Triterpenes from the genus *Ficus* and Their Bioactivities

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Abstract Triterpenoids exist commonly in the genus *Ficus*. Till now, ninety-seven triterpenes have been isolated from the genus *Ficus*. The bioactivities of five triterpenes including maslinic acid, oleanolic acid, lupeol, betulinic acid and ursolic acid have been studied extensively. Herein, we provide an overview of triterpenes in the genus *Ficus* and their various bioactivities.

Keywords *Ficus*, triterpenoids, oleanolic acid, bioactivities

Introduction

The genus *Ficus* belongs to Moraceae that comprises about 1000 species, and it distributes mainly in the tropical and semitropical area. This genus can be deciduous or evergreen trees, shrubs, herbs, climbers or creepers,^[1] and their medicinal plants are often used in traditional folk medicine to treat pneumonia, cancer, tonsillitis, diarrhea, leukoderma, and cough.^[2] Previous phytochemical studies on *Ficus* genus have revealed the presence of coumarins, flavonoids, and triterpenoids. Triterpenoids, whose basic structures are usually established by thirty carbons with five isoprene units, exist widely in the genus *Ficus* and exhibit antineoplastic, antiviral, antibacterial, and anti-inflammatory activities. In this minireview, we summarized the triterpenes from the genus *Ficus* and their bioactivities.

Triterpenoids isolated from the genus *Ficus*

Up to now, twelve species of the genus were reported of the presence of triterpenes. Kuo group investigated *F. microcarpa* extensively and isolated thirty-five triterpenes (1—35) from its aerial roots and nine triterpenes (36—44) from its bark (Figure 1).^[3-8] Among these triterpenes, compounds 1—14 belong to taraxastane-type. Compounds 17 and 18 were determined as rare 13,27-cycloursane-type, and compounds 22 and 25 were elucidated by NMR and further confirmed by X-ray crystallography as 3 β -acetoxy-1 β ,11 α -epidioxy-12-ursene and 3 β -acetoxy-18 α -hydroperoxy-12-oleanen-11-one. Higa *et al.*^[9] isolated seven triterpenes from the ethanol extract of *F. microcarpa* leaves and elucidated them as taraxerol (45), glutinol (46), betulinic acid (47), oleanolic acid (48), epifriedelinol (49), friedelin (50), and lupeol acetate (51). From the fresh leaves and stems of *F. thunbergii*, Kitajima *et al.*^[10] obtained rhoiptelenol (52), α -amyrin (53), α -amyrin acetate (54), ursolic acid (55) and 3 α -hydroxyisohop-22(29)-en-24-oic acid (56). From the fruit of *F. pumila* L., two cycloartane-type triterpenoids (57 and 58), six acetylated dammarane-type triterpenoids (59—62), one euphane-type triterpenoid (63) and another two triterpenes (64 and 65) were isolated from its methanolic extract.^[11,12] From the leaves or stems of *F. pumila* L.,

11 α -hydroxy- β -amyrin (66) and a new neohopane (3 β ,29-dihydroxy-17- α -methylhop-13(18)-ene, 67) were obtained by silica gel chromatography.^[13,14] From its fresh leaves, compounds 68—73 were isolated from the ether extract.^[15] Tuyen *et al.*^[16] investigated the bark of *F. fistulosa* and purified seven triterpenes (74—80) from its MeOH extract by silica gel column chromatography and HPLC. The fractionation and purification of the leaf, stem bark and fruit extracts of *F. natalensis* led to the isolation and identification of the triterpenes (81—83).^[17] A novel lanostane derivative (lanost-20-en-3 β -acetate, 84), along with three other triterpenes (85—87) were isolated and characterized from the root bark of *F. racemosa*.^[18] From the fresh stem of *F. spetica*, a rare triterpene skeleton derivative, 13,27-cycloursan-3 β -yl-acetate (88) was isolated from natural sources for the first time.^[19] Study on the fresh and undried leaves of *F. carica* afforded baurenol (89).^[20] From the air-dried powdered leaves of *F. pandurata* Hance, isolation and purification of its ethyl acetate-soluble fraction afforded β -amyron (90) and 2 α ,3 α -dihydroxy-lup-20(29)-en-28-oate (91).^[21] A new antimicrobial triterpenic acid named as (9,11), (18,19)-disecoolean-12-en-28-oic acid (92) was afforded from the leaves of *F. benjamina*.^[22] 3-O-[β -D-glucopyranosyl]-quinovic acid-28-O-[β -L-rhamnopyranosyl] ester (93) was isolated from the aerial roots of *F. elastic*.^[23] Investigation on the EtOH extract of the air dried stems of *F. tsiangii* afforded 3-acetoxy-12-oleanene-11-ketone (94), 3-acetoxy-lup-12,20(29)-diene (95).^[24] Epilupeol acetate (96) was isolated and identified from *F. drupacea* L with antifungal activities against *Aspergillus versicolor* and *A. ochraceus*.^[25] A novel triterpene lactone was isolated and determined as moretenolactone (97) from the leaves of *F. insipida*.^[26]

Bioactivities of triterpenes from the genus *Ficus*

Triterpenoids have extensive biological activities. Researches show that they possess antineoplastic, antidiabetic, antibacterial, antiviral, antiparasitic, antifertility, hepatoprotective and anti-inflammatory activities.

Antineoplastic activity

Maslinic acid (43) exerted cytotoxicity to A549 cells by

inducing mitochondrial apoptosis and suppressing HIF-1 α expression under normoxic and hypoxic conditions.^[27] Oleanolic acid (**39**) inhibited the proliferation of T24 cells of human bladder cancer through inhibiting Akt/mTOR/S6K and ERK1/2 signal pathway.^[28] Betulinic acid (**38**) decreased the cells in the S-phase and increased the cells in the G2-phase, causing the arrest of cells in the G2-phase, thus inhibited the proliferation of triple-negative breast cancer cells.^[29]

Antidiabetic activity

A triterpene, α -amyrin acetate (**54**) from the fruits of *F. remosa* was evaluated for antihyperglycemic activity in STZ-S model at the dose of 100 mg/kg and found to lower the blood glucose levels by 18.4% and 17% at 5 and 24 h.^[30] Oleanolic acid (**39**) could enhance glucose-stimulated insulin secretion and cell proliferation in insulinoma cells.^[31] Ursolic acid (**55**) slowed the development of diabetic nephropathy and decreased glomerular mesangial cells hypertrophy and proliferation through inhibiting p85PI3K-pAkt-pmTOR signal pathway caused by up-regulating miRNA-21 and down-regulating PTEN protein.^[32]

Hepatoprotective activity

Lupeol (**80**) ameliorated GalN/LPS-induced liver injury through inhibiting IRAK-mediated TLR inflammatory signaling.^[33]

Anti-inflammatory activity

Lupeol (**80**) protected against LPS-induced microglial neuroinflammation via inhibiting the P38-MAPK and JNK pathways, thus having the therapeutic potential to treat various neuroinflammatory disorders.^[34] Maslinic acid (**43**) may protect neural cells by promoting synaptogenesis and axonal regeneration through regulating Akt/GSK-3 β signaling pathway.^[35]

Antibacterial activity

Fontanay *et al.*^[36] investigated the antibacterial activities of betulinic acid (**38**), oleanolic acid (**39**) and ursolic acid (**55**). Their study showed that betulinic acid didn't have antibacterial activity (**38**), whereas oleanolic acid (**39**) and ursolic acid (**55**) showed a moderate to strong antibacterial activity against Gram-positive bacteria through inhibiting the expression of peptidoglycan biosynthesis-related genes of *S. mutans* UA159 at the transcriptional level. Antibacterial and antifungal activities of maslinic acid (**43**) were evaluated by the agar well diffusion method.^[37] The results showed that it inhibited moderately on *Aspergillus flavus* and *Ustilago maydis*.

Antiviral activity

Betulinic acid (**38**) prevented HCV replication by suppressing the NF- κ B and ERK1/2-mediated COX-2 pathway.^[38] Oleanolic acid (**39**) inhibited the secretion of HBsAg and HBeAg in HepG 2.2.15 cell line, indicating potential HBV inhibitory activity.^[39]

Antiparasitic and anti-HIV activity

Yamamoto *et al.*^[40] assayed the activity of oleanolic acid (**39**) and ursolic acid (**55**) in experimental cutaneous leishmaniasis (*in vitro* and *in vivo*). They concluded that oleanolic acid (**39**) eliminated leishmania in the promastigote form, whose mechanism may be associated with programmed cell death.

Among HIV-1 reverse transcriptase (RT)-associated functions, DNA polymerase and Ribonuclease H (RNase H) are both essential for HIV replication. Esposito *et al.*^[41] showed that betulinic acid (**38**) can impair the function of ribonuclease H (RNaseH), which is related to HIV-1 reverse transcription.

Figure 1 Structures of triterpenoids from the genus *Ficus*.

Conclusions and Perspectives

The plants from the genus *Ficus* have a long history in medicinal use. With the improvement of modern instruments and experimental techniques, many chemical constituents have been isolated and elucidated from the genus *Ficus* and some of them have been bio-evaluated. This minireview summarizes 97 triterpenoids (the richest constituents) and their bioactivities as antidiabetic, antineoplastic, anti-inflammatory and antibacterial from twelve species of the genus *Ficus*. However, as we read the published papers, we found that most pharmacological assays still used their crude extracts and the chemical constituents accounting for the bioactivities have yet to be known. In order to get drug candidates from the genus *Ficus*, the chemical constituents of most plants of the genus and their activities still need to be investigated extensively in future.

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