*S*-Pandoline	*M. polyadenus*(L & S)	[22]
40	Vincadifformine N_b-oxide	*M. morsei*(L & S),*M. yunnanensis*(L & T)	[28,32]
41	Tabersonine N_4-oxide	*M. yunnanensis*(L & T)	[32]
42	Melobaline	*M. balansae*(L)	[20]
43	Vincoline	*M. hemsleyanus*(R),*M. morsei*(A), *M. suaveolens*(Tr)	[17,36,37,44]
44	Baloxine	*M. balansae*(L)	[20]
45	3-Oxotabersonine	*M. suaveolens,M. yunnanensis*(L & T)	[29,32]
46	17-Hydroxy-14,15-dihydrotabersonine	*M. yunnanensis*(L & T)	[32]
47	Melodinine M	*M. suaveolens*(N)	[29]
48	Melodinine N	*M. suaveolens*(N)	[29]
49	Melodinine O	*M. suaveolens*(N)	[29]
50	Melodinine P	*M. suaveolens*(N)	[29]
51	Melodinine R	*M. suaveolens*(N)	[29]
52	Melodinine S	*M. suaveolens*(N)	[29]
53	3α-Acetonyltabersonine	*M. suaveolens*(N)	[29]
54	Buxomeline	*M. celastroides*(L)	[40]
55	Melotenine A	*M. tenuicaudatus*(N)	[41]

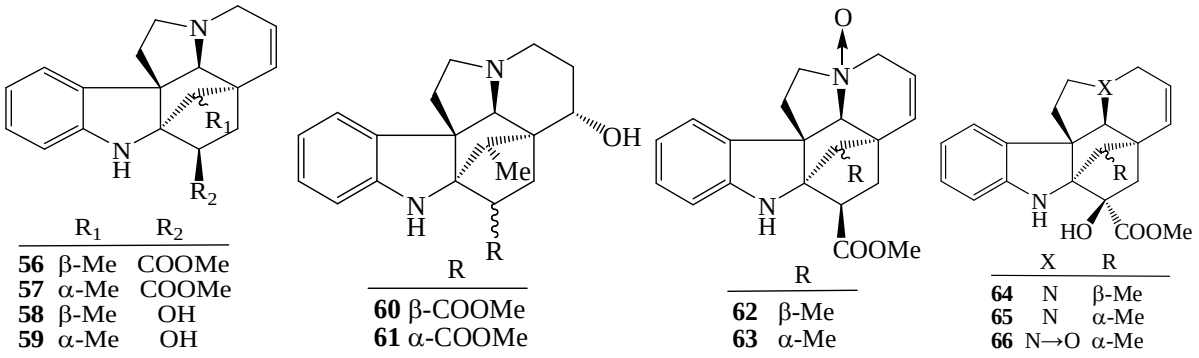

Figure 3: Structures of vindolinine-type alkaloids from *Melodinus* spps

Table 3: Vindolinine-type alkaloids from genus *Melodinus*

No.	Compound name	Species	Ref
56	19*S*-Vindolinine = Vindolinine	*M. balansae*(L),*M. fusiformis*(R & S), *M. hemsleyanus, M. morsei*(N,), *M. Oblongus*(S),*M. hylliraeoides*(L), *M. Suaveolens*(Tr),*M. tenuicaudatus*(B)	[15,16,20, 23,27,28,3 0,37,43]
57	19*R*-Vindolinine = Epivindoline	*M. celastroides*(L),*M. hemsleyanus*(A), *M. morsei*(L & S), *M. phylliraeoides*(L), *M. oblongus*(S)	[16,23,25, 28,30,40]
58	16-Hidroxyvindolinine	*M. oblongus*(S)	[30]
59	16-Hidroxyepivindolinine	*M. oblongus*(S)	[30]
60	15*α*-Hydroxy-14,15-dihydrovindolinine	*M. Morsei*(N)	[16,47]
61	15*α*-Hydroxy-14,15-dihydro-16-epivindolinine	*M. morsei*(N)	[16,47]
62	Vindolinine N_b-oxide	*M. balansae*(L),*M. hemsleyanus*(R), *M. morsei*(N),*M. phylliraeoides*(L), *M. tenuicaudatus*(B)	[16,17,20, 23,43]
63	Epivindolinine N_b-oxide	*M. balansae*(L),*M. morsei*(N),*M. phylliraeoides*(L), *M. tenuicaudatus*(B)	[16,20,23, 43]
64	16*β*-Hydroxy-19*R*-vindolinine	*M. hemsleyanus*(R & A)	[17,25]
65	16*β*-Hydroxy-19*S*-vindolinine	*M. hemsleyanus*(A)	[25]
66	16*β*-Hydroxy-19*S*-vindolinine N-oxide	*M. hemsleyanus*(R)	[17]

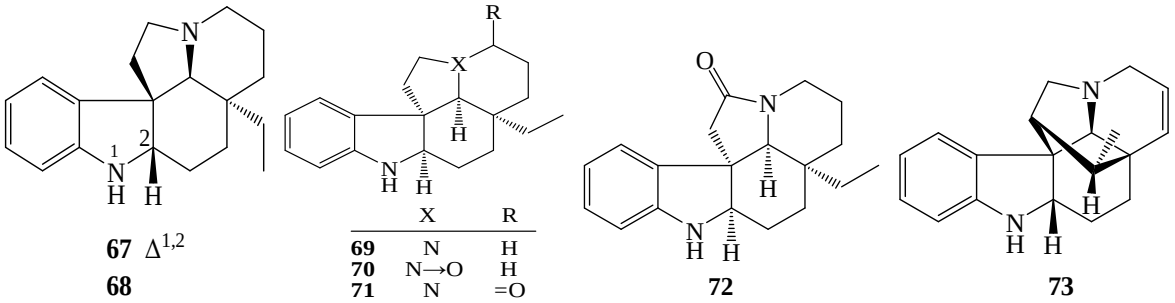

Figure 4: Structures of aspidospermidine-type alkaloids from *Melodinus* spps

isolated [50]. 6,7-Didehydroisotuboxenine (**73**) was only aspidospermidine alkaloid isolated from leaves and twigs of *M. yunnanensis* [32].

Aspidospermidine-type

Aspidospermidine alkaloids, **67-73** (Fig 4), may be derived from vincadifformine by deformylation. Eburenine (1,2-dehydroaspidospermidine) (**67**) and (-)-aspidospermidine (**68**) were isolated from air-dried leaves, twigs and aerial parts of *M. morsei* (L & T), *M. henryi* and air-dried leaves of *M. celastroides* [28,44,48,49]. Previous pharmacological investigations on leaves of *M. celastroides*, epi-20, 21(+)-aspidospermidine (**69**), Nb-oxyepi-20, 21(+)-aspidospermidine (**70**),

melocelinine (**71**) and meloceline (**72**) were isolated [50]. 6,7-Didehydroisotuboxenine (**73**) was only aspidospermidine alkaloid isolated from leaves and twigs of *M. yunnanensis* [32].

Quebrachamine derivatives

The group is exemplified by quebrachamine (**74**) and its derivatives (**75-85**) (Fig 5), which lack the C(7)-C(21) bond of aspidospermidine from *M. australis, M. axillaries, M. fusiformis, M. morsei* and *M. suaveolens* [16,18,28,37,44,45]. In this group, (S)-quebrachamine (**74**) and (+)-17-methoxy- quebrachamine (**75**), rhazidine (**76**), 11-hydroxyrhazidine (**77**) and axillarisinine (**78**) were isolated from roots of *M. australis* [18,45]. The leaves and twigs of *M. yunnanensis* were collected in Honghe (PR China), provided four new quebrachamine derivatives, 14β,15β-20S-quebrachamine (**80**), 3-oxo-voaphylline (**81**), 2α,7α-dihydroxy-dihydrovoaphylline (**82**), 16β,21β-epoxy-vincadine (**83**), and three known compounds (+)-voaphylline (**79**), voalenine (**84**) and voaphylline hydroxyindolenine (**85**) [32]. Suaveolenine (**86**) was that a structure with a lactam ring and an additional five-membered ring containing an oxygen atom had been found from the trunk of *M. suaveolens* [37].

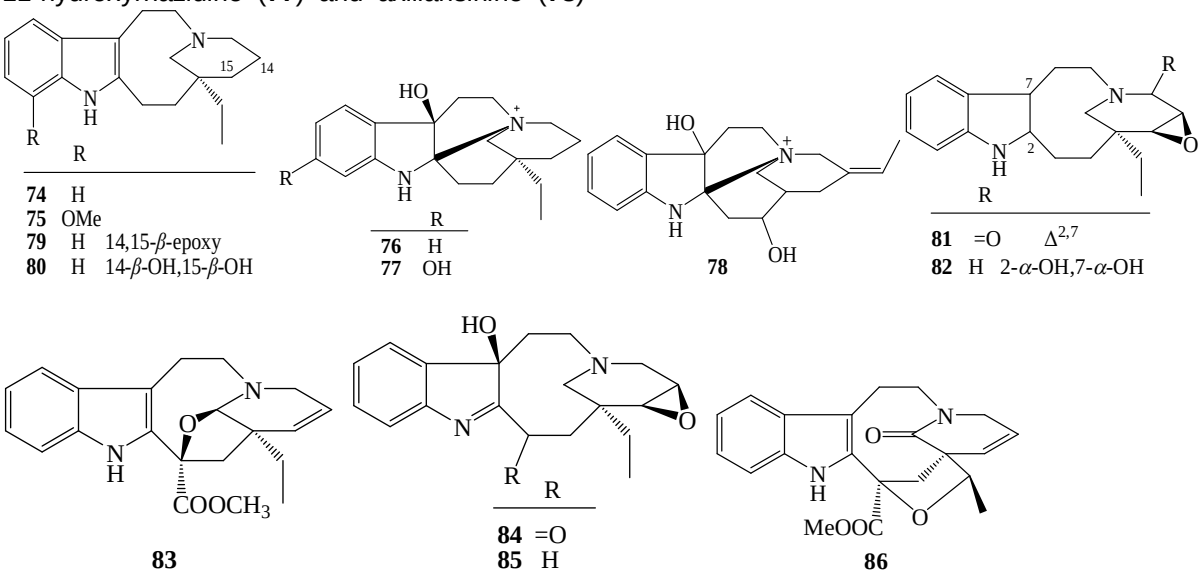

Figure 5: Structures of quebrachamine derivatives alkaloids from *Melodinus* spps

Eburnamine-type, 87- 114 (Table 4. Fig 6)

Five pair of epimers, **87- 96**, were isolated from nine *Melodinus* species. Four eburnamine-type alkaloids including two new ones, melodinines F-G (**97, 98**), together with O-methylepivincanol (**100**), (-)-eburnamenine (**101**) were isolated from *M. henryi* [35, 48]. Δ14-Isoeburnamine (**105**) and (+)-isoeburnamine (**106**) were obtained from *M. celastroides, M. henryi, M. oblongus* and *M. henryi* [30,40,42,52]. Five indole alkaloids, Δ14-vincamenine N4-oxide (**99**), meloyunine (**109**), 14β-hydroxymeloyunine (**110**) and its epimer (**111**), and 16,19-epoxy-Δ14-vincanol (**113**) were described from *M. yunnanensis* [32].

Tubotaiwine-type (Figure 7)

Tubotaiwine (**114**) and tubotaiwine N-oxide (**115**) were isolated from *M. aeneus, M. axillaris, M. fusiformis, M. hemsleyanus, M. oblongus, M. suaveolens* [15,17,26,38,45,55]. From leaves and twigs of *M. yunnanensis* and air-dried of *M. henryi* yielded seven metabolites, 19S-hydroxytubotaiwine (**116**) and its N4-oxide (**117**), 19R-methoxytubotaiwine (**118**) and its 19R-demethylation derivative (**119**), kopsiyunnanine F3 (**120**), melodinine D (**121**) and 20-hydroxy-tubotaiwine (**122**) [32,48]. (±)-Condylocarpine (**123**), (±)-isocondylocarpine (**124**), 19E-isocondylocarpine N4-oxide (**125**) and 19,20-dihydrocondylocapine (**126**) were obtained from *M. australis* (R), *M. henryi* (L & R), *M. khasianus* (B), *M. oblongus* (S), *M. yunnanensis* (L & T) [18,26,32,35,42,51].

Akuammicine-type (Figure 8)

Four akuammicines derivatives, akuammicine (**127**) and its N-oxide (**128**), norfluorocurarine (**129**) and its N-oxide (**130**), stricticine (**131**) and compactinervine (**132**), were isolated from *M. axillaries* (R), *M. henryi* (L), *M. oblongus* (S) and

Table 4: Eburnamine-type and derivatives alkaloids from genus *Melodinus*

No.	Compound name	Species	Ref.
87	*O*-methyl-Δ^{14}-vincanol	*M. tenuicaudatus*(N),*M. yunnanensis*(L & T)	[27,32]
88	16-Epi-*O*-methyl-Δ^{14}-vincanol	*M. khasianus*(B),*M. yunnanensis*(L & T)	[32,51]
89	Δ^{14}-Vincanol= Δ^{14}-Eburnamine	*M. celastroides*(L),*M. henryi*(F & R),*M. insulae- pinorum*(B & A), *M. khasianus*(B),*M. oblongus*(S), *M. tenuicaudatus*(B),*M. yunnanensis*(L & T)	[24,30,32, 39,42,43, 49,51]
90	16-Epi- Δ^{14} -vincanol	*M. celastroides*(L),*M. insulae-pinorum*(B & A), *M. oblongus*(S)	[24,30,49]
91	Δ^{14}-Vincine=14,15-Dehydrovincamine	*M. henryi*(F & R), *M. polyadenus*(L & S),*M. suaveolens*(Tr),*M. tenuicaudatus*(B),*M. yunnanensis*(L & T)	[2,22,32,37,43]
92	Epi-16-dehydro-14,15-vincine	*M. aeneus*(L)	[38]
93	Δ^{14}-Vincamine	*M. henryi*(F & R),*M. yunnanensis*(L & T)	[32,42,52]
94	Epi-16-Δ^{14}-vincamine (+)-16-epi-Δ^{14}-vincamine	*M. aeneus*(L),*M. henryi*(R), *M. yunnanensis*(L & T)	[32,38,52]
95	14-Epieburnamine = (-)-Isoeburnamine; (3*α*,14*β*,16*α*)	*M. henryi*(L)	[35,48]
96	(+)-Eburnamine = (+)-Vincanol	*M. celastroides*(L),*M. henryi*(L)	[35,39]
97	Melodinine F	*M. henryi*(N)	[48]
98	Melodinine G	*M. henryi*(N)	[48]
99	Δ^{14}-Vincamenine N_4-oxide	*M. yunnanensis*(L & T)	[32]
100	*O*-Methylepivincanol	*M. henryi*(N)	[48]
101	(-)-Eburnamenine = Vincamenine	*M. henryi*(L)	[35,48]
102	11-Methoxy-Δ^{14}-vincamenine	*M. guillauminii*(B & A)	[14]
103	11-Methoxy-Δ^{14}-vincanol	*M. guillauminii*(B & A)	[14]
104	Δ^{14}-Vincamenine	*M. yunnanensis*(L & T)	[53]
105	Δ^{14}-Isoeburnamine	*M. celastroides*(L), *M. henryi*(F & R),*M. oblongus*(S)	[30,40,42]
106	(+)-Isoeburnamine	*M. henryi*(R)	[52]
107	20-Oxo-eburnamine	*M. henryi*(L& S)	[34]
108	19-Oxoeburnamine	*M. henryi*(L& S)	[34]
109	Meloyunine	*M. yunnanensis*(L & T)	[32]
110	14*β*-Hydroxymeloyunine	*M. yunnanensis*(L & T)	[32]
111	16-Decarbomethoxy-vincapusine	*M. yunnanensis*(L & T)	[32]
112	16,19-Epoxy-Δ^{14}-vincanol	*M. yunnanensis*(L & T)	[32]
113	14,17-Epoxy-eburnamine	*M. henryi*(F, R & S)	[54]

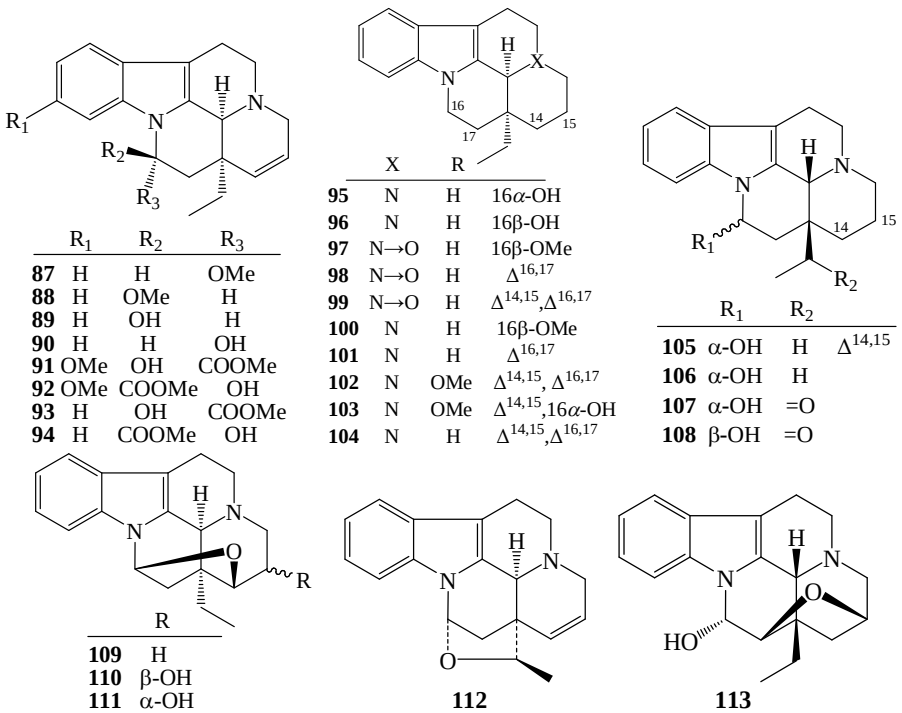

Figure 6: Structures of eburnamine-type alkaloids from *Melodinus* spps

M. tenuicaudatus, M. suaveolens (L & T) and *M. yunnanensis* (L & T) [26,32,35,43,45,46].

Geissoschizine-type and derivatives (Table 5(a) and (b), Figure 9)

Twenty-five constituents, 133- 157, were isolated from *M. acutiflorus, M. australis, M. fusiformis, M. hemsleyanus, M. khasianus, M. oblongus* and *M. tenuicaudatus* [15,20,27,28,32,43,50,54].

Picraline-type (**133-139**) and anhydrojmaline-type alkaloids (*140-141*) are biogenetically considered to be derived from geissoschizine (**144**) with its derivative by ring closure between the C(7) and C(16) positions and between the C(5) and C(16). As a common intermediate, geissoschizine (**144**) would also provide the mavacurine-type alkaloids (**149-150**) and tetrahidroalstonin (**151**).

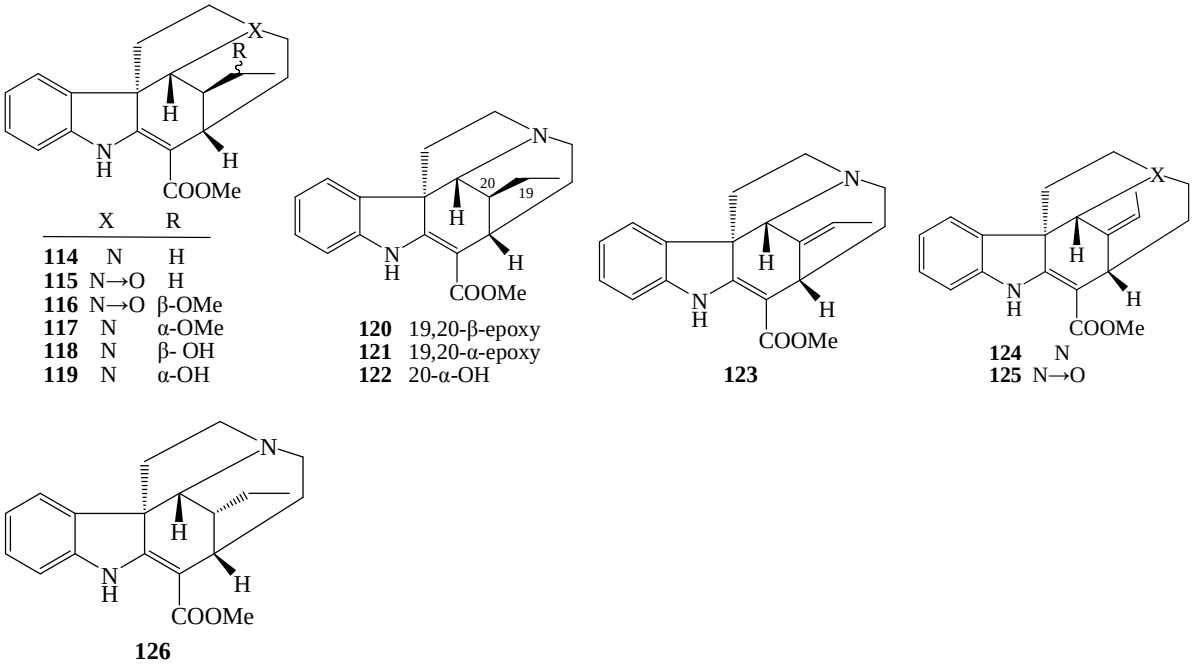

Figure 7: Structures of tubotaiwine -type alkaloids from *Melodinus* spps

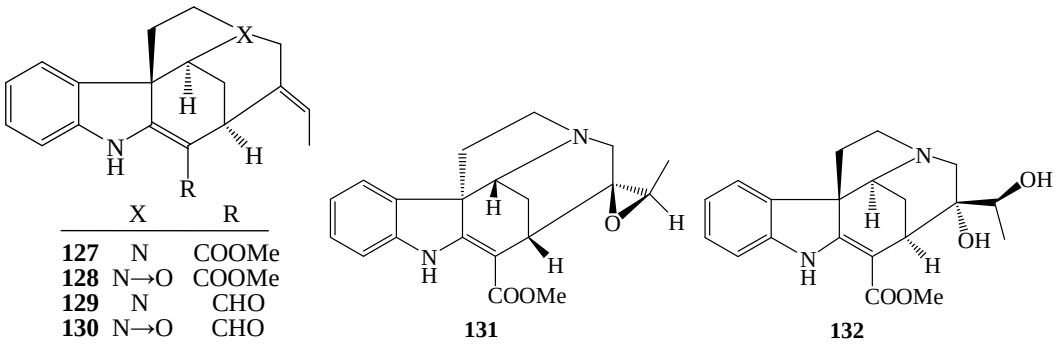

Figure 8: Structures of akuammicine-type alkaloids from *Melodinus* spps

Leuconotis alkaloid 376 and its analogues (Figure 10)

Melodinines A-C (**158-160**, resp.), together with leuconotis alkaloid 376 (**161**), possessed 22 skeletal carbons arranged compactly in six rings, were isolated from *M. henryi* by RP-18 gel and Sephadex LH-20 [48].

Axillarisine (**162**) was found from dry root powder of *M. axillaris* by Yan *et al* [45]. Three other novel alkaloids, melohenine A (**163**), an unusual C24 monoterpenoid indole alkaloid with additional skeletal carbons arranged compactly in eight rings, and henrycinols A- B (**164-165**) with an a cinnamoyl group system were also isolated from roots of *M. henryi* [52,57]. The relative configuration of henrycinols A and B was determined by NOESY analysis.

Table 5: Geissoschizine-type and derivatives alkaloids from genus *Melodinus*

No.	Compound name	Species	Ref
133	Picraline	*M. oblongus*(S)	[30]
134	Picralinal	*M. hemsleyanus*(A),*M. oblongus*(L)	[25,26]
135	Picrinine	*M. hemsleyanus*(A),*M. oblongus*(L)	[25,26]
136	Deacetylpicraline	*M. fusiformis,M. oblongus*(S)	[15,30]
137	Deacetylakuammiline= rhazimol	*M. acutiflorus,M. oblongus*(S), *M. yunnanensis*(L & T)	[30,32,56]
138	16-Epirhazinaline=rhazinaline	*M. acutiflorus*(L),*M. yunnanensis*(L & T)	[32,56]
139	Akuammiline	,*M. khasianus*(B), *M. oblongus*(S)	[30,51]
140	Akuammidine	*M. australis*(N),*M. hemsleyanus*(A)	[18,25]
141	Normacusine B	*M. tenuicaudatus*(B)	[43]
142	Polyneuridine	*M. suaveolens*(L & T)	[55]
143	Isositsirikine	*M. henryi,M. insulae-pinorum*(B & A),*M. phylliraeoides*(L),*M. yunnanensis*(L & T)	[23,24,32,48]
144	(+)-Geissoschizine	*M. phylliraeoides*(L)	[23]
145	Geissoschizol	*M. morsei*(A)	[36,44]
146	Nortetraphyllicine	*M. henryi*(L& S)	[34]
147	N*b*-Methylnortetraphyllicine	*M. henryi*(L& S)	[34]
148	(+)-Ajmaline	*M. Balansae*(L)	[21]
149	Pleiocarpamine	*M. guillauminii*(B & AP),*M. oblongus*(S)	[14,26,30]
150	16-Hidroxymetyl pleocarpamine	*M. oblongus*(L)	[26]
151	Tetrahidroalstonin	*M. oblongus*(L)	[26]
152	Strictosamide	*M. axillaris*(R)	[45]
153	Demethylstrictosidine	*M. axillaris*(R)	[45]
154	Vallesiachotamine	*M. axillaris*(R),*M. henryi*(N)	[45,48]
155	(-)-Antirhine	*M. celastroides*(A)	[31]
156	Descarbomethoxydihydrogambirtannine	*M. henryi*(N)	[48]
157	Renoxidine = Reserpine N-oxide	*M. balansae*(L)	[20]

Other indole alkaloids, 166-178 (Figure 11)

Two known compounds, stemmadenine (**166**) and its N-oxide (**167**), were isolated from *M. henryi* [18,35,48]. N-acyl-indolinique (**168**) and a new diazaspiroindole alkaloid, melodinine E (**169**) were structural type seldom reported from *M. morsei* and *M. henryi*, resp. [28,48]. 6/7-Seco rearranged spiro-indolone alkaloids, meloyunines A (**170**) and B (**171**) were elucidated from leaves and twigs of *M. yunnanensis*. These structures were elucidated based on NMR, FTIR, UV, and MS spectroscopic data [53]. Mehri *et al* reported melonine (**172**) and Nb-oxy-melonine (**173**) from *M. celastroides* possibly artifacts due to the use of CH_2Cl_2 or HCl as an extraction solvent [40,49]. In 1978, Baassou *et al* found (-)-ibogamine (**174**) from *M. aeneus* [38]. Two novel alkaloids arbophylline (**175**) and 15-β-methoxy- 14, 15-dihydroandranginine (**176**) were isolated from leaves and twigs of *M. yunnanensis* [32]. Melodinoxanine (**177**), which derived from an oxygenated derivative of isocarapanaubine (**178**), was a unique oxindole alkaloid with an extra oxygen atom in the C-ring of a heteroyohimbine skeleton from the stems and leaves of *M. henryi* growing in Yunnan, China [34].

Monoterpenoid quinoline alkaloids

***Scandine derivatives*, 179-183** (Figure 12)

In 1969, Bernauer *et al* identified scandine (**179**), which was a naturally occurring biologically active product derived from plants, was important as a possible starting material for the syntheses of valuable pharmaceuticals, from *M. scandens* first time [58]. Then, this compound and 10-hydroxyscandine (**180**) were isolated from the other seven plants of *M. fusiformis, M. hemsleyanus, M. henryi, M. khasianus, M. oblongus, M. tenuicaudatus, M. scandens, M. suaveolens* [2,15,17,19,25,27,28,29,30,43,46, 55,59]. And the absolute configuration has aroused the great concern [60]. The crystal structure and absolute configuration of (+)-scandine have been determined by X-ray diffraction [61,62]. Some fo scandine derivatives, 10-methoxyscandine (**181**), scandine Nb-oxide (**182**), melodinine U (**183**) and T (**184**), melodinhenine C-D (**185-186**) obtained from *M. tenuicaudatus, M. fusiformis, M. henryi, M. suaveolens* [15,27,29,55,63]. The interesting chemical significance of the *Melodinus* plants prompted researchers to initiate a phytochemical study on the twigs and leaves of *M. suaveolens*, which led to the isolation of two new quinoline alkaloids, 14, 15-dihydroscandine (**187**) and 15β-

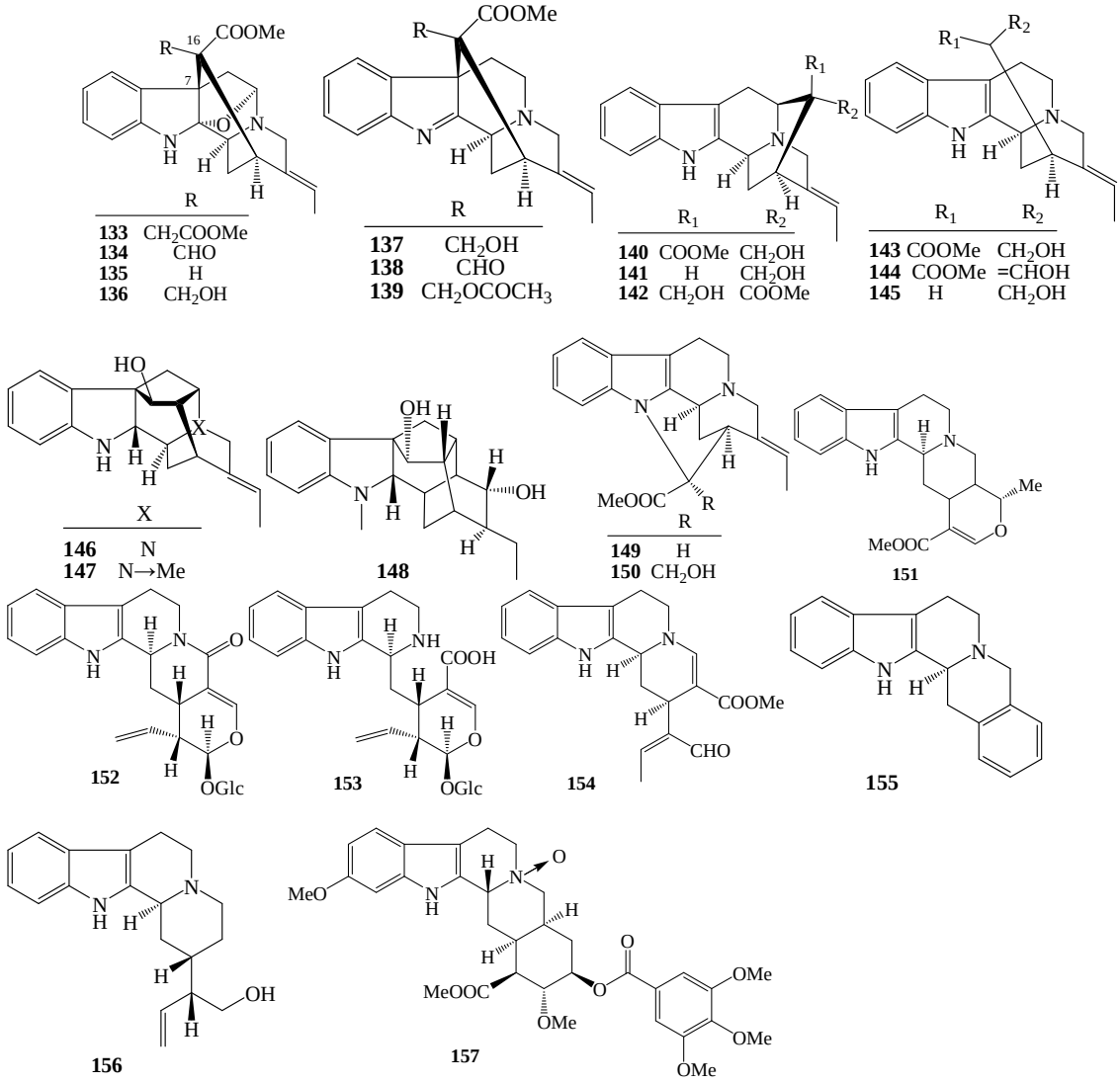

Figure 9: Structures of geissoschizine-type and derivatives alkaloids from *Melodinus* spps

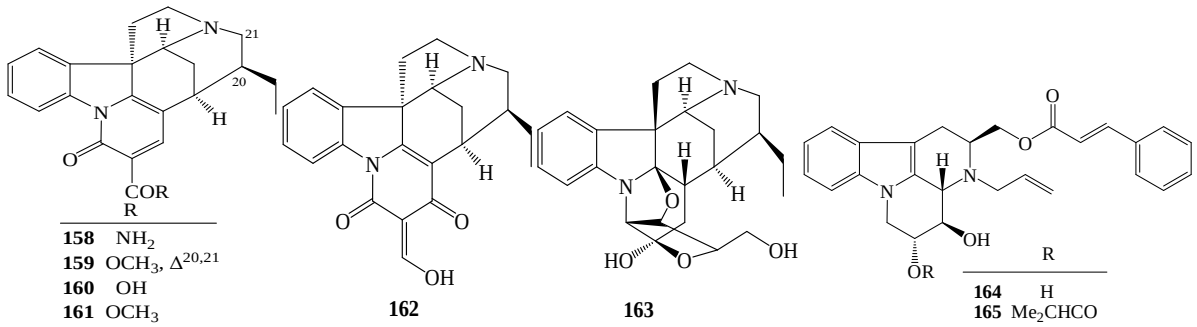

Figure 10: Structures of leuconotis alkaloid 376 and its analogues alkaloids from *Melodinus* spps

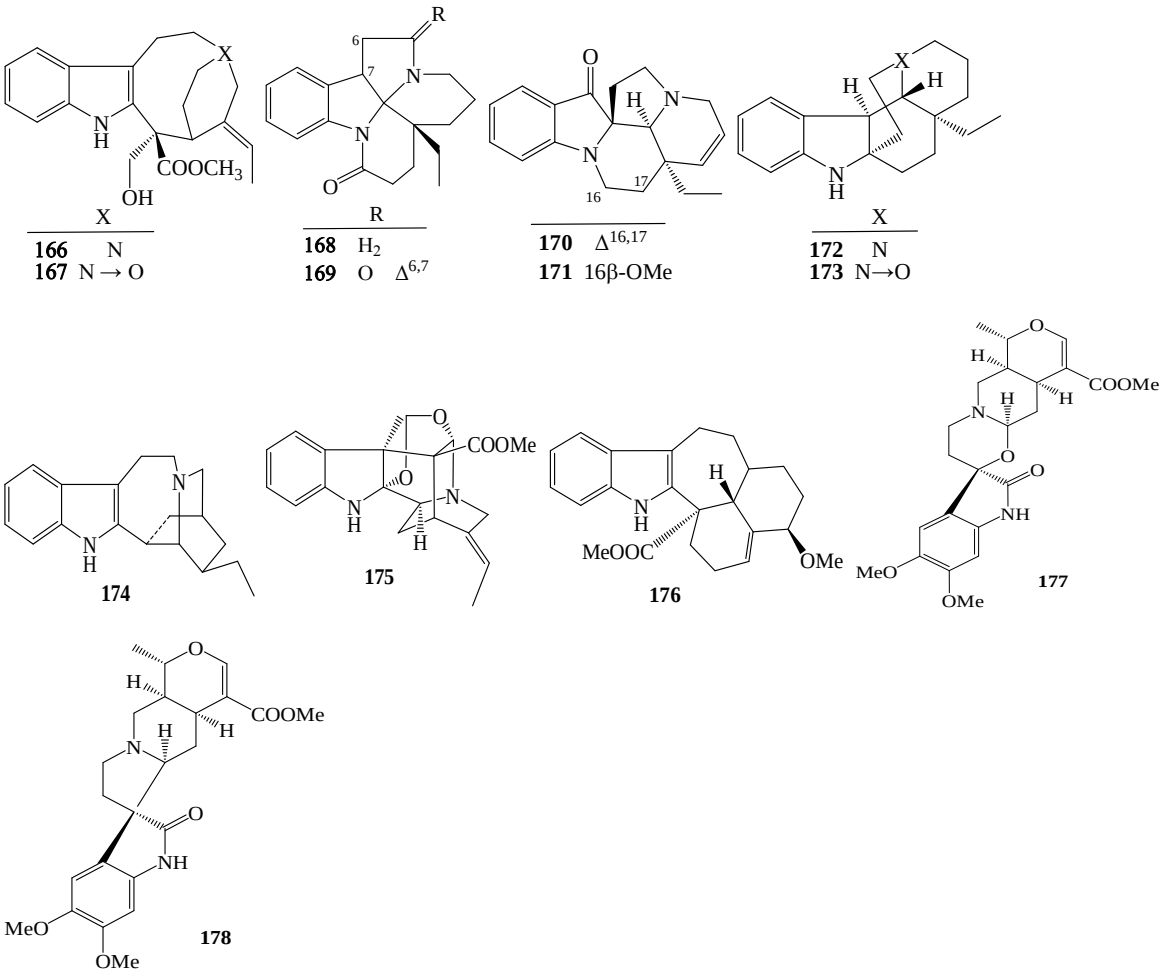

Figure 11: Structures of other indole alkaloids from *Melodinus* spps

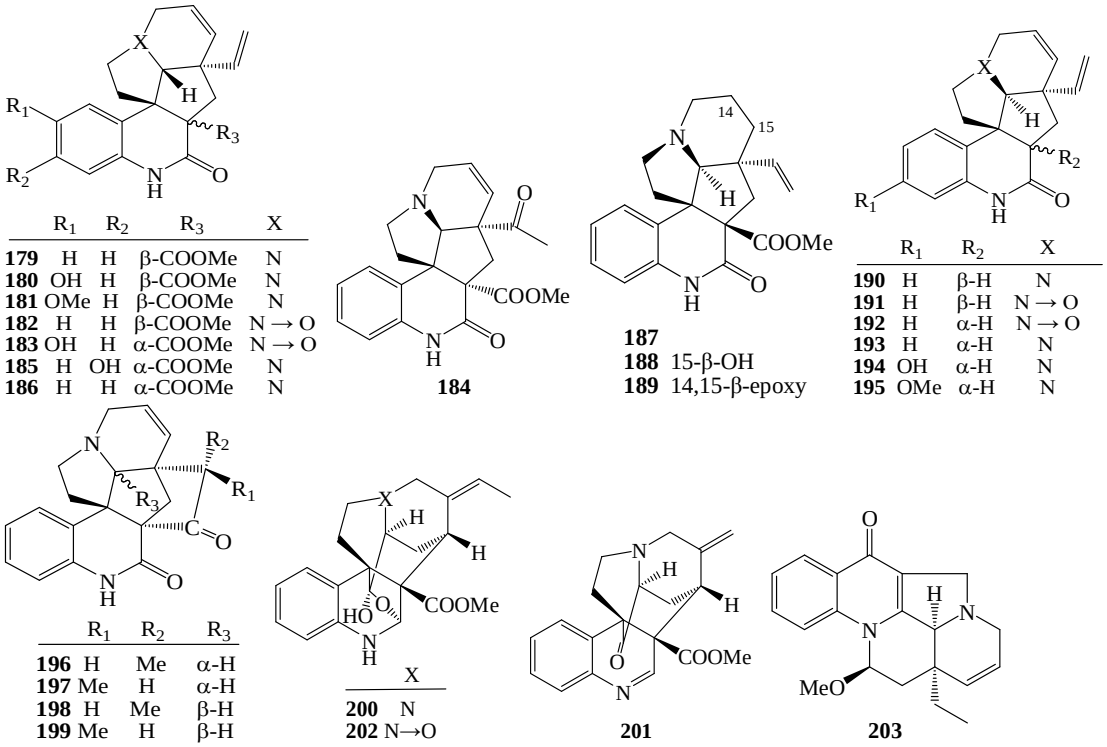

Figure 12: Structures of scandine derivatives quinoline alkaloids from *Melodinus* spps

hydroxy- 14,15-dihydroscandine (**188**), along with a known alkaloids 14, 15-β-epoxyscandine (**189**) [46,55].

***Meloscine derivatives*, 190-195** (Figure 12)

Meloscine (**190**) and its Nb-oxide (**191**) were isolated from *M. hemsleyanus, M. oblongus, M.scandens, M. suaveolens* [25,30,55,59]. Four epi-meloscine compounds, N-oxyepimeloscine (**192**), epimeloscine (**193**), 9-hydroxyepimeloscine (**194**) and 9-methoxy epimeloscine (**195**), were isolated from *M. scandens* [19,58,60,61,64]. Meloscandonine (**196**) was isolated from *M. fusiformis, M. hemsleyanus, M. khasianus, M. scandens, M. oblongus, M. tenuicaudatus* [15,19,25-28,55,58,61]. And the structure of stereochemistry by UV, IR, NMR and X-ray [65,66]. 19-Epimeloscandonine (**197**) and melodinhenine E-F (**198, 199**) obtained from *M. fusiformis, M. hemsleyanus, M. henryi* and *M. oblongus* [25,28,63]. On the structure elucidation of the main alkaloids of *M. acutiflorus*, which led to a revision of the structures of rhazicine (**200**) and rhazimine (**201**), were first isolated. Further investigation of the extract of leaves of *M. acutiflorus* gave a new alkaloid, rhazicine N-oxide (**202**) [56,67]. To our knowledge, the first report of the co-occurrence of monoterpenoid indoles meloyunine C (**203**) and precursor Δ14-vincamenine (**104**) in same plant, supporting the biosynthesis of quinoline from *M. yunnanensis* and concurring with previous *in vivo* tracer experiments in the literature [53].

***Other monomeric alkaloids*, 204-210** (Figure 13)

(-)-Rhazinilam (**204**) was a natural compound isolated from *M. australis* and *M. henryi*, whose tetracyclic structure possesses an axially chiral phenyl-pyrrole subunit bridged by a nine-membered lactam ring [18,35,48,68]. Melohenine B (**205**), 14, 15-dehydromelohenine B (**206**) and 14-O-ethyl-substituted (3α,14α,16α)-2,7-secoeburnamine derivative (**207**) with an unprecedented 6/9/6/6 tetracyclic ring system, regarded as a key intermediate from indole to quinoline alkaloids were obtained from *M. henryi* and *M. yunnanensis* [35,52,55]. Three simple alkaloids, venoterpine (**208**), (□)-R/S-1-(3-pyridyl)ethanol (**209**) and 2, 5-diphenyloxazole (**210**), were also isolated from *M. aeneus, M. axillaris* and *M. celastroides* [33,38,45].

Bisindole alkaloids

Eburnamine derivative dimeric alkaloids (Figure 14)

Fifteen bisindole alkaloids, melonines C-D (**211−212**), having an eburnamine-aspido-spermidine linkage, guillauminiine (**213**), paucivenine (**214**), tenuicausine (**215**), demethylteuicausine (**216**) and melodinine J (**217**), possessing an eburnamine-tabersonine skeleton, melodinine H-I (**218-219**), melodinhenine A-B (**220-221**) of the eburnamine-vindolinine type, and melonine A (**222**), melaxillarinine (**223**) and melaxillaridine (**224**) with an eburnamine-quebrachamine derivatives, were isolated from eight *Melodinus* species by column chromatography (CC),TLC, RP-18 gel, Sephadex LH-20 [6,14,21,27,42,43,45,65,68-71].The absolute configuration of **220** and **221** was determined using ECD exciton chirality method. *M. insulaepinorum* furnished an eburnamine-kopsinine bisalkaloid, insulopinine (**225**) [24]. From *M. celastroides*, celastromeline (**226**) and celastromelidine (**227**) were the tertiary analogues of Le chlorure de chloromethyl celastromelinium (**228**) and Le chlorure de chloromethyl celastromelidinium (**229**), and their quasi-dimeric structures were not likely to be artifacts [49]. The laster eburnamine-diazaspiroindole bisindole alkaloids, melonine B (**230**) was isolated as a pale-red powder from *M. henryi* [71].

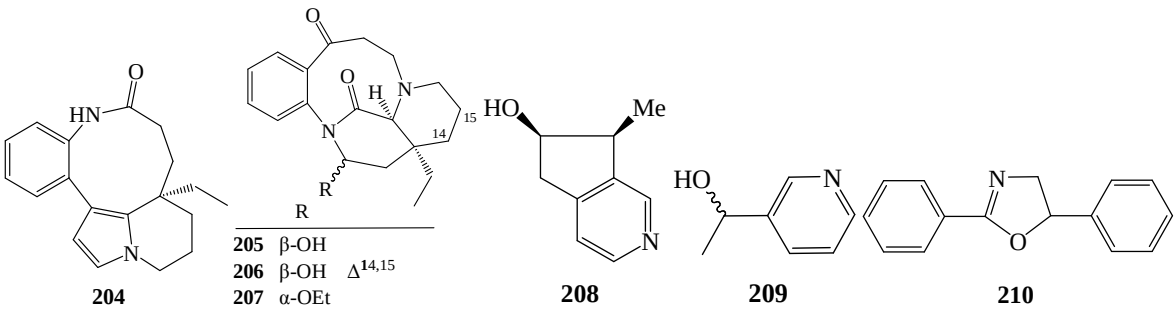

Figure 13: Structures of other monomeric alkaloids alkaloids from *Melodinus* spps

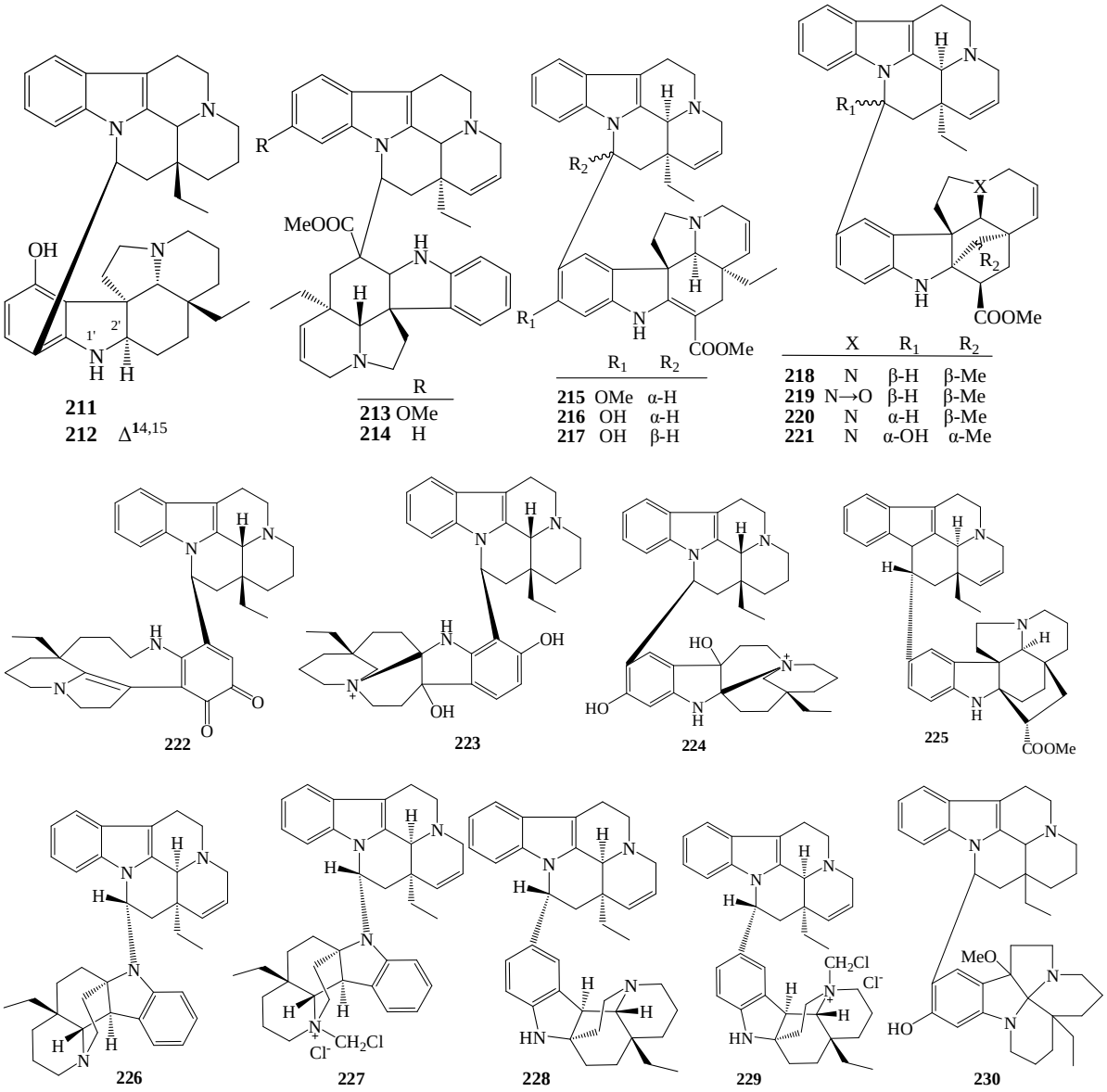

Figure 14: Structures of eburnamine-type dimeric alkaloids from *Melodinus* spps

***Tabersonine derivative dimeric alkaloids*, 231-247** (Figure 15)

In this part, we list all tabersonine derivative dimeric alkaloids except eburnamine-tabersonine type. Tabersonine-tabersonine skeleton, melodinine K (**231**) and melomorsine I (**232**) were isolated from *M. tenuicaudatus* and *M. fusiformis*, resp. [27,28]. In 2013, melosuavine D-F (**233-235**) were identified by Liu *et al* from twigs and leaves of *M. suaveolens* [69]. From *M. suaveolens* and *M. scandens*, three tabersonine-scandine, melosuavine A-C (**236-238**), and three tabersonine-vindolinine type, melosuavine G-H (**239-240**) and scandomelidine (**241**) were obtained [69,72]. The isolation and structural determination of lochnericine-kopsinine derivatives from *M. yunnanensis* and *M. morsei*, meloyine (**242**) and melornorsine (**243**), were studied [32,44]. Four 18, 19-dehydrotabersonin-vincadifformine derivatives, scandomelonine (**244**) and its epimer (**245**), scandomeline (**246**) and its epimer (**247**), were isolated from *M. scandens* [72,73].

Other dimeric alkaloids (248-252), (Figure 15)

Melaxilline (**248**) and melaxillinine (**249**) were obtained from *M. axillaris* [45]. To investigate antitumor indole alkaloids from the leaves and twigs of *M. morsei*, melofusine I (**250**) was subjected to RP-18 silica gel CC on eluting with 70 % - 75 % aq. MeOH [28]. *M. celastroides* contained two other dimeric alkaloids, Dichlorure de methylene Nb,Nb' [bis-[(+)-meloninium] (**251**) and methylene 10,10'-bis-[(+)-Na-norvallesami-

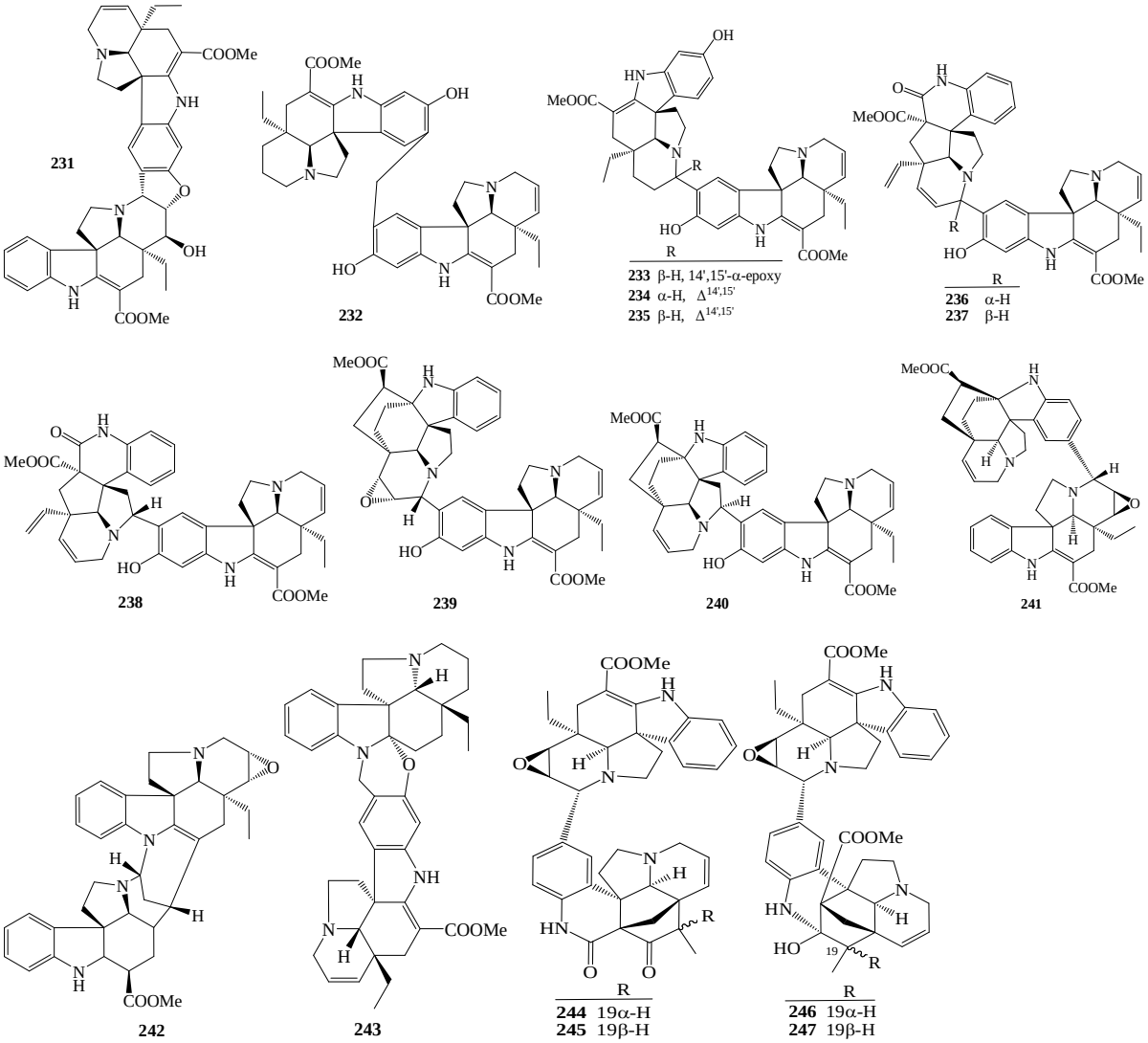

Figure 15: Structures of eburnamine-type dimeric alkaloids from *Melodinus* spps

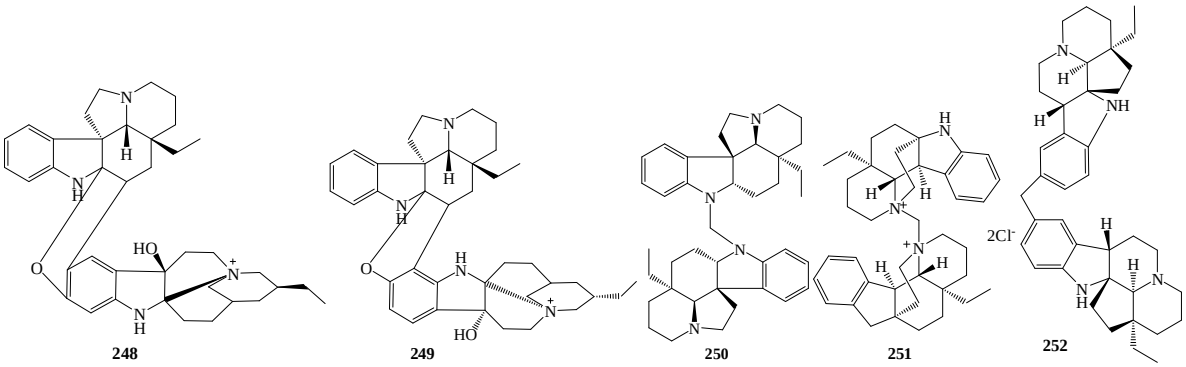

Figure 16: Structures of other dimeric alkaloids from *Melodinus* spps

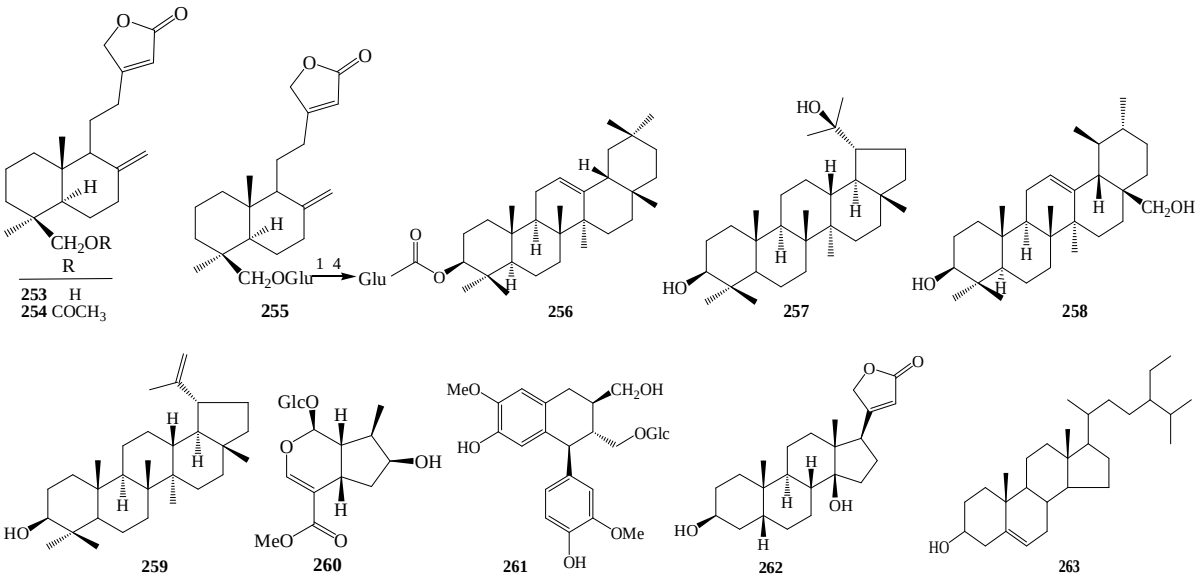

Figure 17: Structures of terpenoids and other compounds from *Melodinus* spps

dine (**252**). And alkaloid 251 was a quaternary ammonium and **252** possibly artifacts due to the use of CH_2Cl_2 as an extraction solvent [49].

Diterpenoids, triterpenes and others compounds (Figure 17)

A novel labdane diterpene, medigenin (**253**), O-acetyl-medigenin (**254**) and its glycoside, medinin (**255**), have been isolated from the ether extract of *M. monogynus* [74,75]. Four triterpenes, β-amyrin acetate (**256**), uvaol (**257**), monogynols A (**258**) and B (**259**), were isolated from *M. henryi, M. monogynus* and *M. reticulatus* [2,13,76-78]. One iridoid glycosides named loganin (**260**), a lignan glycoside, isolariciresinol-monoglucoside (**261**), two steroids, digitoxigenin (**262**) and β-sitosterol (**263**), were isolated from *M. henryi, M. monogynus* and *M. morsei* [2,36,78].

Extraction and isolation

Four methods were used for extraction and isolation. Firstly, the air-dried sample was extracted with EtOH or MeOH. The extract was partitioned between organic solvent and HCl solution. The acidic water-soluble materials, adjusted to pH 9 - 10 with ammonia solution, were extracted with EtOAc, MeOH or $CHCl_3$ to give an alkaloidal extract. Then, the extract was subjected to silica gel column chromatography (CC), TLC, MPLC with RP-18 gel CC, Sephadex LH-20 CC [27-29,32,34]. Secondly, *M. fusiformis* were extracted exhaustively with EtOH. After concentration, the material was obtained which was then dissolved in citric acid or tartaric acid, filtered and the solution adjusted to pH 5 and 7 with NH_4OH, and then extracted with $CHCL_3$, repeatedly. The extract was subjected to silica gel column chromatography (CC). Lastly, some dried *Melodinus* spps were ground and extracted with acetone or EtOH. The extract was filtered and concentrated and the residue extracted with similarity principle. The extract was subjected to silica gel column chromatography (CC), Et_2O, $CHCL_3$ and MeOH being used as eluents.

Pharmacological aspects

Cytotoxic activity

Continuous investigation of bioactive indole alkaloids from the genus *Melodinus*, include tests against seven human tumor cell lines, HL-60, SMMC-7721, A-549, MCF-7, SW480, SK-BR-3 and PANC-1.The results showed that these compounds exhibited stronger inhibitory activity with low IC_{50} than that of cisplatin (Table 6).

Pharmacological screening revealed 11-hydroxytabersonine (**24**) displayed antitumor activity [17].

Compound **32**, 11-hydroxy-14,15α-epoxytabersonine, and rhazinilam (**204**) were the source of potent antitumor compounds against P-338 cell and KB cell line [15,79,80]. Evaluated for cytotoxicity by using the WT cell, compound **207** exhibited moderate cytotoxic activity [35]. Demethylteuicausine (**216**), a new bisindole alkaloid was isolated from *M. hemsleyanus*, showed antitumor activities in pharmacological tests KB cell and HCT [6].

Table 6: Cytotoxicity of compounds (IC_{50}, μM) from *Melodinus* spps

No.	HL-60	SMMC-7721	A-549	MCF-7	SW480	SK-BR-3	PANC-1	Ref
23	4.6	5.6	14.8	9.9	12.1	-	-	[28]
25	0.2	13.1	12.8	2.1	12.7	-	-	[27]
25	0.5	1.1	1.0	0.2	2.4	-	-	[29]
51	0.7	3.3	3.9	1.8	1.6	-	-	[29]
53	0.2	0.3	0.6	0.4	0.5	-	-	[29]
55	0.9	5.2	10.7	-	-	2.8	3.6	[41]
56	6.8	20.7	26.3	21.9	15.2	-	-	[28]
154	2.0	16.8	25.9	-	-	24.7		[48]
171	15.48	19.08	40.0	14.24	13.29	-	-	[53]
211	0.66	2.73	3.01	-	-	3.63	3.77	[71]
212	2.77	18.13	11.07	-	-	23.22	23.41	[71]
217	3.0	8.5	9.1	10.0	14.8	-	-	[27]
218	1.1	3.2	4.8	2.9	1.4	-	-	[27]
222	2.84	11.54	20.07	-	-	15.41	>40	[71]
230	2.53	7.40	14.70	-	-	7.78	14.45	[71]
231	0.1	3.0	5.0	2.7	5.7	-	-	[27]

Anti-inflammatory effects

Two new compounds **187-188** exhibited significant, dose-dependent inhibition of the production of lipopolysaccharide (LPS)-induced NO, IL-6 and IL-8 in mice macrophages. The results suggested that these new quinoline alkaloids could be new potential candidates for development as anti-inflammatory agents [46].

Other activities

11,19R-dihydroxytabersonine (**30**) had significant anti-fertility activity. The results of spermicidal effect *in vitro* showed that spermicidal concentration of 0.2 mg/ml [15]. Rhazinilam (**204**) evaluated against the disassembly of microtubules into tubulin with IC_{50} value of 2 - 3 µM [79,80]. Metabolism studies were conducted in order to investigate the reasons for the *in vivo* lack of activity of (-)-rhazinilam. The oxidative metabolism of (-)-rhazinilam were markedly less active than it *in vitro*, which might explain its *in vivo* inactivity [80].

CONCLUSION

Plants of the family Apocynaceae have been proven to be good sources of indole alkaloids, quinoline alkaloids, which originated from the condensation of tryptophan with secologanin. Some have been reported to display *in vitro* cytotoxicity against several human cancer cell lines, anti-inflammatory effects and antifertility activity. However, there still arise questions concerning the structure-activity relationships and elucidation of the action mechanism. There are 23 species of this genus whose isolation and activities have not previously been reported. Thus, much attention should be paid to the other *Melodinus* species via further phytochemical, pharmacological and structure-activity relationship studies.

ACKNOWLEDGEMENT

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