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Review article

Pharmacology of oleanolic acid and ursolic acid

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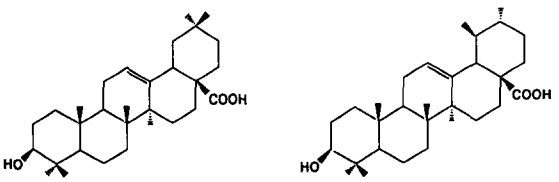
Abstract

Oleanolic acid and ursolic acid are triterpenoid compounds that exist widely in food, medicinal herbs and other plants. This review summarizes the pharmacological studies on these two triterpenoids. Both oleanolic acid and ursolic acid are effective in protecting against chemically induced liver injury in laboratory animals. Oleanolic acid has been marketed in China as an oral drug for human liver disorders. The mechanism of hepatoprotection by these two compounds may involve the inhibition of toxicant activation and the enhancement of the body defense systems. Oleanolic acid and ursolic acid have also been long-recognized to have antiinflammatory and antihyperlipidemic properties in laboratory animals, and more research is warranted to develop a therapy for patients. Recently, both compounds have been noted for their antitumor-promotion effects, which are stimulating additional research in this field. Oleanolic acid and ursolic acid are relatively non-toxic, and have been used in cosmetics and health products. The possible mechanisms for the pharmacological effects and the prospects for these two compounds are discussed.

Keywords: Oleanolic acid; Ursolic acid; Triterpenoid; Hepatoprotection; Antiinflammatory; Antihyperlipidemia; Antitumor-promotion

1. Introduction

Oleanolic acid (3β-hydroxy-olea-12-en-28-oic acid) and its isomer, ursolic acid (3β-hydroxy-urs-12-en-28-oic acid) (Fig. 1), are triterpenoid compounds which exist widely in natural plants in the form of free acid or aglycones for triterpenoid saponins (Price et al., 1987; Mahato et al., 1988; Wang and Jiang, 1992). Saponins can be chemically categorized as comprising an aglycone linked to one or more sugar chains. There are two groups of



Oleanolic acid Ursolic acid

Fig. 1. Structures of oleanolic acid and ursolic acid.

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saponins, one contains a steroidal aglycone, and the other contains a triterpenoid aglycone (Price et al., 1987). Squalene is considered as the common precursor for biosynthesis of both steroid and triterpenoid systems (Price et al., 1987). Like steroids, triterpenoids have many biological effects, and interest in triterpenoids is growing (Price et al., 1987; Mahato et al., 1988). In this review, discussion will be focused on pharmacology of the two triterpenoids, oleanolic acid and its isomer, ursolic acid, largely because they share many common pharmacological properties. Other triterpenoids may have similar properties but in general they have not been studied in as much detail.

2. Occurrence in folk medicine

Ginseng, the roots of *Panax ginseng* C.A. Meyer, has been well known among the people in East Asian countries since ancient times as a precious drug for longevity or cureall. The effective principles of ginseng are thought to be saponins, with 20-S-protopanaxadiol, 20-S-protopanaxtriol and oleanolic acid as the main aglycones (Shibata, 1977). Oleanolic acid, the aglycone for many triterpenoid saponins in medicinal plants, has been shown to be an active ingredient in producing biological effects (Table 1). Oleanolic acid has been isolated from more than

Table 1
Partial survey on medicinal plants containing oleanolic acid as an active ingredient

Names of the plant	Biological activity	References
Aralia chinensis L. var *nuda* Nakai (Araliaceae)	Hepatoprotection	Wang and Jiang, 1992; Liu et al., 1994b
Beta vulgaris L. var. cicla L. (Chenopooliaceae)	Hepatoprotection	Yabuchi et al., 1988
Calendula officinalis L. (Compositae)	Antifugal activity	Favel et al., 1993
Eugenia jaumbolana Lam. (Myrtaceae)	Inhibition of lipid peroxidation and protection against adriamycin toxicity	alanehru and Nagarajan, 1991; 1992
	Antifertility activity	Rajasekaran et al., 1988
Ganoderma lucidum Karst.	Anticariogenic activity	Hada et al., 1990
Glechoma hederacea L. (Labiatae)	Inhibition of azoxymethane-induced carcinogenesis in rats	Yoshimi et al., 1992
	Antitumor promotion	Ohigashi et al., 1986; Tokuda et al., 1986
Ligustrum lucidum Ait. (Oleaceae)	Antiinflammation	Dai et al., 1988, 1989
	Antihyperglucemia	Liu et al., 1994
	Inhibition of mutagenicity by B[a]P	Niikawa et al., 1993
Luffa cyclindrica Roem. (Cucurbitaceae)	Antiinflammation and inhibition of C3-convertase of the complement pathway	Singh et al., 1992; Kapil et al., 1994.
Oleandra neriifolia L.	Antiinflammation	Gupta et al., 1969
Panax ginseng C.A. Meyer (Araliaceae)	Hepatoprotection, tonic effects etc.	Shibata, 1977
Sapindus mukorossi Gaertn (Sapindaceae)	Antiinflammation	Takagi et al., 1980
Swertia mileensis He et Shi (Gentianaceae)	Hepatoprotection	Human Med Inst, 1975, 1977; Ma et al., 1982
Swertia japonica Makino (Gentianaceae)	Hepatoprotection	Hikino et al., 1984b
Tetrapanax papyriferum L. (Araliaceae)	Hepatoprotection	Hikino et al., 1984a
Tinospora sagittata G. (Menispermaceae)	Antihyperglucemia	Hao, 1991

120 plant species (Wang and Jiang, 1992); listed in Table 1 is the result of a partial survey on the existence of oleanolic acid in folk medicine, and its biological activity.

The plant *Sambucus chinesis* Lindl. is used to treat inflammatory disorders and acute hepatitis in folk medicine. Both oleanolic acid and ursolic acid have been identified as active components in producing hepatoprotective effects (Ma et al., 1986). Ursolic acid is similar to oleanolic acid chemically and pharmacologically. Table 2 summarizes the result of a partial survey on medicinal plants containing ursolic acid as an active ingredient.

The traditional uses of plants containing oleanolic acid or ursolic acid in folk medicines are multiple, in terms of antiinflammatory, hepatoprotection, analgesia, cardiotonic, sedative and tonic effects, etc. Many of these therapeutic effects have been confirmed by contemporary scientific research. With the isolation of oleanolic acid or ursolic acid from medicinal plants, new pharmacological properties of these two compounds have also been discovered, which will be discussed in this review.

3. Hepatoprotective effects

The hepatoprotective effect of oleanolic acid was first reported in 1975 in the study of *Swertia mileensis* He et Shi, a traditional herbal medicine used for hepatitis. Of three compounds isolated from this herb, oleanolic acid was most effective in protecting against CCl_4-induced liver injury in rats (Hunan Med. Inst., 1975). Since then, oleanolic acid has been further demonstrated to decrease CCl_4-induced liver parenchymal cell necrosis, steatosis and degeneration (Ma et al., 1982), and prevents CCl_4 plus alcohol-induced chronic cirrhosis in rats (Han et al., 1981). Among seven Chinese hepatoprotective compounds, oleanolic acid is very effective in protecting against chemically induced liver injury in mice (Liu et al.,

Table 2
Partial survey on medicinal plants containing ursolic acid as an active ingredient

Names of the plant	Biological activity	References
Calluna vulgaris (Ericaceae)	Inhibition of lipoxygenase and cyclooxygenase in HL60 leukemic cells	Simon et al., 1992; Najid et al., 1992
Eribotrya japonica Lindl. (Rosaceae)	Inhibition of mutagenesis in bacteria	Young et al., 1994
Eucalyptus hybrid (Myrtaceae)	Hepatoprotection	Shukla et al., 1992
Glechoma hederacea L. (Labiatae)	Antitumor-promotion	Ohigashi et al., 1986; Tokuda et al., 1986
Melaleuca leucadendron L. (Myrtaceae)	Inhibition of histamine release	Tsuruga et al., 1991
Ocimum sanctum L. (Labiatae)	Inhibition of lipid peroxidation and protection against adriamycin toxicity	Balanehru and Nagarajan, 1991; 1992
Rosmarinus officinalis L. (Labiatae)	Antimicrobial activity	Collins and Charles, 1987
	Inhibition of mouse skin tumorigenesis	
	Antiinflammation	Huang et al., 1994
Pyrola rotundifolia (Pyrolaceae)	Antiinflammation	Kosuge et al., 1985
Psychotria serpens L. (Rubiaceae)	Cytotoxic to leukemia cells	Lee et al., 1988
Sambucus chinesis Lindl (Caprifoliaceae)	Hepatoprotection	Ma et al., 1986
Solanum incanum L. (Solanaceae)	Hepatoprotection	Lin et al., 1987
Tripterospermum taiwanense (Gentianaceae)	Hepatoprotection	Gan and Lin, 1988

1994b). Oleanolic acid protects against the hepatotoxicity produced not only by CCl_4, but also by acetaminophen, cadmium, bromobenzene, phalloidin, thioacetamide, furosemide, colchicine and D-galactosamine plus endotoxin. However, it is ineffective in decreasing the hepatotoxicity produced by allyl alcohol, dimethylnitrosamine, α-amanitin and chloroform (Liu et al., 1995a). The hepatoprotective profiles indicate that oleanolic acid protects many, but not all of the hepatotoxicants, and suggest that multiple mechanisms may be involved in the hepatoprotective effect of oleanolic acid. In rat primary hepatocyte cultures, oleanolic acid also decreases the cytotoxicity produced by CCl_4 and D-galactosamine (Hikino et al., 1984a, 1984b).

Ursolic acid, the isomer of oleanolic acid, was also identified as an active hepatoprotective component in the preparation of *Sambucus chinesis* Lindl. (Ma et al., 1986), *Solanum incanum* L. (Lin et al., 1988), *Tripterospermum taiwanense* (Gan and Lin, 1988), and *Eucalyptus* hybrid (Shukla et al., 1992). In addition to its protection against CCl_4-induced liver injury, ursolic acid also protects against D-galactosamine-induced liver injury in rats, and prevents acetaminophen-induced cholestasis (Shukla et al., 1992). In comparison, ursolic acid is even more potent than oleanolic acid in decreasing chemically induced liver injury in mice (Liu et al., 1994a).

After satisfactory therapeutic effects in clinical trials were achieved (Hunan Med. Inst., 1977), oleanolic acid has been successfully used as an oral drug to treat human liver diseases in China, including acute and chronic hepatitis, as well as other liver disorders (Qu, 1981; Wu and Li, 1986; Chen and Wang, 1989). Treatment of patients with oleanolic acid for 3 months or longer has been shown to have more beneficial effects than placebo controls: the elevated serum aminotransferase activity is returned to the normal level, the occurrence of cirrhosis from chronic hepatitis is decreased, and the clinical symptoms of hepatitis are improved (Qu, 1981; Wu and Li, 1986). Extraction of oleanolic acid from *Beta vulgaris* L. var. cicla L. (sugar beets) for treatment of liver failure and liver disorders has also been patented in Japan (Yabuchi et al., 1988).

The mechanisms for the hepatoprotection by oleanolic acid and/or ursolic acid appear to be multiple. It is known that many hepatotoxicants require metabolic activation, especially through liver cytochrome P-450 systems. Treatment of mice with the disodium semisuccinate of oleanolic acid decreased liver microsomal P-450 levels (Zhang and Liu, 1984). Oleanolic acid also produced a dose-dependent reduction in liver microsomal P-450 (25–37%) and cytochrome b_5 (20%), but had no effect on NADPH-cytochrome *c* reductase (Liu et al., 1995b). Treatment of mice with oleanolic acid suppresses CYP1A and CYP2A enzymes, while having no appreciable effect on CYP3A enzymes (Liu et al., 1995b). Similar results are also observed for ursolic acid (Liu et al., unpublished data). As a corollary, oleanolic acid protects against acetaminophen hepatotoxicity by decreasing its toxication metabolism via liver cytochrome P-450 enzymes (Liu et al., 1993a). The protective effects of oleanolic acid against the hepatotoxicity of bromobenzene, thioacetamide, CCl_4 and furosemide in mice may be partially attributed to suppression of hepatic cytochrome P-450 enzymes (Liu et al., 1995a,b).

The suppressive effect of oleanolic acid on cytochrome P-450 (20–30%), however, is not dramatic and does not explain the mechanism(s) by which oleanolic acid protects against hepatotoxicants that do not require metabolic activation, such as cadmium. Therefore, secondary consideration should be given to the effects of oleanolic acid on the body defense systems. Treatment of mice with oleanolic acid increases some antioxidant components in the liver, such as glutathione, metallothionein, zinc, glutathione *S*-transferase towards 1-chloro-2,4-dinitrobenzene (DNCB) and the glucuronosyltransferase towards acetaminophen (Zhang and Li, 1992; Liu et al., 1993a, 1995b). However, oleanolic acid had no appreciable effects on hepatic glutathione peroxidase, glutathione reductase, superoxide dismutase and DT-diaphorase (Liu et al., 1995b). Nevertheless, the modulation of some of these defense mechanisms by oleanolic acid may contribute to its hepatoprotective effects against some hepatotoxicants. For example, oleanolic acid induces metallothionein, which sequesters Cd in the

cytosol, and thus reduces cadmium toxicity (Liu et al., 1993b). Oleanolic acid increases and/or maintains the hepatic glutathione, which plays an important role in protecting against CCl_4 and acetaminophen-induced liver injury (Zhang and Li, 1992; Liu et al., 1993a). Inhibition of lipid peroxidation by oleanolic acid is also proposed to play a role in preventing CCl_4 and D-galactosamine plus endotoxin-induced liver injury (Balanehru and Nagarajan 1991; Zhang and Li 1992; Liu et al., 1993c).

Preventing liver lesions from progressing to fibrosis and cirrhosis, and repairing parenchymal cell damage by stimulating liver regeneration are important mechanisms for hepatoprotection. Treatment of rats for 6 weeks with oleanolic acid protects against CCl_4 plus alcohol-induced chronic liver injury, as evidenced by decreased necrosis, degeneration, fibrosis and cirrhosis (Han et al., 1981). Oleanolic acid also decreased tyrosine content in plasma and brain of the cirrhotic rats, but had no effect on the absorption of collagen fibers (Han et al., 1981). In hepatotectomy rats, oleanolic acid (100 mg/kg, s.c. × 2) enhanced liver regeneration, as indicated by increased mitosis (Han et al., 1981).

The mechanisms of hepatoprotection by oleanolic acid and ursolic acid are still not completely understood and more studies in this area are warranted.

4. Anti-inflammatory effects

The anti-inflammatory effect is a common property of many triterpenoids (Price et al., 1987; Mahato et al., 1988). Oleanolic acid and ursolic acid are among the most notable triterpenoid compounds.

The anti-inflammatory effect of oleanolic acid was first reported in 1960s. Gupta et al. (1969) reported the inhibitory effects of oleanolic acid on carrageenan-induced rat paw edema and formaldehyde-induced arthritis. The anti-inflammatory effects of oleanolic acid have also been confirmed in later studies (Takagi et al., 1980; Dai et al., 1989a; Singh et al., 1992). Additionally, oleanolic acid has also been shown to inhibit rat paw edema produced by dextran, and to suppress adjuvant-induced arthritis in rats and mice (Singh et al., 1992). Oral administration of oleanolic acid is not as effective as i.p. or s.c. injection in inhibiting inflammatory reactions (Takagi et al., 1980; Sigh et al., 1992). The acetic acid-induced vascular permeability in mice and histamine-induced vascular permeability in rats are decreased approximately 50% by oleanolic acid pretreatment (Dai et al., 1989a). The allergic responses, such as Forssman cutaneous vasculitis in guinea pigs and the active Arthus reaction in rats, are prevented by oleanolic acid treatment. The delayed hypersensitivity reaction in mice, induced by sRBC injection or topical application of dinitrochlorobenzene, is also suppressed by oleanolic acid (Dai et al., 1988).

Ursolic acid was identified as an active component of *Pyrola rotundifolia* L. in preventing carrageen-induced paw edema in rats, as well as acetic acid-induced writhing in mice (Kosuge et al., 1985). In the medicinal preparations from *Rosmarinus officinalis* L. (Rosemary), ursolic acid is one of the active components in preventing 12-*o*-tetradecanoylphorbol-13-acetate (TPA)-induced mouse ear edema (Hirota et al., 1990; Huang et al., 1994).

The mechanisms of anti-inflammatory effects of oleanolic acid and/or ursolic acid have been attributed to the following aspects: (1) Inhibition of histamine release from mast cells induced by the compound 48/80 and concanavalin A (Dai et al., 1989b; Rajasekaran et al., 1990; Tsuruga et al., 1991), or by adriamycin (Balanehru and Nagarajan, 1994); (2) inhibition of lipoxygenase and cyclooxygenase activity (Simon et al., 1992; Najid et al., 1992), thus reducing some inflammatory factors produced during arachidonic acid cascade. For example, the synthesis and release of PGE_2 and leukotriene B are suppressed by oleanolic acid (Dai et al., 1989a; Zhou et al., 1993); (3) inhibition of elastase, the IC_{50} for elastase inhibition by ursolic acid and oleanolic acid were quite similar (4.4 vs. 6.4 μM). Elastase is thought to play a role in tissue inflammatory response in rheumatic diseases (Ying et al., 1991); (4) inhibition of complement activity (Dai et al., 1989b), possibly through the inhibition on C_3-convertase of the classical complement pathway (Kapil et al., 1994). In addition, high doses of oleanolic acid produce thymus atrophy (Dai et al., 1989a, 1989b).

5. Antitumor activity

Both tumor initiation and promotion are inhibited by oleanolic acid and ursolic acid to various degrees. The most notable effect of these two triterpenoids is antitumor-promotion.

Oleanolic acid and ursolic acid are identified as active components of *Ligustrum lucidum* Ait. in inhibiting mutagenicity produced by benzo[a]pyrene (B[a]P) in bacteria (Niikawa et al., 1993). The amounts of oleanolic acid and ursolic acid at 90% suppression in each solvent fraction is 65 μg and 30 μg, respectively (Niikawa et al., 1993). Ursolic acid is also identified as an active component of *Eriobotrya japonica* Lindl. in inhibiting aflatoxin B_1-induced mutagenicity in *Salmonella typhimurium* TA100 or TA98 assay system (Young et al., 1994). Ursolic acid extracted from *Rosmarinus officinalis* L. is effective in inhibiting the covalent binding of B[a]P to epidermal DNA and in inhibiting tumor initiation by B[a]P and 7,12-dimethyl-benz[a]anthracene (DMBA) (Huang et al., 1994). Bioassay-directed fractionation of the cytotoxic antileukemic extracts of *Prunella vulgaris, Psychotria serpens*, and *Hyptis capitata* has led to the isolation of ursolic acid as one of the cytotoxic principles towards the leukemia cells P-388 and L-1210, as well as the human lung carcinoma cell A-549 (Lee et al., 1988). Treatment of rats with oleanolic acid (200 ppm) in diet for 3 weeks decreases the incidence and multiplicity of azoxymethane-induced intestinal tumor (Yoshimi et al., 1992).

Oleanolic acid and ursolic acid have been shown to be the active components of *Glechoma hederacea* L. in inhibiting tumor-promoting effects by 12-*o*-tetradecanoyl phorbol-13-acetate (TPA), both in vitro (Ito et al., 1983; Ohigashi et al., 1986) and in vivo (Tokuda et al., 1986). TPA-induced Epstein-Barr virus (EBV)-associated activation in Raji cells was inhibited by oleanolic acid and ursolic acid at about 1000-fold molar ratio to TPA or another tumor promotor, teleocidin B-4 (Ohigashi et al., 1986; Konoshima et al., 1987). In the two-stage mouse skin tumorigenic experiment, initiating with DMBA followed by promoting with TPA, the percentage of papilloma-bearing mice and average number of papillomas/mouse were significantly decreased by topical application of oleanolic acid or ursolic acid (Tokuda et al., 1986). This effect was comparable to that of retinoid acid, and ursolic acid is more effective following a single application (Tokuda et al., 1986). The subsequent studies confirm and extend their findings (Hirota et al., 1990; Huang et al., 1994; Shibata et al., 1994), and the structure-activity relationship of oleanane-type triterpenes for the inhibition of tumor promotion is analyzed (Nishino et al., 1988).

The mechanisms by which oleanolic acid and ursolic acid suppress the tumor promotion are not known, but may be due to the following effects: (1) inhibition of inflammation produced by tumor promoters (Huang et al., 1994; Shibata et al., 1994); (2) inhibition of tumor promoter (TPA)-induced ornithine decarboxylase activity in mouse skin (Huang et al., 1994); (3) suppression of certain oncogene expression, such as c-*jun* and c-*fos* (Rhew et al., 1993); (4) induction of the differentiation, this effect may be related to partial remissions of some kinds of tumors (Lee et al., 1994). For example, ursolic acid or oleanolic acid caused the morphological change of F9 teratocarcinoma stem cells into endoderm cell (Lee et al., 1994), induced the differentiation of M1 cells into macrophage-like cells (Umehara et al., 1992); (5) modulation of body defense systems, such as antioxidant potential and immune functions. Treatment of mice with ursolic acid inhibits mitochondrial lipid peroxidation in tumor-bearing rats, and returns the increased superoxide dismutase to normal levels (Dominic et al., 1993). However, ursolic acid differs from linoleic acid in modulating T subsets in sarcoma 180-transplanted mice; it is not as effective as linoleic acid in modulating T subsets (Kim et al., 1993). This is not surprising, as the two acids are chemically very different.

The use of triterpenoid compounds, such as oleanolic acid and ursolic acid, has been recommended for skin cancer therapy in Japan (Muto et al., 1990). Cosmetic preparations containing ursolic acid/oleanolic acid are patented in Japan for the prevention of skin cancer for topical use (Ishida et al., 1990). Pharmaceutical preparation containing oleanolic acid is patented for the treat-

ment of non-lymphatic leukemia (Liu, 1986). Nevertheless, more focused research is needed to develop an anticancer chemotherapy using oleanolic acid or ursolic acid.

6. Anti-hyperlipidemic effects

The hypolipidemic and anti-atherosclerotic properties of triterpenoids, such as ursolic acid and glycyrram, were first reported by scientists in the Soviet Union in 1979. Ursolic acid fed to rabbits and rats prevented the experimental atherosclerosis, and lowered blood cholesterol (44%) and β-lipoprotein levels (50%) (Parfenteva, 1979; Vasilenko et al., 1981). They further tested another 14 triterpenoid compounds, and found that all of them, including oleanolic acid, were effective in preventing hyperlipidemia in rabbits, guinea pigs and rats (Vasilenko et al., 1982). Treatment of experimental hyperlipidemic rats with oleanolic acid (50 mg/kg, p.o. for 9 days) decreases the elevated blood cholesterol and β-lipoprotein levels by more than 40%; this effect is similar to that produced by clofibrate, and better than that produced by berberine (Liu et al., 1987). Oleanolic acid does not affect the blood lipoprotein levels in normal rabbits, but decreases the elevated blood cholesterol levels and prevents lipid precipitation in blood vessels and major organs of experimental hyperlipidemic rabbits. The serum concentrations of high density lipoprotein are increased, while the low density lipoproteins are decreased following oleanolic acid treatment (Ma, 1986). The anti-hyperlipidemic effect of oleanolic acid and ursolic acid has stimulated considerable clinical interest (Ma, 1986).

7. Other effects

7.1. Anti-ulcer effects

Oleanolic acid, ursolic acid and their derivatives have been shown to be effective in producing anti-ulcer activity (Gupta et al., 1981; Snyckers and Fourie, 1984; Wrzeciono et al., 1985). The heat-, chemical- (aspirin, indomethacin, reserpine, acetic acid), and stress-induced ulcers in rats were decreased by oleanolic acid treatment (Snyckers and Fourie, 1984). This inhibitory effect can be accomplished without compromising the anti-thrombotic and anti-inflammatory effect of aspirin, and it even increases the analgesic activity of aspirin (Snyckers and Fourie, 1984). In comparison to aspirin, oleanolic acid (Singh et al., 1992) or ursolic acid (Gupta et al., 1981) exerts anti-inflammatory effects without causing ulcerogenic effects. Ursolic acid administered orally to rats also decreases the incidence of gastric ulceration induced by pyloric ligation (Gupta et al., 1981). The hemisuccinates of oleanolic acid derivatives were more effective in producing antiulcer effects in rats than that produced by carbenoxalone, a known antiulcer agent (Wrzeciono et al., 1985).

7.2. Anti-microbial activity

Ursolic acid and its derivatives have been shown to have anti-microbial activity, such as growth inhibition of *Staphylococcus aureus*, gram-negative organisms and *Microsporium lenosum* (Zaletova et al., 1986). Ursolic acid was identified as one of the active components in rosemary to inhibit the growth of some food-associated bacteria and yeast (Collins and Charles, 1987). Ursolic acid also decreased the cytopathalic effects in Vero cells exposed to Hepes simplex virus (Poehland et al., 1987), but its derivatives had no effect on HIV and Sindbis virus replication (deTommasi et al., 1992). Two oleanolic acid 3-hemiesters exerted a high protection index on vaccina virus (Serra et al., 1994). Oleanolic acid-type saponins also exhibited a broad spectrum of antifungal activity (Anisimov et al., 1979), especially against the strain of *Candida glabrata* (Favel et al., 1994).

7.3. Hypoglycemic effect

Oleanolic acid treatment (50 and 100 mg/kg, s.c. × 7d) before or after the treatment of alloxan decreased the blood glucose level in alloxan-induced diabetic mice; the elevation of blood glucose caused by adrenaline (0.2 mg/kg, i.p.) or glucose (2 g/kg, i.p.) was also attenuated by oleanolic acid treatment (Hao et al., 1989). When rats were intoxicated with alloxan (170 mg/kg, i.p.), followed by oleanolic acid treatment (100 mg/kg, p.o., 4 × per day for 1 week), the elevation of blood glucose was also ameliorated, and hepatic glycogen

and insulin were higher than the pathological controls (Liu et al., 1994).

7.4. Protection against cyclophosphamide-induced toxicity in mice

Oleanolic acid has been identified as an active component of *Ligustrum lucidum* Ait. in preventing cyclophosphamide-induced lethal toxicity in mice, and in elevating the numbers of plasma leukocytes in cyclophosphamide-intoxicated mice (Dai et al., 1982). Cyclophosphamide-induced chromosome damage in mice was also reduced by oleanolic acid treatment (Hang et al., 1987).

7.5. Anti-cariogenic activity

Oleanolic acid was identified as an active component of *Ganoderma lucidum* Karst. in preventing dental caries in an *in vitro* anti-plaque assay (Hada et al., 1990). Oleanolic acid and ursolic acid has been shown to inhibit glucosyltransferase from *Streptococcus mutans*, a primary cariogenic bacteria (Kozai et al., 1987). Another triterpenoid com-

Table 3
Summary on pharmacology of oleanolic acid and ursolic acid

Pharmacological effects	Proposed mechanism	References
Hepatoprotection	Protect against chemically induced liver necrosis	Human Med Inst., 1977; Ma et al., 1982; 1986; Lin, 1987; Shukla et al., 1992; Liu et al., 1994; 1995
	Suppression of cytochrome P-450	Zhang & Liu, 1984; Liu et al., 1995b
	Enhancement of hepatic glutathione system	Zhang & Li, 1992; Liu et al., 1993a; 1995b
	Inhibition of lipid peroxidation	Balanehru and Nagaraji, 1991; Zhang & Li, 1992
	Induction of metallothionein	Liu et al., 1993b
	Prevention of fibrosis	Han et al., 1981
	Stimulation of liver regeneration	Han et al., 1981
Antiinflammation	Prevention of chemically induced rat paw edem	Gupta et al., 1969; Takagi et al., 1980; Dai et al., 1989a; Kosuge et al., 1985; Singh et al., 1992
	Reduction of vascular permeability	Dai et al., 1988; 1989a; Huang et al., 1994
	Inhibition of histamine release	Rajasekaran et al., 1990; Tsuruga et al., 1990
	Suppression of lipoxygenase & cyclooxygenase	Simon et al., 1992; 1992; Zhou et al., 1993
	Inhibition of elastase	Ying et al., 1991
	Inhibition of complement activity & C3-convertase	Dai et al., 1989b; Kapil et al., 1994
Antitumor activity	Inhibition of mutagenicity by B[a]P or aflatoxin B1	Niikawa et al., 1993; Young et al., 1994
	Inhibition of covelent binding of B[a]P to DNA	Huang et al., 1994
	Inhibition of TPA-induced EBV activation	Ohigashi et al., 1986; Konoshima et al., 1987
	Suppression of skin tumor promotion by TPA	Tokuda et al., 1986; Huang et al., 1994
	Reduction of TPA-induced inflammation	Huang et al., 1994
	Induction of differentiation	Umehara et al., 1992; Lee et al., 1994
Antihyperlipidemia	Prevention of experimental atherosclerosis	Parfenteva, 1979; Vasilenko et al., 1981
	Reduction of blood cholesterol	Vailenko et al., 1982
	Decrease in blood low density lipid proteins	Vailenko et al., 1982; Liu et al., 1986
	Increase in blood high density lipid proteins	Ma, 1986

pound glycyrrhizin is under clinical trial for treating dental caries (Steinberg et al., 1989).

7.6. Anti-fertility activity

Oleanolic acid, extracted from *Eugenia jambolana* Lam. was shown to have anti-fertility effects in male rats (Rajasekaran et al., 1988). Oleanolic acid and other triterpenoids have also been shown to be an inhibitor of testosterone 5α-reductase, and to have anti-male hormone activities (Ohyo, 1985).

8. Toxicity

Oleanolic acid is relatively non-toxic. A single s.c. injection of oleanolic acid (1.0 g/kg) to mice or to rats, no mortality was observed during 5-day period (Hunan Med. Inst., 1975; Singh et al., 1992). During multiple administration of oleanolic acid (180 mg/kg, p.o.) for 10 days, no abnormalities were observed in brain, heart, lung, liver, kidney, thyroid, testes, stomach, spleen or intestine (Hunan Med. Inst., 1977). However, parenteral injection of higher doses of oleanolic acid (300 μmol/kg, s.c. × 3 d) to mice causes cholestasis in some animals (Liu et al., unpublished data). A 70-case clinical trial using oleanolic acid (60–90 mg/day, for 30 days) for acute jaundice hepatitis demonstrated that it was therapeutically effective in the absence of apparent side effects (Xu and Wan, 1980). The long-term use of oleanolic acid (> 3 months) in 188 cases of chronic hepatitis indicates that oleanolic acid is safe (Xu, 1985).

Because of its efficacy and apparent low side effects, oleanolic acid has been patented in Japan as an additive to health drinks (Okudo et al., 1990) and hair tonics (Okazaki et al., 1987). It is also marketed in China for liver disorders.

9. Conclusions

Triterpenoids are an interesting group of compounds in nature. During the last two decades, pharmacological studies of oleanolic acid and ursolic acid indicate that these two triterpenoids have many beneficial effects, notably hepatoprotection, antiinflammation, antitumor-promotion and antihyperlipidemia (summarized in Table 3). These two triterpenoids are relatively non-toxic, and oleanolic acid has been marketed in China for human hepatitis. In the future, more mechanistic-oriented basic research is needed to elucidate the mechanisms of action. The studies on derivatives of these two compounds and on other triterpenoid acids are also desired to elucidate the structure-activity relationships and to guide the development of novel therapeutic agents.

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