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Phytochemistry, Pharmacological Potency, and Potential Toxicity of Myoporum spp.

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Abstract: Genus *Myoporum* family Myoporaceae, includes approximately 32 species of woody small trees or shrubs, most of them are native to Australia and surrounding territories. Only certain species have been thoroughly studied and rich in flavonoids, phenylethanoids, Phenylpropanoids, terpenoids, iridoids, essential oil, and trace alkaloids. The essential oils are characterized by sesquiterpenes type components, either in ketone or alcoholic forms usually combined to a furanoid moiety. *Myoporum* spp. have been utilized in folk medicine for treatment of various diseases and were used as antidermatitis, antibacterial, antipyretic, anti-pulpitis, antipsychotic, anti-inflammatory, detoxicant, and others. Despite all these benefits, *Myoporum* spp. must be cautiously employed due to their potential toxicities, which arise from the presence of furanosesquiterpenoid contents, particularly in their essential oil. The toxicity influences liver and can extend to kidney and lung causing injury. The present review aims to explore the phytochemistry, beneficial uses and the toxic potentials of *Myoporum* spp.

Keywords: *Myoporum*; Myoporaceae; secondary metabolites; furanosesquiterpenoids; biological activities; toxicity.

1. Introduction

Family Myoporaceae is slightly a small family, consisting mainly of three genera; *Bontia*, *Eremophila*, and *Myoporum*. Myoporaceous plants are shrubs or small trees widely endemic to Australia. Genus *Myoporum* was discovered in 1786 by George Foster [1-3]. It is a widely distributed genus including approximately 30 species as reported by Chinnock and Grady [4-7], 31 species as stated by Richmond and Ghisalberti [8], or 32 species as claimed by Laurence [9-11]. It is distributed mainly in Australia, extended to Melanesia, the Pacific and Indian Ocean areas, New Guinea, Mauritius, New Zealand, and Eastern Asia. About 18 species of *Myoporum* are native and endemic to Australia, while the others are distributed to various regions and territories. For example, *M. boninense* Koidz. and *M. bontioides* (Sieb. et Zucc.) A. Gray is native to Japan, where they are regarded as endangered plants [12,13]. Like all Myoporaceous members, *Myoporum* species are rich in flavonoids; and phenylethanoids; terpenoids, iridoids and alkaloid contents [3,12-19]. Besides these secondary metabolites, most of *myoporum* species are characterized by secretory ducts that secrete essential oil mixture. The best known of which are the sesquiterpenes with or without furanoid moiety in their structures, which may be of ketone or alcohol. Although *Myoporum* spp. have been reported for their toxicity, most plant members have acquired a good reputation by aborigines [20]. The essential oil of

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Table 1. List of *Myoporum* species, common names/ growing areas

No.	*Myoporum* spp.	Common name / Area	References
1.	*M. acuminatum* R.Br.	pointed boobialla / Australia	[4]
2.	*M. bateae* F.Muell.	New South Wales	
3.	*M. betcheanum* L.S.Sm.	mountain boobialla / New South Wales, Melanesia and Queensland	
4.	*M. boninense* Koidz.	New South Wales, Queensland, Bonin to Mariana Islands	
5.	*M. brevipes* Benth.	pale *myoporum* / mainly South Australia	
6.	*M. caprarioides* Benth.	slender *myoporum* / Western Australia	
7.	*M. cordifolium* (F.Muell.) Druce	Jerramungup *myoporum* / Western Australia	
8.	*M. crassifolium* G.Forst.	New Caledonia, Vanuatu	
9.	*M. degeneri* (G.L.Webster) O.Deg. & I.Deg.	Maui/Hawaii	
10.	*M. floribundum* A.Cunn. ex Benth.	weeping boobialla / New South Wales, (Victoria)	
11.	*M. insulare* R.Br.	boobialla, blueberry tree / Australia	
12.	*M. laetum* G.Forst.	Ngaio / New Zealand	
13.	*M. mauritianum* A.DC.	Mauritius and Rodrigues	
14.	*M. montanum* R.Br.	native myrtle / Australia, New Guinea and Timor	
15.	*M. obscurum* Endl.	bastard ironwood, popwood / Norfolk Island	
16.	*M. oppositifolium* R.Br.	twin-leaf *myoporum* / Australia	
17.	*M. parvifolium* R.Br.	creeping boobialla / Australia	
18.	*M. petiolatum* R.J.Chinnock	sticky boobialla / Australia	
19.	*M. platycarpum* R.Br.	sugar wood (Australia)	
20.	*M. rapense* F.Br.	French Polynesia & Kermadec island in New Zealand	
21.	*M. rimatarensis* F.Br.	French Polynesia	
22.	*M. sandwicense* A.Gray	naio / Hawaii and Mangaia	
23.	*M. stellatum* (G.L.Webster) O.Deg. & I.Deg.	O'ahu/Hawaii	
24.	*M. stokesii* F.Br.	French Polynesia	
25.	*M. tenuifolium* G.Forst.	New Caledonia and Loyalty Islands	
26.	*M. tetrandrum* (Labill.)	Domin boobialla / coastal regions of Australia	
27.	*M. turbinatum* R.J.Chinnock	salt *myoporum* / Western Australia	
28.	*M. velutinum* R.J.Chinnock	Western Australia	
29.	*M. viscosum* R.Br.	sticky boobialla / South Australia	
30.	*M. wilderi* Skottsb.	Cook Islands	
31.	*M. bontioides* (Sieb. et Zucc.) A. Gray A. Gray	bitter blue plant / Northwest of China, Japan	[12,25,28]
32.	*M. deserti* A. Cunn.	Ellangowan poison bush / Japan China, Australia, Hawaiian Islands, New Zealand	[15,16,29]
33.	*M. serratum* R. Br.	New Holland	[30,31]

M. crassifolium is incorporated in the composition of many pharmaceutical preparations employed in skin disorders associated with inflammation resulting from pruritus, sunburns, acne, eczema, redness, psoriasis, improving the signs of aging and skin scars [21,22]. Owing to the easily burning of their inner wood, some of *Myoporum* plants e.g. *M. crassifolium*, was used as a lighter and fire source on

beaches. The small cut sticks and laths of *M. crassifolium* and *M. platycarpum* are also employed as candles or torches in ceremonies in the New Caledonia southern coast and Australia [13].

The Australian youths have used the resin of *M. platycarpum* to reach manhood [4,23]. The wood of *M. laetum* and *M. sandwicenes* are used as timber in New Zealand Hawaiian [4,10]. *M. bontioides*, has been used in folk medicine as antidermatitis, anti-bacterial, antipyretic, anti-pulpitis, antipsychotic, relieving restlessness, anti-inflammatory, treating sciatica and detoxicant [4,17,24,25] in Northwest China. Additionally, *Myoporum* spp. can be used as a moisturizing agent in cosmetic preparations [24]. In Australia, the decoction of *M. montanum* leaves was used by the aboriginal people as a medicinal wash. In contrast the smoking branches for management of general ailments [4], the aqueous leaves extract has been used in respiratory and gastrointestinal disorders, laxative, analgesic in headache, an antidote for poisons and in venereal diseases [4,10,20]. Generally, *Myoporum* species were employed as horticultural plants, ornamental shelterbelts on roadsides to break winds [10]. In New Zealand, the juice of *M. laetum* leaves has been used as insecticide while the outer bark was applied for curing skin ulcers and eruptions. The oils of *M. laetum* leaves were used for septic wounds [4].

The survey stated that the nutritional value of Myoporaceous plants is limited; the fruits of *M. montanum,* and the sugary manna of *M. platycarpum* are irregularly eaten [4,8]. The aboriginal people have applied *M. montanum, M. tenuifolium, M. sandwicense* leaves, and the inner bark of *M. laetum* decoctions to relieve toothache [4, 10]. Biological evaluation of Myoporum species revealed that they possess various biological impacts as anticancer, antibacterial, insecticidal and anti-inflammatory [24]. *M. laetum* exhibited mosquitos' repellent effect while *M. desertii* was considered insect pests deterrent with high activity against locusts [26]. *M. bontioides* extract displayed a strong pesticidal, insect-repellent, and antifeedant activities [26]. *M. laetum* possesses anti-quorum sensing (anti-QS) activity against the *Chromobacterium violaceum* [27].

The *Myoporum* essential oil particularly those with epingaione content as in *M. bontioides*, exhibited potent insecticidal effect against grasshoppers, *Pieris rapae* and leaf-cutting ants [10]. Chinnock has mentioned thirty species of Myoporum with their common names and area of distribution [4]. Additional four species have been entitled in various articles and were listed in Table 1. This review aims to explore the phytochemistry, biological activities, and potential toxicity of *Myoporum* spp.

2. Biological Activities of *Myoporum* spp. Secondary Metabolites

Various biological and phytochemical studies on *Myoporum* spp. have been performed, either to support the folk medicinal uses or to warn the aboriginals from their abuse. Generally, the Furanosesquiterpenoids of *Myoporum* are found to have insecticidal metabolites against the leaf-cutting ants. Unfortunately, the previous biological investigations of *Myoporum* spp. are scarce and have been focused mainly on certain spp. concerning *M. bontioides, M. montanum, M. insulare, M. laetum, M. acuminatum and M. crassifolium*. *M. bontioides* has been extensively investigated, the extract of which possessed a strong repellent activity against *Plutella xylostella*, and antifungal effect against *Fusarium oxysporum, Sphaceloma fawcettii, Thielaviopsis paradoxa, Mycosphaerella sentina, Colletotrichum musae, Pestalotia mangiferae and Alternaria alternata* [26,28,32], due to the presence of (−)-epingaione. It also exhibited anti-methicillin resistant *Staphylococcus aureus* (anti-MRSA) activity, the isolated sesquiterpene alkaloids (Myoporumine A and B) as well as epingaione and dehydroepingaione of *M. bontioides* also exhibited potent anti-MRSA effect with MIC values close to that of the standard vancomycin [17]. Additionally, the flavones of *M. bontioides* including 3,4`-dimethoxy-3`,5,7-trihydroxyflavone exhibited potent antiproliferative effect against breast cancer cell line MCF-7 [24], While (2R,3R)-3,5,7-trihydroxyflavanone-3-acetate showed potent antifungal activity against *Magnaporthe grisea* [33]. Moreover, the essential oil and ethyl acetate fraction of which showed potent antifeedant and larvicidal activities against *Spodoptera litura* [34,35]. The plant also was incorporated in herbal mixture to treat intractable headache, sciatica and upper respiratory tract infection [36-38]. The aqueous extract *M. montanum* leaves exhibited significant antibacterial activity against *Staphylococcus epidermidis, Enterococcus faecalis, and Moraxella catarrhalis*, due to

presence of (-)-10,11-dehydromyoporone, (±)-myoporone and 11-hydroxymyoporone [20]. The serrulatane diterpenes content of *M. insulare* exhibited significant anticancer activity against various types of cell lines [34,35]. The essential oil of *M. laetum* leaves showed antiviral, antimicrobial and antifungal activities [39,40]. The essential oil of *M. acuminatum* leaves and fruits displayed promising antimicrobial activity against G+ve bacteria: *Bacillus subtilis and Streptococcus pneumonia,* G-ve bacteria: *E. coli* and fungi: *Syncephalastrum racemosum*, *Aspergillus fumigates* and *Geotricum candidum* [34,41]. The resinous content of *M. crassifolium* was incorporated in pharmaceutical creams to treat skin disorders and inflammation [16].

3. Secondary Metabolites Isolated from *Myoporum*

Myoporum spp. are well known by various secondary metabolites contents including flavonoids, phenylethanoids, Phenylpropanoids, terpenoids, iridoids, trace alkaloids and essential oil [12,13,15-17,42]. the oils are characterized by sesquiterpenes type compounds, either as ketone or alcoholic forms, usually combined to a furanoid moiety, to which the toxicity of *Myoporum* was attributed [20]. The essential oil is nearly distributed in all Myoporaceous plants. Flavonoids have been isolated from *M. tenuifolium*, *M. deserti*, *M. acuminatum*, *M. bontioides* and *M. serratum*. Organic acids and phenylethanoids have been obtained from *M. bontioides*. Serrulatane type diterpene were isolated from *M. insulare*. Iridoid glycosides have been isolated from *M. bontioides*, *M. deserti* and *M. insulare*. β-sitosterol and the sesquiterpene alkaloids (myoporumine A and B) were detected and isolated from *M. bontioides*, while the furanosesquiterpenoids have been isolated from most of *myoporum* spp. as mentioned in Table 2 and chemical structures of the compounds are given Figure 1. [12,28,43-45].

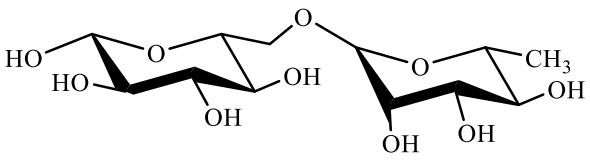
Table 2. Secondary metabolites isolated from *Myoporum* spp.

No	Compound name	Distribution / Plant name	References
	Flavones		
1.	Apigenin	*M. bontioides* & *M. tenuifolium* leaves	[12, 28, 45]
2.	Apigenin-7-*O*-rutinoside	*M. tenuifolium* leaves	[45]
3.	Apigenin-7-*O*- glucoside	*M. bontioides* leaves	[12, 44]
4.	Apigenin-7-*O*- glucuronide	*M. bontioides* leaves and flowers	[12]
5.	(1→6)-rhamnosyl-6-amino-6-deoxyglucosyl-7-O-apigenin.	*M. tenuifolium* leaves	[8, 50]
6.	chrysoeriol	*M. bontioides* Gray leaves *M. tenuifolium* leaves	[12, 45]
7.	chrysoeriol-7-*O*-gentiobioside	*M. tenuifolium* leaves	[45, 51]
8.	chrysoeriol-7-*O*-rutinoside	*M. tenuifolium* leaves	[45, 51]
9.	chrysoeriol-7-*O*-glucoside	*M. bontioides* leaves	[12]
10.	chrysoeriol-7-*O*-glucuronide	*M. bontioides* leaves	[12]
11.	(1→6)-rhamnosyl-6-amino-6-deoxyglucosyl-7-O-chrysoeriol	*M. tenuifolium* leaves	[50]
12.	norartocarpetin	*M. bontioides* leaves acetone extract	[24]
13.	luteolin	*M. tenuifolium* leaves *M. deserti* *M. acuminatum* *M. bontioides* leaves	[12, 24, 28, 43, 45, 51]
14.	luteolin-7-*O*-glucoside	*M. tenuifolium leaves* *M. bontioides* leaves	[12, 45, 51]
15.	luteolin-7-*O*-rutinoside	*M. tenuifolium* leaves	[45]
16.	luteolin-7-O-glucuronide	*M. bontioides* A. Gray leaves and flowers	[12], 107

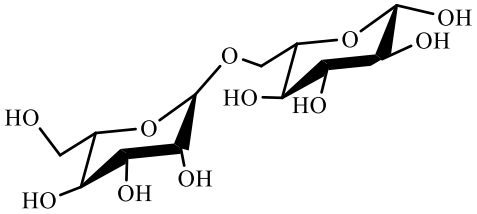
17.	(1-6)-glucosyl-6-amino-6-deoxyglucosyl-7-O-chrysoeriol	*M. bontioides* leaves	[52]
18.	(1-6)-glucosyl-6-amino-6-deoxyglucosyl-7-O-luteolin	*M. bontioides* leaves	[52]
19.	5-hydroxy-6,7,3′,4′-tetramethoxyflavone	*M. bontioides* leaves and flowers	[28]
20.	Tricin	*M. tenuifolium* leaves	[24, 45]
21.	tricin-7-*O*-glucuronide	*M. tenuifolium* leaves *M. bontioides*	[12, 45]
22.	diosmetin	*M. bontioides* leaves acetone extract	[24]
23.	tangeretin	*M. bontioides* leaves	[28]
24.	sinensetin	*M. bontioides* leaves	[28]
25.	Nobiletin	*M. bontioides* leaves	[28]
26.	5-demethylnobiletin	*M. bontioides* leaves	[28]
27.	5,4′-dihydroxy-6,7,8,3′-tetramethoxy flavone	*M. bontioides* leaves	[28]
28.	4′,5,7,8-pentamethoxyflavone	*M. bontioides* leaves	[28]
29.	selagin-7-*O*-glucoside	*M. bontioides* leaves	[12]
30.	selagin-7-*O*-glucuronide	*M. bontioides* leaves	[12]
31.	3,4`-dimethoxy-3`,5,7-trihydroxyflavone	*M. bontioides* leaves	[24, 43]
	Flavonols		
32.	galangin	*M. bontioides*	[12, 53]
33.	galangin-3-methylether	*M. bontioides*	[53]
34.	ermanin	*M. bontioides*	[12]
35.	quercetin-3-methyl ether	*M. bontioides* leaves	[12]
36.	quercetin-3,4`-dimethyl ether	*M. bontioides* leaves	[12]
37.	3,3′-dimethoxyquercetin	*M. bontioides* leaves acetone extract	[24]
38.	Isorhamnetin	*M. bontioides* leaves	[43]
39.	Kaempferol	*M. serratum*	[12]
40.	3,4`-dimethoxy kaempferol	*M. bontioides* leaves	106
41.	Dihydrokaempferol	*M. bontioides* leaves	[28]
42.	Isokaempferide	*M. bontioides* leaves	[12]
43.	rhamnocitrin	*M. bontioides* leaves acetone extract	[24]
		Flavanones	
44.	eriodictyol-7-*O*-rutinoside	*Myoporum tenuifolium*	[45]
45.	(2R,3R)-3,5,7-trihydroxyflavanone 3-acetate	*M. bontioides*	[53, 54]
46.	pinocembrin	*M. bontioides* leaves	[12, 53]
47.	Pinobanksin	*M. bontioides* leaves	[53]
48.	Sakuranetin	*M. bontioides* leaves	[53]
	Anthocyanin		
49.	cyanidin-3,5-di-*O*-glucoside	*M. bontioides* flowers	[12]
	Organic acids, phenylpropanoids and phenylethanoids		
50.	verbascoside, isoverbascoside and oxoverbascoside	*M. bontioides* leaves and flowers	[12, 44, 55]
51.	Sesamin	*M. bontioides* leaves	[53, 55]
52.	chlorogenic acid	*M. bontioides* leaves	[12]
53.	Cimidahurine	*M. bontioides* leaves	[44]
54.	Meliotoside	*M. bontioides* leaves	[44]

55.	ferulic acid β-D-glucopyranosyl ester (phenylpropanoids)	*M. bontioides* leaves	[44]
	Serrulatane diterpenes		
56.	7,8,18-trihydroxyserrulat-14-ene	*Myoporum insulare* resins/exudates	[19, 31, 35, 56]
57.	5,18-epoxyserrulat-14-en-8,18-diol	*Myoporum insulare* resins/exudates	[19, 35, 57]
58.	5,18-epoxy-8-hydroxyserrulat-14-ene	*Myoporum insulare* resins/exudates	[19,35]
59.	7,8-dihydroxyserrulat-14-ene	*Myoporum insulare* resins/exudates	[19,35]
60.	Serrulat-14-en-5,8-dione	*Myoporum insulare* resins/exudates	[19,35]
61.	5,18-epoxyserrulat-14-en-7,8-dione	*Myoporum insulare* resins/exudates	[31, 56]
		Steroids	
62.	β-sitosterol	*M. bontioides* leaves acetone extract	[24, 53]
63.	Stigmasterol	*M. bontioides* leaves	[53]
	Sesquiterpene alkaloids		
64.	Myoporumine A	acetone fraction of *M. bontioides*	[17]
65.	Myoporumine B	acetone fraction of *M. bontioides*	[17]
	Iridoids		
66.	Myopochlorin	*M. bontioides*	[3, 44]
67.	Myobontioside A & B	*M. bontioides*	[3, 44]
68.	(1*R*)-1-methoxymyodesert-3-ene	*M. deserti* essential oil	[15, 16]
69.	(+)-(1*R*)-1-acetoxymyodesert-3-ene	*M. deserti* essential oil	[15, 16]
70.	(-)-(1*S*)-1-acetoxymyodesert-3-ene	*M. deserti* essential oil	[15, 16]
71.	Harpagide	*M. insulare* *M. bontioides*	[47, 55]
72.	8-acetylharpagide	*M. insulare* *M. bontioides*	[47, 55]
73.	macfadyenoside (5-hydroxycatalpol)	*M. insulare*	[47]
74.	myoporoside (6-epimer of ajugol)	*M. insulare*	[47]
	Furanoid sesquiterpene ketones		
75.	Epingaione	*M. bontioides* leaves acetone fraction	[17]
76.	Dehydroepingaione	*M. bontioides* leaves acetone fraction	[17]
77.	Myoporone	acetone fraction of *M. bontioides* & *M. montanum* leaves	[17, 20, 24]
78.	Dehydromyoporone	acetone fraction of *M. bontioides* & *M. montanum* leaves	[17, 20]
79.	9-(3-furanyl)-2,6-dimethyl-4-nonanone	*M. bontioides* leaves acetone fraction	[17]
80.	Dihydrocrassifolone	*M. bontioides* leaves acetone fraction	[17]
81.	10,11-dehydroisomyodesmone	acetone extract & essential oil of *M. montanum* leaves	[20]
82.	10,11-dehydromyodesmone	acetone extract & essential oil of *M. montanum* leaves	[20]

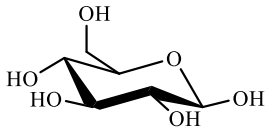
	Furanoid sesquiterpene ketols isolated from *Myoporum*		
83.	10,11-dehydromyoporum ketol	acetone extract & essential oil of *M. montanum* leaves	[20]
84.	myoporum ketol	acetone extract & essential oil of *M. montanum* leaves	[20]
85.	Crassifolone	*M. crassifolium* essential oil	[13]
86.	dihydrocrassifolone	*M. crassifolium* essential oil	[13]
87.	(-)- epi-α-bisabolol (−)-anymol	*M. crassifolium* essential oil (65.1%)	[13]
88.	Dendrolasin	*M. crassifolium* essential oil	[13]
89.	α-bisabolol oxide-B	*M. crassifolium* essential oil (7.3%)	[13]
	Major essential oil contents		
90.	Ngaione	*M. deserti* *M. acuminatum* (leaves & fruits) *M. laetum*	[13, 29, 34, 40, 58]
91.	(+)-myomontanone	*M. acuminatum* fruits essential oil *M. montanum* (70% of the oil) *M. betcheanum*	[34, 46]
92.	(+)-10,ll-didehydromyomontanone	*M. montanum*	[46, 59]
93.	isomyomontanone	*M. montanum* (3% of the oil)	[46]
94.	dehydrongaione	*M. deserti*	[29]
95.	epingaione	*M. deserti and M. bontioides* (81.52 %)	[26, 29, 43, 60, 61]
96.	dehydroepingaione	*M. deserti*	[29]
97.	myodesmone	*M. deserti* *M. acuminatum*	[29, 62, 63]
98.	dehydromyodesmone	*M. deserti*	[62]
99.	isomyodesmone	*M. deserti* *M. acuminatum*	[62]
100.	dehydroisomyodesmone	*M. deserti*	[62]
101.	myoporone	*M. deserti* *M. montanum* (22% of the oil) *M. betcheanum*	[29, 46, 63, 64]
	Miscellaneous		
102.	myobontioside C (acetogenin glucoside)	*M. bontioides*	[44]
103.	myobontioside D (monoterpene glucoside)	*M. bontioides*	[44]
104.	Prunasin	*M. bontioides*	[50]



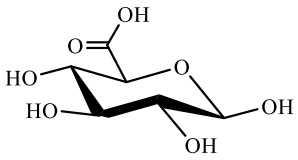
rutinoside moiety



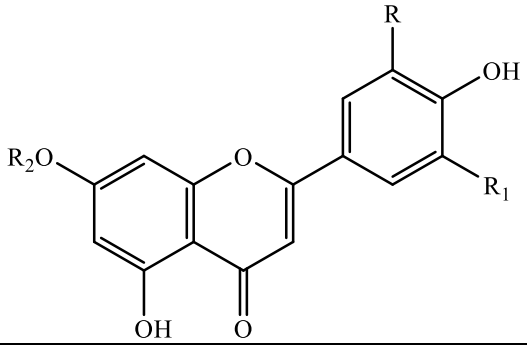
gentiobioside moiety



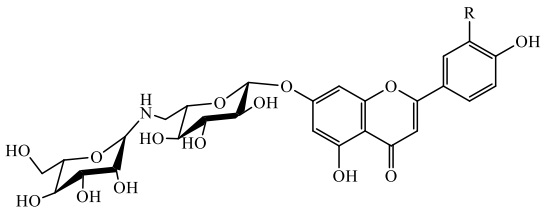
β-D-glucose moiety



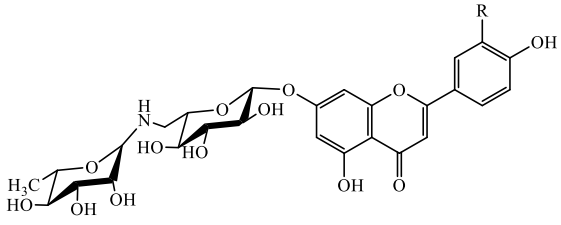
glucuronide moiety



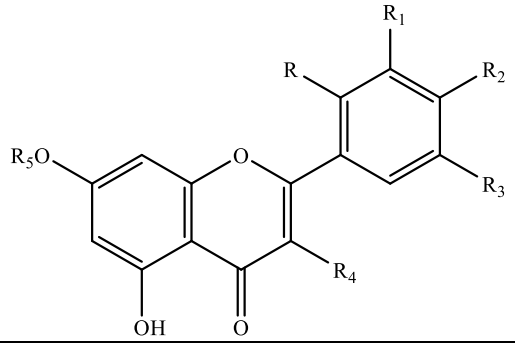
Compound No	R	R_1	R_2
1	H	H	H
2	H	H	rutinoside
3	H	H	β-D-glucoside
4	H	H	glucuronide
6	OCH_3	H	H
7	OCH_3	H	gentiobioside
8	OCH_3	H	rutinoside
9	OCH_3	H	glucoside
10	OCH_3	H	glucuronide
13	OH	H	H
14	OH	H	β-D-glucoside
15	OH	H	rutinoside
16	OH	H	glucuronide
20	OCH_3	OCH_3	H
21	OCH_3	OCH_3	glucuronide
29	OCH_3	OH	glucoside
30	OCH_3	OH	glucuronide



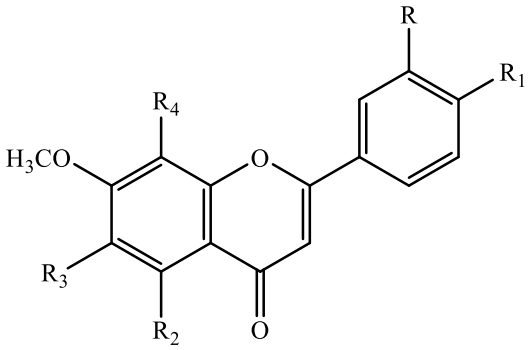
17:R= OCH_3 **18:** R= OH



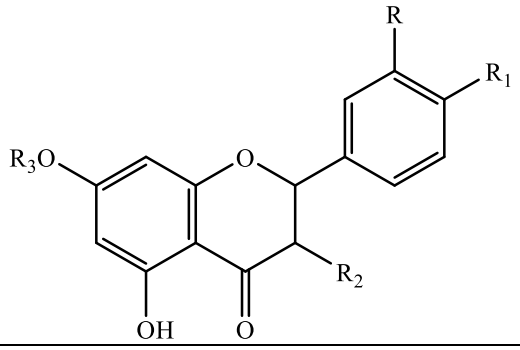
5 : R= H, **11:** R= OCH_3



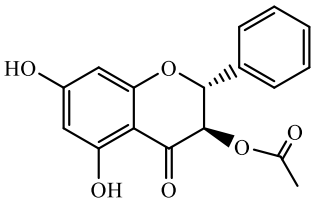
Compound No	R	R1	R2	R3	R4	R5
31	H	OH	OCH_3	H	OCH_3	H
43	H	H	OH	H	OH	CH_3
12	OH	H	OH	H	H	H
22	H	OH	OCH_3	H	H	H
37	OH	OCH_3	OH	OH	OCH_3	H
34	H	H	OCH_3	H	OCH_3	H
42	H	H	OH	H	OCH_3	H
38	H	H	OH	OCH_3	OH	H
35	H	OH	OH	H	OCH_3	H
36	H	OH	OH	OCH_3	OCH_3	H
32	H	H	H	H	OH	H
33	H	H	H	H	OCH_3	H
39	H	H	OH	H	OH	H
40	H	H	OCH_3	H	OCH_3	H



Compound No	R	R1	R2	R3	R4
27	OCH_3	OH	OH	OCH_3	OCH_3
26	OCH_3	OCH_3	OH	OCH_3	OCH_3
19	OCH_3	OCH_3	OH	H	OCH_3
23	H	OCH_3	OCH_3	OCH_3	OCH_3
24	OCH_3	OCH_3	OCH_3	H	OCH_3
28	H	OCH_3	OCH_3	OCH_3	H
25	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3



Compound No.	R	R_1	R_2	R_3
41	H	OH	OH	H
44	OH	OH	H	rutinoside
46	H	H	H	H
47	H	H	OH	H
48	H	H	H	CH_3



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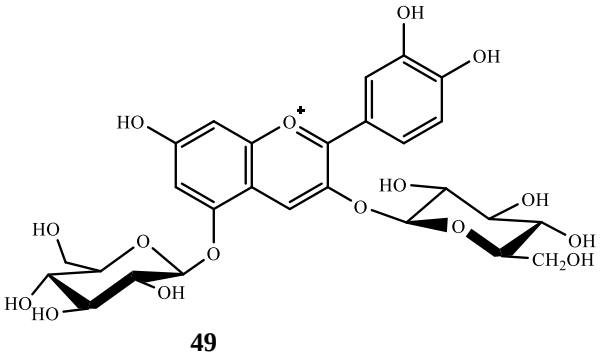

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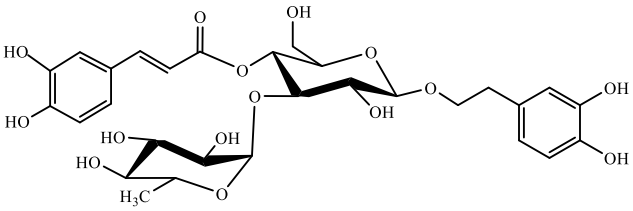

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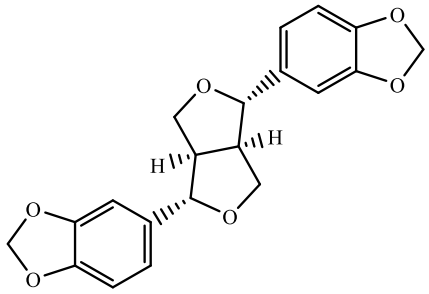

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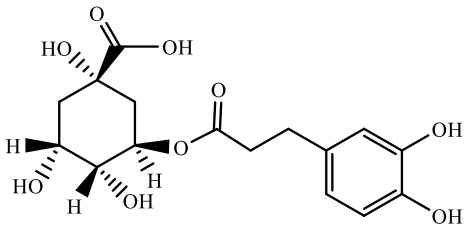

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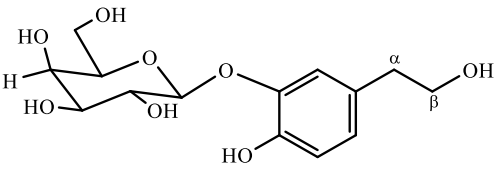

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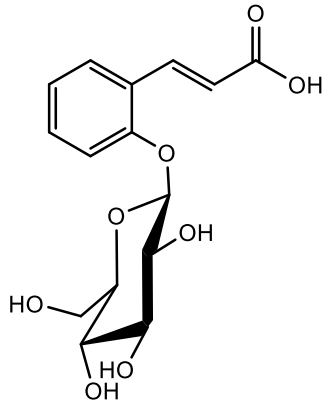

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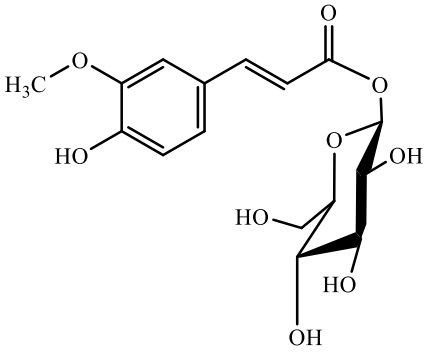

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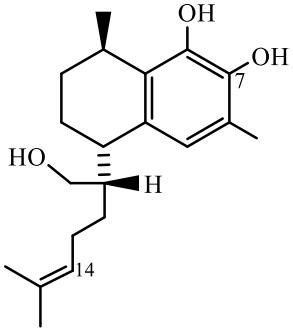

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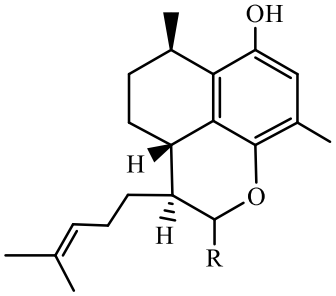
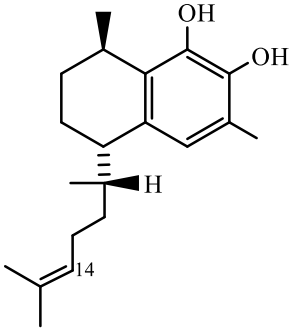


57 R = OH

58 R = H



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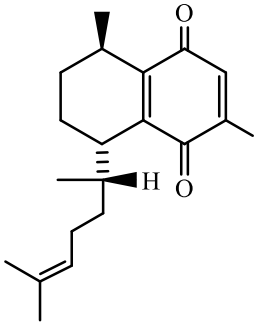

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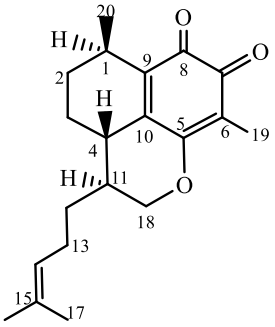

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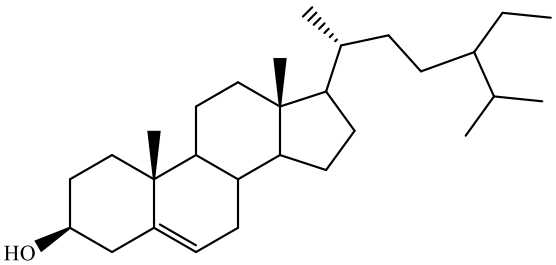

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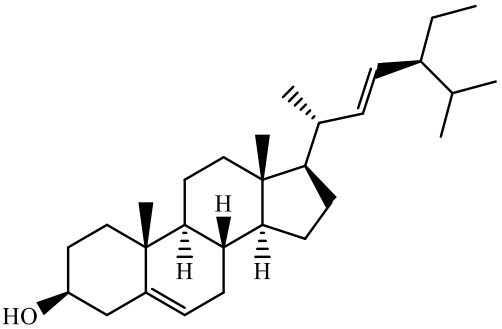

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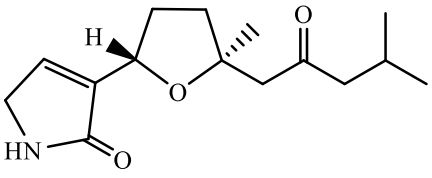

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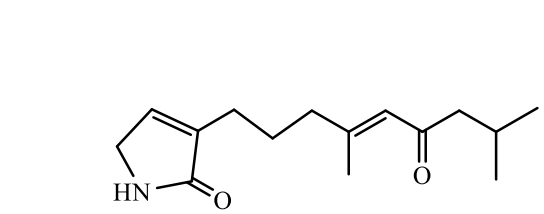
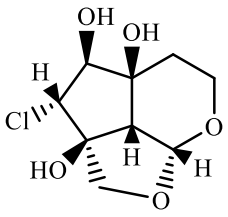
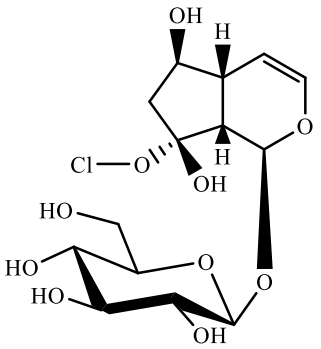
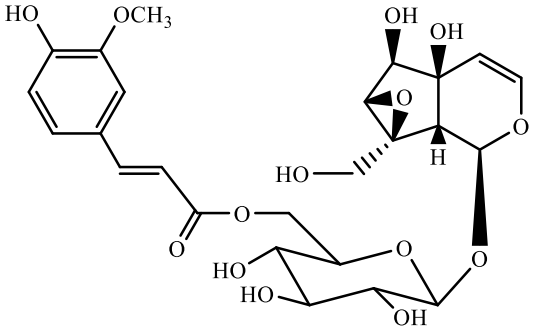
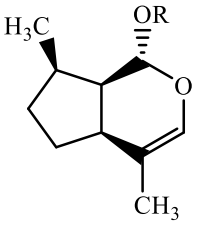


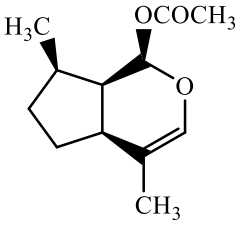




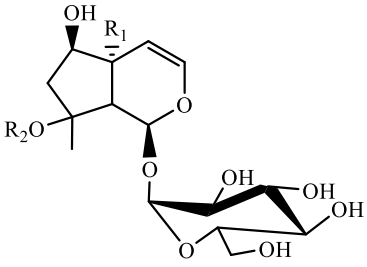
65 **66** **67a**

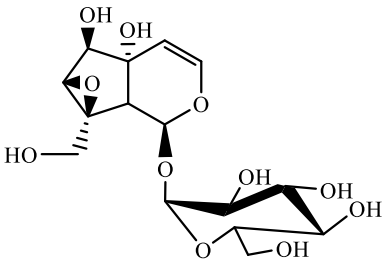


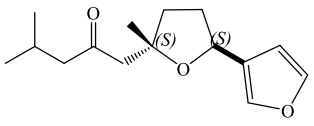




67b **68** R= CH_3 **69**
70 R= Ac



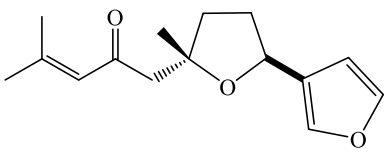


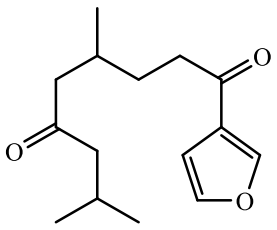


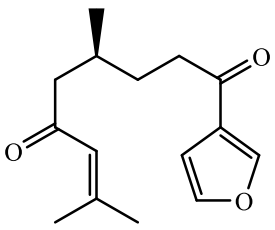
	R_1	R_2
71	OH	H
72	OH	Ac
74	H	H

macfadyenoside **73**

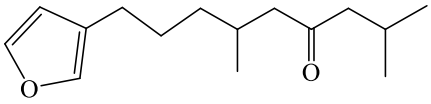
(+)-epingaione **95, 75**







96, 76 **101, 77** **78**



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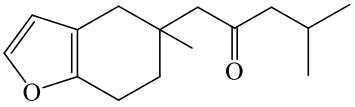

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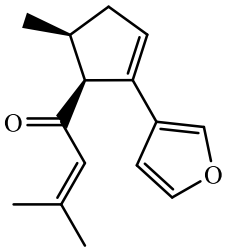

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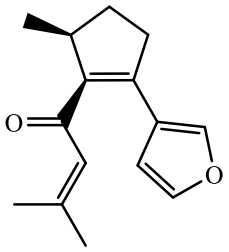

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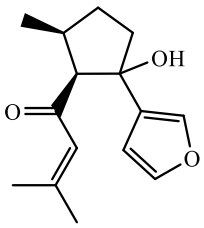

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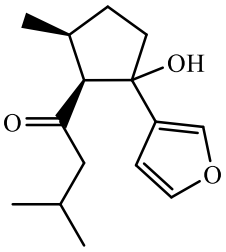

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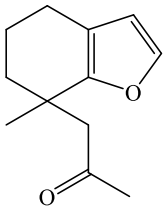

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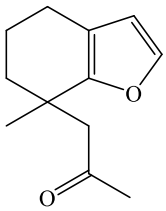

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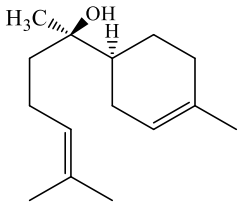

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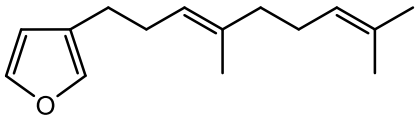

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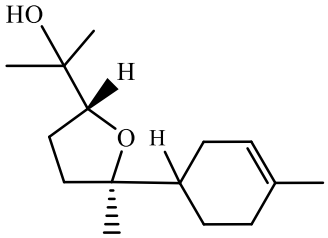

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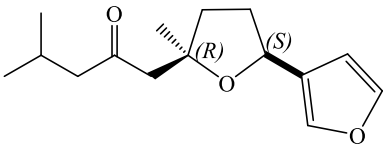

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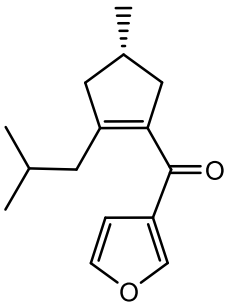

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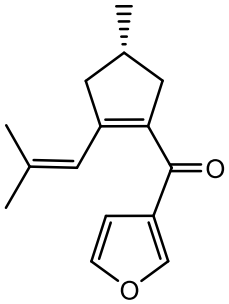

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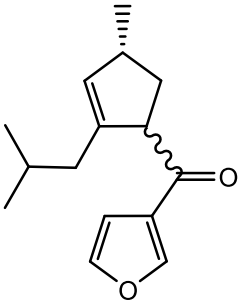

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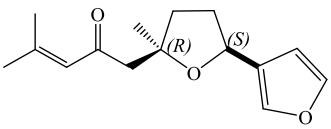

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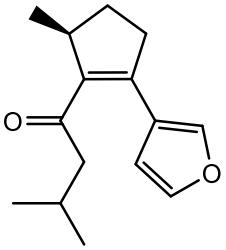

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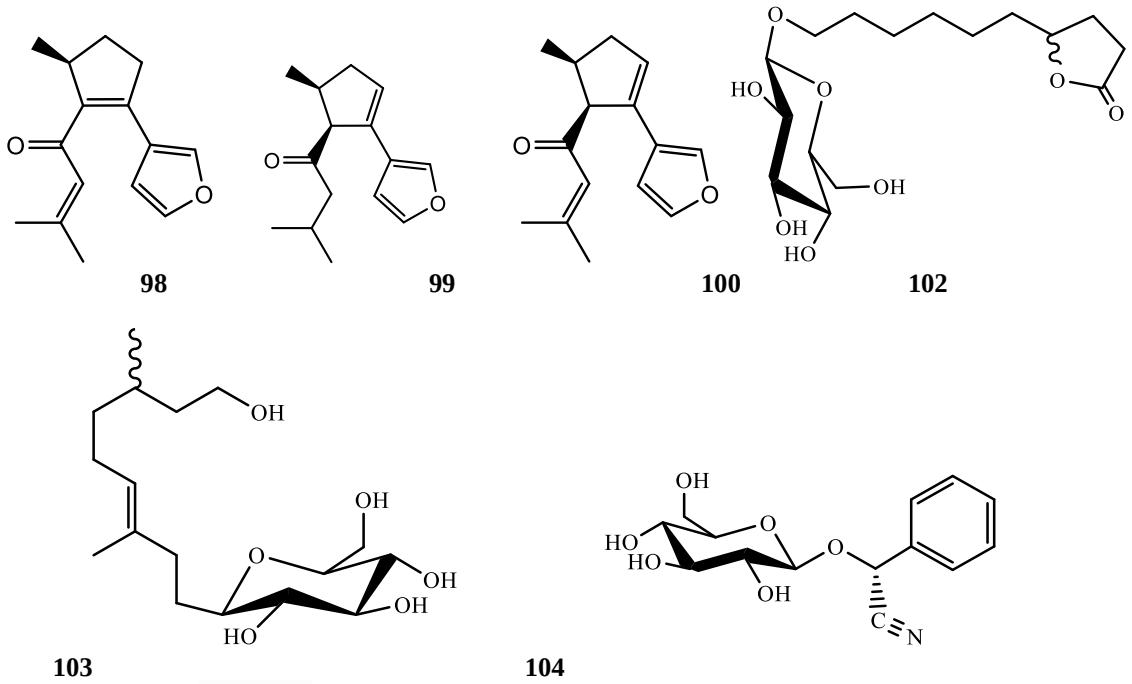

Figure 1. Chemical structures diversity present in *Myoporum* spp.

3.1. Essential oils of Myoporum spp.

Essential oils are nearly distributed in all Myoporaceous plants, the previous studies have focused mainly on the composition of essential oil of *Myoporum* leaves [4], while researches on fruits oil are scarce [18, 34]. The oils are famous for their contents of toxic furanoid sesquiterpenes which may be of ketone (oxygenated farnesols) or alcohol types [13,40]. Furanosesquiterpenoid ketones such as (±)-myoporone, dehydromyoporone, myodesmone, dehydromyodesmone, ngaione, epingaione, dehydrongaione, dehydroepingaione were detected and isolated from *M. acuminatum, M. laetum, M. tenuifolium, M. betcheanum, M. deserti, M. tetrandrum, M. crassifolium, M. bontioides* [46-48]. The oils of *M. acuminatum* were characterized by high percentage of myoporone and myodesmone. *M. betcheanum* and *M. maculatum* were rich in myoporone as the major essential oil content, the high percentage of dehydrongaione and dehydromyodesmone were detected in *M. deserti* and *M. maculatum*. Myomontanone, isomyodesmone, dehydroisomyodesmone, dehydromyodesmone, myoporone and dehydromyoporone were detected in high percentage in *M. montanum* and *M. acuminatum* [10,21,47,49]. The other sesquiterpenoid members such as crassifolone, dihydrocrassifolone and dendrolasin were also found in *M. crassifolium* [13]. The essential oil of Egyptian *M. laetum* leaves produced the highest percentage (0.23%) when collected in August [40]. it was rich in oxygenated sesquiterpene compounds including ngaione, elemicin, dehydromyoporone, myoporone and myomontanone in ratios of 79.63%, 10.74%, 1.92% 0.80% and 0.02%, respectively [39]. The alcohol sesquiterpenoids were detected in the essential oil of *M. crassifolium* inner wood and *M. montanum* leaves [40]. *M. crassifolium* yielded about 1.54% essential oil, with the major component of (-)- epi-α-bisabolol or its epimer (−)-anymol in concentration of (65.1%), bisabolol oxide isomers B1 and B2 in concentrations of 7.3% and 9.1%, respectively [10, 13, 21, 49]. While *M. montanum* was rich in 10,11-dehydromyoporum ketol (2.5%) and *Myoporum* ketol (3.6%). The essential oil of *M. deserti*, consisting mainly of furanosesquiterpene ketones (-)-ngaione, (-)-dehydrongaione, myodesmone, myoporone, (-)-epingaione, and (-)-dehydroepingaione [13, 29]. It also contains monoterpene iridoid, (1*R*)-1-methoxymyodesert-3-ene which is nontoxic to the sheep and hemiacetal esters iridoid, (+)-(1*R*)- and (-)-(1*S*)-1-acetoxymyodesert-3-ene [15, 16]. It has been stated that *M. deserti* was responsible for the severe stock poisoning and the loss of numerous sheep and cattle, despite its high nutritional value as fodder [15, 16].

4. Potential Toxicity of *Myoporum* spp.

Liver is the largest organ in the human belly consisting of two lobes and located at the right abdominal side. It is reddish-brown with rubbery touch and being enclosed by the rib cage [65,66]. The main function of the liver is associated with digestion, blood filtration, metabolism, detoxification of the body from the harmful chemicals and production of vital proteins such as albumin and others involved in blood clotting [67,68]. Hepatic disorders may arise from injury by drugs, chemicals, phytotoxins, pesticides contaminated foods and environmental pollution. The injured liver may be manifested by abdominal pain, hepatitis which is characterized by an elevation in alanine aminotransferase (ALT), alkaline phosphatase (ALP) and aspartate amino transferase (AST) levels in the blood, anorexia, nausea, fatigue, weakness, cholestasis, high bilirubin level, jaundice, icterus and itching [57,65,69-72]. So, exploring the plants risks is of great importance and is considered as significant as exploring their beneficial effects. Either to warn the populations from the hazards of their abuse, or to regulate the prescribed therapeutic doses. Additionally, the literature survey found no distinct cuts between the medicinally used plants and the toxic ones, as most of them were considered toxic with low safety index, and the toxicity may arise from the accumulation of certain metabolites by the time in the living body [73,74]. Most of the *Myoporum* essential oils are characterized by their sesquiterpenoid contents, which may be hydrocarbons or furanosesquiterpenoid ketones or alcohols. The furan-containing sesquiterpenoids are regarded as toxic phytochemicals [75-77]. The most commonly and the best known toxic furanosesquiterpenoid ketones are ngaione, epingaione, dehydrongaione, deisopropylngaione, dehydroepingaione, myomontanone, isomyomontanone, myodesmone and dehydromyodesmone. Only myoporone and its analogues were found to be less or non-toxic to the sheep. The major toxic *Myoporum* spp. with high content of furanosesquiterpenoid ketones are *M. deserti*, *M. acuminatum*, *M. montanum*, *M. tenuifolium*, *M. insulare*, *M. tetrandrum*, *M. laetum*, *M. crassifolium*, *M. bontioides* and *M. betcheanum* [46,75,78]. *Myoporum* toxicity is concerned mainly with the liver, kidney and lung, causing pulmonary oedema [4, 75, 78]. The highly toxic plant organs were the aerial parts including leaves, where the oil components are concentrated. The toxicity of Myoporum spp. is mainly attributed to the presence of ngaione (furanosesquiterpenoid ketones), which is responsible for the typical *Myoporum* toxicity signs and symptoms [78-80]. So, the *Myoporum* members which contain ngaione or its analogues are regarded as typical toxicants. The toxicity of *Myoporum* was firstly discovered and recognized when outbreaks of photosensitization and death have been developed in cattle in many Australian farms during the period (1979-1982). About 2-6 days after feeding on the nearest and hanging branches of *M. insulare*, the cattle have developed intoxication signs of photosensitization, depression, jaundice, petechia, anorexia and agalactia (failure of cows to produce milk). The severe intoxication was manifested by liver haemorrhage and necrosis with bile duct hyperplasia. When the experimental cows were tested for *Myoporum* intoxication, they have developed the same symptoms upon treatment with minced and wetted fresh leaves of *M. insulare* by oral intubation. The symptoms have been developed 72 h following intubation [79, 80]. The histopathological examination of the autopsied cows showed yellow pigmentation and necrotic liver, either in periportal, midzonal or centrilobular part. Proliferation of the bile duct was also observed, and the SGT, AST and CPK enzymes were elevated [78-80]. In case of *M. deserti and M. acuminatum*, the symptoms of toxicity were developed 24 h following the feeding of the experimental cattle, while death occurred within 48 h after consumption [81, 82]. The degree of intoxication depending mainly on the furanosesquiterpenoid contents as well as the activity of liver microsomal mixed-function oxygenase enzymes (MMFO) during the consumption time of grazing plants, which in turn may be influenced by nutritional style of the animal [75, 76, 83]. So, intoxication may be fully or partially reduced upon inactivation of this enzyme by pretreatment with inhibitors [63, 76, 84]. Upon enhancement of liver MMFO, the toxicity may be periportal rather than centrilobular lesions [83]. From the literature survey, certain *Myoporum* spp. were considered extremely toxic, for example, the two varieties of *M. deserti* (Jackson & Theodore) were classified as livestock-poisoning due to their major toxic furanosesquiterpenoid ketones; (-)-ngaione, (-)-epingaione, (-)-dehydrongaione, and (-)-dehydroepingaione [29]. This toxicity was estimated by the histopathological examination of the liver and renal lesions, of the intraperitoneally injected mice with these individual sesquiterpenoid ketones [29]. Additionally, *M. laetum* was regarded as totally toxic plant; it causes liver injury associated with thrombosis after being consumed by cattle due to the high ngaione content [85]. The toxicity of which

has been considered at the early stages of the last century, it was observed that when the livestock (horses, cattle, pigs and sheep) tend to feed on the leaves of hanging branches of *M. laetum*, severe fatal toxicity have been developed in most cases and manifested by photosensitivity, liver damage, jaundice and icterus [86-88]. Moreover, the essential oil *M. tetrandrum* was categorized as toxic as *M. deserti* due to the presence of dehydrongaione (78%) and ngaione (7%) as the main contents, its toxicity was manifested by liver damage with extensive haemorrhagic centrilobular necrosis in calves [29,83], associated with pulmonary edema in most cases [83]. With the exception of some furanosesquiterpenoids, Blackburne 1972 has reported myoporone and its derivatives as nontoxic metabolites to the sheep if orally consumed [89]. Only the I.P. injected mice with myoporone or its analogues showed ngaione-like toxicity while sheep didn't [89]. *M. montanum* was found to be rich in toxic furanosesquiterpenoids which are livestock poisoning. Owing to the fact that toxic furanoid members are degraded at temperature higher than 20 °C and its aqueous extract contains only (±)-Myoporone (-)-10,11-dehydromyoporone and 11-hydroxymyoporone which are benign and non-toxic to the sheep [20], the infusion-prepared tea of which has been applied safely in folk medicine by the aborigines in treatment of skin infection, otitis and dermatitis topically, and in gastritis and respiratory system orally [20].

4.1. Mechanism of Myoporum Toxicity

Furanosesquiterpenoid derivatives are nearly distributed in all *Myoporum* spp. as per the literature survey. The ketone type sesquiterpenes are believed to cause renal injury and pulmonary lesions in mice by direct tubular toxicity (Figure 2), as reported by Ogunsan 2012 for Deisopropylngaione (DIN) [90,91]. Dongju and Weiwei 2016 have proven that the presence of furan moiety in certain phytochemicals such as 8-epidiosbulbin E acetate induces hepatotoxicity [92,93]. Weiwei concluded that, the furanoid diosbulbin B (DIOB) compound which is the main phytochemical of *Dioscorea bulbifera* produced liver damage in humans and experimental animals, while the same hydrogenated tetrahydrofuran moiety of DIOB hasn't developed any toxicity. Consequently, Weiwei suggested that liver injury is attributed to the presence of furan moiety, which can be converted into reactive toxic metabolites by the cytochrome P450 3A enzymes [93]. Additionally, WU claimed that furan ring is necessary for induction of toxicity through the oxidation step by cytochrome P450 to form the reactive intermediate, which causing the toxic effects [94, 95]. Consequently, the furanosesquiterpenoids of *Myoporum* were supposed to induce their toxicity by the same mechanism [96-97].

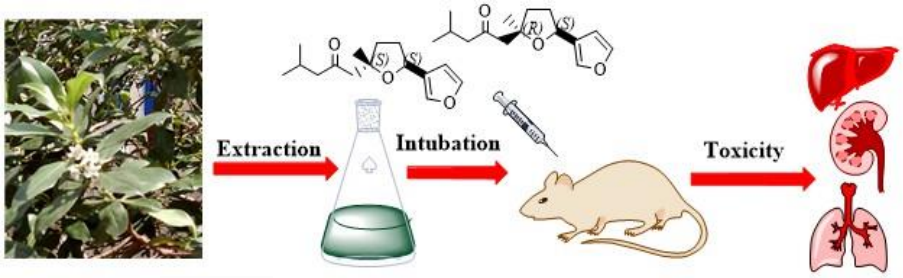

Figure 2. *in vivo* furanosesquiterpenoid toxicity of *Myoporum* spp.

5. Conclusion

It has become apparent that the application of plants in folk medicine is not always safe and must be cautiously used. All furanosesquiterpenoid-containing *Myoporum* are regarded as potentially toxic plants and can induce ngaione-like symptoms and toxicity, except myoporone and its analogues.

Most of Myoporaceous plants, particularly those of genus *Myoporum* are categorized as liver, kidney and lung poisoning plants due to their furanosesquiterpenoid contents. About 32 *Myoporum* spp. were reported in literature, most of them haven't been resolved yet in the plant list; a standard website for listing all plant spp. Additionally, some of these species haven't been fully studied, and the investigation concerning their toxic profile is strongly recommended to save the livestock. Despite the severe toxicity of most *Myoporum* spp., their aqueous extract can be safely applied in folk medicine for the treatment of several diseases if prepared by infusion. Finally, the use of natural remedies doesn't convey a guarantee of safety.

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Conflict of interest

The author declares that there is no conflict of interest.

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