

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 (3 $\beta$ -hydroxy-olea-12-en-28-oic acid) and its isomer, ursolic acid (3 $\beta$ -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

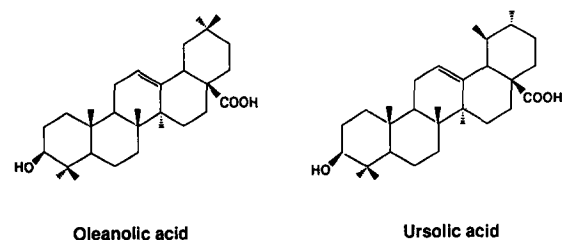


Fig. 1. Structures of oleanolic acid and ursolic acid.

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

macological 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<sub>4</sub>-induced liver injury in rats (Hunan Med. Inst., 1975). Since then, oleanolic acid has been further demonstrated to decrease CCl<sub>4</sub>-induced liver parenchymal cell necrosis, steatosis and degeneration (Ma et al., 1982), and prevents CCl<sub>4</sub> 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
<i>Calluna vulgaris</i> (Ericaceae)	Inhibition of lipoxygenase and cyclooxygenase in HL60 leukemic cells	Simon et al., 1992; Najid et al., 1992
<i>Eribotrya japonica</i> Lindl. (Rosaceae)	Inhibition of mutagenesis in bacteria	Young et al., 1994
<i>Eucalyptus</i> hybrid (Myrtaceae)	Hepatoprotection	Shukla et al., 1992
<i>Glechoma hederacea</i> L. (Labiatae)	Antitumor-promotion	Ohigashi et al., 1986; Tokuda et al., 1986
<i>Melaleuca leucadendron</i> L. (Myrtaceae)	Inhibition of histamine release	Tsuruga et al., 1991
<i>Ocimum sanctum</i> L. (Labiatae)	Inhibition of lipid peroxidation and protection against adriamycin toxicity	Balanehru and Nagarajan, 1991; 1992
<i>Rosmarinus officinalis</i> L. (Labiatae)	Antimicrobial activity Inhibition of mouse skin tumorigenesis	Collins and Charles, 1987
<i>Pyrola rotundifolia</i> (Pyrolaceae)	Antiinflammation Antiinflammation	Huang et al., 1994 Kosuge et al., 1985
<i>Psychotria serpens</i> L. (Rubiaceae)	Cytotoxic to leukemia cells	Lee et al., 1988
<i>Sambucus chinensis</i> Lindl (Caprifoliaceae)	Hepatoprotection	Ma et al., 1986
<i>Solanum incanum</i> L. (Solanaceae)	Hepatoprotection	Lin et al., 1987
<i>Tripterospermum taiwanense</i> (Gentianaceae)	Hepatoprotection	Gan and Lin, 1988

1994b). Oleanolic acid protects against the hepatotoxicity produced not only by  $\text{CCl}_4$ , 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,  $\alpha$ -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  $\text{CCl}_4$  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 chinensis* 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  $\text{CCl}_4$ -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,  $\text{CCl}_4$  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  $\text{CCl}_4$  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  $\text{CCl}_4$  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  $\text{CCl}_4$  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 hepatotomy rats, oleanolic acid (100 mg/kg, s.c.  $\times$  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 *Pyñola 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  $\text{PGE}_2$  and leukotriene B are suppressed by oleanolic acid (Dai et al., 1989a; Zhou et al., 1993); (3) inhibition of elastase, the  $\text{IC}_{50}$  for elastase inhibition by ursolic acid and oleanolic acid were quite similar (4.4 vs. 6.4  $\mu\text{M}$ ). 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  $\text{C}_3$ -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  $\mu\text{g}$  and 30  $\mu\text{g}$ , respectively (Niikawa et al., 1993). Ursolic acid is also identified as an active component of *Eriobotrya japonica* Lindl. in inhibiting aflatoxin B<sub>1</sub>-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  $\beta$ -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  $\beta$ -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 ac-

complished 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 anti-ulcer 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 cytopathic 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 vaccinia 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.  $\times$  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  $\times$  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
Antiinflammation	Prevention of fibrosis	Han et al., 1981
	Stimulation of liver regeneration	Han et al., 1981
	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
Antitumor activity	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
	Inhibition of mutagenicity by B[a]P or aflatoxin B1	Niikawa et al., 1993; Young et al., 1994
	Inhibition of covalent binding of B[a]P to DNA	Huang et al., 1994
Antihyperlipidemia	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
	Prevention of experimental atherosclerosis	Parfenteva, 1979; Vailenko 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 5 $\alpha$ -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  $\mu$ mol/kg, s.c.  $\times$  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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### References

- Anisimov, M.M., Shcheglov, V.V., Strigina, L.I. et al. (1979) Chemical structure and antifungal activity of a number of triterpenoids. *Biological Bulletin Academia Science USSR* 6, 464–468.
- Balancheu, S. and Nagarajan, B. (1991) Protective effect of oleanolic acid and ursolic acid against lipid peroxidation. *Biochemistry International* 24, 981–990.
- Balancheu, S. and Nagarajan, B. (1994) Triterpenes intervene in adriamycin-induced histamine release in rodents. *Medical Science Research* 24, 981–990.
- Chen, C.P. and Wang, H.Y. (1989) The effects of oleanolic acid and dimethyl dicarbonate biphenyls on acute liver injury. *Zhong Cheng Yao Study* 10, 11(S)-14(S)1331.
- Collins, M.A. and Charles, H.P. (1987) Antimicrobial activity of carnosol and ursolic acid: two anti-oxidant constituents of *Rosmarinus officinalis*. *Food Microbiology* 4, 311–315.
- Dai, P.X., Chen, L. and Lan, S.S. (1982) Oleanolic acid, the active components of *Ligustrum lucidum* in preventing cyclophosphamide-induced toxicity. *Zhong Cheng Yao Study* 1, 42–47.
- Dai, Y., Hang, B.Q., Meng, Q.Y., Ma, S.P. and Tan, L.W. (1988) Inhibition of hypersensitivity reactions by oleanolic acid. *Acta Pharmacologica Sinica* 9, 562–565.
- Dai, Y., Hang, B.Q. and Tan, L.W. (1989a) Anti-inflammatory effect of oleanolic acid. *Chinese Journal of Pharmacology and Toxicology* 3, 96–99.
- Dai, Y., Hang, B.Q., Li, P.Z. and Tan, L.W. (1989b) Effects of oleanolic acid on immune system and type I allergic reaction. *Acta Pharmacologica Sinica* 10, 381–384.
- Dominic, Y.A. and Subbaiyan, M. (1993) Studies on mitochondrial lipid peroxidation in tumor-bearing rats treated with ursolic acid and ursolic acetate. *Medical Science Research* 21, 213–215.
- Favel, A., Steinmetz, M.D., Regli, P., Vidal-Ollivier, E., Elias,

- R. and Balansard, G. (1994) In vitro antifungal activity of triterpenoid saponins. *Planta Medica* 60, 50–53.
- Gan, K.H. and Lin, C.N. (1988) Studies on the constituents of Formosan gentianaceous plants. XI. Constituents of *Gentiana flavo-maculata* and *Tripterospermum taiwanense* and the antihepatotoxic activity of ursolic acid derivatives. *Chinese Pharmaceutical Journal* 40, 77–84.
- Gupta, M.B., Bhalla, T.N., Gupta, G.P., Mitra, C.R. and Bhargava, K.P. (1969) Antiinflammatory activity of natural products (I) Triterpenoids. *European Journal of Pharmacology* 6, 67–70.
- Gupta, M.B., Nath, R., Gupta, G.P. and Bhargava, K.P. (1981) Antiulcer activity of some plant triterpenoids. *Indian Journal of Medical Research* 73, 649–52.
- Hada, S., Hattori, T. and Namba, T. (1990) Dental caries prevention by traditional medicines. Effect of components of *Ganoderma lucidum* on glucosyltransferase from *Streptococcus mutans*. *Chemical Abstracts* 113, 91423f.
- Hang, B.X., Dai, Y. and Tan, L.W. (1987) Oleanolic acid protects against chromosomal damage produced by cyclophosphamide and urethane. *Zhouguo Yaokexue Xuebao (Bulletin University of Chinese Pharmaceutical Sciences)* 18, 222–224.
- Han, D.W., Ma, X.H., Zhao, Y.C. and Yin, L. (1981) The protective effects of oleanolic acid on experimental cirrhosis. *Journal of Traditional Chinese Medicine* 3, 217–223.
- Hao, Z., Hang, B. and Wang, Y. (1989) Hypoglycemic effect of oleanolic acid. *Zhouguo Yaokexue Xuebao* 22, 210–212.
- Hikino, H., Kiso, Y., Amagaya, S. and Ogihara, Y. (1984a) Antihepatotoxic actions of papyriogenins and papyrioides, triterpenoids of *tetrapanax papyrifera* leaves. *Journal of Ethnopharmacology* 12, 231–235.
- Hikino, H., Ohsawa, T., Kiso, Y. and Oshima, Y. (1984b) Analgesic and antihepatotoxic actions of dianosides, triterpenoid saponins of *dianthus superbus* var *logicalycinus* herbs. *Planta Medica* 50, 353–354.
- Hirota, M., Mori, T., Yoshio, M. and Iriye, R. (1990) Suppression of tumor promoter-induced inflammation of mouse ear by ursolic acid and 4,4-dimethylcholestane derivatives. *Agricultural and Biological Chemistry* 54, 1073–1075.
- Huang, M.T., Ho, C.T., Wang, Z.Y., Ferraro, T., Lou, Y.R., Stauber, K., Ma, W., Georgiadis, C., Laskin, J.D. and Conney, A.H. (1994) Inhibition of skin tumorigenesis by rosemary and its constituents carnosol and ursolic acid. *Cancer Research* 54, 701–708.
- Hunan Med. Inst. (1975) Pharmacological studies of hepatoprotective compounds from *Swertia mileensis*. *Traditional Medicine (Zhong Chao Yao)* 6, 47–62.
- Hunan Med. Inst. (1977) Effects of oleanolic acid on experimental liver injury and therapeutic value in human hepatitis. *Traditional Medicine (Zhong Chao Yao)* 8, 32–37.
- Ito, Y., Yanase, S., Tokuda, H., Kishishita, M., Ohigashi, H., Irota, M. and Koshimizu, K. (1983) Epstein-Barr virus activation by tung oil, extracts of *Aleurites fordii* and its diterpene ester 12-O-hexadecanoyl-16-hydroxyphorbol-13-acetate. *Cancer Letters* 18, 87–95.
- Ishida, M., Okubo, T., Koshimizu, K., Daito, H., Tokuda, H., Kin, T., Yamamoto, T. and Yamazaki, N. (1990) Topical preparations containing ursolic acid and/or oleanolic acid for prevention of skin cancer. *Chemical Abstract* 113, 12173y.
- Kapil, A. and Sharma, S. (1994) Anti-complement activity of oleanolic acid: an inhibitor of C3-convertase of the classical complement pathway. *Journal of Pharmacy and Pharmacology* 46, 922–923.
- Kim, K.H., Chang, M.W., Kim, E.Y., Park, K.Y. and Sunwoo, Y.I. (1993) Effects of linoleic acid and ursolic acid on T subsets in sarcoma 180-transplanted mice. *Chemical Abstracts* 119, 262145x.
- Konoshima, T., Takasaki, M., Kozuka, M. and Tokuda, H. (1987) Studies on inhibitors of skin-tumor promotion. I. Inhibitory effects of triterpenes from *Eupteies polyandra* on Epstein-Barr virus activation. *Journal of Natural Products* 50, 1167–1170.
- Kosuge, T., Yokota, M., Sugiyama, K., Mure, T., Yamazawa, H. and Yamamoto, T. (1985) Studies on bioactive substances in crude drugs used for arthritic diseases in traditional Chinese medicine. III. Isolation and identification of anti-inflammatory and analgesic principles from the whole herb of *Pyrola rotundifolia* L. *Chemical and Pharmaceutical Bulletin* 33, 5355–5357.
- Kozai, K., Miyake, Y., Kohda, H., Kametaka, S., Yamasaki, K., Suginaka, H. and Nagasaka, N. (1987) Inhibition of glucosyltransferase from *Streptococcus mutans* by oleanolic acid and ursolic acid. *Caries Research* 21, 104–108.
- Lee, H.Y., Chung, H.Y., Kim, K.H., Lee, J.J. and Kim, K.W. (1994) Induction of differentiation in the cultured F9 teratocarcinoma stem cells. *Japan Cancer Research and Clinical Oncology* 120, 513–518.
- Lee, K.H., Lin, Y.M., Wu, T.S., Zhang, D.C., Yamagishi, T., Hayashi, T., Hall, I.H., Chang, J.-J., Wu, R.-Y., Yang, T.-S. (1988) The cytotoxic principles of *Prunella vulgaris*, *Psychotria serpens* and *Hyptis capitata*: Ursolic acid and related derivatives. *Planta Medica* 54, 308–311.
- Lin, C.N., Chung, M.I. and Gan, K.H. (1988) Novel anti-hepatotoxic principles of *Solanum incanum*. *Planta Medica* 54, 222.
- Liu, J., Chen, X.F., Xia, L., Geng, X.Z. and Li, Z.S. (1987) Effect of oleanolic acid on serum glyceride cholesterol and  $\beta$ -lipo-proteins in normal and experimental hyperlipidemia rats. *Chinese Pharmacological Bulletin* 4, 14–15.
- Liu, J., Liu, Y.P., Madhu, C. and Klaassen, C.D. (1993a) Protective effects of oleanolic acid on acetaminophen hepatotoxicity in mice. *Journal of Pharmacology and Experimental Therapeutics* 266, 1607–1613.
- Liu, Y.P., Kreppel, H., Liu, J., Choudhuri, S. and Klaassen, C.D. (1993b) Oleanolic acid protects against cadmium-induced liver injury in mice. *Journal of Pharmacology and Experimental Therapeutics* 266, 400–408.
- Liu, Y.P., Liu, J. and Klaassen, C.D. (1993c) The protection of oleanolic acid on D-galactosamine/endotoxin-induced hepatotoxicity. *Toxicologist* 13, 720.
- Liu, J., Liu, Y.P., Mao, Q. and Klaassen, C.D. (1994a) The

- protective effect of ten triterpenoid compounds on experimental liver injury in mice. *Fundamental and Applied Toxicology* 22, 34–40.
- Liu, J., Liu, Y.P. and Klaassen, C.D. (1994b) The effect of Chinese hepatoprotective medicines on experimental liver injury in mice. *Journal of Ethnopharmacology* 42, 183–191.
- Liu, J., Liu, Y.P. and Klaassen, C.D. (1995a) The effect of oleanolic acid on chemical-induced liver injury in mice. *Acta Pharmacologica Sinica* 15, 16–23.
- Liu, J., Liu, Y.P., Parkinson, A. and Klaassen, C.D. (1995b) Effect of oleanolic acid on hepatic toxicant-activating and detoxifying systems in mice. *Journal of Pharmacology and Experimental Therapeutics* (in press)
- Liu, Y.G. (1986) Pharmaceutical composition for treating non-lymphatic leukemia and its components. *Chemical Abstracts* 106, 90209j.
- Liu, Z., Wang, D., Wang, S., Ha, S. and Li, P. (1994) Oleanolic acid in decreasing hyperglycemia. *Chinese Pharmaceutical Journal* 29, 725–726.
- Ma, B.L. (1986) Hypolipidemic effects of oleanolic acid. *Traditional Medicine and Pharmacology* 2, 28–29.
- Ma, X.H., Zhao, Y.C., Yin, L., Han, D.W. and Ji, C.X. (1982) Studies on the effect of oleanolic acid on experimental liver injury. *Acta Pharmaceutica Sinica* 17, 93–97.
- Ma, X.H., Zhao, Y.C., Yin, L., Han, D.W. and Wang, M.S. (1986) Studies on the preventive and therapeutic effects of ursolic acid on acute hepatic injury in rats. *Acta Pharmaceutica Sinica* 21, 332–335.
- Mahato, S.B., Sarkar, S.K. and Poddar, G. (1988) Triterpenoid saponins. *Phytochemistry* 27, 3037–3067.
- Muto, Y., Ninomiya, M. and Fujiki, H. (1990) Present status research on cancer chemoprevention in Japan. *Japanese Journal of Clinical Oncology* 20, 219–224.
- Najid, A., Simon, A., Cook, J., Chable-Rabinovitch, H., Delage, C., Chulia, A.J. and Rigaud, M. (1992) Characterization of ursolic acid as a lipoxygenase and cyclooxygenase inhibitor using macrophages, platelets and differentiated HL 60 leukemic cells. *Federation of European Biochemical Societies* 299, 213–217.
- Niikawa, M., Hayashi, H., Sato, T., Nagase, H. and Kito, H. (1993) Isolation of substances from glossy privet (*Ligustrum lucidum* Ait) inhibiting the mutagenicity of benzo[a]pyrene in bacteria. *Mutation Research* 319, 1–9.
- Nishino, H., Nishino, A., Takayasu, J., Hasegawa, T., Iwashima, A., Hirabayashi, K., Iwata, S. and Shibata, S. (1988) Inhibition of the tumor-promoting action of 12-*o*-tetradecanoylphorbol-13-acetate by some oleanane-type triterpenoid compounds. *Cancer Research* 48, 5210–5215.
- Ohigashi, H., Takamura, H., Koshimizu, K., Tokuda, H. and Ito, Y. (1986) Search for possible antitumor promoters by inhibition of 12-*o*-tetradecanoylphorbol-13-acetate-induced Epstein-Barr virus activation: ursolic acid and oleanolic acid from an anti-inflammatory Chinese medicinal plant, *Glechoma hederaceae* L. *Cancer Letters* 30, 143–151.
- Ohyo, K.K.K. (1985) Triterpenes with anti-male hormone activity and as testosterone 5 $\alpha$ -reductase inhibitors. *Chemical Abstracts* 104, 39718f.
- Okazaki, T., Suetsugu, M. and Yoshida, T. (1987) Hair tonics containing oleanolic acid derivatives. *Chemical Abstracts* 107, P161369v.
- Okudo, T., Koshimizu, K., Daito, H., Kin, B., Nishimoto, K. and Yamazaki, N. (1990) Health drinks containing ursolic acid and/or oleanolic acid. *Chemical Abstracts* 112, P54097m.
- Parfente'eva, E.P. (1979) Effect of ursolic acid and its derivatives on lipid metabolism in experimental atherosclerosis. *Chemical Abstracts* 91, 9279r.
- Price, K.R., Johnson, I.T. and Fenwick, G.R. (1987) The chemistry and biological significance of saponins in foods and feedingstuffs. *CRC Critical Review Food Science and Nutrition* 26, 27–135.
- Poehland, B.L., Carte, B.K., Francis, T.A., Hyland, L.J., Allaudeen, H.S. and Troupe, N. (1987) In vitro antiviral activity of dammar resin triterpenes. *Journal of Natural Products* 50, 706–713.
- Qu, R.Y. (1981) Oleanolic acid in treating virus hepatitis. *Guangzhou Med.* 3, 41–43.
- Rajasekaran, M., Bapna, J.S., Lakshmanan, S., Ramachandran, N.A., Veliath, A.J. and Panchanadam, M. (1988) Antifertility effect in male rats of oleanolic acid, a triterpene from *Eugenia jambolana* flowers. *Journal of Ethnopharmacology* 24, 115–121.
- Rajasekaran, M., Sudhakaran, C., Pradhan, S.C., Bapna, J.S. and Nair, A.G.R. (1990) Mast cell protective activity of ursolic acid — a triterpene from the leaves of *Ocimum sanctum*. *Chemical Abstracts* 112, 91452u.
- Rhew, T.H., Park, S.M., Park, K.Y., Chung, H.Y., Hah, J.C. and Lee, C.K. (1993) Effects of ursolic acid on oncogene expression detected by in situ hybridization in mice. *Chemical Abstracts* 119, 151741u.
- Serra, C., Lampis, G., Pompei, R. and Pinza, M. (1994) Antiviral activity of new triterpenic derivatives. *Pharmacology Research* 29, 359–366.
- Shibata, S. (1977) Saponins with biological and pharmacological activity. In: H. Wagner and P. Wolff (Eds.), *New natural products and plant drugs with pharmacological or therapeutical activity*. Springer-Verlag, New York pp. 177–196.
- Shibata, S. (1994) Antitumor-promoting and anti-inflammatory activities of licorice principles and their modified compounds. *Chemical Abstracts* 120, 124297t.
- Shukla, B., Viser, S., Patnaik, G.K., Tripathi, S.C., Srimal, R.C., Day, S. and Dobhal, P.C. (1992) Hepatoprotective activity in the rat of ursolic acid isolated from *Eucalyptus* hybrid. *Phytotherapy Research* 6, 74–79.
- Simon, A., Najid, A., Chulia, A.J., Delage, C. and Rigaud, M. (1992) Inhibition of lipoxygenase activity and HL60 leukemic cell proliferation by ursolic acid isolated from heather flowers (*Calluna vulgaris*). *Biochimica et Biophysica Acta* 1125, 68–72.
- Singh, G.B., Singh, S., Bani, S., Gupta, B.D. and Banerjee, S.K. (1992) Anti-inflammatory activity of oleanolic acid in rats and mice. *Journal of Pharmacy and Pharmacology* 44, 456–458.

- Snyckers, F.O. and Fourie, T.G. (1984) Ulcer prevention and treatment with oleanolic acid. *Chemical Abstracts* 100, 39613k.
- Steinberg, D., Sgan-Cohen, H.D., Stabholz, A., Pizanty, S., Segal, R. and Sela, M.N. (1989) The anticariogenic activity of glycyrrhizin: Preliminary clinical trials. *Israel Journal Dental Science* 2, 153–157.
- Takagi, K., Park, E.-H. and Kato, H. (1980) Anti-inflammatory activities of hederagenin and crude saponin isolated from *Sapindus mukorossi* Gaertn. *Chemical and Pharmacological Bulletin* 28, 1183–1188.
- deTommasi, N., deSimone, F., Pizza, C., Mahmood, N., Moore, P.S., Conti, C., Orsi, N. and Stein, M.L. (1992) Constituents of *Eriobotrya japonica*. A study of their antiviral properties. *Journal of Natural Product* 55, 1063–1073.
- Tokuda, H., Ohigashi, H., Koshimizu, K. and Yohei, I. (1986) Inhibitory effects of ursolic and oleanolic acid on skin tumor promotion by 12-*o*-tetradecanoylphorbol-13-acetate. *Cancer Letters* 33, 279–285.
- Tsuruga, T., Chun, Y.T., Ebizuka, Y. and Sankawa, U. (1991) Biologically active constituents of *Melaleuca leucadendron*: inhibitors of induced histamine release from rat mast cells. *Chemical and Pharmacological Bulletin* 39, 3276–3278.
- Umeheera, K., Takagi, R., Kuroyanagi, M., Ueno, A., Taki, T. and Chen, Y.J. (1992) Studies on differentiation-inducing activities of triterpenes. *Chemical and Pharmacological Bulletin* 40, 401–405.
- Vasilenko, Yu. K., Lisevitskaya, L.I., Frolova, L.M., Parfenteva, E.P., Skulte, I.V., Vasilenko, A. Yu., Kozharskii, V.V. and Voskanyan, V.L. (1982) Hypolipemic properties of triterpenoids. *Farmakology and Toksikology* 45, 66–70.
- Vasilenko, Yu. K., Ponomarev, V.D. and Oganessian, E.T. (1981) Comparative study of the hypolipidemic properties of triterpenoids. *Chemical Abstracts* 91, 49279r.
- Wang, B. and Jiang, Z.H. (1992) Studies on oleanolic acid. *Chinese Pharmaceutical Journal* 27, 393–397.
- Wrzeczono, U., Malecki, I., Budzianowski, J., Kierylowicz, H., Zaprutko, L., Beimvik, E. and Kostepska, H. (1985) Nitrogenous triterpene derivatives. Part 10: Hemisuccinates of some derivatives of oleanolic acid and their anti-ulcer effects. *Pharmazie* 40, 542–544.
- Wu, K.H. and Li, Z.S. (1986) Oleanolic acid, a new drug for hepatitis. In: *Oleanolic acid*. Guiyang Pharmaceut. Co., pp. 1–5.
- Xu, L.Z. and Wan, Z.X. (1980) The effect of oleanolic acid on acute hepatitis (70 cases). *Human Medicine* 7, 50–52.
- Xu, S. L. (1985) Effects of oleanolic acid on chronic hepatitis: 188 case reports. *Symposium on oleanolic acid* 23–25.
- Yabuchi, T., Tanaka, T., Sasatsuka, T., Yamahara, J. and Fujimura, H. (1988) Extraction of oleanolic acid from sugar beets for treatment of liver failure. *Chemical Abstracts* 108, 82082p.
- Ying, Q.L., Rinehart, A.R., Simon, S.R. and Cheronis, J.C. (1991) Inhibition of human leucocyte elastase by ursolic acid. *Biochemistry Journal* 277, 521–526.
- Yoshimi, N., Wang, A., Morishita, Y., Tanaka, T., Sugie, S., Kawai, K., Yamahara, J. and Mori, H. (1992) Modifying effects of fungal and herb metabolites on azoxymethane-induced intestinal carcinogenesis in rats. *Japanese Journal of Cancer Research* 83, 1273–1278.
- Young, H.S., Chung, H.Y., Lee, C.K., Park, K.Y., Yokozawa, T. and Oura, H. (1994) Ursolic acid inhibits aflatoxin B1-induced mutagenicity in a Salmonella assay system. *Biological Pharmacology Bulletin* 17, 990–992.
- Zaletova, N.I., Shchavlinskii, A.N., Tolkachev, O.N. et al. (1986) Preparation of some derivatives of ursolic acid and their antimicrobial activity. *Chemical Abstracts* 106, 18867e.
- Zhang, L.Z. and Li, X.F. (1992) Study on the mechanism of oleanolic acid against experimental liver injury in rats. *Traditional Medicine and Clinical Pharmacology* 8, 24–26.
- Zhang J. and Liu, G-T. (1984) The inhibitory effect of disodium semisuccinate of oleanolic acid on cytochromes P-450. *Chinese Pharmacological Bulletin* 1, 300–301.
- Zhou, C., Sun, X., Liu, W., Shi, H., Gao, H. and Miao, Y. (1993) Effects of oleanolic acid on the immune complex allergic reaction and inflammation. *Journal of Clinical Pharmacological Sciences* 2, 69–79.