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The Genus *Melodinus* (Apocynaceae): Chemical and Pharmacological Perspectives

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Abstract

The plants of the genus *Melodinus* (Apocynaceae) are widely distributed, and have long been used in folk medicine for the treatment of various ailments such as meningitis in children and rheumatic heart diseases, hernia, infantile malnutrition, dyspepsia and testitis. Over 100 alkaloids together with flavonoids, lignans, steroids, terpenoids and coumarins have been identified in the genus, and many of these have been evaluated for biological activity. This review presents comprehensive information on the chemistry and pharmacology of the genus together with the traditional uses of many of its plants. In addition, this review discusses the structure-activity relationship of different compounds as well as recent developments and the scope for future research in this aspect.

Keywords

***Melodinus*, Apocynaceae, Ethnopharmacology, Anti-Cancer**

1. Introduction

1.1. General Introduction of the Family Apocynaceae Juss. and Genus *Melodinus*

The genus *Melodinus* belongs to family Apocynaceae, a large family of a family of flowering plants that includes trees, shrubs, herbs, stem succulents, and vines, commonly called the dogbane family [1]. The family comprises some 1500 species divided over about 424 genera. The former family Asclepiadaceae is included in Apocynaceae according to the APG III system [2]. Members of the family are native to European, Asian, African, Australian and American tropics or subtropics, with some temperate members [1]. Many species are tall

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trees found in tropical rainforests, but some grow in tropical dry (xeric) environments [3]. There are also perennial herbs from temperate zones [4]. Some are sources of important drugs, such as cardiac glycosides, which affect heart function [5]. These include the *Acokanthera*, *Apocynum*, *Cerbera*, *Nerium*, *Thevetia* and *Strophantus*. *Rauvolfia serpentina*, or Indian Snakeroot, yields the alkaloids reserpine and rescinnamine, which are useful tools in the treatment of high blood pressure and even some forms of psychosis. *Catharanthus roseus* yields alkaloids used in treating cancer [6] [7].

Melodinus clade embraces 109 species which are mainly found in tropical Asia and Oceania [8].

1.2. Botanical Features of *Melodinus*

The members of the genus *Melodinus* consist of stout climber or lianas. Branches dark gray, glabrous; young branch lets and leaves scaly. Petiole 5 mm - 10 mm; leaf blade oblong or narrowly elliptic, 7 cm - 18 cm × 2.5 cm - 5.2 cm, papery, base rounded, apex acuminate; lateral veins 10 - 15 pairs, nearly flat on both surfaces. Cymes umbellate, terminal and axillary, 5 cm - 6.5 cm; peduncle 1.5 cm - 2 cm, glabrous; bracts and bracteoles 3 mm - 7 mm. Pedicel 5 mm - 7 mm, pubescent. Flower buds cylindric, ca. 2 cm, glabrous outside. Sepals broadly ovate, ca. 7 5 mm, ciliate, apex acute. Corolla white, tube ca. 1.2 cm, pubescent inside; lobes oblong, ca. 1.1 cm; corona scales linear, decurrent to lower part of corolla tube, included. Ovary glabrous. Style very short. Berries globose, ca. 10.5 cm in diam [9]-[11].

This study is an attempt to compile an up-to-date and comprehensive review of the genus Stephania that covers its traditional medicinal uses, chemistry and pharmacology. Many plants of this genus are pharmacologically known but chemically unknown and vice-versa. Therefore, the scope of future research in this aspect is also discussed here.

2. Traditional and Medicinal Uses

Melodinus suaveolens and *Melodinus henryi*, have been used in Chinese folk medicine for the treatment of meningitis in children and rheumatic heart diseases [11]. They can also “invigorate the circulation of blood”, “stimulate sucking and treat fracture” [12]. It was also used in Chinese folk medicine for the treatment of hernia, infantile malnutrition, dyspepsia and testitis [11].

Melodinus reticulatus was used to treat cancers as alkaloids were detected in 1983 [13]. Next, several alkalois were detected successively from *Melodinus acutiflorus* and *Melodinus tenuicaudatus* [14] [15].

3. Chemical Constituents

Isolation and structure elucidations of secondary metabolites in *Melodinus* have been carried out since the 80s [16]. Majority of investigations include the acrial part of the species. To date about 100 compounds have been isolated from 12 species, which are *Melodinus acutiflorus* F. Muell, *Melodinus aeneus* Baill, *Melodinus balansae* Baill, *Melodinus celastroides* Baill, *Melodinus fusiformis* Champ. ex Benth, *Melodinus guillauminii* Boiteau, *Melodinus hemsleyanus* Diels, *Melodinus morsei* Tsiang, *Melodinus monogynus* Roxb, *Melodinus scandens* J.R. Forst. & G. Forst., *Melodinus suaveolens* (Hance) Champ. ex Benth, *Melodinus yunnanensis* Tsiang & P.T. Li.

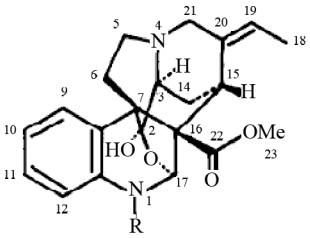
The isolation and separation technique is very much dependent on the type of fractions. Substances are separated with liquid chromatography using different solvent mixtures with silica gel [13], charcoal [17] and sephadex [14] [18]. Other types of analytical techniques include thin layer chromatography (TLC) and high performance liquid chromatography (HPLC) [19]-[22].

The structures are mainly established by mass spectroscopy (MS), ultra-violet spectroscopy (UV), infrared spectroscopy (IR) and ^{1}H and/or ^{13}C nuclear magnetic resonance (NMR). ^{1}H and/or ^{13}C spectroscopy is probably the most useful method in structure elucidation [13]-[15] [17]-[20] [22]-[30].

Among the secondary metabolites isolated from members of the genus *Melodinus* are mainly focused on alkaloids (indoles, steroids, diterpenes). The main secondary metabolites isolated so far from the genus *Melodinus*. consists of 30 - 35 compounds. The profile of all known secondary metabolites of *Melodinus* as found in literature and their structures are included following.

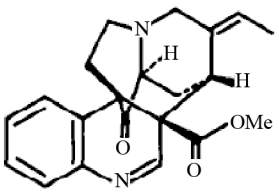
3.1. *Melodinus acutiflorus* F. Muell

Rhaxicine 1), rhaximine 2), 16-epi rhazinaline 3), N(l)-methyl-rhazicine 4) [14] [32].

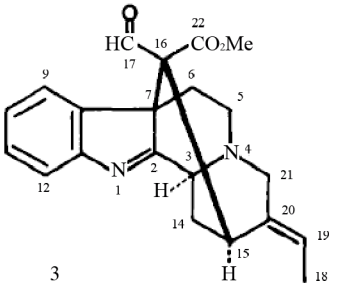


1 R=H,

4 R=Me



2 Rhazlmine

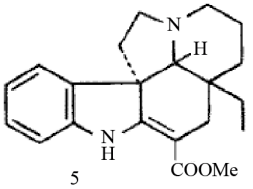


3

16-*epi*-rhazinallne

3.2. *Melodinus aeneus* Baill

(+) vincadifformine (**5**), (−) tabersonine (**6**), (−) methoxy-11 tabersonine (**7**), (−) lochnericine (**8**), (−) lochneinine (**9**), (−) ibogamine (**10**), venoterpine (**11**), (+) tubotaiwine (**12**), (+) N-oxy tubotaiwine (**13**), (+) epi-16dehydro l4-15 vincamine (**14**), (+) epi-16dehydro l4-15 vincine (**15**) [33].



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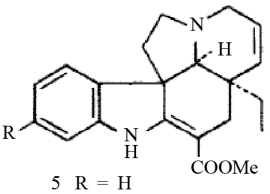
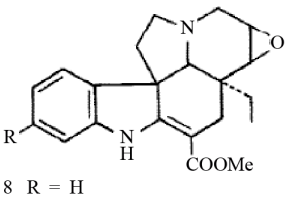


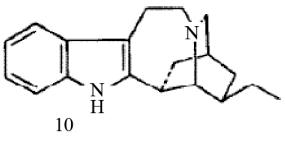
5 R = H

7 R = OMe



8 R = H

9 R = OMe



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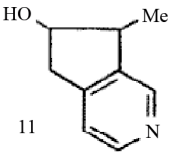

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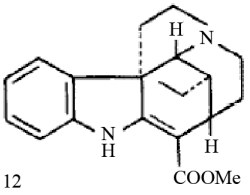
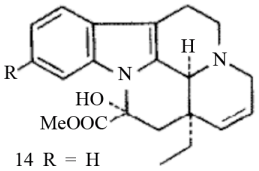


12

13 N_b -Oxyde

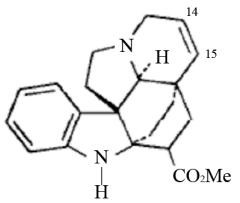


14 R = H

15 R = OMe

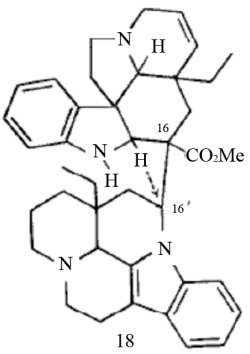
3.3. *Melodinus balansae* Baill

Venalstonine dehydro 14-15 (**16**), venalstonidine epoxy 14-15*α* (**17**), paucivenine (**18**), pleiomutine (**19**) [34].

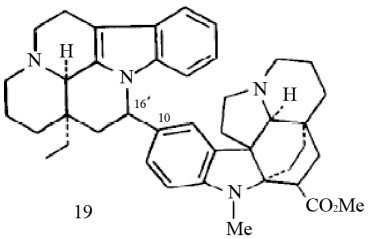


16 venalstonine déhydro 14-15

17 venalstonidine époxy 14-15α



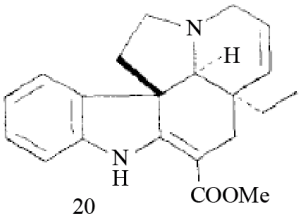
18



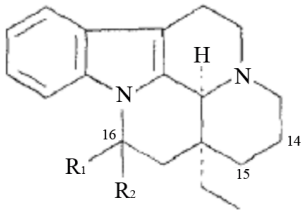
19

3.4. *Melodinus celastroides* Baill

(−) tabersoninel (**20**), leburnamine (**21**), lisoeburnamine (**22**), leburnamonine (**23**) [35].



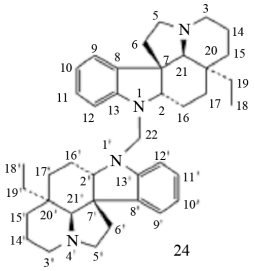
20



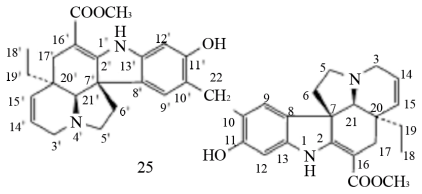
21 R_1 = H ax,; R_{12} = OH eg.
22 R_1 = OH ax.; R_{12} = OH eg.
23 R_1 R_2 = 0

3.5. *Melodinus fusiformis* Champ. ex Benth

Melofusine I (**24**), melomorsine I (**25**), tabersonine (**26**), 11-hydroxytabersonine (**27**), 19-acetyltabersonine (**28**), 11-hydroxy-19-acetyl-tabersonine (**29**), vincadifformine (**30**), 11-hydroxyvincadifformine (**31**), vincadifformineNb-oxide (**32**), lochnericine (**33**), 11-hydroxy-14, 15-epoxytabersonine (**34**), venalstonine (**35**), venalstonidine (**36**), 19*S*-vindolinine (**37**), 19*R*-vindolinine (**38**), eburenine (**39**), (−)-aspidospermidine (**40**), (+)-voaphylline (**41**), (*S*)-quebrachamine (**42**), *N*-acyl-indolinique (**43**), scandine (**44**), 10-hydroxyscandine (**45**), meloscandonine (**46**), and 19-*epi*-meloscandonine (**47**) [20] [26] [30] [36]-[50].



24



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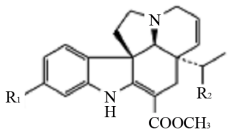
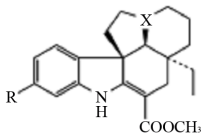
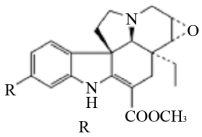


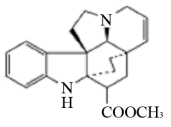
	R_1	R_2
26	H	H
27	OH	H
28	H	Ac
29	OH	Ac



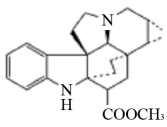
	R	X
30	H	N
31	OH	N
32	H	N=O



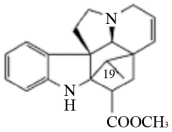
	R
33	H
34	OH



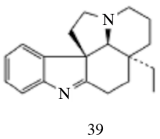
35



36



37 C-19s
38 C-19R



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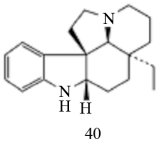

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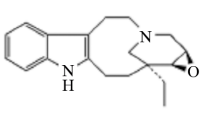

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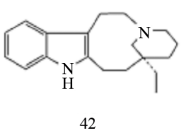
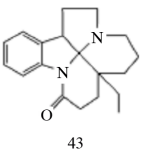


42



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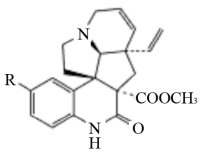
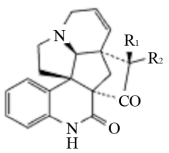


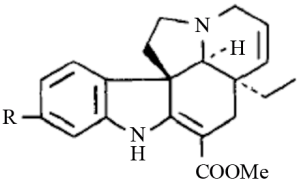
	R
44	H
45	OH



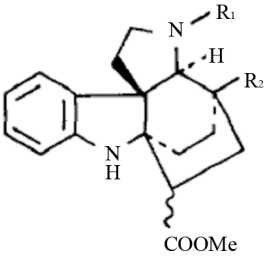
	R1	R2
46	H	CH_3
47	CH_3	H

3.6. *Melodinus guillauminii* Boiteau

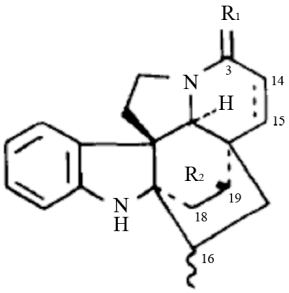
11-hydroxytabersonme (**48**), venalstomne (**49**), venalstomdme (**50**), 14,15-seco-3-oxokopsmal (**51**), 3-oxovenalstomne (**52**), 11-methoxy-Δ^{14}-vmcamenme (**53**), 3-0x0-hydroxykopsmme (**54**), ll-methoxyd14-vmcanol (**55**), kopsmme (**56**), 15-a-hydroxykopsmme (**57**), 16-epi-Δ^{14}-vmcanol (**58**), Δ^{14}-vmcanol (**59**), Δ^{14}-vmcmone (**60**), Δ^{14}-vmcamenme (**61**), Δ^{14}-16-Eplvmcme (**62**), 11-methoxytabersonme (**63**), 19-*β*-hydroxyvenalstomne (**64**), plemcarpamme (**65**) [51].



48 R = OH
63 R = OMe



51 R_1 = COMe, R_2 = CHO



49 R_1 = H_2, R_2 = H, Δ^{14},16 β H

50 R_1 = H_2, R_2 = H, 14 α, 15α epoxy, 16 β H

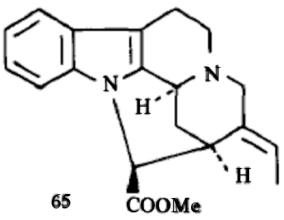
52 R_1 = O, R_2 = H, Δ^{14}, 16 β H

54 R_1 = O, R_2 = H, + OH indetermined

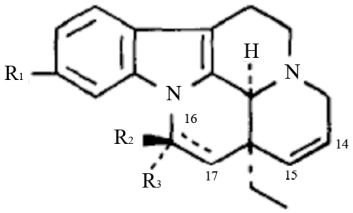
56 R_1 = H_2, R_2 = H, 16 β H

57 R_1 = H_2, R_2 = H, 15α OH, 16 β H

64 R_1 = H_2 R_2 = OH, Δ^{14}, 16 β H



65 COOMe



53 R_1 = OMe, Δ^{16}

55 R_1 = OMe, R_2 = H, R_3 = OH

58 R_1 = H, R_2 = OH, R_3 = H

59 R_1 = H, R_2 = H, R_3 = OH

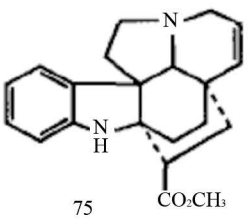
60 R_1 = OMe, R_2 R_3 = O

61 R_1 = H, Δ^{16}

62 R_1 = OMe, R_2 = COOMe, R_3 = OH

3.7. *Melodinus hemsleyanus* Diels

Tabersonine (**66**), 11-methoxytabersonine (**67**), 11-hydroxytabersonine (**68**), 11,19R-dihydroxytabersonine (**69**), ll-hydroxy-14,15-*α*-epoxytabersonine (**70**), scandine (**71**), 10-hydroxyscandine (**72**), meloscine (**73**), meloscandonine (**74**), venalstonine (**75**), venalstonidine (**76**), vindolinine (**77**), picralinal (**78**), picrinine (**79**), akuammidine (**80**), ll-hydroxyvincadifformine (**81**), 14,15-epoxyscandine (**82**), 19-epimeloscandonine (**83**), 16*β*-hydroxy-19R-vindolinine (**84**) and 16*β*-hydroxy-19S-vindolinine (**85**) [39].



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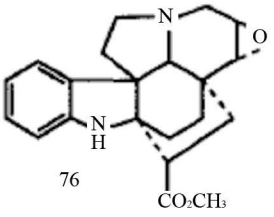
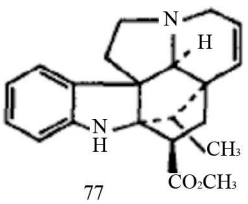
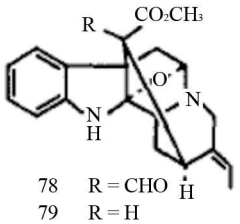


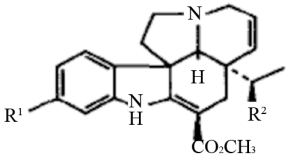
76



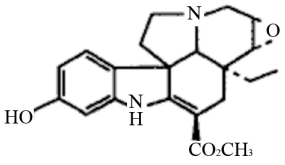
77



78 R = CHO
79 R = H



	R^1	R^2
66	H	H
67	OCH_3	H
68	OH	H
69	OH	OH



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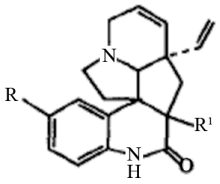
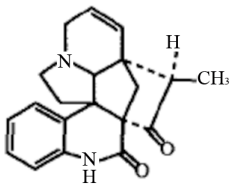


	R	R^1
71	H	CO_2CH_3
72	OH	CO_2CH_3
73	H	H



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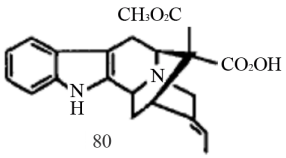

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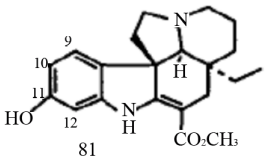

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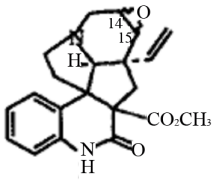

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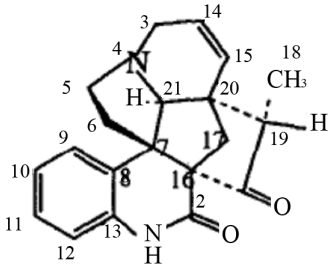
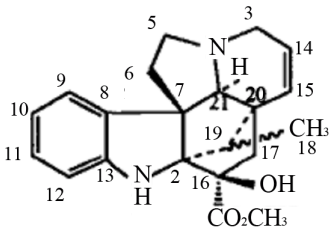


83



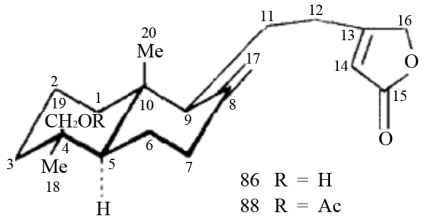
84 19R
85 19S

3.8. *Melodinus morsei* Tsiang

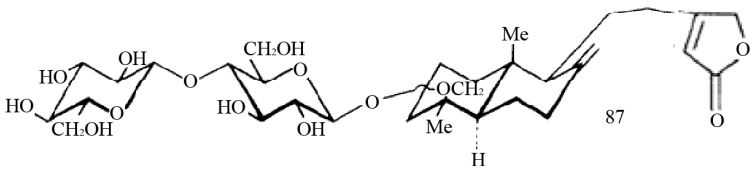
Melofusine I (**24**), melomorsine I (**25**), tabersonine (**26**), 11-hydroxytabersonine (**27**), 19-acetyltabersonine (**28**), 11-hydroxy-19-acetyl-tabersonine (**29**), vincadifformine (**30**), 11-hydroxyvincadifformine (**31**), vincadifformineNb-oxide (**32**), lochnericine (**33**), 11-hydroxy-14,15-epoxytabersonine (**34**), venalstonine (**35**), venalstonidine (**36**), 19*S*-vindolinine (**37**), 19*R*-vindolinine (**38**), eburenine (**39**), (−)-aspidospermidine (**40**), (+)-voaphylline (**41**), (*S*)-quebrachamine (**42**), *N*-acyl-indolinique (**43**), scandine (**44**), 10-hydroxyscandine (**45**), meloscandonine (**46**), and 19-*epi*-meloscandonine (**47**) [17] [20] [26] [30] [36]-[50] [52].

3.9. *Melodinus monogynus* Roxb

Medigenin (**86**), Medinin (**87**), medigenin acetate (**88**) [53].



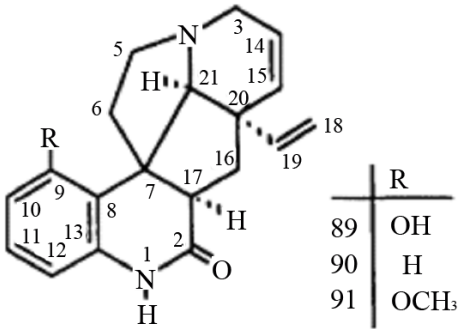
86 R = H
88 R = Ac



87

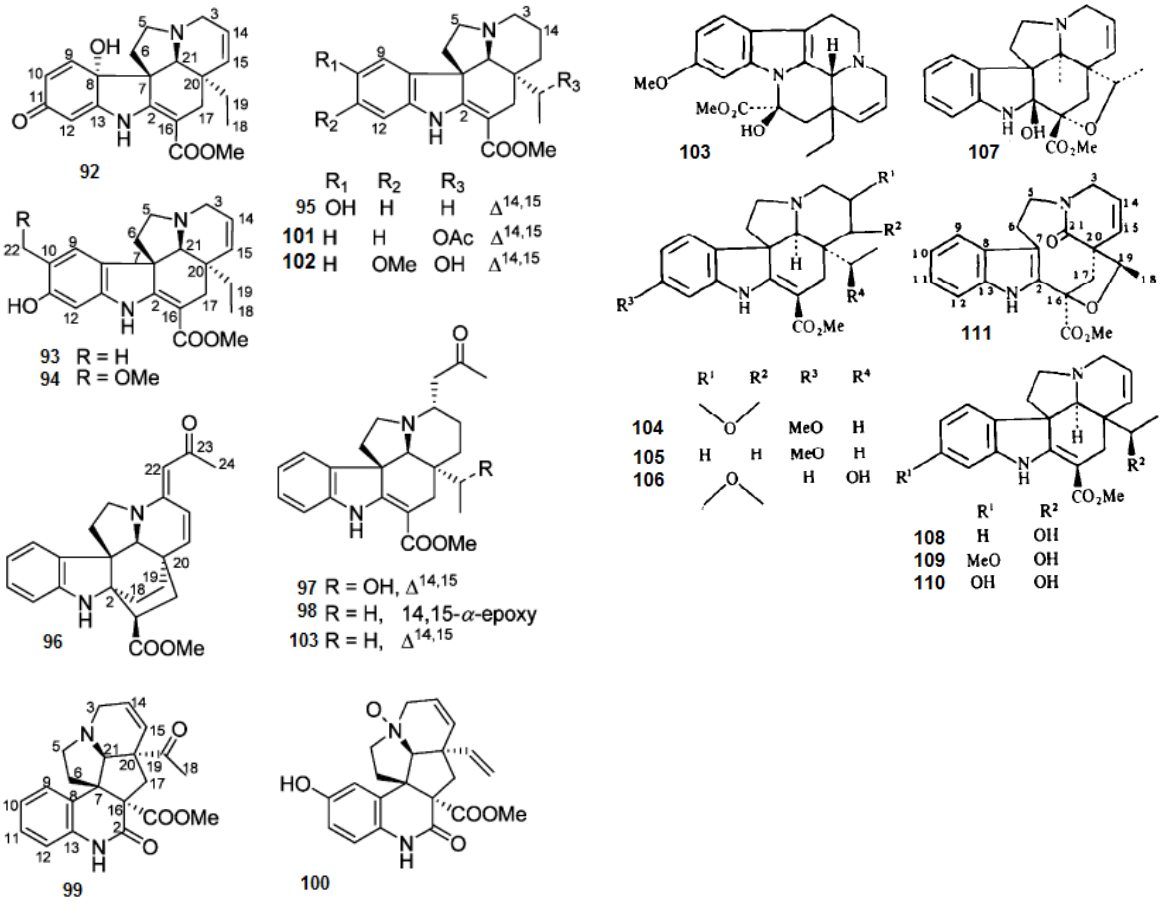
3.10. *Melodinus scandens* J.R. Forst. & G. Forst.

9-hydroxyepimeloscine (**89**); epimeloscine (**90**), 9-methoxyepimeloscine (**91**) [27].



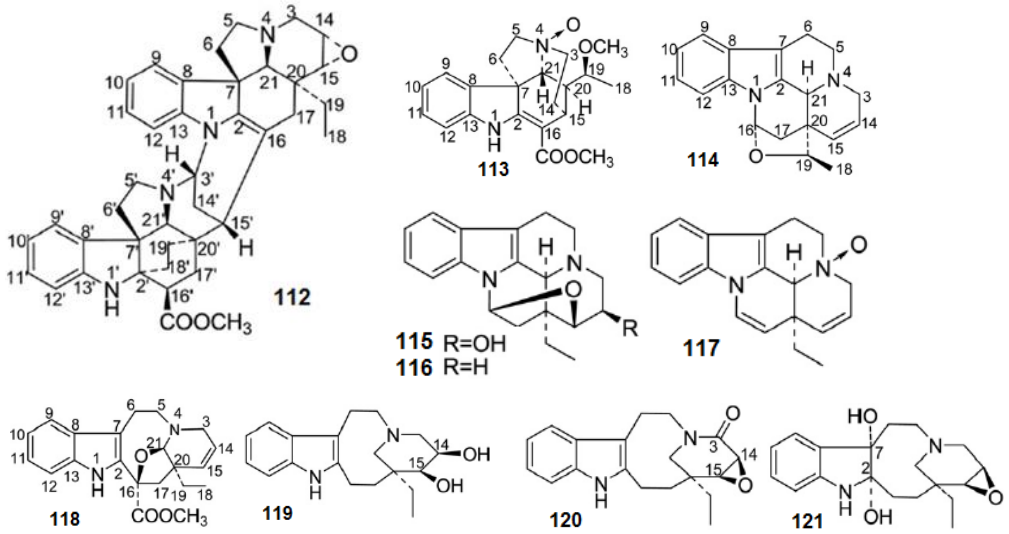
3.11. *Melodinus suaveolens* (Hance) Champ. ex Benth

Melodinine M (**92**), Melodinine N (**93**), Melodinine O (**94**), Melodinine P (**95**), Melodinine Q (**96**), Melodinine R (**97**), Melodinine S (**98**), Melodinine T (**99**), Melodinine U (**100**), 11-hydroxytabersonine (**27**), 11-methoxytabersonine (**67**), tabersonine (**26**), 19-(R)-acetoxytabersonine (**101**), 11-methoxy-19-(R)-hydroxytabersonine (**102**), lochnericine (**33**), Δ^{14}-vincine (**103**), vindolinine (**77**), 11-methoxytabersonine (**67**), vincadifformine (**30**), hazuntine (**104**), 11-hydroxytabersonine (**27**). 11-methoxyvincadifformine (**105**), cathovalinine (**106**), vincoline (**107**), 19R-hydroxytabersonine (**108**), 1l-methoxy-19R-hydroxytabersonine (**109**), 11,19R-dihydroxytabersonine (**110**), tabersonine (**26**), suaveolenine (**111**) [25] [26] [54].



3.12. *Melodinus yunnanensis* Tsiang & P.T. Li

Meloyine I (**112**), 19S-Methoxytubotaiwine N_4-oxide (**113**), 16,19-Epoxy-Δ^{14}-vincanol (**114**), 14*β*-Hydroxy-meloyunine (**115**), Meloyunine (**116**), Δ^{14}-Vincamenine N_4-oxide (**117**), 16*β*,21*β*-Epoxy-vincadine (**118**), 14*β*,15*β*-20S-Quebrachamine (**119**), 3-Oxo-voaphylline (**120**), 2*α*,7*α*-Dihydroxy-dihydrovoaphylline (**121**) [16] [17] [55].



4. Biological Activities

In vitro pharmacological activities of *Melodinus*.

Four species from *Melodinus* have been studied for their pharmacological activities. Extracts and pure compounds derived from *Melodinus* were reported to have a concentrate pharmacological activity of antitumor.

4.1. Anticancer Activities

It is known that nature is able to produce a wide variety of chemical entities of novel structure. Many of the new and novel compounds isolated from natural sources might otherwise have never been discovered, especially those of considerable complexity requiring the development of methods for the creation of new ring systems. Natural products appeared to be a promising source for new types of compounds with antitumor activity [56] [57].

MTT assay is dependent on the reduction of the tetrazolium salt MTT (3-(4,5-dimethylthazol-2-yl)-2,5-diphenyl tetrazolium bromide) by the mitochondrial dehydrogenase of viable cells to form a blue formazan product. The assay measures cell respiration and the amount of formazan produced is proportional to the number of living cells present in culture which will result in lower optical density (OD) [58].

Anticancer activities were reported in 1998, Demethyltenuicausine (I), a new bisindole alkaloid, was isolated from *Melodinus hemsleyanus* revealed antitumor activities in pharmacological tests [24].

Antitumor potential was demonstrated by the indole alkaloids from the leaves and twigs of *Melodinus fusiformis* and *Melodinus tenuicaudatus* via the MTT biological assay showed significant cytotoxicity against five human tumor cell lines: SW480, SMMC-7721, HL-60, MCF-7 and A-549 [17] [18].

Nine isolated from *Melodinus suaveolens* revealed a positive cytotoxicity with IC_{50} all around 10 μM against five human cancer cell lines: Five human cancer cell lines, human myeloid leukemia HL-60, hepatocellular carcinoma SMMC-7721, lung cancer A-549, breast cancer MCF-7, and colon cancer SW480 cells [25].

4.2. Other Biological Activities

A pharmacological test revealed that 11-hydroxyvincadifformine which was isolated from the aerial parts of *Melodinus hemsleyanus* has significant antifertility activity [19].

5. Future Perspectives and Conclusions

There is no relative report mentioned the *Melodinus* products. However, according to its potential, *Melodinus*, can be published as a high-value export crop for medicinal use.

Although, several research work has been done on some plants of this genus to date, but a large number of species are still chemically and/or pharmacologically unknown. Consequently, a broad field of future research remains possible in which the isolation of new active principles from these species would be of great scientific merit. The alkaloids are of particular interest as many are highly potent bioactive and perhaps responsible for most of activities shown by the plants of this genus. However, the mechanism of their action is still unknown. Hence, a detailed study is required to understand the structure-activity relationship of these constituents. As literature showed, many plant extracts having cytotoxic activity, hence, the particular constituent responsible for the activity may be isolated for further process. In addition, some plant extracts were only screened for their preliminary *in vitro* activities, so, the advance clinical trial of them deserves to be further investigated. Herein, we described the possible applications in clinical research but further investigations on phytochemical discovery and subsequent screening are needed for opening new opportunities to develop pharmaceuticals based on Stephania constituents.

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