**Study on Chemical Constituents and Bioactivities from Eucalyptus globulus**

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Abstract  Eucalyptus globulus (E. globulus) is a tall timber tree of genus Eucalyptus (Myrtaceae), and it is mainly distributed in the southern and southwestern China. The dry fruits of E. globulus, called as ‘Yi-Kou-Zhong’ in Chinese, have been commonly used as a traditional Chinese medicine to treat inflammation, eczema, and influenza. Herein, we summarized the chemical constituents and bioactivities of the Eucalyptus globulus.

Keywords  Eucalyptus globulus, chemical constituents, bioactivities

**Introduction**

Eucalyptus globulus is one of the most widely planted Eucalyptuses in the world. E. globulus is native to Tasmania and Australia. It was recorded that this plant was firstly introduced to China in late 1890s.[1] Nowadays, it is widely cultivated in southern and southwestern China, especially in Yunnan and Jiangxi provinces. It is commonly known as button seven, red trumpet flowers, victory fruit, and so on.[2] The chemical composition in E. globulus can be divided into volatile oil, triterpenoids, monoterpenes, sesquiterpenes, phloroglucinol derivatives, flavonoids, tannins. It is reported that this plant has anti-tumor, anti-inflammatory, anti-AIDS, anti-bacterial, anti-virus and other functions.[3]

Herein, we utilized “chemical constituents of Eucalyptus globulus” and “activities of “Eucalyptus globulus” as keywords, and relevant literatures and books were searched on SciFinder, Web of Science, China National Knowledge Infrastructure academic database and website. Herein, we summarized the chemical constituents and activities of E. globulus.

**Chemical Constituents**

Up to date, about 123 compounds have been isolated from E. globulus, including terpenes, flavonoids, organic acids, sesquiterpene, tannins, triterpene and phloroglucinol derivatives.[3]

**Monoterpenes and sesquiterpenes**

Five monoterpenes and sesquiterpenes have been isolated from E. globulus, which were identified as camphor (1), camphene (2), 1,8-eleuteropic acid (3), elemol (4), globulol (5).[4-6] Their structures are shown in Figure 1.

**Triterpenoids**

13 compounds were isolated from the fruits of E. globulus, named as 3β-acetoxyurs-11-en-28,13-olide (6), betulonic acid (7), betulinic acid (8), alpinolic acid (9), 2α,3β-dihydroxyurs-12-en-28-oic acid (10), usoric acid (11), 11,12-dehydroursolic acid lactone (12), eucapinic acid (13), 3-oxo-ursolic acid (14), corosolic acid (15), 3β,13β-dihydroxy-urs-11-en-28-oic acid-13-lactone (16), ileptatifol D (17), colosolic acid (18).[2-7] Above-mentioned compounds 14 and 18 were isolated from the fruits of E. globulus for the first time. 16 compounds were isolated from the stem bark of E. globulus, named as β-amyrin (19), acetylursolic acid (20), acetylectanolic acid (21), acetylbetulinic acid (22), erythrodilid (23), uvaol (24), 11α-methoxyacetylursolic acid methyl ester (25), betulinic acid methyl ester (26), cis-p-methoxy-cinnamoolxyursolic acid methyl ester (27), cis-p-methoxy-cinnamoyloxyacetic acid methyl ester (28), usoric acid methyl ester (29), methyl 3β,23-diacetoxy-12-ursen-28-bate (30), oleanolic acids (31), betulin (32), 2α,3α-isopropylidenedioxy-lup-20(29)-en-28-oic acid (33), 3β-formyloxurs-11-en-28,13-olide (34).[24] Their structures are shown in Figure 2.

![Figure 1: Chemical structures of monoterpenes and sesquiterpenes isolated from E. globulus.](image)

![Figure 2: Chemical structures of triterpenoids.](image)
Minireview

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Figure 2 Chemical structures of triterpenoids isolated from E. globulus.

Phloroglucinol derivatives

Phloroglucinol derivatives are the main compounds of E. globulus. Tian et al.\(^9,10\) obtained five new phloroglucinol glycoroglucinol, named as eucalmainsides A (35), eucalmainsides B (36), eucalmainsides C (37), eucalmainsides D (38), eucalmainsides E (39), and a carbon glycoside, named 8-β-C-glucopyranosyl-5,7-dihydroxy-2-isobutylchromone (40). Eight compounds were isolated from E. globulus, which were identified as eucalyptal A (41), eucalyptal B (42), eucalyptal C (43),\(^{11}\) eucalyptals D (44), eucalyptals E\(^{45}\),\(^{12}\) eucalyptin A (46),\(^{13}\) euglobal R1 (47), euglobal R2 (48). Qin et al.\(^{14}\) obtained ten new formyl-phloroglucinol-terpene meroterpenoids, named eucalyptoglobulusals A−J (49−58). Pham et al.\(^{15}\) obtained five new phloroglucinol derivatives, named as eucalyptins E−G (59−61), and thirteen known compounds were also isolated from the fruits of E. globulus, named as eucalyptone A (62), macrocarpal A (63), macrocarpal B (64), macrocarpal C (65), macrocarpal D (66), macrocarpal E (67), macrocarpal Q (68), eucarobustol E (69), euglobal-V (70), euglobal-III (71), 1-(2,6-dihydroxy-4-methoxy-3,5-dimethylphenyl)-2-methylbutan-1-one (72), 1-(2,4-dihydroxy-6-methoxy-3,5-dimethylphenyl)-3-meth-yibutan-1-one (73), cypricarp C (74). Seven phloroglucinol derivatives were accessed from the leaves of E. globulus, named as eucalyptone (75), macrocarpal H (76), macrocarpal I (77), macrocarpal J (78), euglobal-IvB (79), euglobal-VII (80), euglobal-IX (81). Two compounds were isolated from the stem bark of E. globulus, named eucalyptone G (82), rhodomyrtone (83).\(^{23,35}\) Their structures are shown in Figure 3.
Flavonoids are one of the earlier developed components in E. globulus. Sixteen flavonoids were isolated from the fruits of E. globulus, which were identified as 5-hydroxy-4',7-dimethoxy-6-methylavone (84), 8-β-C-glucosyl-5,7-dihydroxy-2-methylchro-manone (85), 6,6-C-glucosyl-5,7-dihydroxy-2-methylchromanone (86), 8-β-C-glycosyranosyl-5,7-dihydroxy-2-isobutyrylchromone (87), 8-β-C-glycosyranosyl-5,7-dihydroxy-2-isopropylchromone (88), quercetin 3-O-β-D-glucopyranoside (89), quercetin 3-O-β-D-glucuronide-6'-methyl ester (90), rhamnazin (91), rhamnetin (92), eriodictyo (93), quercetin (94), taxifolin (95), engelittin (96), catechin (97), kaempferol (98), 5-hydroxy-4',7-dimethoxy-6,8-dimethylavone (99) [16-20].

Seven compounds were isolated from the stem bark of E. globulus, which were identified as ellagic acid (107), 3-O-methylellagic acid-4′-O-α-L-rhamnopyranoside (108), valoneic acid dilateon (109), 3-O-methylellagic acid-4′-O-2″-O-acetyl-α-L-rhamnopyranoside (110), 3-O-methylglucic acid (111), 3-O-methylellagic acid 4′-O-α-L-2″-O-acetyllhamproyanoside (112), 3-O-methylellagic acid 4′-O-α-rhamnopyranoside (113), 3,4″,3″-trimethylellagic acid (116), 3,3′-O-trimethylellagic acid (117), 3,3′,4,4′-tetrathemylellagic acid (118), 3,3′-O-methylglucic acid 3′-O-α-rhamno-pyranoside (119), 3-O-methylellagic acid 3′-O-α-3″-O-acetyllhamproyanoside (120), 3-O-methylellagic acid 3′-O-α-2″-O-acetyllhamproyanoside (121), 3-O-methylellagic acid 3′-O-α-4″-O-acetyllhamproyanoside (122), methyl-ellagic acid (123). Their structures are shown in Figure 5.

Figure 4  Chemical structures of flavonoids isolated from E. globulus.

Tannins

Seven acid compounds were isolated from the fruits of E. globulus, which were identified as ellagic acid (107), 3-O-methylellagic acid-4′-O-α-L-rhamnopyranoside (108), valoneic acid dilateon (109), 3-O-methylellagic acid-4′-O-2″-O-acetyl-α-L-rhamnopyranoside (110), 3-O-methylglucic acid (111), 3-O-methylellagic acid 4′-O-α-L-2″-O-acetyllhamproyanoside (112), 3-O-methylellagic acid 4′-O-α-rhamnopyranoside (113), 3,4″,3″-trimethylellagic acid (116), 3,3′-O-trimethylellagic acid (117), 3,3′,4,4′-tetrathemylellagic acid (118), 3,3′-O-methylglucic acid 3′-O-α-rhamno-pyranoside (119), 3-O-methylellagic acid 3′-O-α-3″-O-acetyllhamproyanoside (120), 3-O-methylellagic acid 3′-O-α-2″-O-acetyllhamproyanoside (121), 3-O-methylellagic acid 3′-O-α-4″-O-acetyllhamproyanoside (122), methyl-ellagic acid (123). Their structures are shown in Figure 5.
F. galli-62d, and eucalyptin B (50:50) exerted moderate cytotoxic effects in A549 (29.9 and 13.8 μM), in 4T1 (18.77 and 8.45 μM), and in B16F10 (8.86 and 29.33 μM), respectively. However, macrocarpal C (65) displayed significant cytotoxicity in all three A549, 4T1 and B16F10 cells with IC50 values of 4.59, 1.54, 3.73 μM, respectively.

Wang et al.12 reported that two new phloroglucinols, eucalyptals D (44) and E (45), along with a related known compound, were isolated from E. globulus and their cytotoxic activity were evaluated. The results revealed that compounds 49, 50, 52 exhibited significant in vitro cytotoxicities against a few human cancer cell lines (Huh-7; Jurkat, BGC-823 and KE-97) using the CellTiter-GloTM luminescent cell viability assay method.

Qi et al.14 reported that eucalyptoborusal F (54) exhibited cytotoxicity against the human acute lymphoblastic cell line (CCRF-CEM) with an IC50 value of 3.3 μM. Taken together, these compounds showed significant in vitro cytotoxicities against a few human cancer cell lines. The obtained findings may lead to the development of new anticancer drugs.

Other activities
Qi et al.14 reported that eucalyptoborusal A (49), macrocarpal A (63), macrocarpal B (64), and macrocarpal D (66) displayed significant cytotoxicity against the human acute lymphoblastic cell line (CCRF-CEM) with an IC50 value of 3.3 μM. Taken together, these compounds showed significant in vitro cytotoxicities against a few human cancer cell lines. The obtained findings may lead to the development of new anticancer drugs.

Immunosuppressive activity

Compounds 62—74 were investigated for their immune suppressive effects in vitro, and eucalyptin B (62) and macrocarpal A (63) displayed moderate inhibitory activities with IC50 values of 11.8, 10.2, 18.2 and 19.1 μM, respectively.15

Antibacterial activity

Li et al.25 reported that E. globulus extract was effective against the two Gram-positive strains (S. aureus, B. subtilis). The results revealed that the extract of eucalyptin and gallic acid exert bactericidal effects against S. aureus (MBC/MIC = 1 and 1.4, respectively), while tannic acid exerts a bacteriostatic effect on the same bacterium (MBC/MIC = 3.33). The extract and tannic acid had a bacteriostatic effect against B. subtilis (MBC/MIC = 13.33 and 40, respectively), whereas gallic acid exhibited a bactericidal effect against this bacteria (MBC/MIC = 1.33).

Antitumor activity

Migration and invasion of cancer cells into surrounding tissue and vasculature is an important initial step in cancer metastasis. Metastasis is the leading cause of cancer related death.21 Yang et al.22 reported that eucalyptin A (46), together with two known compounds macrocarpal A (63) and macrocarpal B (64) exhibiting potent inhibition on HGF/c-Met axis. Compound 46 showed potent inhibition on HGF-induced c-Met activation and further suppressed HGF-stimulated cell motility and invasive behaviors.

Pham et al.23 evaluated the cytotoxic activity of compound eucalyptin B (62), which exhibited potent cytotoxicity against A549 cells with an IC50 value of 1.51 μM and induced concentration dependent apoptosis of up to 49%. Compounds euglobal-V (70) and euglobal-III (71) exhibited moderate cytotoxic effects in A549 (29.9 and 13.8 μM), in 4T1 (18.77 and 8.45 μM), and in B16F10 (8.86 and 29.33 μM), respectively.

However, macrocarpal C (65) displayed significant cytotoxicity in all three A549, 4T1 and B16F10 cells with IC50 values of 4.59, 1.54, 3.73 μM, respectively.
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