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Infarma CIÊNCIAS FARMACÊUTICAS

Revisão

A Review of the Phytochemical Properties and Pharmacological Uses of the Genus *Pistacia* L. (Anacardiaceae)

Uma revisão sobre as propriedades fitoquímicas e os usos farmacológicos do gênero Pistacia *L. (Anacardiaceae)*

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ABSTRACT

The *Pistacia* genus belongs to the Anacardiaceae family is made up of about twenty species, with the most common including *P. atlantica, P. chinensis, P. integerrima, P. khinjuk, P. lentiscus, P. terebinthus, P. vera,* and *P. weinmanifolia*. Various parts of these different species have been found to be rich in many phytochemical compounds, including essential oil constituents, monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids, tetraterpenoids, flavonoids, phenolic compounds, tannins, fatty acids, steroids, and miscellaneous compounds. Published literature has revealed many pharmacological uses for various species. The most studied plant parts in terms of chemical composition were leaves, with 36%, followed by fruits, with 19%. These uses include antioxidant effects, hepatoprotection, anti-inflammatory effects, antimicrobial effects, wound healing/analgesic properties, anticancer properties, digestive aid, and treatment of various chronic conditions. After the full investigation on this genus, the phytochemical properties and pharmacological uses of nine Pistacia species are outlined in this comprehensive literature review.

Keywords: *Pistacia;*antioxidant; anti-inflammatory; antimicrobial; flavonoid; monoterpenoid.

RESUMO

O gênero *Pistacia* pertence à família Anacardiaceae e é composto por cerca de vinte espécies, sendo as mais comuns *P. atlantica*, *P. chinensis*, *P. integerrima*, *P. khinjuk*, P. *lentiscus*, *P. terebinthus*, *P. vera* e *P. weinmanifolia*. Várias partes dessas diferentes espécies são ricas em importantes compostos

fitoquímicos, incluindo constituintes de óleo essencial, monoterpenoides, sesquiterpenoides, diterpenoides, triterpenoides, tetraterpenoides, flavonoides, compostos fenólicos, taninos, ácidos graxos, esteroides e outros compostos. A literatura publicada revelou muitos usos farmacológicos para várias espécies. As partes das plantas mais estudadas quanto à composição química foram as folhas, com 36%, seguidas dos frutos, com 19 %. Esses usos incluem efeitos antioxidantes, hepatoproteção, efeitos anti-inflamatórios, efeitos antimicrobianos, propriedades cicatrizantes/analgésicas, propriedades anticancerígenas, digestivo e tratamento de várias condições crônicas. Após a investigação completa sobre este gênero, as propriedades fitoquímicas e usos farmacológicos de nove espécies de *Pistacia* foram descritas nesta abrangente revisão da literatura.

Palavras-chave: *Pistacia*; antioxidante; anti-inflamatório; antimicrobiano; flavonoide; monoterpenoide.

INTRODUÇÃO

The *Pistacia* genus, part of the Anacardiaceae family, is made up of about twenty species of flowering shrubs and small trees that range from 5 to 15 meters in height. Depending on the species, they can be evergreen or deciduous; all species are dioecious. Common *Pistacia* species include *P. atlantica* Desf., *P. chinensis* Burge, *P. integerrima* J.L. Stewart ex. Brandis, *P. khinjuk* Stocks, *P. lentiscus* L., *P. terebinthus* L., *P. vera* L., and *P. weinmanifolia* J. Poisson ex. Franch. The genus is native to north Africa, central Asia, Middle Eastern and Mediterranean regions (1). *Pistacia* is traditionally used for food, medicinal, and ornamental purposes (2).

Our review provides a comprehensive look at the phytochemical compounds isolated from these plants and the pharmacological uses of the genus *Pistacia*, with a focus on literature published between 2000 and 2022 via a literature search using the database ScienceDirect. A total of 207 papers were evaluated in this literature review.

PHYTOCHEMISTRY

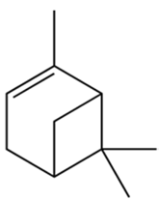
From the literature review, a total of 302 chemical compounds have been identified or isolated from different species of the genus *Pistacia*. These are summarized below in Table 1 and Figure 1. According to the literature, the most common method used to identify phytochemicals from the genus *Pistacia*, notably from its essential oils, was gas chromatography-mass spectroscopy (GC-MS). Phytochemicals were also isolated from various parts of the plants, including leaves (36%), fruits (19%), resin (12%), hulls (5%), aerial parts (5%), nuts (4%), galls (4%), leaf-buds (3%), bark (2%), stems (2%), young shoots (2%), flowers (2%), twigs (2%), and branches (2%).

Table 1. List of compounds identified/isolated from various species of the genus Pistacia.

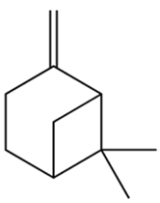
Species	Numbers of Compounds Isolated
P. atlantica	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 209, 210, 234, 235, 236, 243, 244, 250, 251, 252, 253, 254, 264, 267, 269, 278, 279, 280, 281
P. chinensis	3, 85, 134, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 193, 255, 256, 280, 284
P. eurycarpa	1, 118, 211, 212, 270
P. integerrima	128, 129, 132, 134, 136, 149, 150, 151, 152, 153, 154, 155, 156, 193, 213, 237, 245, 271, 280, 283
P. khinjuk	1, 2, 8, 14, 16, 29, 30, 46, 52, 56, 63, 64, 65, 132, 143, 144, 193, 196, 234, 236, 255, 256, 264, 286
P. lentiscus	1, 2, 8, 11, 13, 14, 16, 18, 19, 22, 27, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 48, 53, 56, 58, 62, 63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 85, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 119, 126, 128, 132, 133, 134, 136, 138, 143, 144, 145, 157, 158, 159, 160, 161, 162, 163, 164, 165, 193, 194, 197, 198, 203, 205, 206, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 235, 236, 240, 241, 242, 246, 251, 252, 255, 256, 257, 258, 264, 265, 266, 267, 268, 269, 272, 273, 278, 279, 280, 282, 287, 288, 289, 293
P. terebinthus	1, 2, 8, 10, 11, 18, 22, 34, 39, 40, 41, 42, 43, 44, 46, 48, 83, 84, 120, 121, 126, 127, 132, 134, 136, 166, 167, 168, 169, 170, 171, 193, 202, 264, 265, 267, 269, 272, 287, 290, 291, 292, 294
P. vera	1, 2, 8, 12, 13, 14, 17, 18, 26, 34, 36, 38, 43, 44, 117, 120, 121, 122, 123, 124, 126, 128, 129, 131, 132, 133, 134, 135, 136, 138, 143, 145, 150, 163, 164, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 195, 207, 208, 214, 227, 228, 229, 230, 231, 232, 233, 247, 248, 249, 258, 259, 263, 264, 265, 266, 267, 268, 269, 270, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 285, 286, 287, 288, 290, 291, 292, 295, 296, 297, 298, 299, 300, 301, 302
P. weinmannifolia	1, 260, 261, 262

Figure 1. Identified/isolated compounds from species of *Pistacia genus* (Anacardiaceae)

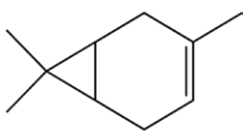
Essential Oil Constituents, Monoterpenoids, and Sesquiterpenoids



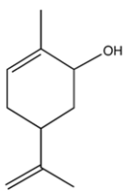
α-Pinene(1)



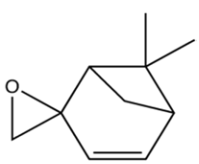
β-Pinene (2)



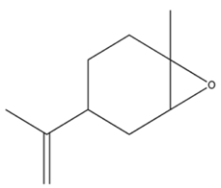
Δ^3-Carene (3)



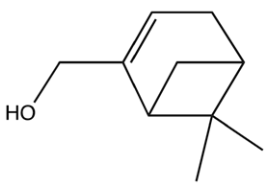
Carveol (4)



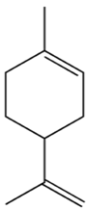
Epoxypinene (5)



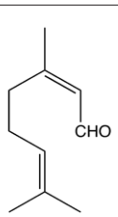
Limonene oxide (6)



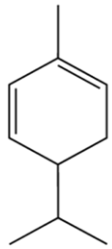
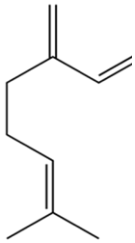
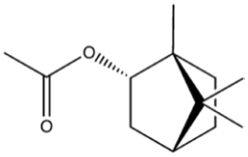
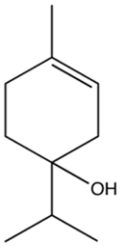
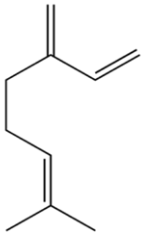
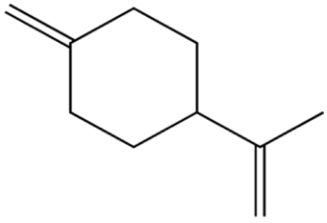
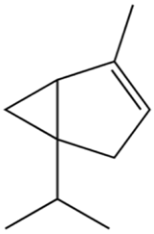
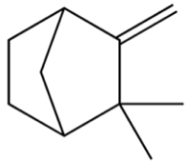
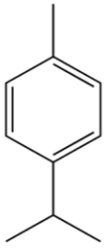
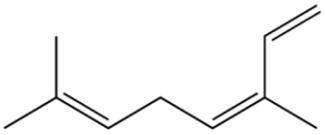
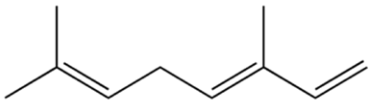
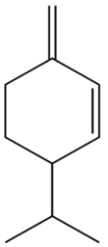
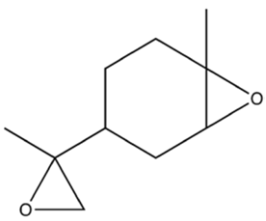
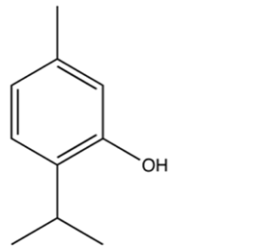
Myrtenol (7)

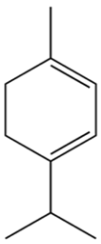
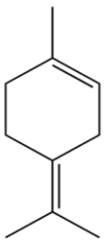
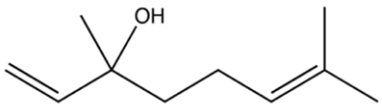
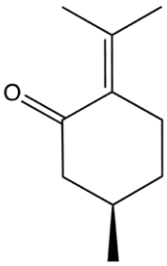
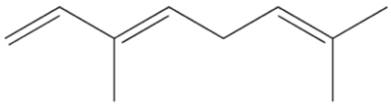
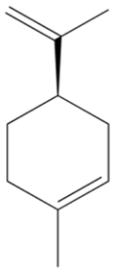
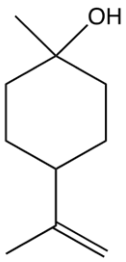
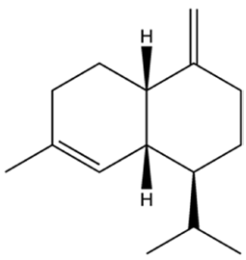
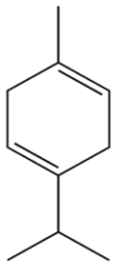
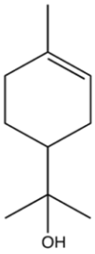
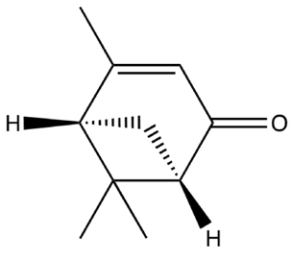
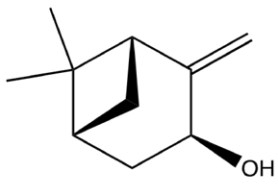
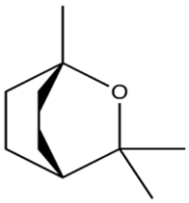
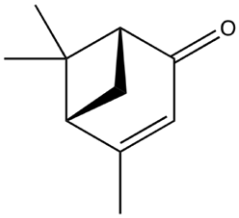
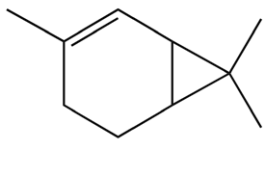


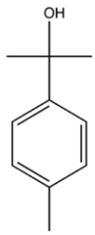
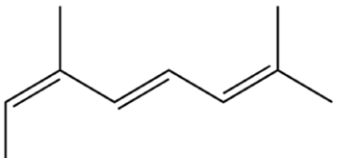
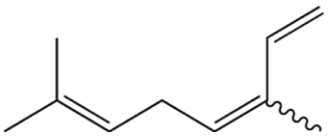
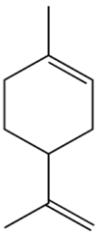
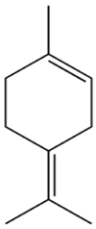
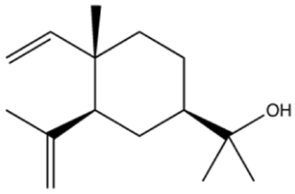
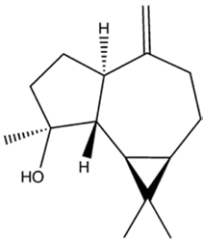
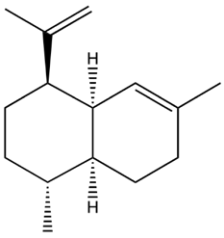
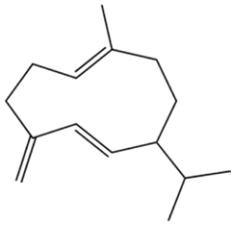
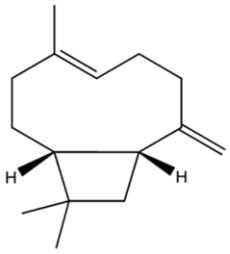
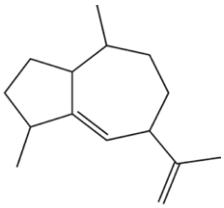
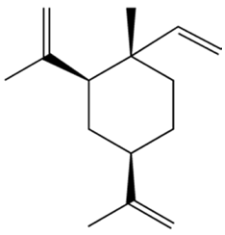
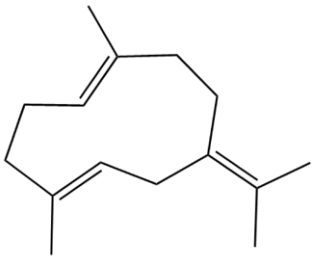
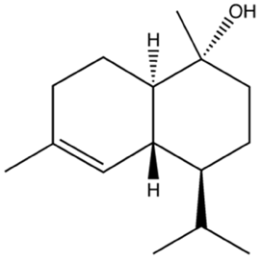
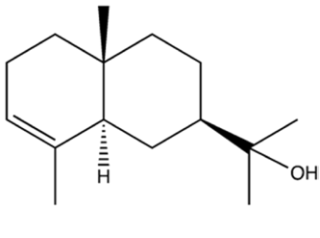
Limonene (8)

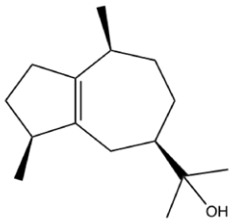
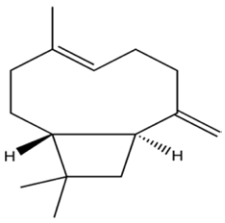
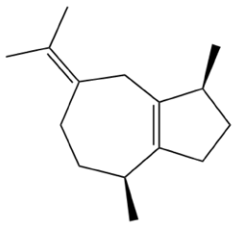
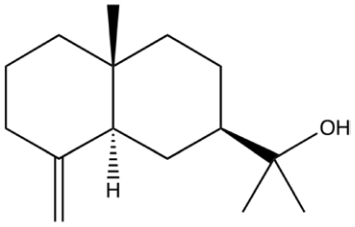
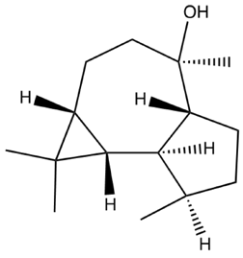
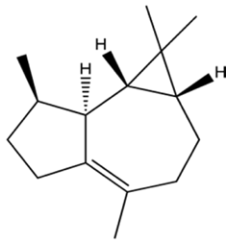
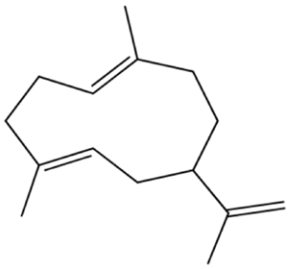
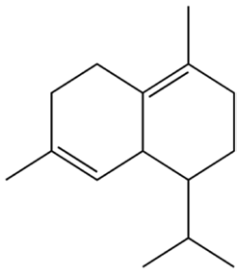
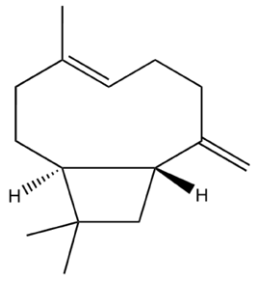
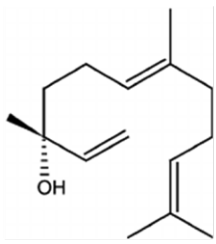
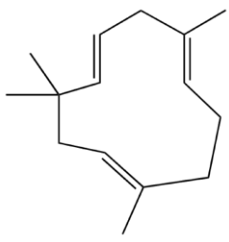
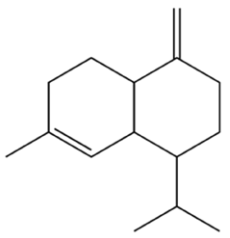
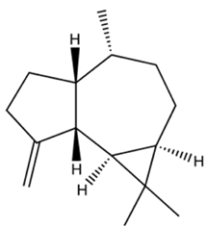
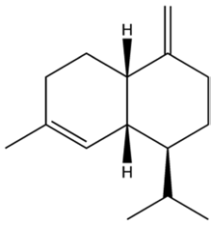
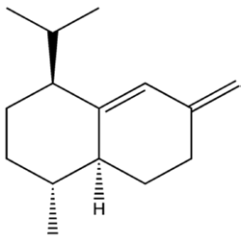


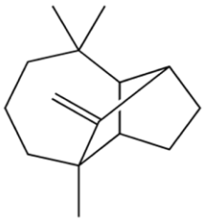
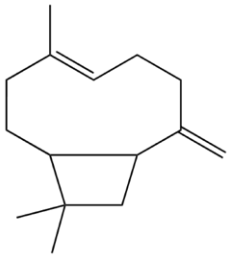
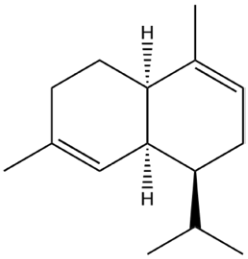
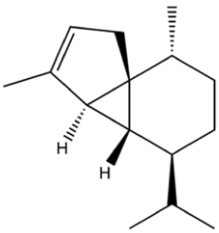
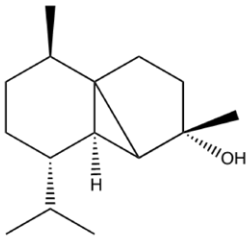
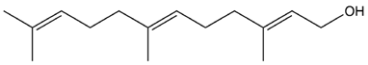
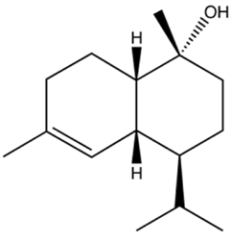
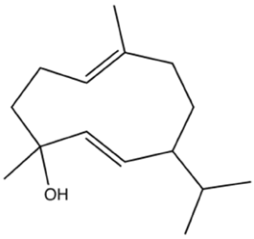
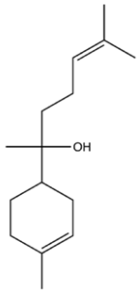
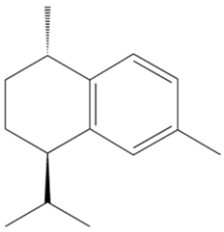
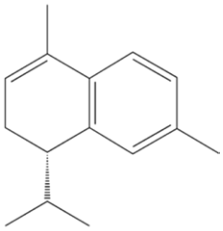
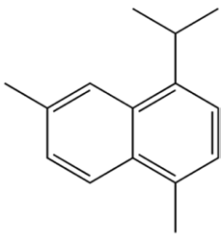
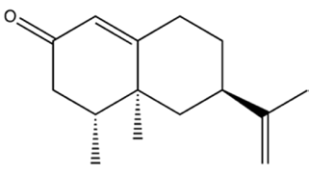
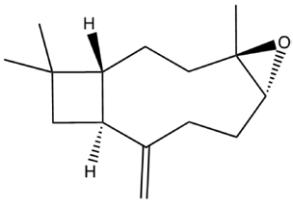
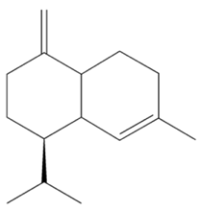
Citral (9)

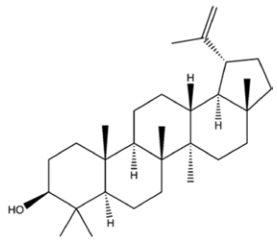
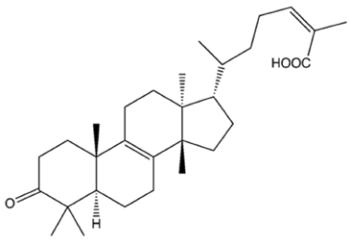
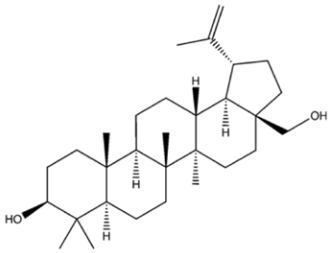
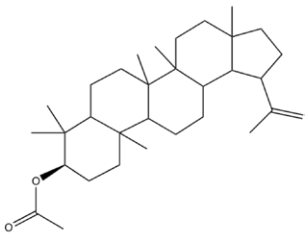
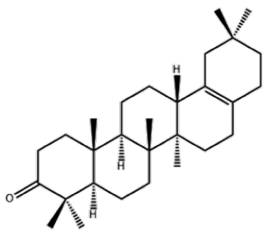
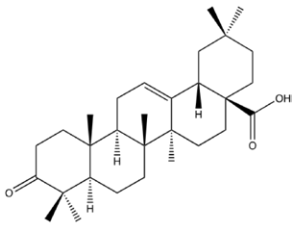
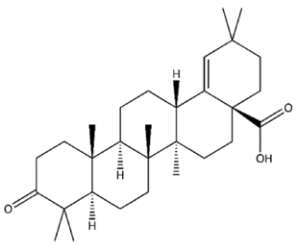
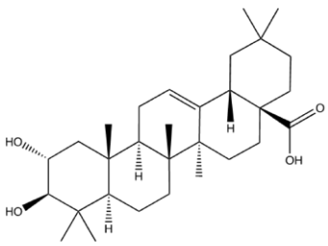
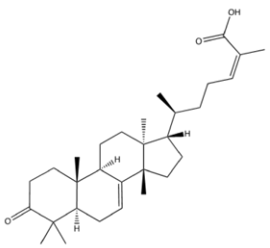
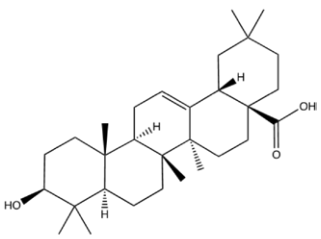
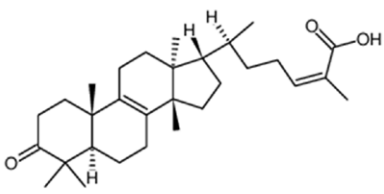
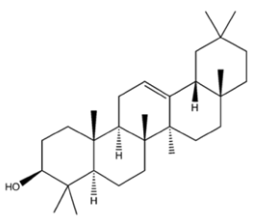
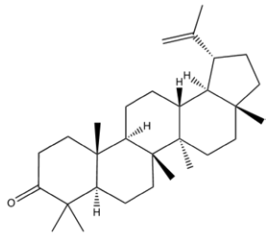
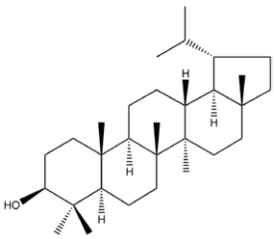
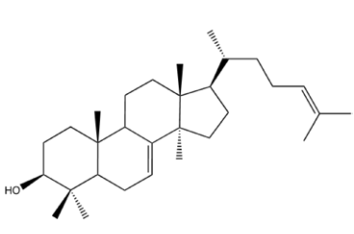
		
α-Phellandrene (10)	β-Myrcene (11)	Bornyl acetate (12)
		
Terpinen-4-ol (13)	Myrcene (14)	p-Mentha-1(7),8-diene (15)
		
Sabinene (16)	α-Thujene (17)	Camphene (18)
		
p-Cymene (19)	cis-Cimene (20)	trans-Ocimene (21)
		
β-Phellandrene (22)	Limonene dioxide (23)	Thymol (24)

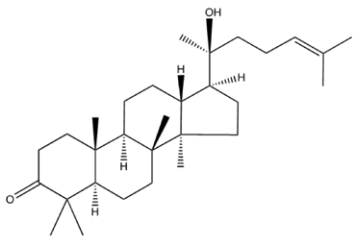
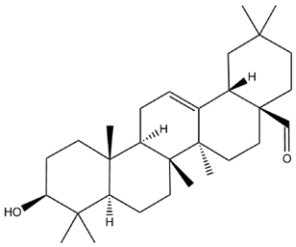
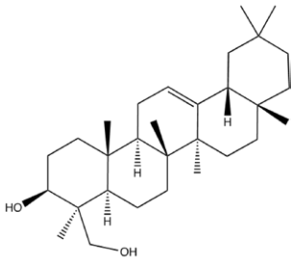
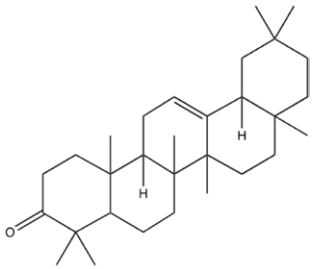
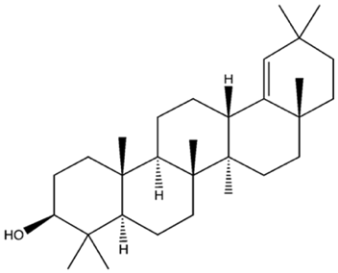
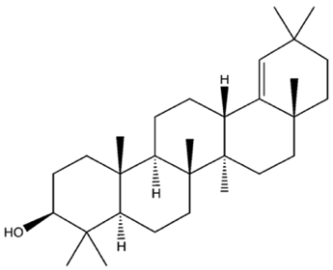
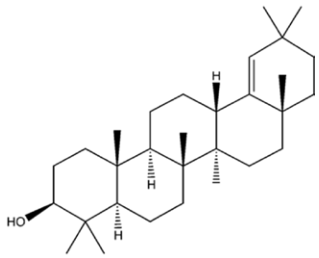
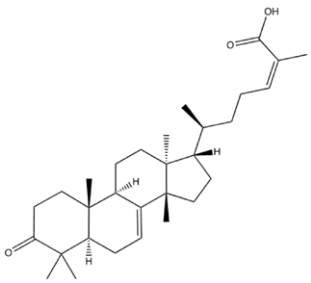
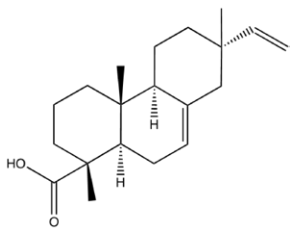
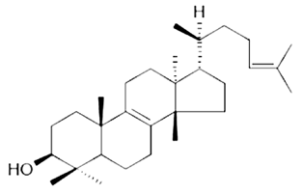
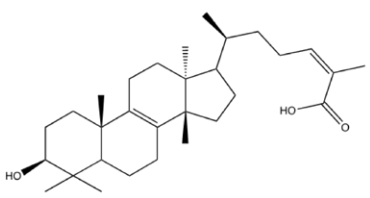
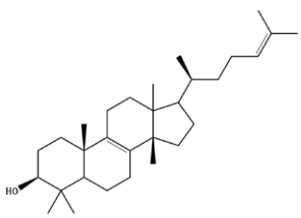
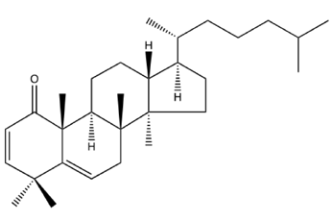
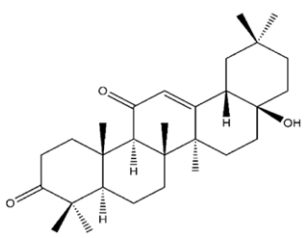
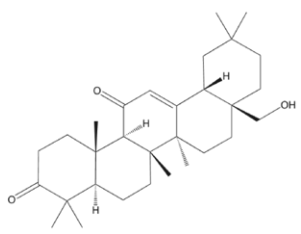
		
α-Terpinene (25)	α-Terpinolene (26)	Linalool (27)
		
Pulegone (28)	trans-β-Ocimene (29)	D-Limonene (30)
		
trans-β-Terpineol (31)	γ-Muurolene (32)	γ-Terpinene (33)
		
α-Terpineol (34)	Verbenone (35)	trans-Pinocarveol (36)
		
1,8-Cineole (37)	trans-Verbenol (38)	2-Carene (39)

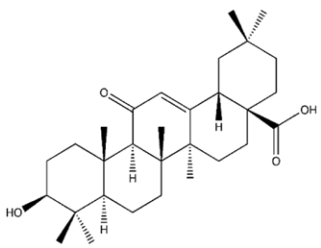
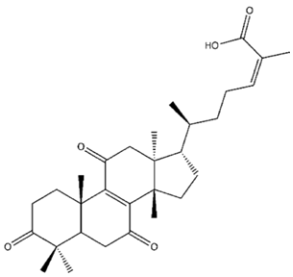
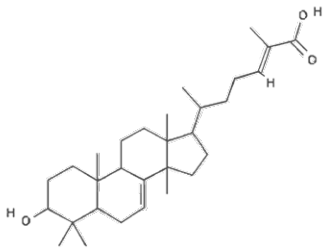
		
p-Cymen-8-ol (40)	allo-Ocimene (41)	β-Ocimene (42)
		
d,l-Limonene (43)	Terpinolene (44)	Elemol (45)
		
Spathulenol (46)	γ-Amorphene (47)	Germacrene D (48)
		
(E)-2-epi-β-Caryophyllene (49)	γ-Gurjunene (50)	β-Elemene (51)
		
Germacrene B (52)	α-Cadinol (53)	α-Eudesmol (54)

		
Guaiol (55)	(–)-β-Caryophyllene (56)	β-Guiaiene (57)
		
β-Eudesmol (58)	Globulol (59)	Ledene (60)
		
Germacrene A (61)	δ–Cadinene (62)	(+)-β-Caryophyllene (63)
		
D-Nerolidol (64)	α-Humulene (65)	γ-Cadinene (66)
		
β-Gurjunene (67)	Muurolene (68)	Epi-Bicyclosesquiphellandrene (69)

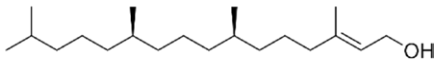
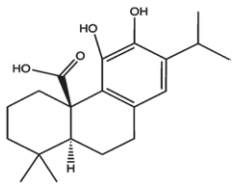
		
Longifolene (70)	β-Caryophyllene (71)	α-Amorphene (72)
		
α-Cubebene (73)	Cubebol (74)	Farnesol (75)
		
Cedreanol (76)	Germacrene D-4-ol (77)	α-Bisabolol (78)
		
trans-Calamenene (79)	α-Calacorene (80)	Cadalene (81)
		
Nootkatone (82)	Caryophyllene oxide (83)	δ-Muurolene (84)

Triterpenoids		
		
Lupeol (85)	Pistagremic acid (86)	Betulin (87)
		
Lup-20(29)-en-3-ol, acetate, (3.beta.) (88)	28-Norolean-17-en-3-one (89)	Oleanonic acid (90)
		
Moronic acid (91)	maslinic acid (92)	Masticadienonic acid (93)
		
Oleanolic acid (94)	(iso)-Masticadienonic acid (95)	β-amyrin (96)
		
Lupenone (97)	Lupanol (98)	Butyrospermol (99)

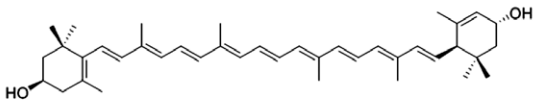
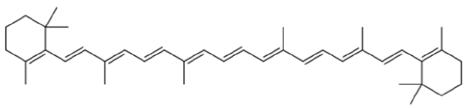
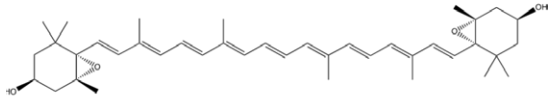
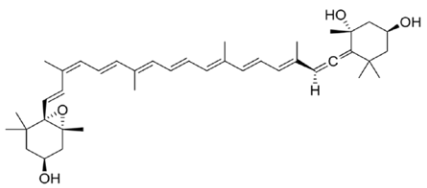
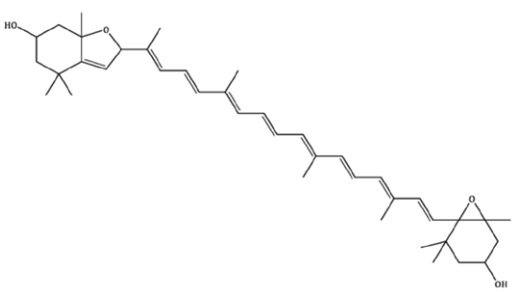
		
Dipterocarpol (100)	Oleanolic aldehyde (101)	-β-amyrone (102)
		
β-Amyrone (103)	Germanicol (104)	Betulonal (105)
		
Lup-20(29)-ene-3-one (106)	24-Z-Masticadienonic acid (107)	Isopimaric acid (108)
		
24-Z-Masticadienolic acid (109)	24-Z-Isomasticadienolic acid (110)	Tirucallol (111)
		
Dammaradienone (112)	3,11-Dioxo-28-norolean-12-en-17-ol (113)	Krukovine A (114)

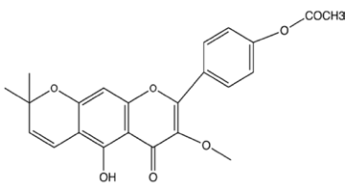
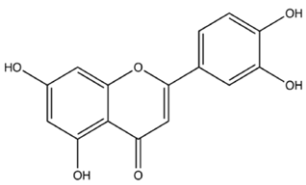
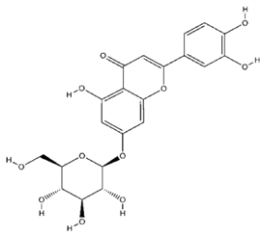
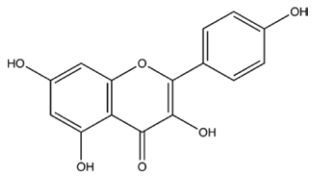
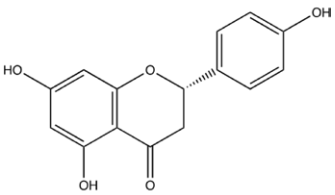
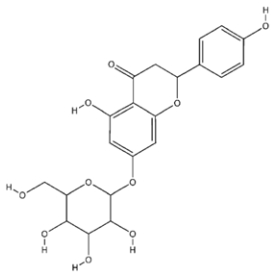
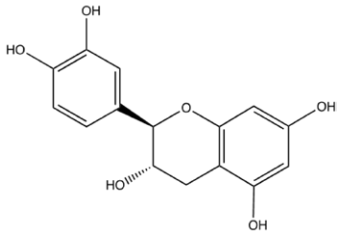
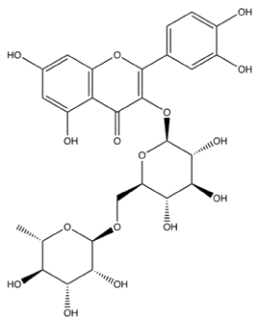
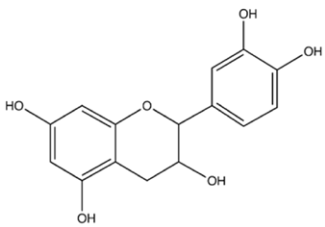
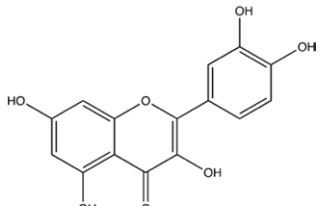
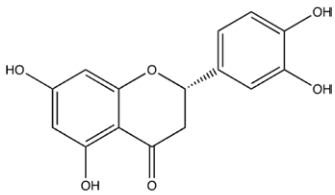
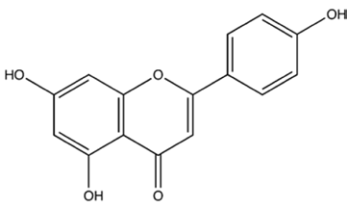
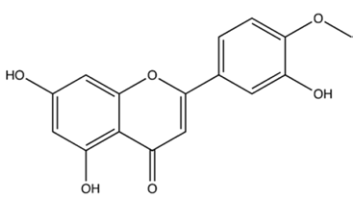
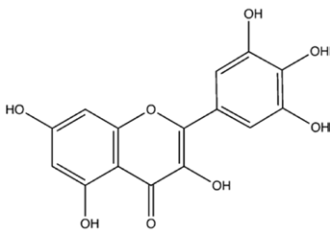
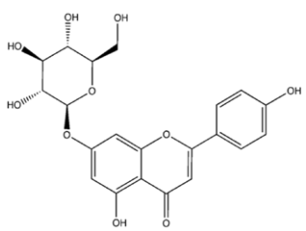
		
3β-Hydroxy-11-oxo-olean-12-en-28-oic acid (115)	3,7,11-Trioxo-8,24(Z)-tirucalladien-26-oic acid (116)	3-Epimasticadienolic acid (117)

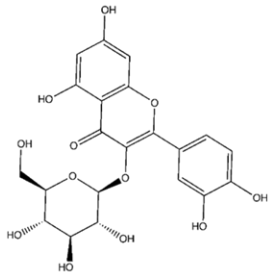
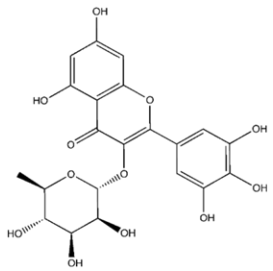
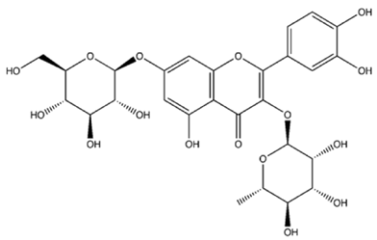
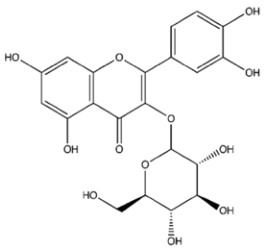
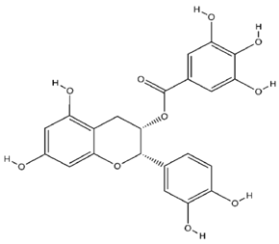
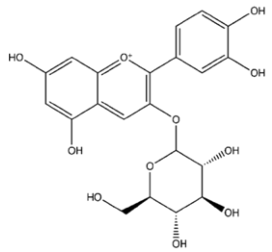
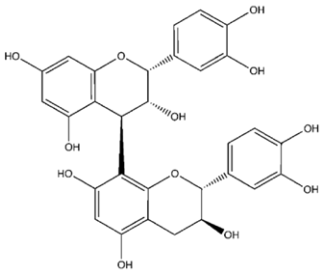
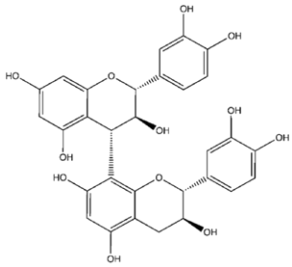
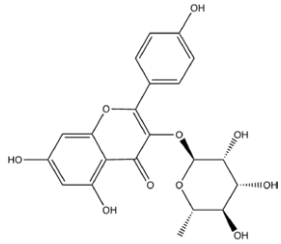
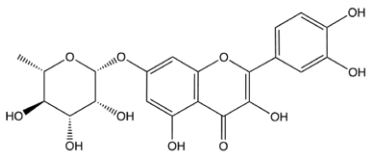
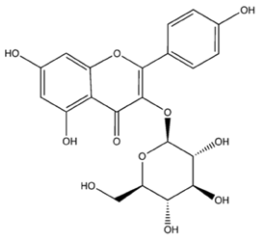
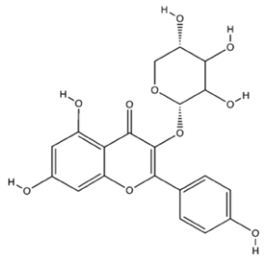
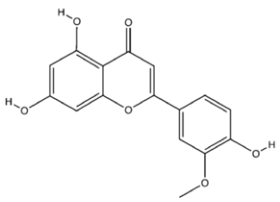
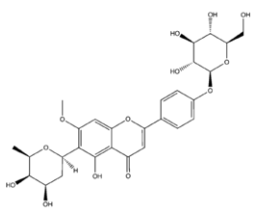
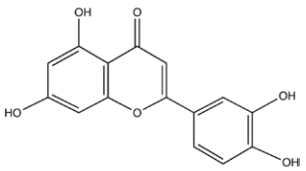
Diterpenoids

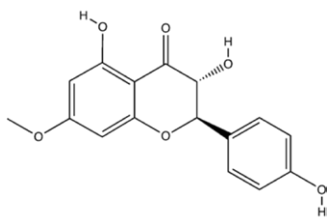
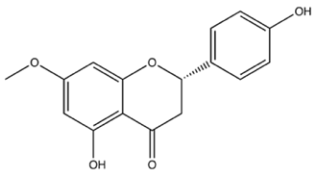
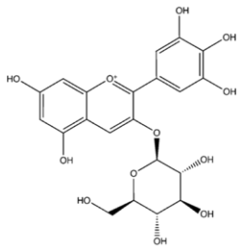
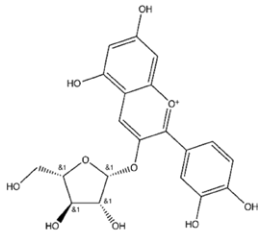
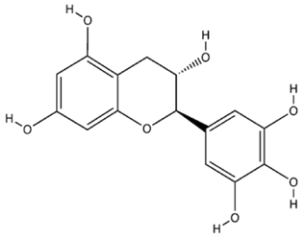
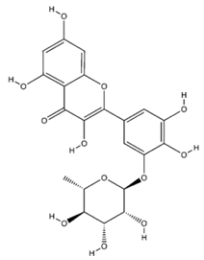
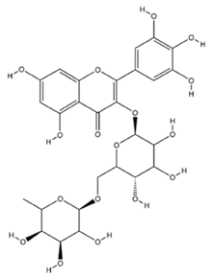
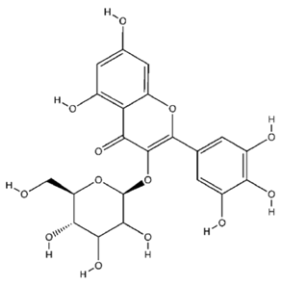
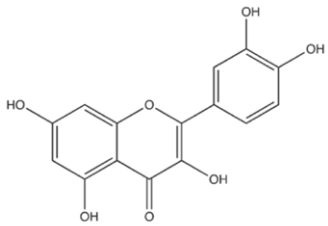
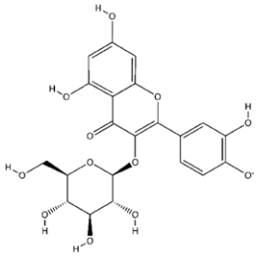
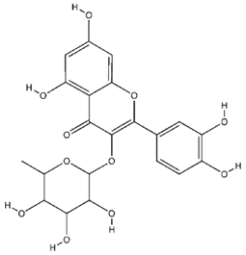
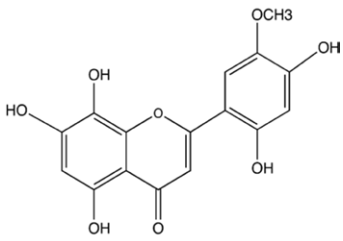
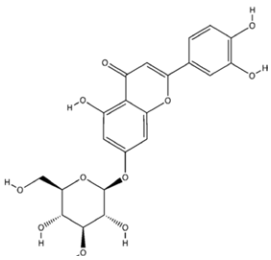
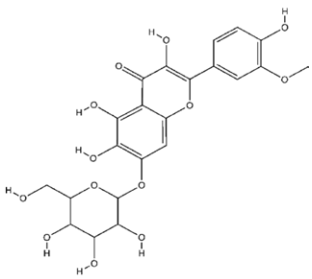
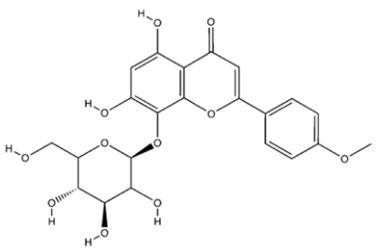
	
Phytol (118)	Carnosic acid (119)

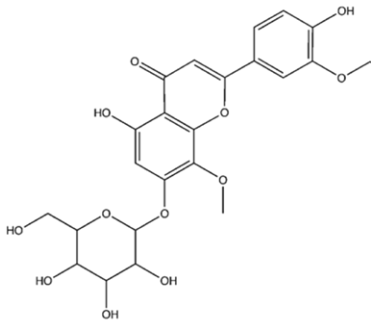
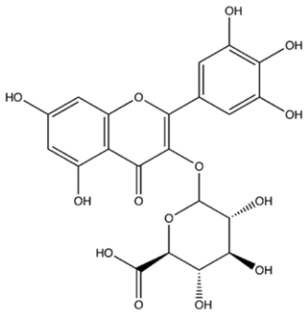
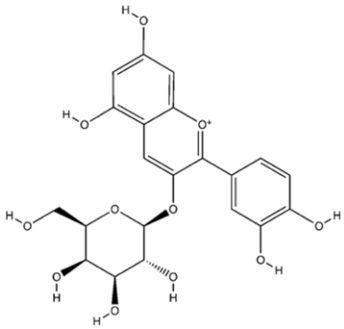
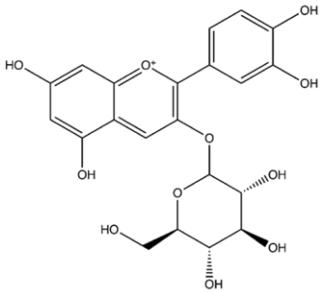
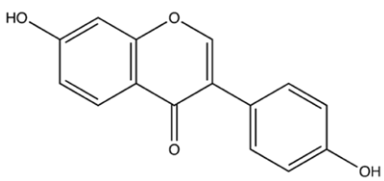
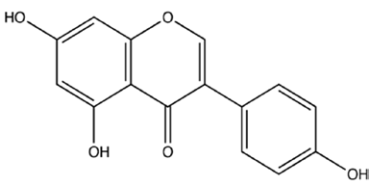
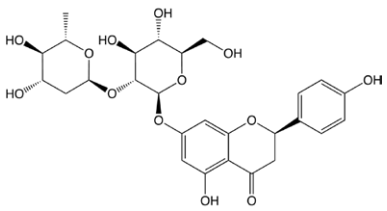
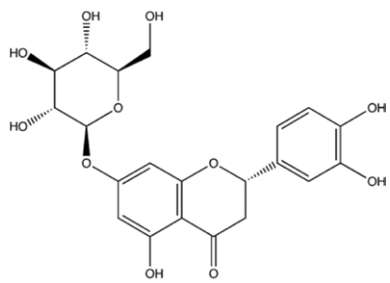
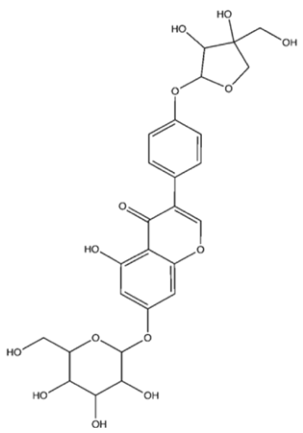
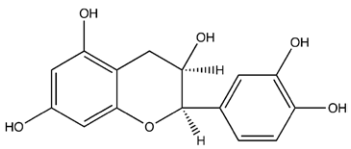
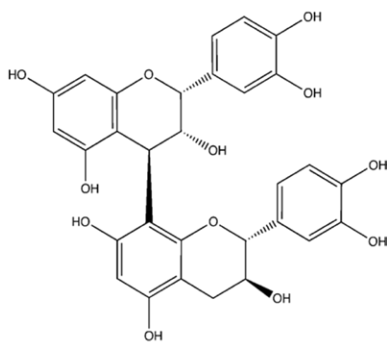
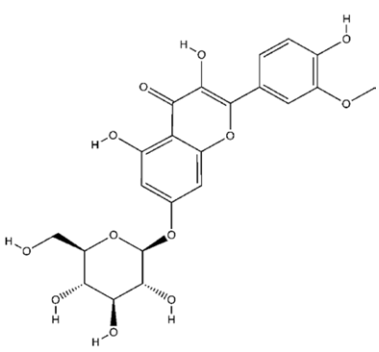
Tetraterpenoids

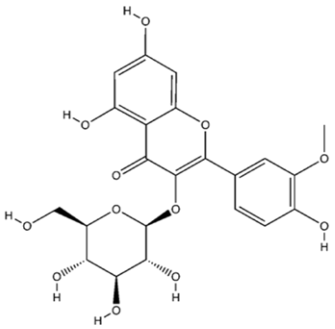
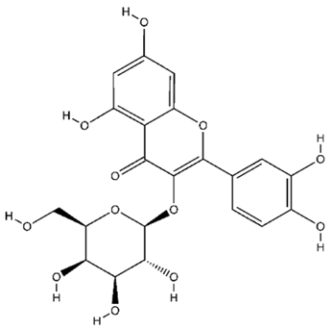
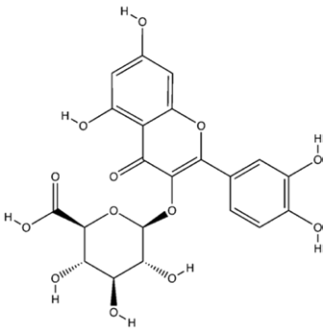
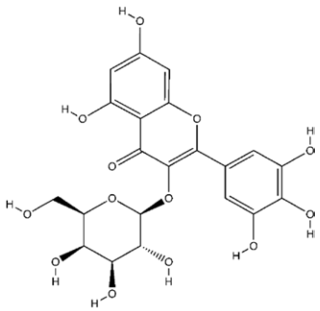
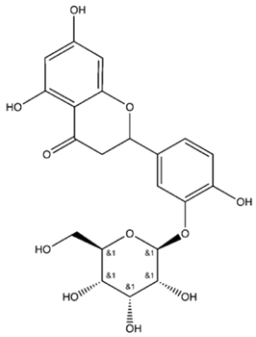
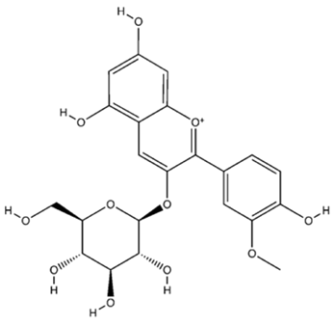
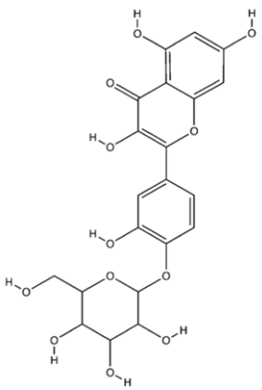
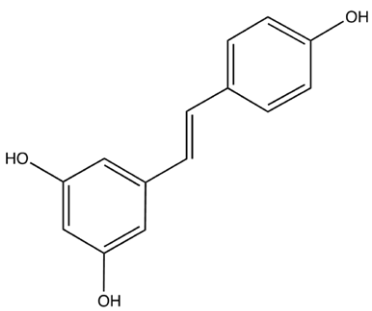
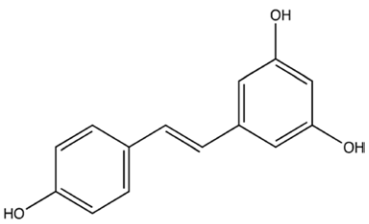
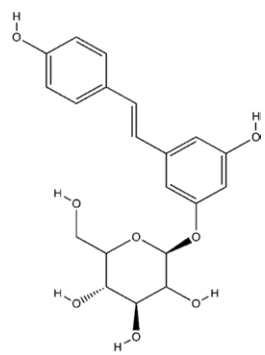
	
Lutein (120)	β-Carotene (121)
	
Violaxanthin (122)	Neoxanthin (123)
	
Luteoxanthin (124)	

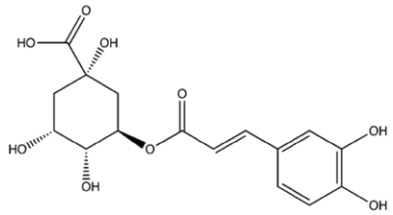
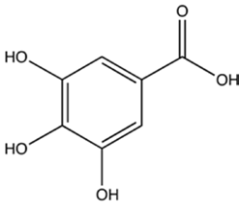
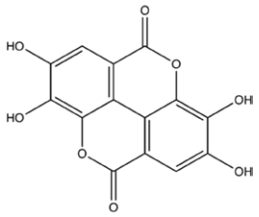
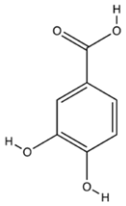
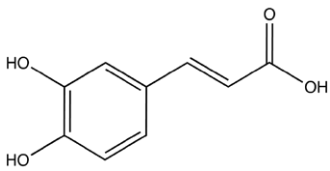
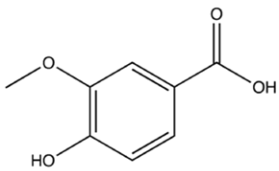
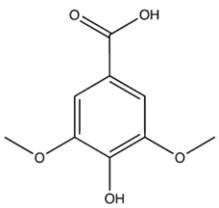
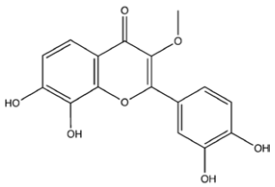
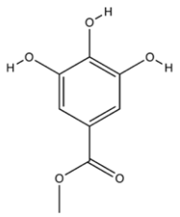
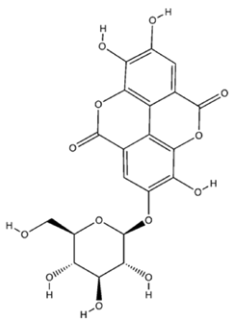
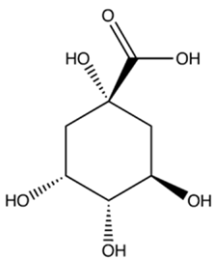
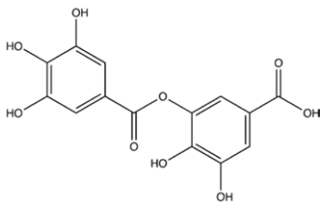
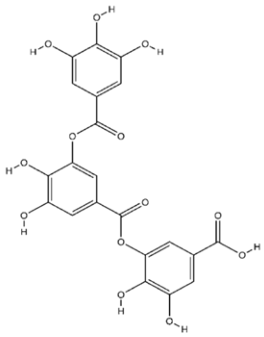
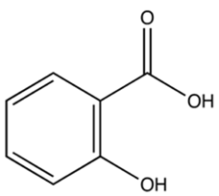
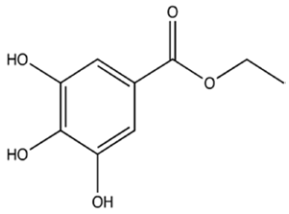
Flavonoids		
		
Carpachromene (125)	Luteolin (126)	Luteolin-7-glucoside (127)
		
Kaempferol (128)	Naringenin (129)	Naringenin 7-glucoside (130)
		
(+)-Catechin (131)	Rutin (132)	Catechin (133)
		
Quercetin (134)	Eriodictyol (135)	Apigenin (136)
		
Diosmetin (137)	Myricetin (138)	Apigenin 7-O-β-glucoside (139)

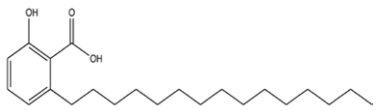
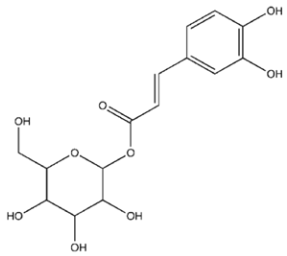
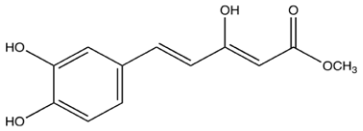
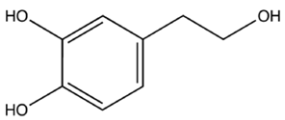
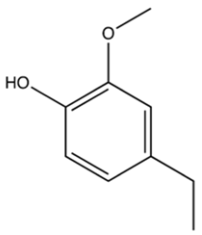
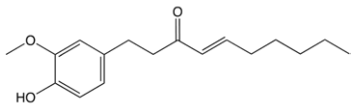
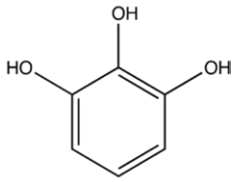
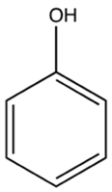
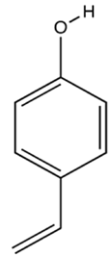
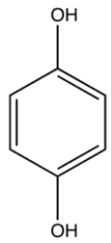
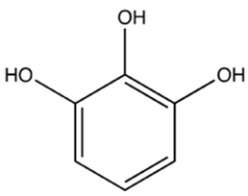
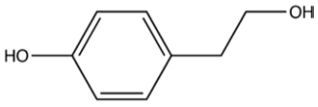
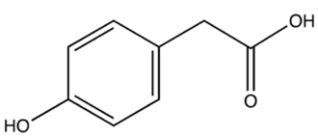
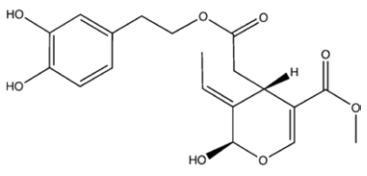
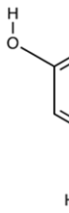
		
Quercetin 3-O-β-glucoside (140)	Myricetin 3-O-α-rhamnoside (141)	Quercetin 3-O-glucoside-7-O-rhamnoside (142)
		
Quercetin 3-O-glucoside (143)	Epicatechin-3-gallate (144)	Cyanidin-3-O-glucoside (145)
		
Procyanidin B1 (146)	Procyanidin B3 (147)	Afzelin (148)
		
Quercetin 7-O-β-L-rhamnopyranoside (149)	Kaempferol-3-O-β-d-glucoside (150)	Kaempferol-3-O-(4"-O-galloyl)-α-l-arabinopyranoside (151)
		
Chrysoeriol (152)	Diandraflavone A (153)	3',5,7,4'-Tetrahydroxy-flavanone (154)

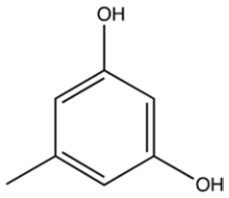
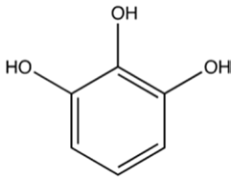
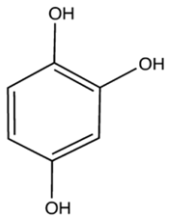
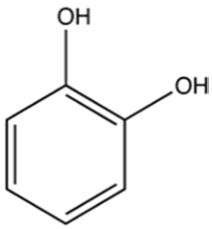
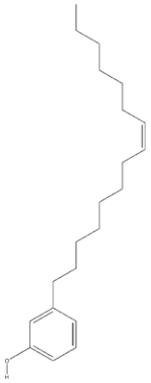
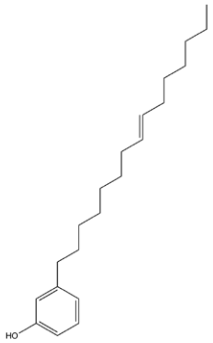
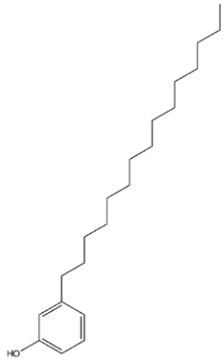
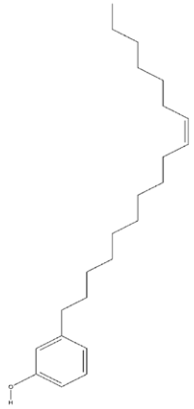
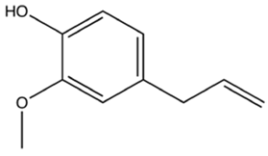
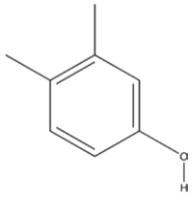
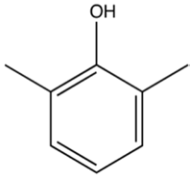
		
3,5,4'-Trihydroxi-7-methoxy-flavanone (155)	Sakuranetin (156)	Delphinidin-3-O-glucoside (157)
		
Cyanidin-3-O-arabinoside (158)	D-Gallocatechin (159)	Myricetin-rhamnoside (160)
		
Myricetin-rutinoside (161)	Myricetin-glucoside (162)	Quercetin Derivative (163)
		
Quercetin-glucoside (164)	Quercetin-rhamnoside (165)	6'-Hydroxyhypolaetin 3'-methyl ether (166)
		
Luteolin-7-glucoside (167)	Quercetagetin 3-methyl ether 7-O-glucoside (168)	Isoscutellarein 8-O-glucoside (169)

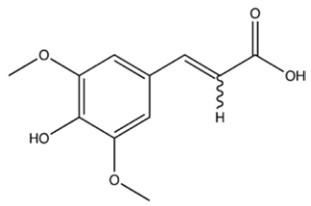
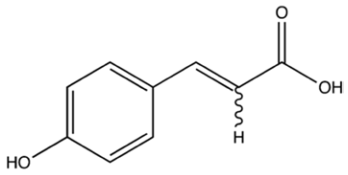
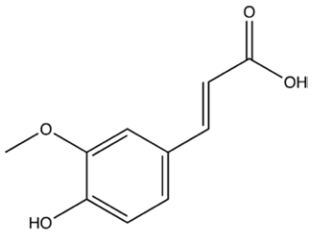
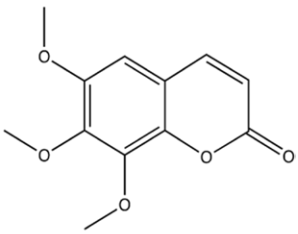
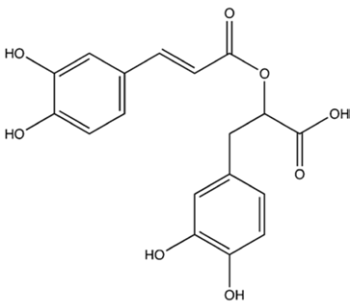
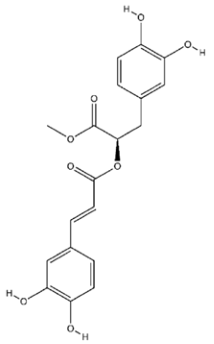
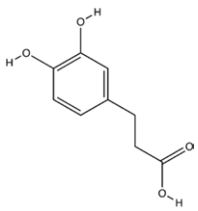
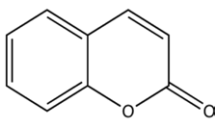
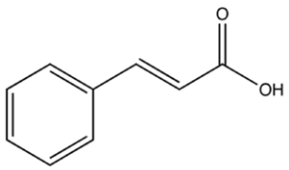
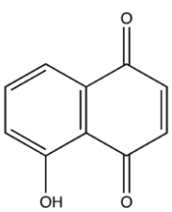
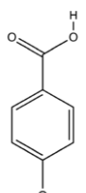
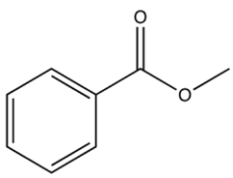
		
Apigenin-7-glucoside (170)	Myricetin-O-glucoronide (171)	Cyanidin-3-galactoside (172)
		
Cyanidin-3-glucoside (173)	Daidzein (174)	Genistein (175)
		
Naringenin-7-O-neohesperidoside (176)	Eriodictyol-7-O-glucoside (177)	Genistein-7-O-glucoside (178)
		
Epicatechin (179)	Procyanidin dimer (180)	Isorhamnetin-7-O-glucoside (181)

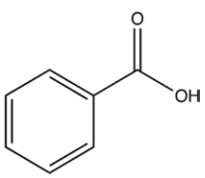
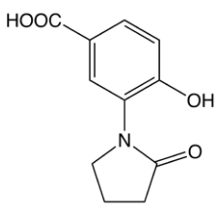
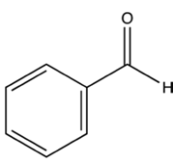
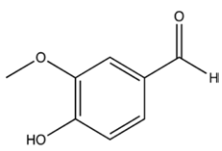
		
Isorhamnetin-3-O-glucoside (182)	Quercetin-3-O-galactoside (183)	Quercetin 3-O-glucuronide (184)
		
Myricetin 3-O-galactoside (185)	Eriodictyol-3-O-glucoside (186)	Peonidin-3-glucoside (187)
		
Quercetin-4'-glucoside (188)	Resveratrol (189)	Trans-resveratrol (190)
		
Trans-resveratrol-3-O-β-glucoside (191)		

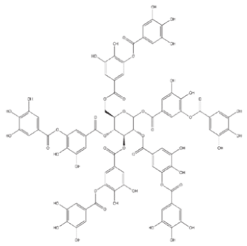
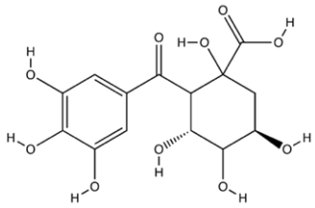
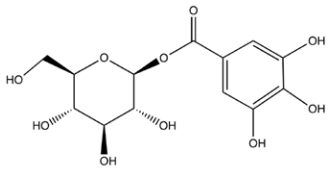
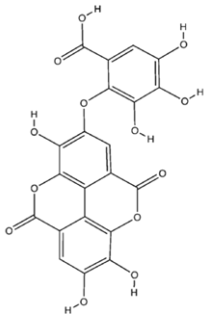
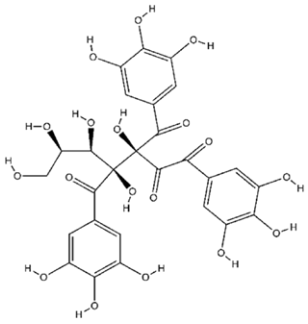
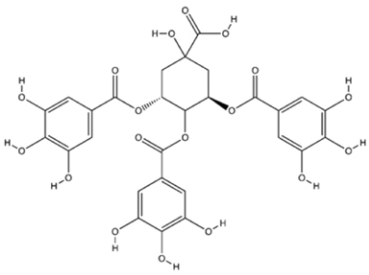
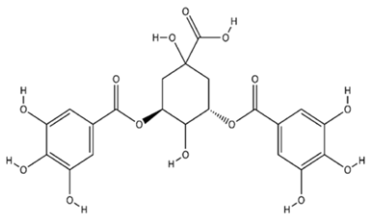
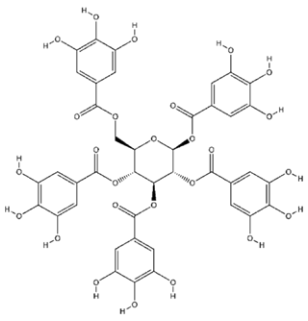
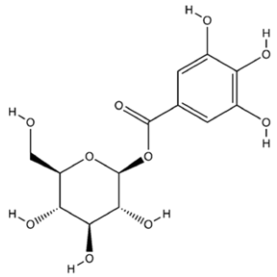
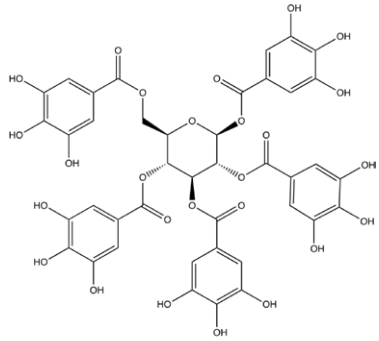
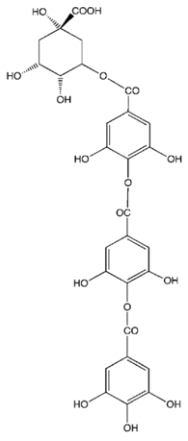
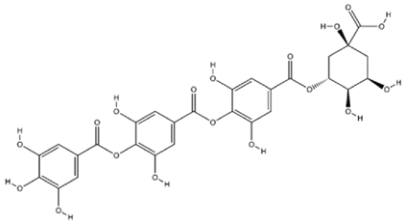
Phenolic Compounds		
		
Chlorogenic acid (192)	Gallic acid (193)	Ellagic acid (194)
		
Protocatechuic acid (195)	Caffeic acid (196)	Vanillic acid (197)
		
Syringic acid (198)	Transilitin (199)	Methyl gallate (200)
		
Ellagic acid glucoside (201)	Quinic acid (202)	Digallic acid (203)
		
Trigallic acid (204)	Salicylic acid (205)	Ethyl gallate (206)

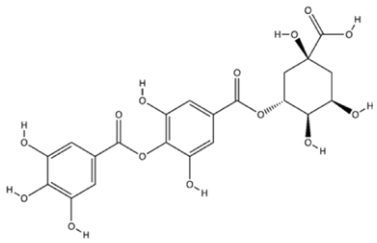
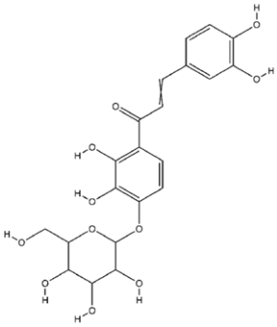
		
Anacardic acid (207)	Caffeic acid hexoside (208)	Methyl 5-(3,4-dihydroxyphenyl)-3-hydroxypenta-2,4-dienoate (209)
		
Hydroxytyrosol (210)	4-ethyl-2-methoxyphenol (211)	Trans-6-shogaol (212)
		
Pyrogallol (213)	Phenol (214)	4-vinylphenol (215)
		
Hydroquinone (216)	Benzetrienol (217)	Tyrosol (218))
		
4-Hydroxyphenylacetic acid (219)	Oleuropein aglycon (220)	Naphtoresorcinol (221)

		
Orcinol (222)	1,2,3-Benzenetriol (223)	Hydroxyquinol (224)
		
Catechol (225)	(Z)-3-(Pentadec-8-en-1-yl)phenol (226)	3-(8-Pentadecenyl)-phenol (227)
		
3-(10-pentadecenyl)-phenol (228)	3-pentadecyl-phenol (229)	3-(10-heptadecenyl)-phenol (230)
		
Eugenol (231)	3,4-dimethylphenol (232)	2,6-dimethylphenol (233)

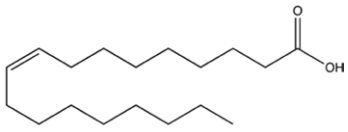
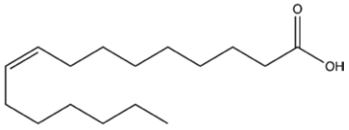
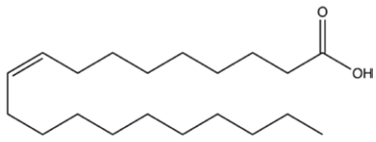
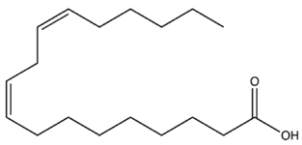
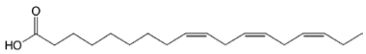
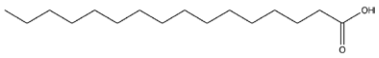
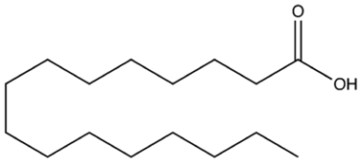
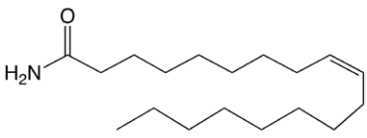
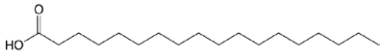
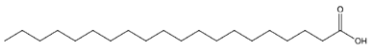
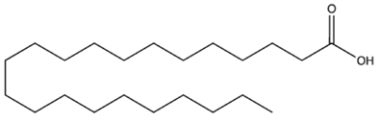
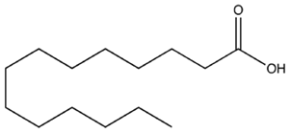
		
Sinapic acid (234)	p-Coumaric acid (235)	Ferulic acid (236
		
6,7,8-Trimethoxycoumarin (237)	Rosmarinic acid (238)	Methyl rosmarinate (239)
		
3,4-Dihydroxyhydro-cinnamic acid (240)	Coumarin (241)	trans-Cinnamic acid (242)
		
Juglone (243)	p-Hydroxybenzoic acid (244)	Methyl benzoate (245)

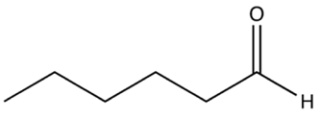
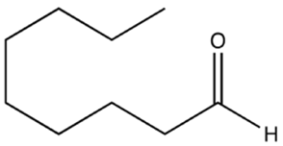
			
Benzoic acid (246)	4-hydroxy-5-(2-oxo-1-pyrrolidinyl)-benzoic acid, (247)	Benzaldehyde (248)	Vanillin (249)

Tannins		
		
Tannic acid (250)	Galloylquinic acid (251)	Glucogallin (252)
		
Valoneic acid dilactone (253)	Trigalloylglucose (254)	3,4,5-O-Trigalloyl quinic acid (255)
		
3,5-O- digalloyl quinic acid (256)	1,2,3,4,6-Pentagalloylglucose (257)	β-glucogallin (258)
		
Penta-O-galloyl-β-D-glucose (259)	Pistafolia A (260)	Pistafolin A (261)

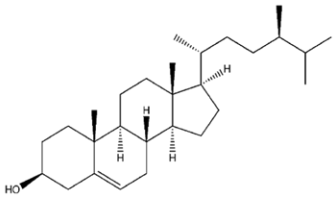
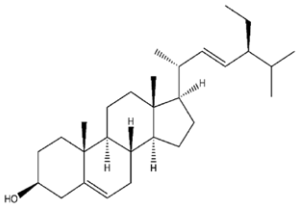
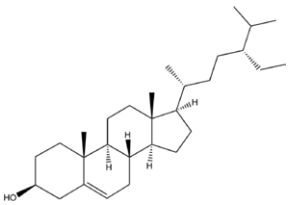
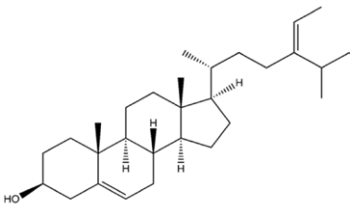
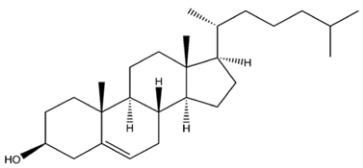
		
Pistafolin B (262)	Okanin 4'-galactoside (263)	

Fatty Acids

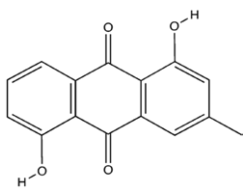
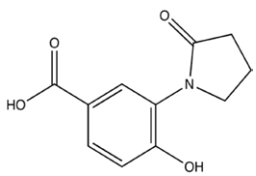
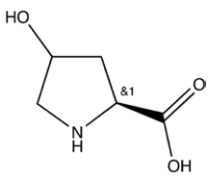
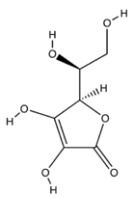
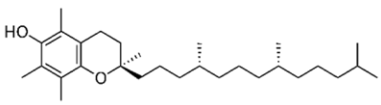
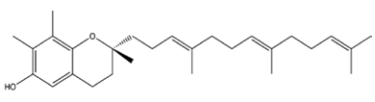
		
Oleic acid (264)	Palmitoleic acid (265)	Gadoleic acid (266)
		
Linoleic acid (267)	Linolenic acid (268)	Palmitic acid (269)
		
Hexadecanoic acid (270)	9-octadecenamide, (Z) (271)	Stearic acid (272)
		
Arachidic acid (273)	Behenic acid (274)	Myristic acid (275)

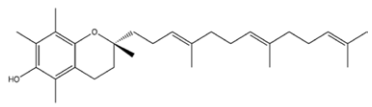
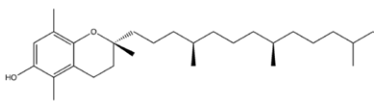
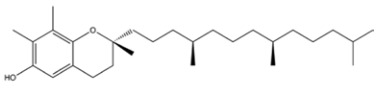
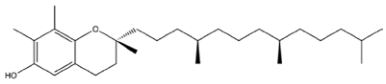
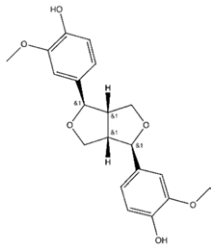
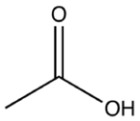
		
Hexanal (276)	Nonanal (277)	

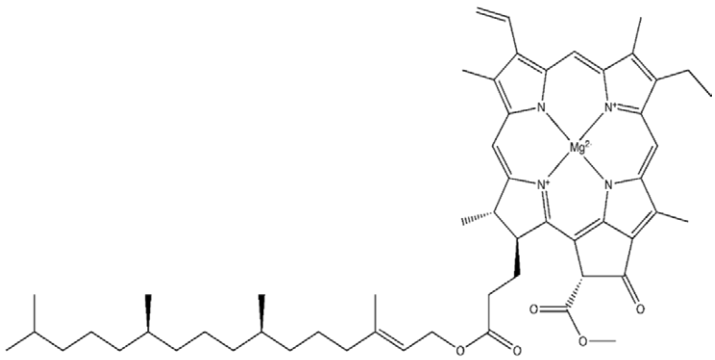
Steroids

		
Campesterol (278)	Stigmasterol (279)	β-Sitosterol (280)
		
Δ5-Avenasterol (281)	Cholesterol (282)	

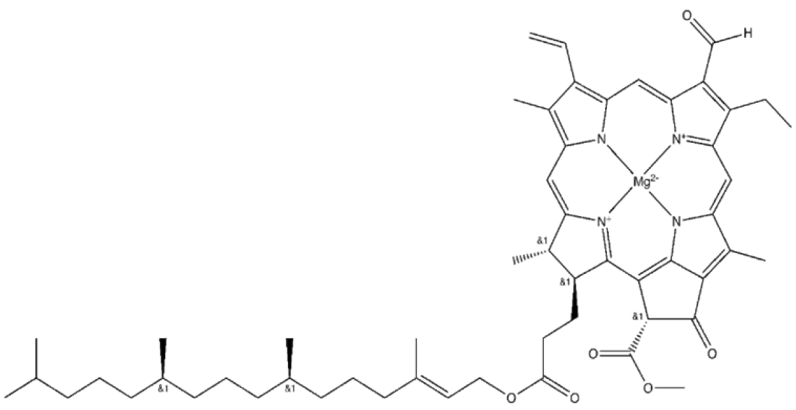
Miscellaneous Compounds

		
1,5-Dihydroxy-3-methylanthraquinone(283)	4-Hydroxy-5-(2-oxo-1-pyrrolidinyl)-benzoic acid (Pistaciamide) (284)	4-Hydroxy-L-proline (285)
		
Ascorbic acid (286)	α-Tocopherol (287)	γ-Tocotrienol (288)

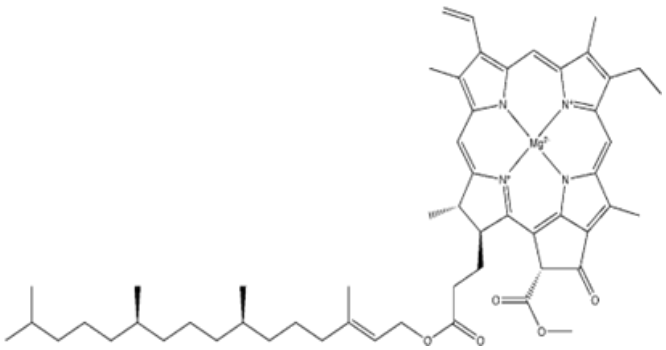
		
α-Tocotrienol (289)	β-Tocopherol (290)	γ-Tocopherol (291)
		
δ-Tocopherol (292)	Pinoresinol (293)	Acetic acid (294)



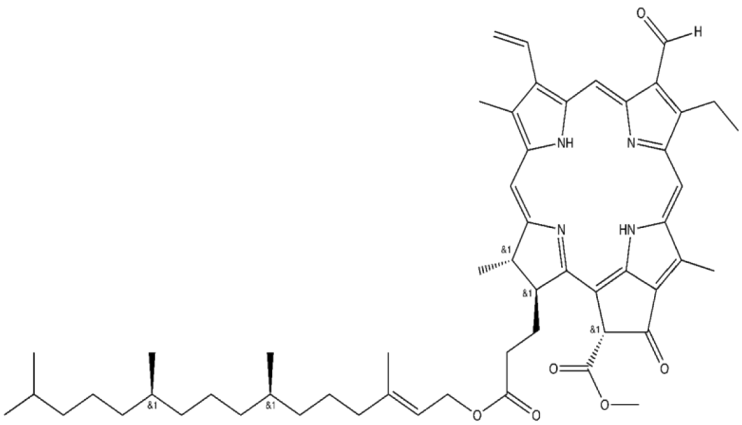
Chlorophyll a (295)



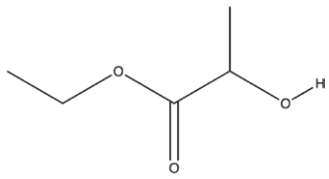
Chlorophyll b (296)



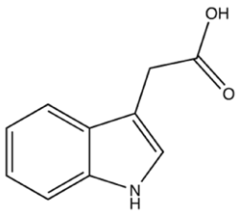
Pheophytin a (297)



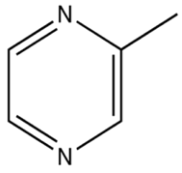
Pheophytin b (298)



Ethyl lactate (299)



Indole-3-acetic acid (300)



Methylpyrazine (301)

(E,E)-2,4-Nonadienal (302)

PISTACIA ATLANTICA

A total of 90 compounds have been identified in *P. atlantica*, including essential oil constituents, monoterpenoids, sesquiterpenoids, flavonoids, phenolic compounds, tannins, fatty acids, and steroids. Among essential oil constituents, monoterpenoids, and sesquiterpenoids. *Pistacia atlantica* is found to have α-pinene **(1)** (3, 4, 6, 7, 10, 13, 14, 16-18, 24-26, 30)**,** β-pinene **(2)** (3, 4, 7, 10, 13 14, 25), Δ3-carene **(3)** (3), carveol **(4)** (3), epoxypinene **(5)** (3), limonene oxide **(6)** (3), myrteol **(7)** (3), limonene **(8)** (3, 16, 17, 25, 26), citral **(9)** (3), α-phellandrene **(10)** (3, 26), β-myrcene **(11)** (3, 16, 17), bornyl acetate **(12)** (4), terpinen-4-ol **(13)** (6, 14, 25), myrcene **(14)** (6, 14, 25), p-mentha-1(7),8-diene **(15)** (6), sabinene **(16)** (6, 12, 26), α-thujene **(17)** (10, 26), camphene **(18)** (10. 13, 14, 17, 25, 26), p-cymene **(19)** (10), cis-ocimene **(20)** (17), trans-ocimene **(21)** (17), β-phellandrene **(22)** (26), limonene dioxide **(23)** (26), thymol **(24)** (26), α-terpinene **(25)** (26), α-terpinolene **(26)**(26), linalool **(27)** (26), pulegone **(28)** (26), elemol **(45)** (4), spathulenol **(46)** (10, 13, 26), γ-amorphene **(47)** (13), germacrene D **(48)** (13, 19, 26), E-caryophyllene **(49)** (19), γ-gurjunene **(50)** (26), β-elemene **(51)** (26), germacrene B **(52)** (26), α-cadinol **(53)** (26), α-eudesmol **(54)** (26), guaiol **(55)** (26), caryophyllene **(56)** (26), β-guiaiene **(57)** (26), β-eudesmol **(58)** (26), globulol **(59)** (26), ledene **(60)**(26), germacrene A **(61)** (26), and δ−cadinene **(62)** (26).

Among flavonoids, *P. atlantica* is found to have 5-hydroxy-8-(4-hydroxyphenyl)-7-methoxy-2H-2,2-dimethylpyrano-6H-[2,3-g] chromen-6-one (3-methoxy-carpa-chromene) **(125)** (8), luteolin **(126) (**9, 18, 20, 23), luteolin-7-glucoside **(127)** (9), kaempferol **(128)** (9), naringenin **(129)** (9, 21), naringenin 7-glucoside **(130)** (9), (+)-catechin **(131)** (9), rutin **(132)** (15, 21, 22, 27, 28), catechin **(133)** (21), quercetin **(134)** (21, 22), eriodictyol **(135)** (23), and apigenin **(136)** (23).

Among other phenolic compounds, *P. atlantica* is found to have chlorogenic acid **(192)** (9, 11), gallic acid **(193)** (11, 15, 20-23, 27, 29), ellagic acid **(194)** (11, 23), protocatechuic acid **(195)** (11), caffeic acid **(196)** (15, 28), vanillic acid **(197)** (15, 21), syringic acid **(198)** (15, 21), transilitin **(199)** (18), methyl gallate **(200)** (23, 27, 29), ellagic acid glucoside **(201)** (23), quinic acid **(202)** (27, 29), digallic acid **(203)** (27), trigallic acid **(204)** (27), methyl 5-(3,4-dihydroxyphenyl)-3-hydroxypenta-2,4-dienoate **(209)**(9), hydroxytyrosol **(210)** (26), sinapic acid **(234)** (11, 15), p-coumaric acid **(235)** (15, 21), ferulic acid **(236)** (15, 21), juglone **(243)** (11), and p-hydroxybenzoic acid **(244)** (15)**.**

Considering tannins, *P. atlantica* is found to have tannic acid **(250)** (21), galloylquinic acid **(251)** (27, 29), glucogallin **(252)** (27, 29), valoneic acid dilactone **(253)** (29), and trigalloylglucose **(254)** (29). Among fatty acids, oleic acid **(264)** (5), linoleic acid **(267)** (5), and palmitic acid **(269)** (5). Among steroids, *P. atlantica* is found to have campesterol **(278)** (5), stigmasterol **(279)** (5), β-sitosterol **(280)** (5), and Δ5-avenasterol **(281)** (5).

PISTACIA CHINENSIS

A total of 21 compounds have been identified in *P. chinensis*, including essential oil constituents, monoterpenoids, sesquiterpenoids, triterpenoids, flavonoids, phenolic compounds, tannins, steroids, and miscellaneous compounds.

Among essential oil constituents, monoterpenoids, and sesquiterpenoids, *P. chinensis*presents Δ3-carene **(3)**. Among triterpenoids and sterols, the species has lupeol **(85)** (33) and β-sitosterol **(280)** (33). Among flavonoids, *P. chinensis* is found to have quercetin **(134)** (33), apigenin **(136)** (32), diosmetin **(137)** (32), myricetin **(138)** (32, 33), apigenin 7-O-β-glucoside **(139)** (32), quercetin 3-O-β-glucoside **(140)** (32, 33), myricetin 3-O-α-rhamnoside **(141)**(32, 33), quercetin 3-O-β-glucoside-7-O-α-rhamnoside **(142)** (32), quercetin 3-O-glucoside **(143)** (34, 35), epicatechin-3-gallate **(144)** (34), cyanidin-3-O-glucoside **(145)** (35), procyanidin B1 **(146)** (35), procyanidin B3 **(147)** (35), and afzelin **(148)**.

Among other phenolic compounds, *P. chinensis* is found to have gallic acid **(193)**. Among tannins, *P. chinensis* is found to have 3,4,5-O-trigalloyl quinic acid **(255)** and 3,5-O- digalloyl quinic acid **(256)** (34). Among

miscellaneous compounds, P. chinensis is found to have 4-hydroxy-5-(2-oxo-1-pyrrolidinyl)-benzoic acid (Pistaciamide) **(284)** (31).

PISTACIA EURYCARPA

A total of 5 compounds have been identified in *P. eurycarpa*. Among essential oil constituets, monoterpenoids, and sesquiterpenoids, *P. eurycarpa*presents α-pinene **(1)** (36). Among diterpenoids, *P. eurycarpa* is found to have phytol **(118)** (36). Among phenolic compounds, *P. eurycarpa* is found to have 4-ethyl-2-methoxyphenol **(211)** (36). Among fatty acids, *P. eurycarpa* is found to have hexadecanoic acid **(270)** (36).

PISTACIA INTEGERRIMA

A total of 20 compounds have been identified in *P. integerrima*, including flavonoids, phenolic compounds, fatty acids, steroids, and miscellaneous compounds.

Among flavonoids, *P. integerrima* is found to have kaempferol **(128)** (37), naringenin **(129)** (42), rutin **(132)** (37), quercetin **(134)** (37, 40), apigenin **(136)** (37), quercetin-3-O-β-d-glucopyranoside **(149)** (37)**,** kaempferol-3-O-β-d-glucoside **(150)** (37), kaempferol-3-O-(4″-O-galloyl)-α-l-arabinopyranoside **(151)** (37), chrysoeriol **(152)** (39), diandraflavone A **(153)** (39), 3,5,7,4′-tetrahydroxy-flavanone **(154)** (42)**,** 3,5,4′-trihydroxy,7-methoxy-flavanone **(155)** (42), and Sakuranetin **(156)**(42). Other phenolic compounds also were identified in this species: gallic acid **(193)** (41), pyrogallol **(213)** (40), 6,7,8-trimethoxycoumarin **(237)** (41), and methyl benzoate **(245)** (41).

Among fatty acids, *P. integerrima*presents 9-octadecenamide, (Z) **(271)** (43). Among steroids, *P. integerrima* is found to have β-sitosterol **(280)** (43). Among miscellaneous compounds, *P. integerrima* is found to have 1,5-dihydroxy-3-methylanthraquinone **(283)** (41).

PISTACIA KHINJUK

A total of 24 compounds have been identified in *P. khinjuk*, including essential oil compounds, monoterpenoids, sesquiterpenoids, flavonoids, phenolic compounds, tannins, fatty acids, and miscellaneous compounds. Among essential oil constituents, monoterpenoids, and sesquiterpenoids, *P. khinjuk* is found to have α-pinene **(1)** (44, 48), β-pinene **(2)** (44, 47, 49), limonene **(8)** (48), myrcene **(14)** (44, 48), sabinene **(16)** (47), trans-β-ocimene **(29)** (47), D-limonene **(30)** (47), spathulenol **(46)** (44, 47), germacrene B **(52)** (44), caryophyllene **(56)** (47) β-caryophyllene **(63)** (44, 48, 49), D-nerolidol **(64)** (47), and α-humulene **(65)** (48)**.**

Among flavonoids, *P. khinjuk* is found to have rutin **(132)** (46), quercetin 3-O-glucoside **(143)** (34), and epicatechin-3-gallate **(144)** (34). And others phenolic compounds, such as gallic acid **(193)**(46), caffeic acid **(196)** (46), sinapic acid **(234)**(46), and ferulic acid **(236)** (46). Among tannins, *P. khinjuk* is found to have 3,4,5-O-trigalloyl quinic acid **(255)** (34) and 3,5-O- digalloyl quinic acid **(256)** (34). Among fatty acids, *P. khinjuk* is found to have oleic acid **(264)** (45). Among miscellaneous compounds, *P. khinjuk* is found to have ascorbic acid **(286)** (46).

PISTACIA LENTISCUS

A total of 142 compounds were identified in *P. lentiscus*, including essential oil constituents, monoterpenoids, sesquiterpenoids, triterpenoids, diterpenoids, flavonoids, phenolic compounds, tannins, fatty acids, steroids,and miscellaneous compounds. Among essential oil constituents, monoterpenoids, and sesquiterpenoids, *P. lentiscus* is found to have α-pinene **(1)** (51, 53, 54, 57, 58, 60, 63, 69, 71, 73, 77, 79, 81, 83-86, 90, 97), β-pinene **(2)** (49, 53, 54, 57, 60 63, 81, 83, 84), limonene **(8)** (51, 53, 57, 60, 67, 73, 86, 97), β-myrcene **(11)** (53, 63, 86, 90), terpinen-4-ol **(13)** (54, 57, 61, 63, 69, 72, 84, 86), myrcene **(14)** (51, 57, 60, 67, 77, 79, 83), sabinene **(16)** (54, 57, 79, 84), camphene **(18)** (60), p-cymene **(19)** (57), β-phellandrene **(22)** (49), linalool **(27)** (59), D-limonene **(30)** (91), trans-β-terpineol **(31)** (54), γ-muurolene **(32)** (54), γ-terpinene **(33)** (57, 91), α-terpineol **(34)** (57, 59, 61, 71), verbenone **(35)** (59, 84), trans-pinocarveol **(36)** (59), 1,8 cineole **(37)** (63), trans-verbenol **(38)** (85), 2-carene **(39)**

(91), germacrene D **(48)** (49, 51, 57, 67, 73, 80, 84, 86, 97), α-cadinol **(53)** (67), caryophyllene **(56)** (84), β-eudesmol **(58)** (79), δ−cadinene **(62)** (67, 69, 73, 79, 80, 84, 97), β-caryophyllene **(63)** (49, 53, 60, 61, 69, 71, 73, 79, 86, 97), α-humulene **(65)** (51), γ-cadinene **(66)** (49, 54, 80), β-gurjunene **(67)** (51), muurolene **(68)** (51), epi-bicyclosesquiphellandrene **(69)** (51), longifolene **(70)** (54), trans-caryophyllene **(71)** (67, 80), α-amorphene **(72)** (67), α-cubebene **(73)** (67), cubebol **(74)** (78), farnesol **(75)** (78), cedreanol **(76)** (79), germacrene D-4-ol **(77)** (80), α-bisabolol **(78)** (80), trans-calamenene **(79)** (91), α-calacorene **(80)** (91), cadalene **(81)** (91), and nootkatone **(82)** (91).

Considering triterpenoids, the species presents lupeol **(85)** (78, 92), 28-norolean-17-en-3-one **(89)** (66, 68), oleanonic acid **(90)** (68, 85), moronic acid **(91)** (68, 74, 85, 92), 11-hydroxyoleanolic acid **(92)** (68), masticadienonic acid **(93)** (68, 74), oleanolic acid **(94)** (74, 92), (iso)-masticadienonic acid **(95)** (74, 85), β-amyrin **(96)** (78, 92), lupenone **(97)** (78), lupanol **(98)** (78), butyrospermol **(99)** (92), dipterocarpol **(100)** (92), oleanolic aldehyde **(101)** (92),28-hydroxy-β-amyrone **(102)** (92), β-amyrone **(103)** (92), germanicol **(104)** (92), betulonal **(105)** (92), lup-20(29)-ene-3-one **(106)** (92), 24Z-masticadienonic acid **(107)** (92), 24Z-isomasticadienonic acid **(108)** (92), 24Z-masticadienolic acid **(109)** (92), 24Z-isomasticadienolic acid **(110)** (92), tirucallol **(111)** (92), dammaradienone **(112)** (92), 3,11-dioxo-28-norolean-12-en-17-ol **(113)** (95), krukovine A **(114)** (95), 3β-hydroxy-11-oxo-olean-12-en-28-oic acid **(115)** (95), and 3,7,11-trioxo-8,24(Z)-tirucalladien-26-oic acid **(116)** (95). One diterpene was found: carnosic acid **(119)** (82).

Among flavonoids, *P. lentiscus*has luteolin **(126)** (70, 75, 82), kaempferol **(128)** (70, 82), rutin **(132)** (96), catechin **(133)** (50, 65, 75, 93), quercetin **(134)** (70, 87, 93), apigenin **(136)** (82), myricetin **(138)** (87, 96), quercetin 3-O-glucoside **(143)** (34), epicatechin-3-gallate **(144)** (34), cyanidin-3-O-glucoside **(145)** (50, 56), delphinidin-3-O-glucoside **(157)**, (50, 56) cyanidin-3-O-arabinoside **(158)** (56), D-gallocatechin **(159)** (70), myricetin-rhamnoside **(160)** (70, 72, 87, 94), myricetin-rutinoside **(161)** (72), myricetin-glucoside **(162)** (72), aquercetin derivative **(163)** (72), quercetin-glucoside **(164)** (72), and quercetin-rhamnoside **(165)** (72, 75, 87, 94).

Among phenolic compounds, *P. lentiscus* is found to have gallic acid **(193)** (50, 55, 72, 75, 82, 87, 88, 93, 96), ellagic acid **(194)** (75), vanillic acid **(197)** (82), syringic acid **(198)** (75), digallic acid **(203)** (62), salicylic acid **(205)** (75, 82), ethyl gallate **(206)** (96), phenol **(214)** (66, 91), 4-vinylphenol **(215)** (64), hydroquinone **(216)** (66), benzetrienol **(217)** (66), tyrosol **(218)** (82), 4-hydroxyphenylacetic acid **(219)** (82), oleuropein aglycon **(220)** (82), naphtoresorcinol **(221)** (82), orcinol **(222)**(91), 1,2,3-benzenetriol **(223)** (91), hydroxyquinol **(224)** (91), catechol **(225)** (91), (Z)-3-(pentadec-8-en-1-yl)phenol **(226)** (91), p-coumaric acid **(235)** (82), ferulic acid **(236)** (82), 3,4-dihydroxyhydro-cinnamic acid **(240)** (75), coumarin **(241)** (82), trans-cinnamic acid **(242)** (82), and benzoic acid **(246)** (75). Among tannins, *P. lentiscus* is found to have galloylquinic acid **(251)** (70, 72), glucogallin **(252)** (72), 3,4,5-O-trigalloyl quinic acid **(255)** (34, 50), 3,5-O- digalloyl quinic acid **(256)** (34), 1,2,3,4,6-Pentagalloylglucose **(257)** (55), and β-glucogallin **(258)** (65).

Among fatty acids, *P. lentiscus* is found to have oleic acid **(264)** (64, 76, 89), palmitoleic acid **(265)** (64), gadoleic acid **(266)** (64), linoleic acid **(267)** (64, 76, 89), linolenic acid **(268)** (64), palmitic acid **(269)** (64, 76, 89), stearic acid **(272)** (64, 89), and arachidic acid **(273)** (64). Among steroids, P. lentiscus is found to have campesterol **(278)** (64), stigmasterol **(279)** (64), β-sitosterol **(280)** (64, 78, 89), and cholesterol **(282)** (64). Among miscellaneous compounds, *P. lentiscus* is found to have α-tocopherol **(287)** (52, 78, 89), γ-tocotrienol **(288)** (89), α-tocotrienol **(289)** (89), and pinoresinol **(293)** (82).

PISTACIA TEREBINTHUS

A total of 44 compounds have been identified in *P. terebinthus.*

Among essential oil constituents, monoterpenoids, and sesquiterpenoids, *P. terebinthus* is found to have α-pinene **(1)** (98, 99, 101,

103, 105, 107-110, 113), β-pinene **(2)** (98, 99, 101, 107, 108, 113), limonene **(8)** (10, 98, 101, 103, 107, 110, 113), α-phellandrene **(10)** (12), β-myrcene **(11)** (109), camphene **(18)** (108, 114), β-phellandrene **(22)** (108), α-terpineol **(34)** (110, 113), 2-carene **(39)** (107), p-cymen-8-ol **(40)** (101), allo-ocimene **(41)** (103), β-ocimene **(42)** (105), D,L-limonene **(43)** (105), terpinolene **(44)** (108), spathulenol **(46)** (101), germacrene D **(48)** (98), caryophyllene oxide **(83)** (101), and δ-muurolene **(84)** (107).

Among tetraterpenoids, *P. terebinthus*-presents lutein **(120)** (104) and β-carotene **(121)** (104). Among flavonoids, *P. terebinthus* is found to have luteolin **(126)** (100, 102, 111, 112), luteolin-7-glucoside **(127)** (102), rutin **(132)** (112), quercetin **(134)** (100, 112), apigenin **(136)** (100), 6′-hydroxyhypolaetin 3′-methyl ether **(166)** (100), luteolin-7-glucoside **(167)** (100), quercetagetin 3-methyl ether 7-O-glucoside **(168)** (100), isoscutellarein 8-O-glucoside **(169)** (100), apigenin-7-glucoside **(170)** (102), and myricetin-O-glucoronide **(171)** (112). Among phenolic compounds, *P. terebinthus* is found to have gallic acid **(193)** (112)and quinic acid **(202)** (112).

Among fatty acids, oleic acid **(264)** (104, 105, 106), palmitoleic acid **(265)** (104), linoleic acid **(267)** (104), palmitic acid **(269)** (104, 105), and stearic acid **(272)** (104). Among miscellaneous compounds, *P. terebinthus* is found to have α-tocopherol **(287)** (104), β-tocopherol **(290)** (104), γ-tocopherol **(291)** (104), δ-tocopherol **(292)** (104), and acetic acid **(294)** (107).

PISTACIA VERA

A total of 105 compounds have been identified in *P. vera*, Among essential oil constituents, monoterpenoids, and sesquiterpenoids, *P. vera* is found to have α-pinene **(1)** (113-115, 125, 133, 139, 145), β-pinene **(2)** (113-115, 145), limonene **(8)** (113, 114, 133), bornyl acetate **(12)** (125), terpinen-4-ol **(13)** (113), myrcene **(14)** (139), α-thujene **(17)** (115, 133), camphene **(18)** (114), α-terpinolene **(26)** (133), α-terpineol **(34)**(113), trans-pinocarveol **(36)** (114), trans-verbenol **(38)** (114), D,L-limonene **(43)** (139), and terpinolene **(44)** (125). Among triterpenoids, *P. vera* is found to have 3-epimasticadienolic acid **(117)** (142). Among tetraterpenoids, *P. vera* is found to have lutein **(120)** (118, 119, 123), β-carotene **(121)** (118, 119), violaxanthin**(122)** (118), neoxanthin **(123)** (118), and luteoxanthin **(124)** (118).

Among flavonoids, *P. vera* is found to have luteolin **(126)** (120, 129), kaempferol **(128)** (129), naringenin **(129)** (120, 129, 132), (+)-catechin **(131)** (130, 137), rutin **(132)** (120), catechin **(133)** (129, 132, 140, 141), quercetin **(134)** (120, 129, 146), eriodictyol **(135)** (120, 129, 141), apigenin **(136)** (120, 129, 146), myricetin **(138)** (130, 146), quercetin 3-O-glucoside **(143)** (130, 135, 137), cyanidin-3-O-glucoside **(145)** (129, 137, 140), kaempferol-3-O-β-d-glucoside **(150)** (137), Quercetin Derivative**(163)** (129, 132), quercetin-glucoside **(164)** (140), cyanidin-3-galactoside **(172)** (117, 120, 123, 129), cyanidin-3-glucoside **(173)** (117, 120, 123), daidzein **(174)** (124, 129), genistein **(175)** (124, 129), naringenin-7-O-neohesperidoside **(176)** (129), eriodictyol-7-O-glucoside **(177)** (129, 132, 139, 141), genistein-7-O-glucoside **(178)** (129), epicatechin **(179)** (129, 137), procyanidin dimer **(180)** (130, 137), isorhamnetin-7-O-glucoside **(181)** (132), isorhamnetin-3-O-glucoside **(182)** (132), quercetin-3-O-galactoside **(183)** (135, 137, 140), quercetin 3-O-glucuronide **(184)** (135), myricetin 3-O-galactoside **(185)** (135), eriodictyol-3-O-glucoside **(186)** (137), peonidin-3-glucoside **(187)** (140), quercetin-4′-glucoside **(188)** (140), resveratrol **(189)** (116), trans-resveratrol **(190)** (124, 126), and trans-resveratrol-3-O-β-glucoside **(191)** (126).

Among phenolic compounds, *P. vera* is found to have gallic acid **(193)** (129, 130, 132, 135, 136, 141, 143), protocatechuic acid **(195)** (132, 135, 139, 143), anacardic acid **(207)** (135), caffeic acid hexoside **(208)** (137), phenol **(214)** (139), 3-(8-pentadecenyl)-phenol **(227)** (127), 3-(10-pentadecenyl)-phenol **(228)** (127), 3-pentadecyl-phenol **(229)** (127), 3-(10-heptadecenyl)-phenol **(230)** (127), eugenol **(231)** (139), 3,4-dimethylphenol **(232)** (139), 2,6-dimethylphenol **(233)** (139), 4-hydroxybenzoic acid **(247)** (132, 143), benzaldehyde **(248)** (139), and vanillin **(249)** (139).

Among tannins, *P. vera* is found to have β-glucogallin **(258)**(135), penta-O-galloyl-β-d-glucose **(259)** (135, 136), and okanin 4′-galactoside **(263)** (140). Among fatty acids, *P. vera* is found to have oleic acid **(264)** (121, 122, 128, 134, 140, 143, 144), palmitoleic acid **(265)** (121, 144), gadoleic acid **(266)** (121), linoleic acid **(267)** (121, 128, 134, 140, 143, 144), linolenic acid **(268)** (121, 144), palmitic acid **(269)** (121, 128, 144), hexadecanoic acid **(270)** (121), stearic acid **(272)** (121, 128, 144), arachidic acid **(273)** (121), behenic acid **(274)** (121), myristic acid **(275)** (121), hexanal **(276)** (139), and nonanal **(277)** (139). Among steroids, *P. vera* is found to have campesterol **(278)** (144), stigmasterol **(279)** (138, 144), β-sitosterol **(280)** (122, 144), Δ5-avenasterol **(281)** (144), and cholesterol **(282)** (144).

Among miscellaneous compounds, *P. vera* is found to have 4-hydroxy-l-proline **(285)** (131), ascorbic acid **(286)** (124), α-tocopherol **(287)** (124), γ-tocotrienol **(288)** (124), β-tocopherol **(290)** (119), γ-tocopherol **(291)** (119, 144), δ-tocopherol **(292)** (119, 144), chlorophyll a **(295)**(118, 123), chlorophyll b **(296)** (118, 123), pheophytin a **(297)**(118), pheophytin b **(298)** (118), ethyl lactate **(299)** (131), indole-3-acetic acid **(300)** (131), methylpyrazine **(301)** (139), and (E,E)-2,4-nonadienal **(302)** (139).

PISTACIA WEIMANNIFOLIA

A total of 4 compounds have been identified in *P. weinmannifolia*, including essential oil constituents, monoterpenoids, sesquiterpenoids, and tannins. Among essential oil constituents, monoterpenoids, and sesquiterpenoids, *P. weinmannifolia* is found to have α-pinene **(1)** (149). Among tannins, *P. weinmannifolia* is found to have pistafolia A **(260)** (147), pistafolin A **(261)** (148), and pistafolin B **(262)** (148).

PHARMACOLOGICAL USES

Pistacia sp chemical compounds present several biological and pharmacological activities, potentially useful. Table 2 presents these activities.

Antioxidant. Antioxidant effects have been tested in various species of *Pistacia*. 2,2-diphenylpicrylhydrazyl (DPPH) assay,2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS)assay, NO scavenging, beta carotene bleaching assay, and ferric reducing antioxidant power (FRAP) are among the various assays used to determine antioxidant power.

Phenolic components, methyl gallate **(200)**, valoneic acid dilactone **(253)**, and quinic acid **(202)** from *P. atlantica* galls proved antioxidant capacity as methyl gallate and valoneic acid were important in the FRAP and ABTS scavenging assays and quinic acid was the main antioxidant activity influencer in the DPPH method (29). The essential oil, rich in monoterpenes and oxygenated sesquiterpenes from leaves, showed higher antioxidant capacity compared to ascorbic acid (41). Total phenolic and flavonoid content can be related to antioxidant activity of *P. atlantica* leaves (150) as oil from air dried leaves was found to be a significant source of natural antioxidants (151). *P. atlantica* subspecies Kurdica also showed antioxidant capacity (152). The hulls also showed significant antioxidant activity (153), and highest antioxidant activity may be attributed to the higher total phenolic and flavonoid content (15). Fruits, leaves, buds, stems, roots, and internal and external trunk barks were also assessed; extracts of leaves and buds had the highest phenolic content (70).

Root buds and fruit extracts of *P. atlantica* also showed antioxidant activities (28). *Pistacia atlantica* stocks showed significant urease inhibitor activity: while the ethyl acetate fraction had 100% urease inhibition, n-hexane and chloroform fractions showed insignificant urease inhibition. Isolated compound transilitin **(199)** reduced urease by 95%, at a concentration of 0.15 mg/mL (18).

Pistacia chinensis bark and leaves were assessed via various antioxidant assays *in vitro* and the ethyl acetate of bark showed the highest results in most assays (154).

Pistacia integerrima flavonoids were assessed for radical scavenging (DPPH) and xanthan oxidase inhibitory activities *in vitro* and were found to have significant radical scavenging and xanthine oxidase inhibitory activity [37]. Ethyl acetate fraction of *P. integerrima* was also

highly potent in scavenging DPPH and SBTS free radicals and acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) [40].

The ethanolic extract of *P. khinjuk* was assessed via DPPH and showed powerful antioxidant activity (155). The essential oil of this species' hull had major components including β-caryophyllene **(63)**, myrcene **(14)**, α-pinene **(1)**, limonene **(8)**, and α-humulene **(65)** and exhibited DPPH scavenging assay activity almost 4 to 5 times higher than ascorbic acid and a 10-fold increase in β-carotene bleaching assay relative to ascorbic acid (48).*P. khinjuk* also showed antioxidant capability in relation to total phenolic and flavonoid content (46).

When comparing *P. khinjuk* and *P. terebinthus*, *P. terebinthus* extracts rich in flavonoid content had the highest antioxidant capacity (106).

Pistacia lentiscus showed remarkable *in vitro* antioxidant effects with myrcene **(14)** and α-pinene **(1)** found to be the main components (156). Fresh leaves showed better performance in antioxidant potential (major components include galloyl quinic acid, D-gallocatechin **(159)**, myricetin **(138)**, quercetin **(134)**, and kaempferol glycoside isomers (70)) compared to those extracted using microwave assisted or ultrasound assisted extraction (67).

When the aerial parts of the *P. lentiscus* species was assessed, the essential oil showed lower antioxidant potential compared to the ethanolic extract, reflecting the potential phenolic content responsible for antioxidant activity (157). When comparing leaf extracts to essential oil, the extract proved more effective than the essential oils and standard (97). Leaves also showed the highest ability to reverse toxic effects caused by Al with myricetin rhamnoside **(160)** component (87). Gallic acid **(193)**, quercetin **(134)**, and catechin **(133)** also showed significant antioxidant potential from *P. lentiscus* leaves (93). Flowers, rich in terpinen-4-ol **(13)**, also possess antioxidant and cell protective activities (84).

Pistacia lentiscus resin restored glutathione (GSH) levels (158) and downregulatedcluster of differentiation 36 (CD36) expression (159). The aqueous extract of the leaves of *P. lentiscus* proved to be a great natural antioxidant compared to the quercetin standard (160). Seed oils are also effective antioxidants (161). *Pistacia lentiscus* oil also reduced AChE activity, decreased oxidative stress, and prevented oxidative stress in the livers of lipopolysaccharides (LPS)-treated rats (162). The strongest antioxidant properties correspond to the leaves macerates, which contained 15 times more phenolic compounds and 20 times more flavonoids, when compared to the fruit (91); however, the fruit extract exhibited antioxidant activities by ability to scavenge DPPH radical and protect against lipid peroxidation (133). Monoterpenes [alpha-pinene **(1)** and limonene **(8)**] from leaves reach their highest percentage at the flowering stage; highest phenolic content and strongest antioxidant activity are observed (57).

Leaves and fruits of *P. lentiscus* were tested for cytoprotective effects against hydrogen peroxide (H2O2)- induced oxidant stress. Cells treated with leaf extracts strongly inhibited H2O2 damage and significantly increased cell survival at 25, 50, 75, and 100 µg/mL. Phenolic compounds were also tested: gallic acid was affecting from 1 µg/mL while quercetin was already active at 0.1 µg/mL and showed the highest protection at 1 µg/mL (130).

Pistacia lentiscus ethanolic fruit extract inhibited calcium oxalate monohydrate (COM) crystals adhesion onto the apical membrane on proximal tubular cells, significantly reversing COM tubulotoxicity (163).

Pistacia terebinthus leaves showed higher antioxidant activities than BHA and ascorbic acid (102). The acetone and ethanol extracts of shells, nuts, and whole fruits showed strong DPPH and ABTS radical scavenging activity (111). The methanol extract of the leaves had higher levels of total phenolic compounds compared to the ethyl acetate extract and exhibited promising antioxidant capacity on DPPH and ABTS antioxidant assays (112). *Pistacia terebinthus* coffee brands showed higher antioxidant activity and exhibited better activity than the fruits of *P. terebinthus*(105). A flavone, 6'-hydroxyhypolaetin 3'-methyl ether **(166)**, showed high activity in β-carotene bleaching (100).

Polyphenol-rich *P. vera* nut extract possesses a higher antioxidant activity than the seeds extracts (164). The methanol extract from the hulls gave the highest yields of gallic acid **(193)**, 4-hydroxybenzoic acid **(247)**, protocatechuic acid **(195)**, naringenin **(129)**, eriodictyol-7-O-glucoside **(177)**, and catechin **(133)** had higher scavenging activity in all antioxidant activities performed (132). Dry pistachio samples were found to be useful in blocking the action of reactive oxygen species involved in cardiovascular disease and cancer with predominant compounds identified being gallic acid **(193)** and catechin **(133)**(130). Phenolic compound content was found to be significantly higher in the skins of pistachios compared to the seeds; the skins had better antioxidant activity compared to the seeds in all tests (129). Gum extract consisted of saponins, tannins, and flavonoids and increased the antioxidant power of the brain (165).

Table 2. Researched uses of various parts of the Pistacia plants

Species	Parts used	Researched uses
P. atlantica	Leaves, gums, fruit, galls, stem, trunk, branches, roots, leaf-buds, oleo-gum-resin, hull, oleoresin, stocks, trunk bark, twigs	Antioxidant, antibacterial, antifungal, anti-plasmodial, analgesic, hepatoprotective, wound healing, anti-hyperuricemia, anti-diabetic, anti-hypertensive, anti-hyperlipidemia, nitric oxide (NO) inhibition
P. chinensis	Leaves and stem bark	Antioxidant
P. integerrima	Leaves, Galls, whole plant, fruit	Antioxidant, analgesic, anti-inflammatory, anti-allergic, anti-angiogenic, anti-asthma, scabies, antibacterial, antifungal, anti-hyperuricemia, gastrointestinal disorders,
P. khinjuk	Leaves, seeds, hull, stocks	Antioxidant, antibacterial, anti-hyperlipidemia
P. lentiscus	Leaves, twigs, wounds of trunk and branches, stems, seeds, seed oil, fruits, mastic, flowers, aerial parts, mastic gum	Antioxidant, antifungal, antibacterial, hepatotoxicity/hepatoprotection, anti-cancer, antilarval, anti-hyperlipidemia, cytoprotective, anti-inflammatory, cardioprotective, nephroprotective, anti-ulcerogenic, anti-diabetic, antiatherogenic, anti-cholinesterase, anti-allergic, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) protein inhibition
P. x saportae	Leaves and twigs	Antifungal
P. terebinthus	Leaves, galls, twigs, fruits	Antifungal
P. vera	Leaves, trunk, nuts, hull, branch, seeds, skins, gum extract, fruits, peduncles. Kernel, shell, whole plant, fruit extract	Antioxidant, anti-inflammatory, antifungal, wound healing, increase monounsaturated fatty acids in visceral adipose tissue, digestive enzyme activity, immune activity, antimicrobial, antiviral, antiprotozoal, cytoprotective activity, scolicidal, regulating body's biological cycle
P. weinmannifolia	Leaves	Antioxidant

Pistacia weinmannifolia leaves exhibited protective effects against oxidative damage of biomacromolecules due to their strong free radical scavenging ability (148).

Hepatoprotective/hepatotoxicity. *Pistacia lentiscus* leaves and fruits were evaluated for their hepatoprotective and hepatotoxic effects in rat models. The leaves have a better hepatoprotective effect than their fruit counterparts, but both showed marked reductions in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and the level of bilirubin (166, 75). Gallic acid **(193)** was identified in both leaves and fruits, while luteolin **(126)** was identified in fruits only (75). On the contrary, *P. lentiscus* leaves were found to contain hepatotoxins that lead to hepatic fibrosis and an inflammatory response, mild cholestasis, and depletion of reduced glutathione associated with an increase in its oxidized form after long term administration in healthy rats. The authors

identified the presence of tannins and speculated their role in inducing hepatotoxicity (167).

Anti-inflammatory. *Pistacia* sp. has been tested for its anti-inflammatory activity. Essential oils from *P. atlantica* galls inhibited NO production with inhibitory effect appearing to be due to their cytotoxicity against macrophage cells and had moderate anti-inflammatory activity compared to quercetin with strong inhibitory activity against 14-lipoxygenase. Low cytotoxicity against healthy cells was observed (168).

Pistacia integerrima leaves and galls were assessed for anti-inflammatory response. Leaves showed less protection than the gall extracts in hind paw edema tests in mice. Leaves at higher doses (200mg/kg), galls extract (100-200 mg/kg), and diclofenac (10 mg/kg) exerted significant anti-inflammatory response (169).

Pistacia vera(α-pinene **(1)** fraction) also exhibited a moderate anti-inflammatory effect in the carrageenan-induced hind paw edema model in mice (170).

Pistacia integerrima galls (ethyl gallate **(203)** was active constituent) inhibited the adhesion of neutrophils to LPS activated endothelium at the functional level indicating ethyl gallate's potential as a therapeutic agent for various inflammatory diseases (171). Pretreatment with flavonoids from galls of *P. integerrima* and *P. lentiscus* also significantly ameliorated post carrageenan induced edema dose dependently at various stages of inflammation with the most dominant effect after the third hour of drug administration (172-174).

Thirteen triterpenoids were isolated from *P. lentiscus* resin; four of the compounds exhibited moderate inhibitory effect against NO production inmurine macrophage cells (RAW 264.7) (95). Sixteen tirucallane triterpenoids from leaves and stems of *P. lentiscus* were assessed for NO inhibitory potential; four of the compounds exhibited stronger inhibitory activities than positive control dexamethasone (175).

Oleanonic acid **(90)** from *P. terebinthus* galls were assessed for activity against mouse ear edema induced by ethyl phenylpropiolate (EPP), triphenylamine (TPA), and diketopyrrolopyrroles (DPPs). The highest activity observed was a 40% reduction in swelling in the DPP ear edema test (176).

Pistacia integerrima extract demonstrated use in asthma related to its ability to reduce TNF-alpha, IL-4, and IL-5 expression levels, which may have contributed to the reduction of airway inflammation and increase aquaporin 1 (AQP1) and aquaporin 5 (AQP5) expression levels, which may be attributed to the reduction of pulmonary edema in mice models (177).

Essential oil extracted from *P. integerrima* galls demonstrated its ability to disrupt the inflammatory cascade at multiple levels via its antioxidant potential, inhibition of 5-lipoxygenase protection of 48/80 induced mast cell degranulation, inhibition of L-type calcium channels on isolated guinea pig ileum, anti-angiogenic activity, reduction in leukocyte infiltration in airways, and reduction in allergen induced airway hyperresponsiveness. The presence of phenolic compounds correlated with the anti-asthmatic activity of *P. integerrima*(178).

Topical treatment with *P. lentiscus* mastic significantly reduced inflammatory and pruritic responses in mice induced with allergic contact dermatitis. There was a significant reduction in ear swelling, itching, immunocyte infiltration, and cytokine production after applying 3% and 30% mastic topical treatment (179).

Antimicrobial. *Pistacia lentiscus* leaves extract and essential oils demonstrated antimicrobial activity against *Listeria monocytogenes*, *Staphylococcus aureus*, *Aspergillus niger*, and *Saccharomyces cerevisiae.* The main compounds responsible for antimicrobial activity include β−myrene **(11)**, α-pinene **(1)**, myrcene **(14)**, and β-pinene **(2)**(63, 83, 180).

Pistacia vera leaf extracts and oleoresin exhibited relative inhibition against staphylococcal strains and reduced biofilm production of *Streptococcus mutans* and *S. sanguinis*, respectively (48, 181).

Pistacia integerrima galls showed significant antimicrobial activity against *Escherichia coli, Klebsiella pneumonia, S. aureus*, and *Bacillus subtilis*. The antimicrobial activity was attributed to the presence of 3,4,7,4-tetrahydroxy-flavanone **(154)** and naringenin **(129)**(42). Flavonoid gly-

cosides (pistacides A and B) isolated from the methanolic extract of *P. integerrima* exhibited significant antimicrobial activity compared to the standard drug zonisamide suggesting potential for use in various disease states (41).

Pistacia atlantica and *P. lentiscus* were evaluated for their use in *Helicobacter pylori* infections and ulcerative colitis. All strains of *H. pylori* were susceptible to *P. atlantica* oleoresin essential oil, with the major compounds responsible for the antimicrobial activity being α−pinene **(1)**, β-pinene **(2)**, limonene **(8)**, camphene **(18)**, and myrcene **(14)**(25).

Pistacia lentiscus gum mastic at a concentration of 125 µg/mL had a minimal bactericidal concentration of 90 µg/mL and killed 50% of *Helicobacter* strains (182). *Pistacia lentiscus* fruits and *P. atlantica* were evaluated for their use in rats induced with ulcerative colitis. In one study of fifteen rats, a histological exam revealed improvement in ulcerative colitis in those who received *P. lentiscus* prior to and on the day of ulcerative colitis induction (76). Myeloperoxidase activity was used as a biomarker of disease activity and severity. The administration of *P. atlantica* at the time of ulcerative colitis induction reduced myeloperoxidase activity by 55% (183). Overall, treatment significantly reduced ulcerated and hemorrhagic areas, displaying significant prophylactic and therapeutic effects against gastric ulcers (184).

The *Pistacia* species have been assessed for activity against other, less common infections. *P. lentiscus* and *P. x saportae* leaves showed antifungal activity against *Cryptococcus neoformans* with a minimum inhibitory concentration (MIC) value of 0.32 µL/mL (185). Palmitic **(269)** and linoleic acids **(267**) from the *P. vera* plant were tested for antifungal and antiviral properties. Noticeable antifungal activity was seen at a concentration range of 128-256 µg/mL and the kernel and seed extracts showed significant antiviral activity compared to the rest of extracts and controls (186).

The *P. vera*, *P. terebinthus* and *P. lentiscus* leaves (petroleum ether, chloroform, ethyl acetate and ethyl alcohol extracts) significantly inhibited the growth of *Phytium ultimum* and *Rhizochtonia solani* (187) and increased growth of *Fusarium sambucinum* (113).

Pistacia vera showed appreciable inhibitory activity against *Plasmodium falciparum* at 4.8 µg/mL and *Trypanossoma brucei* rhodesiense at both 0.8 and 4.8 µg/mL compared to melarsoprol with no activity against *T. cruzi* (188).

Anthelmintic activity was displayed by galloylated tannins from the leaves of *P. lentiscu*s (189).

Quercetin **(134)** and naringenin **(129)** rich-fractions from *P. integerrima* galls facilitated the systemic absorption of polyphenols and flavonoids through mice cuticles more easily producing an enhanced scabicidal effect (190).

Wound Healing and Analgesia. Wound healing is important in preventing more serious infections and various *Pistacia* species have been assessed in the wound healing setting. *Pistacia atlantica* hulls were used to prepare an ointment that was applied to excision wounds in the treatment group of rats; wound contraction rate was significantly increased in the treatment group with wound closure achieved by all doses on the 6th day (191). Leaves from *P. lentiscus* were collected and quercetin **(134)** and myricetin **(138)** were isolated to be tested for *in vivo* wound healing. Centasia cream was used as a positive control; the best healing was observed in the group treated with the pure myricetin **(138)**(94).

Pistacia vera fruits were evaluated for *in vitro* scratch-wound healing with CHCl3, EtOAc, and n-BuOH fractions showing no toxic effects at a concentration range of 0.02–20 µg/mL and effective concentrations of each fraction being 0.02, 0.04 and 0.2 µg/mL, respectively (CHCl3 fraction showed higher wound healing ability than other fractions assessed) (142). Ointments created from oleoresins of *P. vera* were used for excisional wounds created in rabbits. No significant difference was found between Cicatryl (reference drug) treated groups and oleoresin treated groups (145).

Woundsare often accompanied with pain; therefore, it is only fitting that the analgesic effect of *Pistacia* has also been assessed. *P. integerrima* galls showed dose dependent protection in

chemically induced algesia; 200 mg/kg showed significant analgesic activity as compared to pentazocine and diclofenac in thermally induced analgesia (169).

Anticancer. *Pistacia atlantica* tree gums prepared into a nanostructured lipid carrier showed more cytotoxic properti in man breast cancer cells SKBR3 than free essential oil with remarkable apoptotic cell percentage as compared to control cells (192).

Pistacia lentiscus leaves and fruits were assessed for cytotoxicity. Quercetin **(134)** and gallic acid **(193)** were used and doxorubicin and fluorouracil (5-FU) were the reference compounds. Relevant cytotoxic activity of the crude extracts of both parts of the plant was noticed against melanoma tumor B16F10 cell line with IC_{50} values of 56.40 µg/mL and 58.04 µg/mL compared to doxorubicin and 5-FU (IC_{50} = 36.28 and 31.29 µg/mL respectively) (130).

α-Pinene **(1)** and limonene **(8)** from essential oil also exhibited anticancer effects on RD and L20B cell lines (156). Ethanolic extract of Chios mastic gum from *P. lentiscus* inhibited proliferation and induced death of HCT116 human colon cancer cells *in vitro* (193). In high-grade serous ovarian cancer cells, methanolic extract of flavonoids enhanced the sensitivity of platinum-based chemotherapy in the primary cell lines of patients (194). Leaves inhibited mitochondrial redox activity and cell viability of SH-Sy5Y and SK-N-BE(2)-C cell lines and were more effective than vinblastine by 3-fold (78). Terpenes from mastic reduced the level of inflammatory cytokines and induced a protective barrier effect by reducing paracellular permeability in human colon cell models. (195).

Pistacia chinensis, P. khinjuk, P. lentiscus leaves all showed moderate cytotoxic activity against lung, breast, and prostate cancer with only *P. lentiscus* showing moderate activity against liver cancer (196).

Digestive. *Pistacia vera* hulls enhanced amylase and protease digestive enzyme activity in fish models (197). *Pistacia lentiscus* resin has a potential role in the therapy for remission maintenance of irritable bowel syndrome by preventing an increase in amino acid content (198). In addition, essential oils isolated from the galls of *P. integerrima* potentiated isoprenaline-induced relaxation of rabbit jejunum, inhibited calcium-induced contraction of isolated guinea pig ileum and potentiated the reversal of potassium chloride-induced tonic contraction.

Cymene**(19)**, terpineol **(34)**, alpha-terpinene **(25)**, β-caryophyllene **(63)**, and *levo*-bornyl acetate**(12)** are the major constituents assumed to be responsible for the antispasmodic effects (199).

Chronic Conditions. *Pistacia atlantica* and *P. terebinthus* leaves were assessed for their inhibition of α-amylase and α-glucosidase. *In vitro* assays demonstrated inhibition of both enzymes, which play a role in the reduction of postprandial hyperglycemia *in vivo*. Hydroxybenzoic acids, gallotannins, and luteolin **(126)** were identified to be the major compounds responsible for the anti-diabetic effect (111, 200).

Pistacia lentiscus showed dose-dependent *in vivo* inhibition of α-amylase in streptozotocin-induced diabetic rats. The leaf crude extract exhibited higher efficacy in inhibition of α−amylase compared to its fruit counterpart likely related to a higher presence of phenolic compounds. Gallic acid **(193)** was identified in both leaves and fruits, while luteolin **(126)** was identified in fruits only (75). A randomized, triple-blind, placebo-controlled trial included 58 patients with type 2 diabetes mellitus and hyperlipidemia. 29 patients received 500 mg/day *P. atlantica* kurdica fruits capsules for 2 months. Results showed no significant reduction in fasting blood glucose and hemoglobin A1c compared to the placebo group. The same study found a significant decrease in total cholesterol and low-density lipoprotein compared to placebo (201). *Pistacia lentiscus* fruits, *P. lentiscus* leaves, and *P. khinjuk* leaves were also evaluated for their antihyperlipidemic activity *in vivo*. Results demonstrated a decrease in total cholesterol, triglycerides, and low-density lipoprotein, while the gum from the trunk and branches of *P. lentiscus* exhibited a decrease in total cholesterol only (202-205). Furthermore, *P. atlantica* leaves exhibited dose-dependent inhibition of angiotensin-converting enzyme-1 *in vitro*. The maximum inhibition of angiotensin

converting enzyme-1 was 74% at a concentration of 140 µg/mL (200).

Miscellaneous Use. Single studies have shown *Pistacia* use in an array of other conditions. For starters, *P. terebinthus* soap was able to counteract unwanted side effects in patients who developed a grade 2 or 3 skin toxicity to erlotinib. The topical application was found to be both safe and effective (206). In addition, *Pistacia*'s multimodal activity supports its use as a dual-targeted candidate for *in vivo* studies. For example, prior *in vitro* studies promote the use of *P. chinensis, P. lentiscus,* and *P. khinjuk* leaves in the prevention and management of Alzheimer's disease based on its anti-cholinesterase and anti-inflammatory activity (34). Furthermore, the introduction of SARS-COV-2 has led to the analysis of *Pistacia*'s ability to inhibit the replication and transcription processes. 1,2,3,4,6-pentagalloyl glucose **(257)** was identified as the apparent compound from *P. lentiscus* responsible for its binding affinities with helicase, RNA-dependent RNA polymerase (RdRp), envelope (E) protein, and 3CL like protease (3Clpro) (206). Another study identified phytochemicals in *P. integerrima* leaves and fruits with binding affinities for the spike receptor binding domain protein (43). Additional studies are important to identify and solidify *Pistacia*'s role in erlotinib toxicity, Alzheimer's disease, and SARS-COV-2.

CONCLUSION

This comprehensive literature review reveals that *Pistacia* species have numerous uses as a natural medicine. The various chemical compounds isolated from the plant have been proven to be responsible for the antioxidant, anti-inflammatory, anti-cancer, and antimicrobial effects, among many others. Different *Pistacia* species possess a varied number of chemical compounds isolated from them; this is more related to the extent that each species was studied and not to the fact that there are species producing a higher or a lower number of metabolites. Because of that, it is difficult to establish a correlation between the major compounds in each studied species and the pharmacological potential of them. They all seem to be fairly similar in terms of both chemical constituents and pharmacological profile, which in a way is expected from related taxa. Chemical equivalence brings pharmacological equivalence. However, to understand this genus in depth, additional research is required to identify, solidify, and expand its use in medicine.

CONFLICTS OF INTEREST

The authors declare that they do not have any conflicts of interest.

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Infarma CIÊNCIAS FARMACÊUTICAS

Revisão

Lactobacilli species' effects on liver function: a review

Efeito de espécies de Lactobacilos na função hepática: uma revisão

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ABSTRACT

Probiotics are microorganisms that, when ingested, colonize the gastrointestinal tract and bring health benefits. An unbalanced microbiota is synonymous with several diseases, promoting bacterial translocation to other body organs, especially the liver. Given the close correlation between these two factors and the recognized safety of daily intake of probiotics, this literature review aims to collect data on the impact of *Lactobacilli* probiotics on human liver function. The search for clinical studies published between the years 2011 and 2021 was carried out in the following databases and search tools: SciELO (Scientific Electronic Library Online), Google Scholar, PubMed, BVS (Virtual Health Library), Embase, Science Direct, Scopus, CRD (Centre for Reviews and Dissemination) and the Cochrane Library. The articles obtained at the end of the research brought data support the idea that the supplementation of probiotics containing bacteria of the genus *Lactobacilli* is beneficial for patients with a wide range of liver disorders, such as cirrhosis and hepatic encephalopathy. The mechanisms behind this action are diverse, such as decreased intestinal permeability, the growth of pathogenic microorganisms, and pro-inflammatory factors, in addition to stimulating colonization by symbiotic bacteria. Furthermore, studies carried out with healthy patients demonstrate the safety of probiotics, with no adverse effects.

Keywords: *Lactobacillus*; probiotic; liver function.

RESUMO

São chamados de probióticos os microrganismos que, quando ingeridos, colonizam o trato gastrointestinal e trazem benefícios a saúde. Uma microbiota desbalanceada é considerada sinônimo de diversas doenças, ao promover translocação bacteriana para os demais órgãos do corpo, em especial, o fígado. Dada a estreita correlação entre esses dois fatores, bem como a reconhecida segurança da ingestão de probióticos no dia a dia, a presente revisão bibliográfica tem como objetivo o levantamento de dados sobre o impacto dos probióticos Lactobacilos na função hepática humana. A busca por estudos clínicos publicados entre os anos de 2011 e 2021 foi realizada nas seguintes bases de dados: SciELO (*Scientific Electronic Library Onlin*e), Google Acadêmico, PubMed, BVS (Biblioteca

Virtual em Saúde), *Embase, Science Direct, Scopus,* CRD (*Centre for Reviews and Dissemination*) e *Cochrane Library*. Os artigos obtidos ao final da pesquisa trouxeram dados que apoiam a ideia de que a suplementação de probióticos contendo bactérias do gênero Lactobacilos é benéfica para pacientes com as mais variadas desordens hepáticas, tais como cirrose e encefalopatia hepática. Os mecanismos por trás dessa ação são diversos, tais como: diminuição da permeabilidade intestinal, bem como do crescimento de microrganismos patogênicos, e fatores pró-inflamatórios, além do estímulo de colonização por bactérias simbiontes. Ainda, estudos realizados com pacientes saudáveis demonstram a segurança do uso de probióticos, com ausência de efeitos adversos.

Palavras-chave: *Lactobacillus*; probióticos; função hepática.

INTRODUCTION

Liver-related diseases are major health problems that affect a large portion of the population. According to a study conducted in the United States of America (USA) in 2002, about 72 people out of 100.000 had some chronic liver disease. For example, one can cite the 20% prevalence of alcoholic hepatitis in people aged 40 to 60 (1). In 2019, an even more worrying fact emerged: liver cirrhosis is the eleventh leading cause of death worldwide (2). Also, according to data published by the Global Burden of Diseases, Injuries and Risk Factors Study 2017, globally, 1,5 billion people live with chronic hepatitis and liver cirrhosis (3), and another 311 million are infected with hepatitis B and C viruses (4).

Several liver disorders are characterized by the presence of fat in the liver, as well as inflammation, necrosis, and an increase in aminotransferases (5), which lead to loss of quality of life, secondary injuries, and death. These diseases have become as problematic as obesity worldwide (6). It is worth remembering that many hepatic pathologies do not have an established pharmacological therapeutic protocol, with the basic treatment changing in lifestyle (5, 7).

In this context, there is a close relationship between the intestine and the liver since the liver receives blood directly from this portion of the gastrointestinal tract through the portal circulation. The microbiota in this large organ of the digestive system is thought to impact liver function (5) through the interaction between about 2000 species of bacteria. The gut microbiota maintains the homeostasis of various body systems, such as the immune system and digestion. Changes in the composition and balance of the microorganisms involved can lead to or worsen disease conditions such as diabetes, obesity, and irritable bowel syndrome (1). With this in mind, the scientific community turns its eyes to maintaining intestinal microbiota balance through the consumption of probiotics.

Probiotics are microorganisms that benefit the organism when consumed in adequate amounts. Its ability to inhibit the growth of pathogenic bacteria by competing for nutrients and its adherence to the intestinal epithelium can be mentioned, promoting an improvement in bacterial translocation to other tissues (7,8), which culminates in a lower production of inflammatory molecules (5). Among them, the most famous are lactic acid bacteria, especially *Lactobacilli* (9), known for their beneficial role in other pathologies, such as constipation, diarrhea, lactose intolerance, cancer, obesity, and disorders of the lipid profile. In addition, they are considered safe for human consumption and widely used in preparing yogurts, cheeses, and other fermented foods (9-11).

To contribute to the studies related to the Gram-positive bacteria of the genus *Lactobacilli* and seek materials in the context of improving liver function, the present study aimed to investigate the impact of the consumption of probiotics containing *Lactobacilli* on the liver and liver diseases.

METHODS

The databases selected for the research of the materials that make up the collection of this bibliographic review were: SciELO (Scientific Electronic Library Online), Google Scholar, PubMed, BVS (Virtual Health Library), Embase, Science Direct, Scopus, CRD (Center for Reviews and Dissemination) and the Cochrane Library, to have broad coverage on the topic.

INCLUSION CRITERIA

Articles published between 2011 and 2021, written in Portuguese, English and Spanish, focusing on evaluating the impact of *Lactobacilli* species on human liver function through clinical trials, were included.

Exclusion criteria. Exclusion criteria are listed below: (i) books, opinion articles, review articles, and conference banners; (ii) those with a language or date restriction; (iii) studies that did not assess liver function or did not use *Lactobacilli*; (iv) cell culture experiments, *in vitro* or with the use of animals; (v) studies that used probiotic associations with other molecules or prebiotics; (vi) unfinished studies or studies not available for full access.

Sources of information and strategies for search. The search strategy used in each database was adapted to the search needs of each of them. The terms chosen were "*Lactobacillus*" and "Hepatic function", as well as their Portuguese counterparts, which were confirmed through a DeCS/MeSH survey (Table 1).

Studies selection. The first step of this literature review was the search for materials using the terms adapted to each database. Subsequently, the found references were added to EndNote Web, an online citation management program, to exclude duplicates. The title and abstract were read during the third stage, culminating in removing works that did not respect the previously established criteria. Finally, in the fourth step, the last exclusion was made through the entire reading of the remaining materials. Relevant information from the materials that make up the definitive collection of this review was extracted, including year and language of publication, country of study, clinical trials methodology (randomization, blinding, number of participants in each group and their characteristics, species of probiotic bacteria, dosage regimen, duration of interventions), and final outcomes analyzed.

Risk of bias. The assessment of the risk of bias in the clinical trials of this review was performed using the Cochrane Risk of Bias Tool, which evaluated parameters for random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and researchers (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias. For each, a high, low, or uncertain risk rating was assigned (12,13).

RESULTS AND DISCUSSION

With the initial search in databases, 3643 materials were found. After inserting them in the EndNote Web reference manager, 491 duplicate articles were observed. Of the 3152 remaining materials, 3009 were eliminated after analyzing the title and abstracts since it was perceived that they did not fit the pre-established criteria. The 143 remaining articles were entirely read, excluding 115 more materials. The collection of the present review was based on the data obtained from 28 clinical studies (Figure 1).

CHARACTERIZATION OF MATERIALS

The materials included the years 2011 to 2021, written in English. Only 20 articles confirmed in their methodology that they were double-blind studies. At the same time, one of them stated that it was blinded. The other seven works did not provide information. In addition, 26 of the studies were randomized. Only ten results presented methodologies using only *Lactobacilli*; another 18 linked *Lactobacilli* with other beneficial microorganisms.

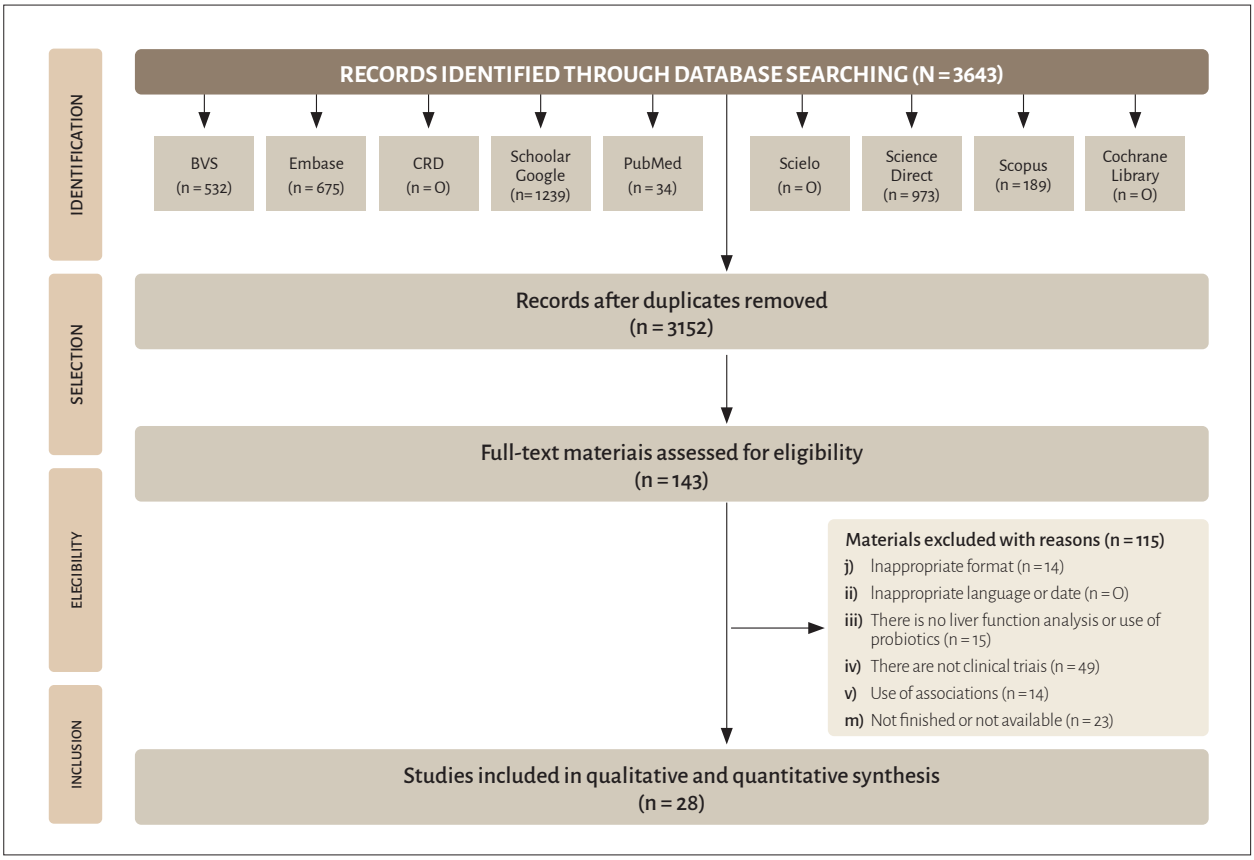
Concerning the place of the study, the obtained reports referred volunteers mainly from Asia (64,29%), followed by Europe (21,43%), Africa (10,71%), and Oceania (3,57%), without studies in America (Figure 2).

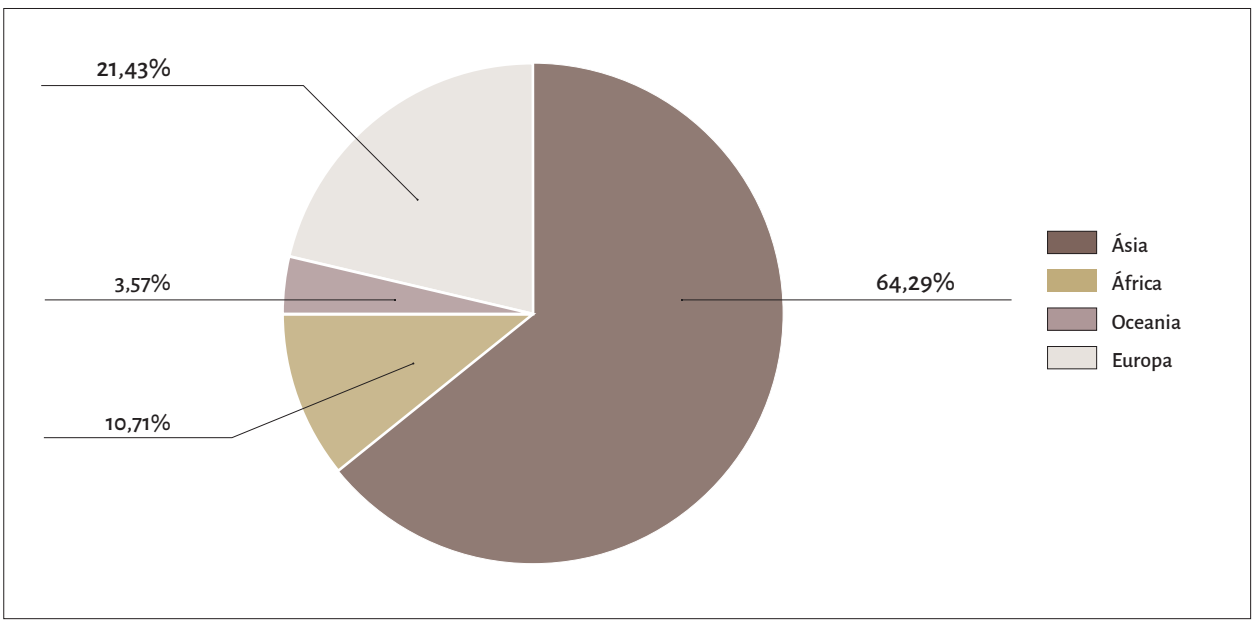
Table 1. Search strategy used in each database.

Database	Search strategy
Google Scholar, Scopus and Science Direct - English	"Lactobacillus" AND "liver function"
Google Scholar, Scopus and Science Direct - Portuguese	"Lactobacillus" AND "função hepática"
PubMed - English	(("lactobacillus"[MeSH Terms] OR "lactobacillus"[All Fields]) AND (("liver"[MeSH Terms] OR "liver"[All Fields] OR "livers"[All Fields] OR "liver s"[All Fields]) AND ("functional"[All Fields] OR "functional s"[All Fields] OR "functionalities"[All Fields] OR "functionality"[All Fields] OR "functionalization"[All Fields] OR "functionalizations"[All Fields] OR "functionalize"[All Fields] OR "functionalized"[All Fields] OR "functionalizes"[All Fields] OR "functionalizing"[All Fields] OR "functionally"[All Fields] OR "functionals"[All Fields] OR "functioned"[All Fields] OR "functioning"[All Fields] OR "functionings"[All Fields] OR "functions"[All Fields] OR "physiology"[MeSH Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "physiology"[MeSH Terms]))) AND ((review[Filter]) AND (2011:2021[pdat]))
PubMed - Portuguese	(("lactobacillus"[MeSH Terms] OR "lactobacillus"[All Fields]) AND ("funcao"[All Fields] AND ("ranunculaceae"[MeSH Terms] OR "ranunculaceae"[All Fields] OR "hepatica"[All Fields]))) AND (review[Filter])
Scielo and BVS - English	(Lactobacillus) AND (liver function)
Scielo and BVS - Portuguese	(Lactobacillus) AND (função hepática)
Cochrane Library - English	Lactobacillus in Title Abstract Keyword AND liver function in Title Abstract Keyword - (Word variations have been searched)
Cochrane Library - Portuguese	Lactobacillus in Title Abstract Keyword AND função hepática in Title Abstract Keyword - (Word variations have been searched)
CRD - English	((Lactobacillus) AND (função hepática)) and ((Systematic review:ZDT and Bibliographic:ZPS) OR (Systematic review:ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN DARE, NHSEED, HTA FROM 2011 TO 2021
CRD - Portuguese	((Lactobacillus) AND (função hepática)) and ((Systematic review:ZDT and Bibliographic:ZPS) OR (Systematic review:ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN DARE, NHSEED, HTA FROM 2011 TO 2021
Embase - English	'lactobacillus AND liver AND function AND [2011-2021]/py
Embase - Portuguese	'lactobacillus AND função AND hepática AND [2011-2021]/py

Adapted from PRISMA (14).

Figure 1. Information sources obtained, excluded, duplicated, and used from this bibliographic review

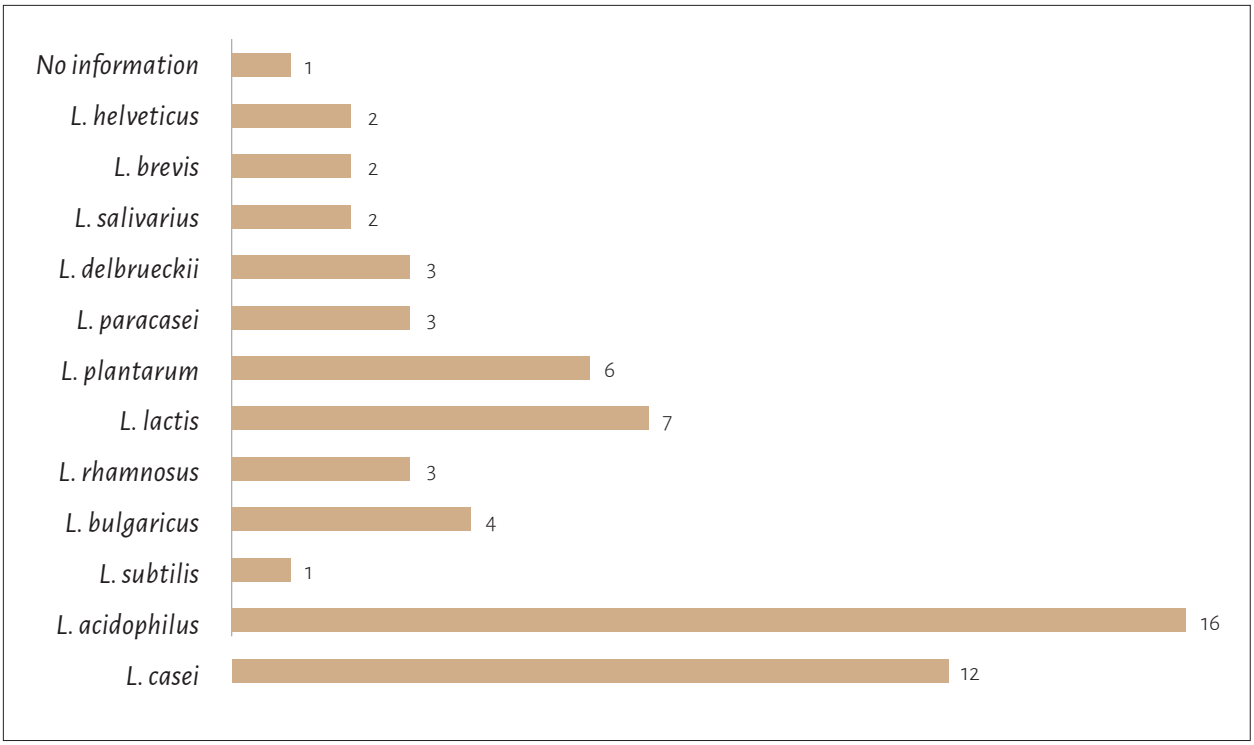




ASIA: SOUTH KOREA (7,14%), JAPAN (10,71%), MALAYSIA (7,14%), ISRAEL (3,57%), CHINA (14,29%), INDIA (10,71%), IRAN (3,57%), SRI LANKA (3,57%), IRAQ (3,57%); EUROPE: SPAIN (3,57%), ITALY (3,57%), POLAND (7,14%), AUSTRIA (3,57%), UNITED KINGDOM (3,57%); AFRICA: EGYPT (10,71%); OCEANIA: AUSTRALIA (3,57%).

Regarding the *Lactobacillus* species used by the researchers, *Lactobacillus acidophilus* stands out, with 16 citations in the methodologies, and *Lactobacillus casei*, with 12 citations (Figure 3). *Lactobacillus casei* is a popular species of study in probiotics due to its commercial value associated with improving capabilities in diarrhea, allergies, and obesity (15).

Figure 3. *Lactobacilli* species used in the methodologies of the articles that make up the collection of this review.



The results obtained by the different authors are shown in Table 2.

It is possible to observe through that most studies found improvement in some physiological parameters in the group treated with probiotics. Only four of twenty-eight studies found no significant differences between the control and treatment groups (8,17,26,32).

Pereg et al. (2011) and Firouzi et al. (2015) attribute the data without a significant difference to a low number of volunteers in the groups (8,26), as well as the short duration of the tests (26). However, other studies in this review found positive results even with a smaller population and a shorter term than the one used by them. The result obtained by Cox et al. (2014) can be explained by the fact that volunteers are healthy people without gastrointestinal, liver or metabolic tract comorbidities. However, such results demonstrated the safety of using probiotics in humans, given the absence of observed adverse effects (17). Finally, the study conducted by Yoshihisa et al. (2012) explained its results by a possible microbial death of the probiotics pashed in capsules over the weeks of study (32).

One study showed a negative effect of a long exposition of probiotics in liver transplants. There is a hypothesis not confirmed by the authors that the ingestion of probiotics can lead to the increase of some intestinal bacteria, such as *Lactobacillus* and *Bifidobacterium*, at the time of transplantation, which can facilitate intestinal lesions by the hepatitis C virus, the cause of death of patients in the study (22).

Regarding the outcomes evaluated by the researchers, liver function was the most estimated parameter, being present in 25 articles. In this regard, liver damage markers and proteins produced by this organ were evaluated. The reduction of inflammatory parameters was searched in 11 of the selected articles. Dysbiosis, on the other hand, was assessed in 10 studies, followed by intestinal permeability (6 papers). Metabolism alterations such as lipid profile and insulin resistance were evaluated in 6 studies. Finally, symptoms and/or exacerbations of hepatic encephalopathy were assessed to a lesser extent in only 5 articles.

Hepatic diseases. The volunteers who comprise the study groups of the present literature review often had some liver disease. Only two studies brought healthy volunteers to carry out their methodology (16,17).

Non-Alcoholic Fatty Liver Disease (NAFLD) is a common hepatic disease around the world, characterized by fat in the liver tissue, necrosis, and increased inflammatory factors; on biochemical tests, there is a marked increase in liver enzymes. It is important to emphasize that there is no well-defined treatment for this pathology, and only lifestyle changes are indicated to reduce the percentage of body fat (5).

Still, other common hepatic pathologies are Alcoholic Hepatitis (AH) and Alcoholic Liver Cirrhosis (ALC). Such pathologies are caused, among other complex factors, by the interaction between alcohol metabolites, oxidants, and inflammatory species. Inflammation usually stems from microbial uncontrollability in the intestine. It happens due to the ability of alcohol to interfere with the intestinal barrier, promoting the translocation of pathogenic bacteria, mainly Gram-negative ones, to the hepatic portal circulation, culminating in the activation of defense cells in the liver through endotoxins, such as lipopolysaccharide (LPS), and, consequently, in liver fibrosis (1,18).

These conditions can lead to the so-called Hepatic Encephalopathy (HE), caused by the accumulation of nitrogenous substances (ammonia) resulting from the breakdown of proteins in the intestine by bacteria when the liver is unable to transform it into urea to be excreted in the urine, and this ends up crossing the blood-brain barrier and reaching the central nervous system. In addition, other substances produced by intestinal microorganisms, such as mercaptans, can lead to a worsening of the case through synergism with ammonia. In mild cases, in the so-called Minimal Hepatic Encephalopathy (MHE), the patient has neurological abnormalities, leading to difficulties in carrying out simple everyday tasks. This condition affects 30% to 84% of patients with liver cirrhosis (19).

Mechanisms of action of probiotics. It is well known that intestinal dysbiosis, an imbalance between the bacteria that make up the gut microbiota, is closely linked to a large number of diseases, such as diabetes, colorectal cancer, and even Alzheimer's. Therefore, the balance of intestinal microorganisms is one of the primary outcomes studied (10). One of the main actions attributed to probiotics is the promotion of a balanced intestinal microbiota by stimulating the growth of the anaerobic bacteria population and reducing pathogenic microorganisms (30). It is known that the uncontrolled increase of the natural microbiota, called Small Intestine Bacterial Overgrowth (SIBO), leads to peritonitis and other inflammation due to increased intestinal permeability; this occurs through the reduction of the junctions between the epithelial cells, essential for the maintenance of the integrity of the barrier (7,15,20).

The body's normal balance is maintained through the intestinal barrier; when there is a failure in this system, there is bacterial translocation to other organs and greater absorption of pro-inflammatory molecules, such as LPS.

Table 2. Synthesis of the methodology of the works of this literature review, as well as the main conclusions obtained by the authors. In the studies that opted for the use of more than one species of probiotic, all were administered together to the volunteers.

Reference	Microorganism	Experimental Design	Results
Han et al., 2015 (1)	*Lactobacillus subtilis* and *Streptococcus faecium*	Group 01: 60 patients with AH, treated with 500 mg of probiotics three times a day for a week; Group 02: 57 patients with AH, with administration of placebo three times a day, for a week;	In the treated and placebo groups, there was a decrease in ALT, AST, γGT, TB, and PT levels, with no significant difference between them. There were no changes in the levels of protein and cholesterol. There was a decrease in the levels of LPS in the treated group, as well as TNF-α and pathogenic bacteria.
Aller et al., 2011 (5)	*Lactobacillus bulgaricus* and *Streptococcus thermophilus*	Group 01: 14 patients with NAFLD, treated with 500 million probiotics once a day for 3 months; Group 02: 14 patients with NAFLD, with administration of placebo (120 mg of starch) once a day for 3 months;	In the treated group, there was a decrease in ALT, AST and γGT levels. There were no changes in the inflammatory levels in either group (TNF-α and IL-6).
Vajro et al., 2011 (6)	*Lactobacillus rhamnosus* strain GG	Group 01: Obese pediatric patients with liver abnormalities, treated with 12 billion CFU of probiotics once daily for 8 weeks; Group 02: Obese children with liver abnormalities treated with placebo once a day for 8 weeks;	There was an improvement in ALT values in the treated group and in SIBO progression.
Mohamad Nor et al., 2021 (7)	*Lactobacillus acidophilus* BCMC 12,130 (107 mg), *L. casei* subsp *L. lactis* BCMC 12,451 (107 mg), *Bifidobacterium bifidum* BCMC 02290 (107 mg), *B. infantis* BCMC 02129 (107 mg) and *B. longum* BCMC 02120 (107 mg)	Group 01: 17 NAFLD patients treated with 30 billion CFU of probiotics twice a day for six months; Group 02: 22 NAFLD patients treated with placebo twice a day for six months;	There were no statistical differences between the treated and control groups regarding AST, ALT, γGT, fibrosis, and steatosis levels. However, the treated group was protected from the increased intestinal permeability observed in the control group.
Pereg et al., 2011 (8)	*Lactobacillus acidophilus, L. bulgaricus, Bifidobacterium bifidum*, and *Streptococcus thermophilus*	Group 01: 20 patients with CLC, treated with 2 x 1010 CFU of probiotics once a day for six months; Group 02: 15 patients with CLC, treated with placebo (non-fermentable wheat-based fibers) once a day for six months;	Between groups, there was no significant difference in plasma albumin, ALT, AST, bilirubin, creatinine, ammonia, and TP levels.
Elhawari and Emad, 2011 (9)	*Lactobacillus acidophilus*	Group 01: 100 HC patients treated with 100 million active probiotics three times a day for 2 weeks; Group 02: 48 healthy patients who did not receive anything;	There were no significant differences in serum bilirubin, ALT, and TP values. However, there was an improvement in HE parameters in the treated group.
Higashikawa et al., 2020(10)	*Lactobacillus plantarum* SN13T	Group 01: 11 patients with a slight increase in liver enzymes, treated with 1,2×1011 of live probiotics once a day for 16 weeks; Group 02: 10 patients with a slight increase in liver enzymes, treated with 1,2×1011 heat-killed probiotics once a day for 16 weeks;	There was a decrease in AST, ALT, and inflammatory parameters (TNF-α) in both groups and a beneficial modulation of the gut microbiota. There was no alteration of γGT.
Caiet al., 2020 (11)	Bifid Triple Viable: *Bifidobacterium*, *Lactobacillus* and *Enterococcus*	Group 01: 70 patients with NAFLD, treated with 1 g of probiotics twice a day, for 3 months + diets and physical exercises; Group 02: 70 patients with NAFLD, treated with diets and physical exercises for 3 months;	The group treated with probiotics had an improvement in the parameters of ALT, AST, γGT, as well as improvement in intestinal dysbiosis, lipid levels, NAFLD and insulin resistance profile. No significant changes in TB.

Reference	Microorganism	Experimental Design	Results
Xiong et al., 2021 (15)	Yakult (*L. casei* Shirota)	Group 01: 106 patients undergoing pharmacological treatment for tuberculosis, treated with 1 x 1010 CFU of probiotics once a day for 2 months; Group 02: 114 patients undergoing pharmacological treatment for tuberculosis, treated with 1 x 1010 CFU of probiotics twice a day for 2 months; Group 03: 105 patients undergoing pharmacological treatment against tuberculosis, without taking any probiotics or placebo;	There was an improvement in AST and TB values, as well as a decrease in inflammatory LPS and improvement in the intestinal microbiota. However, there were no differences between the groups regarding ALT, γGT and cases of hepatic encephalopathy.
Abd-Alwahab, and Fahad, 2018 (16)	Kefir (*Lactobacillus helveticus*, *L. lactis*, *L. casei*, *Streptococcus cremoris*), *Streptococcus lacti*, *Kluyveromyces marxianus*, *Saccharomyces turicensis*, and *Pichia fermentans*	Group 01: 25 healthy volunteers who received 200 mL of tap water once a day for 21 days; Group 02: 50 healthy volunteers, who received 200 mL of kefir fermented drink 5% (25 volunteers) and 7,5% (25 volunteers) once a day for 21 days;	The probiotic-treated group showed improvement in the lipid profile. There were no differences in AST and ALT values between groups.
Cox et al., 2014 (17)	*Bifidobacterium animalis* subsp. *lactis* Bl-04 (2,0 × 109 CFU), *Lactobacillus acidophilus* (5 × 109 UFC) NCFM and *B. animalis* subsp. *lactis* Bi-07 (5 × 109 CFU)	Group 01: 41 healthy volunteers who received probiotics once a day for 5 months; Group 02: 45 healthy volunteers who received placebo once a day for 5 months;	There was no significant difference between groups regarding liver function parameters (ALT, AST, ALP, and TB)
Koga et al., 2013 (18)	Y400: *Lactobacillus casei* Shirota YIT 9029	Group 01: 18 patients with compensated ALC treated with 40 billion CFU of probiotics twice a day for two weeks; Group 02: 19 patients with compensated ALC, with the administration of placebo (lactic acid) twice a day for two weeks;	Both groups had no changes in ALT, AST, γGT, TB and ferritin levels. However, the treated group had a higher level of liver proteins (transthyretin). Furthermore, there was improvement in inflammatory parameters (CRP) and intestinal dysbiosis.
Ziada et al., 2013 (19)	*L. acidophilus*	Group 01: 24 patients with cirrhosis and MHE, treated with 30-60 mL of lactulose once a day for 1 month; Group 02: 26 patients with cirrhosis and MHE, treated with 1x106 of probiotics three times a day for 1 month; Group 03: 25 patients with cirrhosis and MHE as a control group;	In the group treated with probiotics and lactulose, there was an 80% decrease in the probability of developing evident HE, with improvement in psychomotor tests and a reduction in ammonia and glutamine levels, due to the change in the intestinal microbiota. However, the probiotics group had better tolerability and treatment adherence.
Kwak et al., 2014 (20)	*Bifidobacterium lactis* (KCTC 11904BP), *B. bifidum* (KCTC 12199BP), *B. longum* (KCTC 12200BP), *Lactobacillus acidophilus* (KCTC 11906BP), *L. rhamnosus* (KCTC 12202BP), and *Streptococcus thermophilus* (KCTC 11870BP)	Group 01: 25 patients with CLD, treated with 5 × 109 viable cells of probiotics twice a day for four weeks; Group 02: 25 patients with CLD, treated with placebo twice a day for four weeks;	In the treated group, there was an improvement in the SIBO. There was no difference between the groups in terms of improvement in intestinal permeability, nor in the values of AST, ALT, TB, TP.
Grat et al., 2017 (21); and Grat et al., 2020 (22)	ProBacti 4 Enteric: *Lactococcus lactis* PB411 (50,0%), *L. casei* PB121 (25,0%), *Lactobacillus acidophilus* PB111 (12,5%), and *Bifidobacterium bifidum* PB211	Group 01: 26 patients with pre-transplant HC, treated with 3 x 109 CFU of probiotics once a day from two to ten weeks; Group 02: 29 patients with pre-transplantation HC, treated with placebo once a day for two to ten weeks;	In the treated group, there was a reduction in bilirubin levels, AST, and ALT, as well as an improvement in dysbiosis and postoperative infection rates. There was no difference in labor, hospitalization, or time of antimicrobial use. After a 5-year follow-up of patients, it was noted that prolonged administration of probiotics prior to liver transplantation has a negative effect on long-term allograft function.

Reference	Microorganism	Experimental Design	Results
Lunia et al., 2014 (23)	*Bifidobacterium breve*, *B. longum*, *B. infantis*, *Lactobacillus acidophilus*, *L. plantarum*, *L. paracasei*, *L. bulgaricus*, and *Streptococcus thermophilus*	Group 01: 86 HC patients treated with 100 billion CFU of probiotics three times a day for 3 months; Group 02: 74 HC patients who did not receive anything;	There was a decrease in HE occurrence in the probiotic-treated group and in SIBO and ammonia levels.
Asemi et al., 2015 (24)	*Lactobacillus acidophilus* (2×109 UFC), *L. casei* (7× 109 UFC), *L. rhamnosus* (1,5×109 UFC), *L. bulgaricus* (2×108 UFC), *Bifidobacterium breve* (2× 1010 UFC), *B. longum* (7×109 UFC), *Streptococcus thermophilus* (1,5×109 CFU)	Group 01: 28 patients with DM2, treated with probiotics once a day for 8 weeks; Group 02: 30 patients with DM2, treated with placebo once a day for 8 weeks;	In the treated group, there was an increase in calcium levels and a reduction in ALT. There was no change in other parameters of ions, TB, ALP, and AST.
Duseja et al., 2019 (25)	IVOMIXX, VISBIOME and DESIMONE: *Lactobacillus. paracasei* DSM 24733, *L. plantarum* DSM 24730, *L. acidophilus* DSM 24735, *L. delbrueckii* subsp. *bulgaricus* DSM 24734, *Bifidobacterium longum* DSM 24736, *B. infantis* DSM 24737, *B. breve* DSM 24732, and *Streptococcus thermophilus* DSM 24731	Group 01: 17 patients with NAFLD, treated with 675 billion CFU of probiotics once a day for 12 months + physical exercises; Group 02: 13 patients with NAFLD, treated with placebo (microcrystalline cellulose) once a day for 12 months + physical exercises;	The treated group had improvement in liver histology, as well as ALT levels and inflammatory markers (TNF-α, IL-1β, IL-6). There was no difference in terms of insulin resistance.
Firouzi et al., 2015 (26)	Hexbio: *Lactobacillus acidophilus*, *L. casei*, *L. lactis*, *B. bifidum*, *Bifidobacterium longum* and *B. infantis*	Group 01: 48 patients with DM2, treated with 6×1010 CFU of probiotics once a day for 12 weeks; Group 02: 53 patients with DM2, treated with placebo once a day for 12 weeks;	There were no significant differences in ALP, AST, ALT, TB, and albumin values, only a reduction in total proteins.
Horvath et al., 2016 (27)	*Bifidobacterium bifidum* W23, *B. lactis* W52, *Lactobacillus salivarius* W24, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *Lactococcus lactis* W19 and *L. lactis* W5	Group 01: 44 patients with HC, treated with 15 x 109 of CFU of probiotics once a day for 6 months; Group 02: 36 patients with HC, treated with placebo once a day for 6 months;	There was an increase in resting neutrophil bursts in the treated group compared to the control group. However, there were no differences in neutrophil phagocytosis, endotoxin load, intestinal permeability, or inflammatory markers. The liver function had a slight improvement in the treated group.
Li et al., 2021 (28)	*Lactobacillus casei* Shirota	Group 01: 46 patients with ALD, treated with placebo once a day for 2 months; Group 02: 58 patients with ALD, treated with 10 billion probiotics once a day for 2 months; Group 03: 54 patients with ALD, treated with 10 billion probiotics twice a day for 2 months; Group 04: 20 healthy patients who received no treatment;	There was a decrease in ALT, AST, TB, γGT levels, and lipid profile in the groups treated with probiotics. Furthermore, there was an improvement in the microbiota, intestinal permeability, and anti-inflammatory factors (IL-10).
Liu et al., 2015 (29)	*Lactobacillus plantarum*, *L. acidophilus* and *Bifidobacterium longum*	Group 01: 66 patients with CC, treated with 2,6 × 1014 of CFU of probiotics once daily for 16 days (6 preoperative days and 10 postoperative days); Group 02: 68 patients with CC, treated with placebo (maltodextrin) once a day for 16 days (6 days preoperatively and 10 days postoperatively);	There was a decrease in ALT, AST, and plasma endotoxin levels in the treated group. In addition, there was an improvement in intestinal permeability and in the levels of postoperative infection.
Monem, 2017 (30)	*Lactobacillus acidophilus*	Group 01: 15 patients with NASH, treated with 2 billion probiotics three times a day for 1 month; Group 02: 15 patients with NASH who received nothing;	ALT and AST levels decreased in the treated group. There was no change in the parameters of albumin, serum bilirubin, and proteins.

Reference	Microorganism	Experimental Design	Results
Rodrigo et al., 2021 (31)	Bio-Kult 14: *Bacillus subtilis* PXN 21, *B. bifidum* PXN 23, *B. breve* PXN 25, *B. infantis* PXN 27, *B. longum* PXN 30, *Lactobcillus acidophilus* PXN 35, *L. delbrueckii* ssp. *bulgaricus* PXN 39, *L. casei* PXN 37, *L. plantarum* PXN 47, *L. rhamnosus* PXN 54, *L. helveticus* PXN 45, *L. salivarius* PXN 57, *Lactococcus lactis* ssp. *lactis* PXN 63, *Streptococcus thermophilus* PXN 66	Group 01: 43 pediatric patients with NAFLD/NASH, treated with one (under 12 years old) or two capsules (over 12 years old) containing 2x109 CFU of probiotics once a day + diet and physical exercises for 6 months; Group 02: 41 pediatric patients with NAFLD/NASH, treated with one or two capsules containing placebo (microcrystalline cellulose) once a day + diet and physical exercises for 6 months;	Compared to the control group, there was no improvement in AST, ALT, and ALP levels, as well as in the lipid profile and insulin resistance in the treated group. There was improvement only in liver fat levels.
Yoshihisa et al., 2012 (32)	*Lactobacillus brevis* SBC8803	Group 01: 22 patients with increased γGT, treated with 3,3 × 109 CFU of probiotics twelve times a day for 8 weeks; Group 02: 23 patients with increased γGT, treated with placebo twelve times a day for 8 weeks;	There was an improvement in γGT levels after 4 weeks of treatment. Still, there was no significant difference in ALT, AST, and γGT levels after 8 weeks of treatment.
Dhiman et al., 2014 (33)	*Lactobacillus paracasei* DSM 24733, *L. plantarum* DSM 24730, *L. acidophilus* DSM 24735, *L. delbrueckii* ssp. *bulgaricus* DSM 24734, *Bifidobacterium longum* DSM 24736, *B. infantis* DSM 24737, *B. breve* DSM 24732, and *Streptococcus thermophilus* DSM 24731	Group 01: 16 patients with HC who recently recovered from an episode of HE, treated with 9x1011 CFU of probiotics once a day for 6 months; Group 02: 13 patients with HC who recently recovered from an episode of HE, treated with placebo (corn flour) once a day for 6 months;	Patients in the treated group were less likely to be hospitalized due to HE episodes, decreased inflammatory factors (TNF-α, IL1β, and IL6), and improved liver function. There were no significant changes in ammonia levels between both groups.
Macnaughtan et al., 2020 (34)	Yakult Europe: *Lactobacillus casei* Shirota	Group 01: 33 patients with stable HC, who received 6,5 × 109 CFU of probiotics three times a day for 6 months; Group 02: 35 patients with stable HC, who received placebo three times a day for 6 months;	There was an improvement in neutrophil activity in patients with a previous low in the treated group and a decrease in some inflammatory cytokines. There was no difference in the rate of hospitalization, decompensation, or infection between the groups and in liver function parameters, intestinal permeability, and endotoxins.

AH: ALCOHOLIC HEPATITIS; ALD: ALCOHOLIC LIVER DISEASE; ALP: ALKALINE PHOSPHATASE; ALT: ALANINE AMINOTRANSFERASE ; AST: ASPARTATE AMINOTRANSFERASE; CLD: CHRONIC LIVER; DISEASE; CRP: C-REACTIVE PROTEIN; CFU: COLONY FORMING UNIT; DM: DIABETES MELLITUS; HC: HEPATIC CIRRHOSIS ; HE: HEPATIC ENCEPHALOPATHY; IL: INTERLEUKIN; LPS: LIPOPOLYSACCHARIDE; MHE: MINIMAL HEPATIC ENCEPHALOPATHY; NAFLD: NON-ALCOHOLIC FATTY LIVER DISEASE; NASH: NON-ALCOHOLIC STEATOHEPATITIS; PT: PROTHROMBIN; TB: TOTAL BILIRUBIN; TNF-A: TUMOR NECROSIS FACTOR –ALPHA; SIBO: SMALL INTESTINAL BACTERIAL OVERGROWTH; ГGT: GAMMA-GLUTAMYL TRANSFERASE TIME;

The endotoxemia caused by this condition is especially apparent in the liver, as it receives blood directly from the intestine. Although the liver has processes to detoxify itself, the same does not occur in patients with pre-existing liver problems, culminating in several liver pathologies due to the accumulation of pro-inflammatory molecules that damage hepatocytes and can lead to organ dysfunction, fibrosis (31), triggering or aggravating pre-existing conditions, such as cholestasis. Other pathologies associated with bacterial translocation are hepatic encephalopathy, steatosis, hepatic fibrosis, and hepatorenal syndrome (7,15,20).

Some studies in this review demonstrated the ability of *Lactobacilli* to restore the amount of *Clostridium coccoides*, *Clostridium leptum,* and *Bacterioides fragilis*, as well as to reduce levels of Enterobacteriaceae, which are harmful when in imbalance (18). Furthermore, increased levels of *Bacterioides* species are known to positively affect the gastrointestinal tract (21). Kwak et al. (2014) managed to reverse SIBO in treated patients by decreasing hydrogen-producing bacteria (20). As a result, there was a decrease in urease-producing bacteria, such as *Klebsiella* and *Proteus* species, culminating in lower production and absorption of ammonia, which is toxic to the brain. In addition,

the ability of probiotics to decrease inflammation and oxidative stress in hepatocytes by improving ammonia clearance is noted (8,19).

Concerning intestinal permeability, the probable cause of its decrease in the presence of probiotics is the ability these microorganisms have to increase the viability of the intestinal epithelium through essential nutrients for the viability of these cells (19). Literature data states that supplementation with commensal bacteria, such as *Lactobacillus*, *Bifidobacterium,* and *Streptococcus*, can assist intestinal permeability and decrease bacterial translocation. It can be observed in the study carried out by Xiong et al. (2021), who demonstrated the ability of supplementation with *L. casei* to decrease Gram-negative Bacterioidetes species with a role in LPS synthesis and improve intestinal permeability. In addition, there was an increase in the number of beneficial bacteria in the intestines of treated patients (15).

LPS molecules, which are harmful to the body, have different ways of harming the liver. They can reduce the production of bile acid transporters, culminating in their intracellular accumulation in hepatocytes and, consequently, cell death and necrosis. In addition, LPS is responsible for increasing hepatic oxidative stress, as it induces the production of enzymes that produce reactive oxygen species (ROS), such as CYP2E1 (15).

Furthermore, supplementation with probiotics has effects on liver function. Generally, liver health is characterized by simple biochemical tests that quantify liver enzymes such as ALT, AST, ALP, and γGT. As an example, it can be mentioned that the increase in ALP and total bilirubin is linked to liver damage, such as cholestasis (15); still, elevated ALT is a marker of hepatocyte damage (24). Currently, more attention has been given to quantifying γGT, a molecule in hepatocytes and bile cells, which is a biomarker of alcohol-induced liver damage. Its increase is associated with damage from oxidant species, a risk factor for cardiovascular disease, diabetes, and non-alcoholic steatohepatitis (32). The decrease in these parameters, usually exacerbated in liver pathologies, is a positive factor in treating patients.

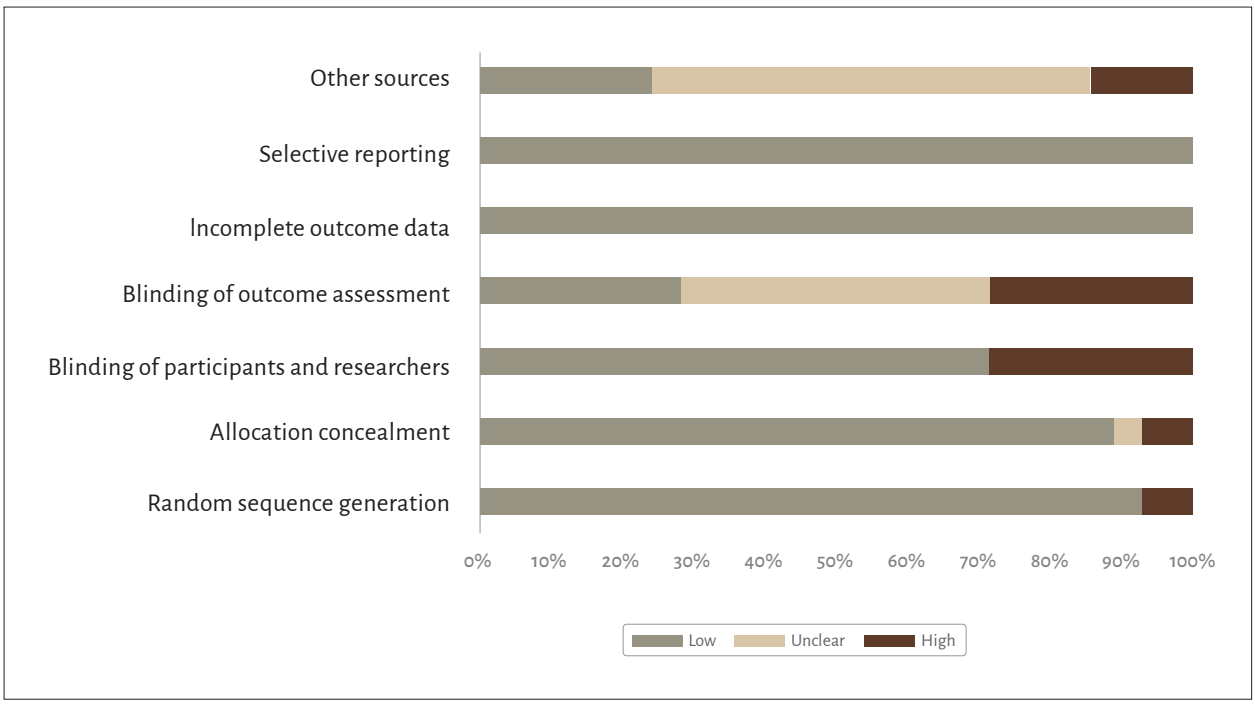
Some studies in the present review presented the improvement of enzymatic parameters with ingesting probiotics, such as *Lactobacilli*. As an example, the work conducted by Aller et al. (2011) can be cited. There was a decrease in ALT enzymes (67,7 IU/L before treatment and 60,4 IU/L after treatment), AST (41,3 IU/L before treatment and 35.6 IU/L L after treatment), and γGT (118,2 IU/L before treatment and 107,7 IU/L after treatment) (5). Vajro et al. (2011) found a substantial decrease in ALT levels (70,3 IU/L before treatment and 40.1 IU/L after treatment) (6). The data obtained by Cai et al. (2020) demonstrate a reduction in ALT (76,38 IU/L before treatment *versus* 34,18 IU/L after treatment), AST (57,23 IU/L before treatment; 32,49 IU/L after treatment), and γGT (30,95 IU/L before treatment; 15,17 IU/L after treatment) (11).

Another way of measuring the outcome of treatment against liver diseases is by quantifying proteins produced by the liver. The increase in production indicates good organ functioning, maintaining usual functions, and being important indicators of nutritional parameters. Among them, transthyretin, an important nutritional factor linked to the metabolism of iron, thyroxine, and retinol, synthesized by hepatocytes, can be mentioned. In addition, other proteins synthesized by the liver are albumin and transferrin (18).

Koga et al. (2013) demonstrated the capacity of consumed probiotics to promote the production of proteins by liver cells; this leads to an improvement in the osmotic pressure of the blood, as well as aiding in the transport of small molecules throughout the body (18).

In some studies, probiotics' consumption reduced inflammatory cytokines' expression. Information from the literature affirms that this occurs through altering the signaling of such communication molecules (25). This decrease in the exposure of liver cells to inflammatory mediators, endotoxins, and oxidative stress leads to an improvement in liver function, as observed in many of the studies presented here (9). Among the inflammatory parameters studied, TNF-α stands out for its role in insulin resistance and the production of oxidant factors, as well as in NAFLD and SHNA; when its levels are high, there is an increase in the severity of these diseases (10,30). Because it is important, it is generally targeted in treating cirrhosis using Infliximab (1). Still, other important cytokines have their production minimized by treatment with probiotics, such as Interleukin 1, 6, and 8 (18).

Figure 4. Graphically representation of risk of bias.



Another outcome observed in some studies was the improvement in the lipid profile of patients treated with probiotics. The translocation of pathogenic bacterial molecules can affect the metabolism of lipids and glucose and interfere with insulin resistance, increasing it. *Lactobacilli* intervene positively in these cases, as their metabolites can inhibit enzymes involved in the production of lipids, such as cholesterol synthetase, in addition to decreasing intestinal absorption of cholesterol. Finally, it is known that beneficial bacteria can also increase the excretion of cholesterol from bile salts in the feces (11), and lowering intestinal pH may increase cholesterol precipitation (16).

Five studies of the present bibliographic review studied such parameters of lipid metabolism. Three of them found significant improvement (11,16,28). In contrast, two others did not observe statistical differences in the improvement of the lipid profile between the probiotic-treated group and the control group (1,31).

Adverse effects. In all studies of the present literature review, no serious adverse effects were observed, proving the safety of these probiotics, even over long periods of treatment (19). It is even more interesting when it is observed that some drugs used in cases of liver dysfunction, such as lactulose, are commonly associated with constant adverse effects, such as flatulence, diarrhea, nausea, and abdominal pain (19,23).

Limitations. Although the results obtained by the studies of this review have been promising in several aspects in improving liver function in sick individuals, it should be noted that the methodological procedure of each of the authors was very different from each other.

The main variations observed were in the species of *Lactobacilli* used and their association with other microorganisms, in addition to the amount used and the chosen dosage regimen, making the comparison of results difficult and the impossibility of reaching definitive conclusions about the use of probiotics in liver diseases.

Another point that makes the comparison between the methodologies of the studies complex is the way of expressing the amount of probiotics administered. Most studies chose to define the amount in CFU (6,8,15,17,18,21-27,29,31-34). Some works have provided such information in

milligrams (1), grams (11), and milliliters (16). Only one of them had both forms of identification (7). Finally, some authors brought only the numerical quantity without a descriptive term (5,9,10,19,28,30). One study highlighted the number of microorganisms associated with the term "viable cells" (20).

Another crucial point of wide variation across studies was the duration of probiotic treatment. Some authors obtained results after a few weeks of ingestion of microorganisms, while others followed their patients for a year.

Therefore, the presented information here should not be generalized to other types of formulations containing different types, amounts, and associations of probiotics and other manufacturing processes of the consumed products.

Risk of bias. The result of the risk of bias analysis, carried out using the Cochrane Risk of Bias Tool, is shown in Figure 4. It is noted that the blinding of participants, researchers, and the outcome evaluation were the points with the highest number of high risks of bias. Regarding other sources of bias, because it is a broad topic, uncertainty appeared in a large percentage, mostly due to the low number of study participants.

CONCLUSION

The clinical studies obtained in this literature review corroborated that the consumption of probiotics containing *Lactobacilli*, isolated or in association with other symbiotic microorganisms, improves liver function parameters in patients with pathologies of this organ, as well as other factors related to the quality of life. Little difference was seen in healthy volunteers who received probiotics compared to the placebo group. Furthermore, they were well tolerated by the vast majority of patients, with few adverse effects, which, when observed, were light and tolerable. It makes probiotics containing *Lactobacillus* species a natural alternative for treating patients with liver disorders, improving the quality of life, even in long-term treatments.

The mechanisms associated with *Lactobacilli* that help to explain their action are diverse, including improvement of intestinal dysbiosis, promoting balance between microbiota species, decreased permeability of the intestine, and, consequently, bacterial translocation through cell membrane stability. In addition, there was a reduction in the inflammatory response profiles, with a decrease in the production of pro-inflammatory cytokines.

Although the data found in this review are promising, more studies are needed with well-established, double-blind methodologies, with a greater range of studied population, to clarify the real benefits in the liver function of using probiotics with Lactobacilli species.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests involved in this work.

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