Journal of Enzyme Inhibition and Medicinal Chemistry, 2011; 26(5): 616–642

ISSN 1475-6366 print/ISSN 1475-6374 online
DOI: 10.3109/14756366.2010.546793

informa
healthcare

REVIEW ARTICLE

Clinically useful anticancer, antitumor, and antiwrinkle agent, ursolic acid and related derivatives as medicinally important natural product

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Abstract

Medicinal plants are becoming an important research area for novel and bioactive molecules for drug discovery. Novel therapeutic strategies and agents are urgently needed to treat different incurable diseases. Many plant derived active compounds are in human clinical trials. Currently ursolic acid is in human clinical trial for treating cancer, tumor, and skin wrinkles. This review includes the clinical use of ursolic acid in various diseases including anticancer, antitumor, and antiwrinkle chemotherapies, and the isolation and purification of this tritepernoid from various plants to update current knowledge on the rapid analysis of ursolic acid by using analytical methods. In addition, the chemical modifications of ursolic acid to make more effective and water soluble derivatives, previous and current information regarding, its natural and semisynthetic analogs, focusing on its anticancer, cytotoxic, antitumor, antioxidant, anti-inflammatory, anti-HIV, acetyl cholinesterase, α-glucosidase, antimicrobial, and hepatoprotective activities, briefly discussion is attempted here for its research perspectives. This review article contains fourteen medicinally important ursolic acid derivatives and 351 references.

Keywords: Ursolic acid, biological significance, *Eriobotrya japonica*

1.Introduction

In the context of our previous communication on bioactivities of oleanolic acid and related derivatives,[1] now we report the bioactivities of ursolic acid (**1**) and related derivatives of ursolic acid along with other triterpenoidal compounds like, ursolic acid glycosides and few sugars were isolated from *Eriobotrya japonica*.[2] Ursolic acid is of interest to scientists in the area of oncology because of its cytotoxicity, induction of differentiation, antimutagenic, antiviral, and anti-invasive activities. It may occur in its free acid form, as shown in **1**, or as aglycones for triterpenoid saponins which are comprised of a triterpenoid aglycone linked to one or more sugar moieties.

A number of ursolic acid derivatives showed high potential anticancer activities against three human cancer cell lines. 2α-hydroxyursolic acid (**7–13**), showed higher antiproliferative activity toward HepG2 cancer cells. Four ursolic type triterpene (**14–17**), showed a marked anti-inflammatory effect on 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation in mice. Ursolic acid and their lipophilic 3-*O*-fatty acid ester chains (C12–C18), were evaluated for their antimicrobial activity against a series of Gram-positive and Gram-negative bacteria. Significantly these compounds (**29–31**) were found to exhibit potent activity against Gram-negative bacteria *Pseudomonas syringae*. Ursolic acid acetate (**33**) and 11,12-dehydroursolic lactone, 3-*O*-acetyl-9,11-dehydro-12α–hydroxyoleanolic lactone (33″), were found to exhibit potent activity against α-glucosidase. The presence of free hydroxy or carboxy groups is necessary for the trypanocidal activity of ursolic acid as could be deduced from the effect of the acetates (**39**), methyl ester (**40**), and aldehyde derivatives. Ursolic acid has been modified at the C-3 position to cinnamate-based esters (**43–51**). The results indicated that modification of the parent structures of ursolic acid to the *p*-coumarate and the ferulate ester analogues resulted in high antimycobacterial activity.

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(Received 04 July 2010; revised 05 December 2010; accepted 07 December 2010)

Several 3-*O*-acyl-ursolic acids were prepared and evaluated for anti-HIV activity. 3-*O*-Diglycoryl-ursolic acid (**62**, Scheme 10) demonstrated relatively potent anti-HIV activity. 3-*O*-(3′, 3′-dimethylsuccinyl) ursolic acid (**60**), displayed only weak anti-HIV activity. The ursolic acid derivatives, dihemisuccinate sodium salt **72** demonstrated a good separation between anti-ulcer and mineralocorticoid activities. In particular, **75** and **76** (Scheme 11, 12), showed a potent anti-ulcer activity, 3- to 25-fold higher than carbenoxolone. The 3-*O*-fatty acid ester derivatives of ursolic acid (**79–84** Scheme 13), Urs-12-ene-28-carboxy-3β-octadecanoate and olean-12-ene-28-carboxy-3β-hexadecanoate were found to exhibit exceptionally potent antifeedant activities. These derivatives have attracted considerable interest due to there biological activity. Only few publications in the compiled form have appeared on the activities of ursolic acid and its derivatives.[3–11]

2.Isolation of ursolic acid from different plant sources

Isolation of ursolic acid from various plants by different workers has been known. Its isolation from *Catharanthus trichophyllus* roots,[12] *Chamobates pusillus*,[13] has been reported. Keller auf dem et al., isolated ursolic acid as content of *Rhododendron ponticum*.[14] Presence of ursolic acid has been reported in *Retanilla ephedra*,[15] *Cestrum diurnum Linn*,[16] in the blossoms of *Viburnum opulus l.* var. *sterile dc* (Caprifoliaceae),[17] and *Viburnum latana*.[18] The presence of ursolic acid in the leaves of *Funtumia latifolia Stapf*, has been reported by Takahashi.[19] Incidence of ursolic acid in the leaves of *Pyrus communis* (L.),[20] has been reported. The leaves of little *periwinkle* and *Vinca minor*, revealed the presence of ursolic acid.[21] Isolation of ursolic acid from leaves of *Ilex aquifolium L. I.* has been reported by Schindler et al.[22] Chemical investigation of bark, peel, and leaf of *Punica granatum* (L.) also revealed the presence of ursolic acid. The other plants contained ursolic acid were *Coussarea paniculata*,[23] *Salvia sochifolia*,[24] *Gentiana tizuensis*,[25] *Alysicarpus monolifer*,[26] *Ilex psammophila*,[27] *Debregeasia salicifolia*,[28] *Uncaria macrophylla*,[29] *Rabdosia excise*,[30] *Schizonepeta tenuifolia Briq*,[31] *Eriobotrya japonica*,[32] *Synurus deltoids*,[33] *Origanum majorana* (L.),[34] *Viscum album* (L.),[35] *Punica granatum* (L.),[36] *Echites hirsuta* (Apocynaceae),[37] *Rabdosia japonica* var. *glaucocalyx*,[38] *Arbutus unedo*,[39] *Paederia scandense*,[40] *Potentilla chinensis*,[41] *Elaeagnus bockii*,[42] *Schizonepeta tenuifolia*,[43] *Mentha haplocalyx*,[44] *Chirita longgangensis* var. *hongyao*,[45] *Launaea nudicaulis*,[46] *Rhaponticum uniflorum*,[47] *Rabdosia japonica* var. *galaucocalyx*,[48] *Ludwigia octovalvis*,[49] *Mallotus apelta Muell*,[50] *Salacia hainanensis*,[51] *Rubus chingi* I,[52] *Incarvillea arguta*,[53] *Tadehagi triquetrum*,[54] *Forsythia viridissima flowers*,[55] *Calophyllum polyanthum*,[56] *Madagascar rain forest*,[57] *Wendlandia formosana*,[58] *Ixora coccinea*,[59] *Lasianthus gardneri*,[60] *Couepia ulei*,[61] *Ilex kudingcha*,[62] *Dalbergia hainanensis*,[63] *Schisandra sphaerandra*,[64] *Psidium guajava*,[65] *Potentilla multifida* (L.),[66] *Ludwigia octovalvis*,[67] *Prunus serrulata* var.,[68] *Salvia przewalskii Maxim*,[69] *Hyssopus officinalis*,[70] *Eucalyptus globulus*[71] *Gaultheria leucocarpa* var.,[72] *Callicarpa bodinieri* Levl.,[73] *Alyxia sinensis*,[74] *Eucommia ulmoides*,[75] *Liquidambaris-lulutong*,[76] *Rabdosia japonica* (Burm.f). *Hara* var. *glaucocalyx* (Maxin) *Hara*,[77] *Acanthopanax sessiliflorus*,[78] *Ilex hainanensis*,[79] *Acanthopanax sessiliflorus*,[80] *Pyrrosia gralla*,[81] *Syzygium buxifolium Hook*,[82] *Eclipta alba*,[83] *Campylotropis hirtella* (Franch. Schindl.),[84] *Isodon oresbius*,[85] *Ilex latifolia*,[86] *Eucalyptus camaldulensis* var. *obtuse*,[87] *Lonicera angustifolia*,[88] *Isodon phyllostachys*,[89] *Syzygium formosanum*,[90] *Baccharis gaudichaudiana*,[91] *Fraxinus ornus* (L.),[92] *Leucoseptrum stellipillum*,[93] *Osbeckia chinensis* (L.),[94] *Hedyotis chrysotricha* (Palib.) *Merr.*,[95] *Actinidia arguta* (Sieb. et Zucc.) *Planch. ex Miquel*,[96] *Lichen Ramalina hierrensis*.,[97] *Isodon albopilosus* (C.Y. Wu et H.W. Li) *Hara*,[98] *Patrinia scabiosaefolia Fischer.*,[99] *Salvia wagneriana*,[100] *Cynomorium songaricum*,[101] *Lantana camara*,[102] *Punica granatum*,[103] *Ilex paraguariensis*,[104] *Aralia decaisneana*,[105] *Fagonia arabica*,[106] *almond hulls*,[107] *Mentha haplocalyx*,[108] *Fagonia glutinosa*,[109] *Potentilla chinesis*,[110] *Origanum majorana (L.)*,[111] *radix Ranunculus ternati*,[112] *Liriope platyphylla*,[113] *Pyrola calliatha*,[114] *Actinidia macrosperma*,[115] *Urtica dioica* (L.),[116] *Sambucus adnata*,[117] *Patrinia villosa*,[118] *Eriophyton wallichii*,[119] *Calligonum polygonoides*,[120] *Psidium guajava*,[121] *Paulownia fortunei* (seem.) *Hemsl*,[122] *Vaccinium iteophyllum*,[123] *Homonoia riparia*,[124] *Uncaria macrophylla*,[125] *Palicourea coriacea* (Rubiaceae),[126] *Carapa guianensis Aubl.* (Meliaceae),[109] *Potentilla chinesis*,[127] *Isodon oresbius*,[128] *Crataegus pinnatifida Bge.* var. *major N. E. Br*,[129] *Satureja khuzistanica.*,[130] *Perovskia abrotanoides*,[131] *Sambucus chinensis Lindl*,[131] *Leucoseptrum stellipillum*,[92] *Ajuga postii*,[132] *Morus nigra*,[133] *Valeriana officinalis*,[134] *Chondrilla piptocoma*,[135] *Rhodobryum roseum*,[136] *Swertia speciosa*[137,138] and *Mitragyna speciosa*.[139]

From the stem bark extract of *Amanoa oblongifolia* a number of non-cytotoxic isolates were found, that comprised the lignans, (+)-sesamin, and paulownin, friedelin, canophyllol, betulinic acid; and the sterols, β-sitosterol, daucosterol, and ursolic acid.[140]

3.Clinical applications of ursolic acid

3.1.Ursolic acid-induced changes in tumor growth, O_2 consumption, and tumor interstitial fluid pressure

The antitumor effect of ursolic acid and ursolic acid-induced changes in tumor physiology in tumor-bearing mice were examined. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium-bromide (MTT) colorimetric assay, clonogenic assay, and growth-delay assay for the determination of tumoricidal effects of ursolic acid were evaluated.[141] See supplementary material 3.1.

3.2.Clinical applications of ursolic acid for treating tumor patients

Ursolic acid is a promising antitumor agent. It is capable of inducing apoptosis in tumor cells on one side and to prevent malignant transformation of normal cells on the other side. It also interferes with numerous enzymes, including the ones serving directly to DNA synthesis. It can inhibit proliferation and induce apoptosis of many tumor cell lines. This compound have been shown to act at various stages of tumor development. They effectively inhibit angiogenesis, invasion of tumor cells and metastasis. It is relatively non-toxic and could be use as chemopreventive/chemoprotective agent in clinical praxis.[142]

Ursolic acid had been isolated from *Glechoma hederacea* as inhibitors of Epstein–Barr virus activation induced by TPA, were tested against inhibitory effect on tumor promotion by TPA *in vivo*.[143]

3.3.The treatment of wrinkles with ursolic acid in clinical trials (liposomal ursolic acid (Merotaine) increases ceramides and collagen in human skin)

Ursolic acid liposomes increased the ceramide content of the skin of human subjects, with increases in hydroxy ceramides occurring after only 3 days of treatment. Both ursolic acid liposomes and retinoic acid decreased markers of keratinocyte differentiation (keratin 1, keratin 10, and involucrin) in cultured normal human epidermal keratinocytes.[144]

Skin wrinkling and xerosis associated with aging result from decreases of dermal collagen and stratum corneum ceramide content. Ursolic acid incorporated into liposomes increases both the ceramide content of cultured normal human epidermal keratinocytes and the collagen content of cultured normal human dermal fibroblasts. In clinical tests, Merotaine increased the ceramide content in human skin over an 11-day period. Merotaine has effects on keratinocyte differentiation and dermal fibroblast collagen synthesis similar to retinoids. However, unlike retinoids, Merotaine increases ceramide content of human keratinocytes. Ursolic acid may bind to members of the glucocorticoid receptor family to initiate changes in keratinocyte gene transcription. As ursolic acid represents a promising chemical entity for the protection of human skin, in agreement with tests done by the cosmetic industry.[145,146]

4.Structure similarity of ursolic acid

4.1.Induction of apoptosis in HeLa cells by 3β-hydroxyurs-12-en-27-oic acid

3-β-Hydroxy urs-12-en-27-oic acid (**4**), was structurally very similar to ursolic acid, with the only difference being the interchange of the COOH and Me group at C-14 and C-17.

3β-Hydroxyurs-12-en-27-oic acid was found to exhibit more distinctive cytotoxicity toward human cervical squamous carcinoma cells than ursolic acid, suggesting that the position of the COOH group significantly affects the cytotoxicity of ursane-type pentacyclic triterpenes with a COOH group.[142] See supplementary material 4.1.

4.2.Antiproliferative and antiviral mechanisms of ursolic acid and dexamethasone in cervical carcinoma cell lines

The structure of ursolic acid is very similar to that of dexamethasone (**5**). Antiproliferative and antiviral effects of ursolic acid and dexamethasone in human papillomavirus associated cervical cancer cells was determined. MTTs assay was performed to measure antiproliferative activity and also characterized apoptosis by DNA fragmentation, 4′-6-diamidino-2-phenylindole staining, and flow cytometry analysis.[147]

5.Rapid analysis of ursolic acid by using different methods

5.1.Study on the extracting of ursolic acid by uniform design

Uniform design method was adopted to research the extraction of ursolic acid. The ethanol concentration, the liquid to solid ratio, and the extraction times were researched. The optimal conditions were achieved by optimization treatment. The ethanol concentration being 75%, liquid to solid ratio being 7, extraction time 60 min, were extracted two times.[148]

5.2.Quantitative determination of ursolic acid by means of the Liebermann–Burchard reaction[149]

5.3.Determination of ursolic acid by reversed phase-high-performance liquid chromatography

The new sesquiterpenoid, together with ursolic acid have been isolated from the roots of *Euphorbia chrysocoma* Lévl. et Vant.[150]

Simple high-performance liquid chromatography (HPLC) methods were developed for the determination of ursolic acid in loquat flower.[151] To evaluate the quality of *Perilla frutescens*, a simple HPLC method was developed for the assessment of ursolic acid.[152] See supplementary material 5.3.

5.4.Determination of free isomeric ursolic acid in Pterocephalus hookeri by capillary zone electrophoresis.[153] See supplementary material 5.4

5.5.Quantitative determination of ursolic acid by spectrophotometry

Ursolic acid was isolated from *Herba cynomorii* and was quantitatively determined by ultraviolet spectrophotometry. The results indicate that the content of ursolic acid is 0.78%. The average recovery rate of ursolic acid is 97.4%, relative standard deviation (RSD) = 0.45% ($n = 4$).[154]

5.6.Determination of ursolic acid of Liuwei Dihuangwan simulation samples by near infrared

Determine the content of ursolic acid of *Liuwei Dihuangwan* by using near infrared with partial least squares, principal component analysis-back-propagation artificial neural network and wavelet transform-back-propagation artificial neural network was carried out. The predication recoveries were 100.7, 100.6, and 100.1% and the RSD were 5.42, 6.49, and 6.52%, respectively.[155]

5.7.Quantitative determination of ursolic acid in Folium ilicis cornutae by thin-layer chromatography method

The content of ursolic acid in *Folium ilicis cornutae* gathered in different periods from Yongfeng country of Jiangxi province was determined by thin-layer chromatography (TLC) method. The result shows that the content appears to be low in samples gathered in April, but about the same in samples of February, June, August, October, and December.[156]

5.8.Comparative analysis of ursolic acid in Crataegus pinnatifida Bge. var. major N.E. Br.

The contents of ursolic acid in *Crataegus pinnatifida* var. major before and after processing determined by CS-920 TLC scanner: 0.274 and 0.265%, coefficients of variation 1.180 and 1.150%, respectively.[157]

The MeOH extract of the leaves of rosemary completely inhibited the motility of cultured epimastigotes of *Trypanosoma cruzi* at the concentration of 2 mg/mL after 2 h of incubation.[158]

5.9.Development of liquid chromatography-mass spectrometry method for determination of ursolic acid

A reproducible liquid chromatography-mass spectrometric assay was developed for the determination of ursolic acid in laboratory-made mixtures and in leaves and twigs extracts of *Staphylea holocarpa* Hemsl.[159]

Another rapid liquid chromatography-mass spectrometry (LC-MS) method for the determination of ursolic acid in rat plasma was developed and validated.[160] See supplementary material 5.9.

5.10.In situ analysis by microspectroscopy reveals triterpenoid compositional patterns.[161] See supplementary material 5.10

5.11.Use of liquid chromatography-atmospheric pressure chemical ionization-ion trap mass spectrometry for identification of ursolic acid

A quantitative method, consisting of supercritical fluid extraction followed by liquid chromatography-atmospheric pressure chemical ionization-ion trap mass spectrometry (LC-APCI-IT-MS) analysis, was developed for identification of ursolic acid in *Anoectochilus roxburghii*.[162]

5.12.Dereplication of pentacyclic triterpenoids in plants by gas chromatography/electron impact/MS

Ursolic acid has been found to exhibit moderate antitubercular activity in a microplate alamar blue assay. To facilitate the discovery of novel antitubercular leads with diverse chemical structures, a new gas chromatography (GC)/electron impact/MS method was developed to dereplicate it as its methyl ester with limits of detection of 25.6, 26.9, and 26.8 ng.[163]

Isolation and GC/MS quantitative determination of ursolic acid in the herb of *Nepeta cataria* var. citriodora have been performed. The content of this compound was in the range 0.95–1.30%.[164] A high performance GC procedure has been developed for the quantitation of ursolic acid in different parts of *Xiakucao* collected in different periods. The study provides a scientific foundation for increased availability and rational collecting periods of *Xiakucao*.[165]

To develop a GC method to determine ursolic acid in *Spica Prunellae*, the sample was derivatized with CH_2N_2 solution. The GC conditions were as follows: comumn-10% SE-30 (2 m × 3 mm) and column temperature –270°C. Ursolic acid well separated and had good linearity in the range of 0.0025–0.4000 mg/mL. The method is good for determining ursolic acid in Chinese medicines.[166]

6.Biological and pharmacological activity of plants extract containing ursolic acid

Some plant extracts containing ursolic acid as one of the constituents have been tested for various biological and microbial activities by different scientists. It has been reported to possess a wide range of diverse pharmacological properties, including strong anti-inflammatory activity, anticancer, antioxidant and is one of the most promising chemopreventive agents for cancer and showed that ursolic acid can inhibit proliferation and induce apoptosis of many tumor cell lines.

6.1.Prevention of dental caries by oriental folk medicines. Active principles of Zizyphi fructus for inhibition of insoluble glucan formation by cariogenic bacterium Streptococcus mutans

The *Z. fructus* extract had inhibitory activity against insoluble glucan formation by glucosyltransferase from the cariogenic bacterium *S. mutans*. The active substances were isolated from the plant and the chemical structures were elucidated to be oleanolic acid and ursolic acid.[167]

6.2.Tumor inhibitory agents from Vauquelinia corymbosa

V. corymbosa Correa plant has shown activity against the P-388 lymphocytic leukemia test system. The constituents responsible for this activity were identified as uvaol, betulinic acid, and ursolic acid.[168]

6.3.Antimicrobial activity of the extract and compounds from Baccharis dracunculifolia D. C.[169,170] See suplementary material 6.3

6.4.Anti-inflammatory activity of extract and fractions from Nepeta sibthorpii Bentham.[171] See supplementary material 6.4

6.5.Central nervous system activity of the extract of Mallotus peltatus (Geist) Muell Arg. Leaf.[172] See supplementary material 6.5

6.6.A potent sperm motility-inhibiting activity of ursolic acid from an ethnomedicine of Onge, Alstonia macrophylla Wall ex A. DC.[173] See suplementary material 6.6

6.7.Antibacterial constituents from fruit bodies of Ascomyce Bulgaria inquinans

Two ergosterins betuinic acid, cerevisterol, (24R) ergosta-7, and triterpenoids 22E-diene-3β, 5α, 6β-triol-3-*O*-palmitate and ursolic acid were isolated from the dried fruit bodies of *Ascomyce Bulgaria inquinans*.[174]

6.8.Antipyretic activity of ursolic acid: an ethnomedicine of Andaman Islands.[175] See supplementary material 6.8

6.9.α-Amylase inhibitory activity of some Malaysian plants used to treat diabetes.[176] See suplementary material 6.9

6.10.A new ursane triterpene inhibits DNA polymerase β–lyase

Bioassay-directed fractionation of a butanone extract of *Monochaetum vulcanicum* resulted in the isolation of a new triterpene, 3β-acetoxy-2α-hydroxyurs-12-en-28-oic acid and four known compounds, ursolic acid, 2α-hydroxyursolic acid, 3-(*p*-coumaroyl) ursolic acid, and β-sitosteryl-β-d-galactoside. Compounds 3β-acetoxy-2α,-hydroxyurs-12-en-28-oic acid, 2α-hydroxy ursolic acid, and β sitosteryl-β-d-galactoside exhibited polymerase β-lyase activity.[177]

6.11.Antiviral activities of extracts and ursolic acid constituents of Ocimum basilicum

O. basilicum extracts were used to identify possible antiviral activities against DNA viruses (herpes viruses, adenoviruses and hepatitis B virus) and RNA viruses (coxsackievirus B1 and enterovirus.[178]

6.12.In vitro transforming growth factor-β1 antagonistic activity of ursolic acid.[4] See suplementary material 6.12

6.13.Dual activity of triterpenoids: apoptotic versus antidifferentiation effects.[179] See suplementary material 6.13

6.14.Apoptosis inducing activity of ursolic acid, from Viscum album (L.).[180] See supplementary materials 6.14

6.15.Antioxidant, anti-inflammatory, and anticancer activities of extracts from Ledum groenlandicum Retzius.[181,182] See suplementary material 6.15

7.Biological and pharmacological significance of isolated ursolic acid

7.1.Ursolic acid: an anti- and pro-inflammatory triterpenoid

Some studies have recently revealed that the effects of ursolic acid on normal cells and tissues are occasionally pro-inflammatory. Thus, ursolic acid may be designated as a double-edged sword with both positive and negative effects, and further evaluations of the effects of ursolic acid on the biological status of target cells or tissues are necessary.[183]

7.2.Effect of ursolic acid on epidermal permeability barrier function and epidermal keratinocyte differentiation via peroxisome proliferator-activated receptor-α.[184] See suplementary material 7.2

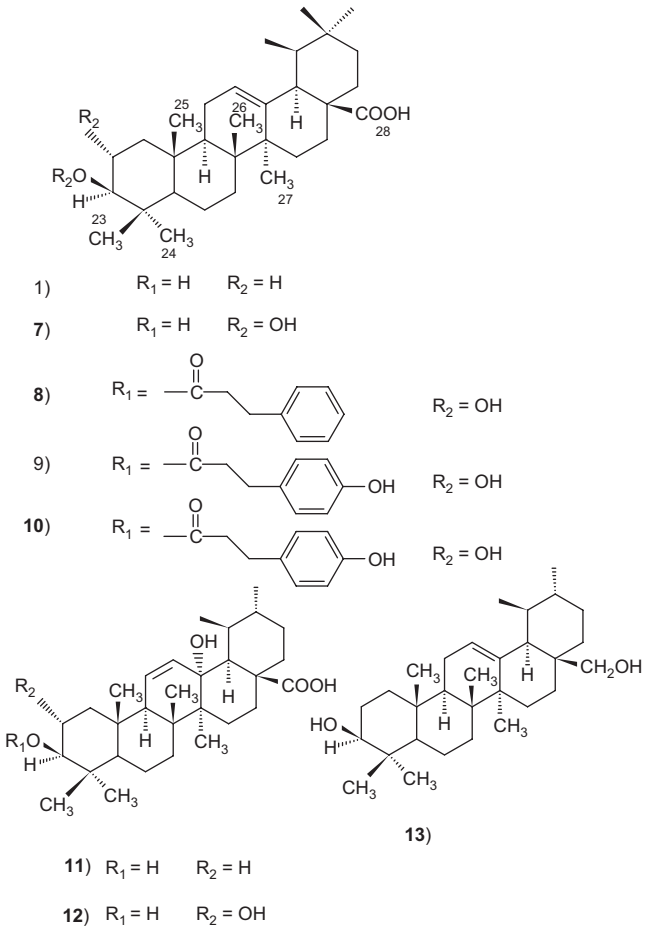
7.3.Non-enzymatic antioxidative and antiglycative effects of ursolic acid.[185] See supplementary material 7.3

7.4.Ursolic acid inhibits the formation of aberrant crypt foci and affects colonic sphingomyelin hydrolyzing enzymes in azoxymethane-treated rats.[186] See suplementary material 7.4

7.5.Evaluation of hepatoprotective activity of ursolic acid.[187–192] See suplementary material 7.5

7.6.Triterpenoids (ursolic acid) from apple peels have potent antiproliferative activity and may be partially responsible for apple's anticancer activity. See suplementary material 7.6

Antiproliferative activities of the thirteen triterpenoids from apple peels against human HepG2 liver cancer cells, MCF-7 breast cancer cells, and Caco-2 colon cancer cells were evaluated. Most of the triterpenoids showed high potential anticancer activities against the three human cancer cell lines. Among the compounds isolated, 2α-hydroxyursolic acid (7, Scheme 1), 2α-hydroxy-3β-[(2E)-3-phenyl-1-oxo-2-propenyl] oxy-olean-12-en-28-oic acid (8) and 3β-trans-p-coumaroyloxy-2α-hydroxyolean-12-en-28-oic acid (9) showed higher antiproliferative activity toward HepG2 cancer cells. Ursolic acid, 2α-hydroxyursolic acid, and 3β-trans-p-coumaroyloxy-2α-hydroxyolean-12-en-28-oic acid exhibited higher antiproliferative activity against MCF-7 cancer cells. All triterpenoids showed antiproliferative activity against Caco-2 cancer cells, especially 2α-hydroxyursolic acid, maslinic acid, 2α-hydroxy-3β-{[(2E)-3-phenyl-1-oxo-2-propenyl]oxy}



Scheme 1. Chemical structures of triterpenes isolated.

olean-12-en-28-oic acid, and 3β-trans-p-coumaroyloxy-2α-hydroxyolean-12-en-28-oic acid, which displayed much higher antiproliferative activities.[186]

7.7.Regulation of the phosphatidylinositol 3-kinase-Akt and the mitogen-activated protein kinase pathways by ursolic acid in human endometrial cancer cells.[193] See supplementary material 7.7

7.8.Ursolic acid demonstrates anticancer activity on human prostate cancer cells.[194] See supplementary material 7.8

7.9.MCF-7 cell-cycle arrested at G1 through ursolic acid, and increased reduction of tetrazolium salts.[195,196] See supplementary material 7.9

7.10.Impact of ursolic acid on chronic ethanol-induced oxidative stress in the rat heart.[197] See supplementary material 7.10

7.11.Ursolic acid ameliorates cognition deficits and attenuates oxidative damage in the brain of senescent mice

Ursolic acid markedly reversed the D-gal induced learning and memory impairment by behavioral tests.[198]

7.12.Amelioration of obesity and glucose intolerance in high-fat-fed C57BL/6 mice by ursolic acid in Cornelian cherry.[199] See supplementary material 7.12

7.13.Effects of ursolic acid on mucin release from airway goblet cells.[200] See supplementary materials 7.13

7.14.Inhibition of cytochrome P_{450} activities by ursolic acid in human liver microsomes.[201] See supplementary material 7.14

7.15.Ursolic acid induces apoptosis through caspase-3 activation and cell-cycle arrest in HaCaT cells

The pro-apoptotic effect of ursolic acid on HaCaT derived keratinocyte cell line was determined.[202] See supplemntary material 7.15.

7.16.Ursolic acid triggers calcium-dependent apoptosis in human Daudi cells

Ursolic acid was found to decrease cell viability in human lymphoma Daudi cells in a dose-dependent manner.[203] See supplemntary material 7.16.

7.17.Cytotoxic ursolic acid from Erica andevalensis

The cytotoxic activity of ursolic acid and α-amyrine has been assessed against three human cancer cell lines, TK-10 (renal adenocarcinoma), MCF-7 (breast adenocarcinoma), and UACC-62 (melanoma) and scientists also evaluated the antimitotic effect in root meristematic cells of *Allium cepa*. Ursolic acid was found to possess the highest cytotoxic activity.[204]

7.18.Proliferative inhibition, cell-cycle dysregulation, and induction of apoptosis by ursolic acid in human non-small cell lung cancer A 549 cells.[205] See supplementary materials 7.18

7.19.Ursolic acid induces Bax-dependent apoptosis through the caspase-3 pathway in endometrial cancer SNG-II cells.[206] See supplementary materials 7.19

7.20.Proteomic analysis of ursolic acid-induced apoptosis in cervical carcinoma cells.[207] See supplementary materials 7.20

7.21.Molecular mechanism of ursolic acid-induced apoptosis in poorly differentiated endometrial cancer HEC108 cells.[208] See supplementary material 7.21

7.22.Inhibition by ursolic acid of calcium-induced mitochondrial permeability transition and release of two pro-apoptotic proteins

The possible inhibition by ursolic acid of mitochondrial permeability transition in mouse liver was investigated to identify the mechanisms underlying the hepatoprotective effect of ursolic acid.[209]

7.23.Ursolic acid induces apoptosis through mitochondrial intrinsic pathway and caspase-3 activation in M4Beu melanoma cells

Ursolic acid effects were investigated on the M4Beu human melanoma cell line. Ursolic acid had a significant antiproliferative effect on M4Beu, associated with the induction of an apoptotic process, characterized by caspase-3 activation, the downstream central effector of apoptosis.[210] See supplementary material 7.23.

7.24.Induction of apoptosis by ursolic acid through activation of caspases and downregulation of c-IAPs in human prostate epithelial cells

The effects of ursolic acid on the growth of human prostate epithelial cells were investigated.[211] See supplementary material 7.24.

7.25.Apoptotic activity of ursolic acid may correlate with the inhibition of DNA replication

The pro-apoptotic effect of ursolic acid on HepG2 human hepatoblastoma cells was investigated.[212] See supplementary material 7.25.

7.26.Mechanisms of inhibiting proliferation and inducing apoptosis of human gastric cancer cell line SGC7901 by ursolic acid

This study was carried out to investigate the effect of ursolic acid on cyclooxygenase-2 (COX-2), Bcl-2 and Bax expression in human gastric cancer cell line SGC7901, and explore its potential mechanisms of inhibiting proliferation and inducing apoptosis.[213]

7.27.Ursolic acid inhibits STAT3 activation pathway leading to suppression of proliferation and chemosensitization of human multiple myeloma cells

Agents that can suppress STAT3 activation have potential for prevention and treatment of cancer. Ursolic acid tested, for its ability to suppress STAT3 activation. Ursolic acid, inhibited both constitutive and interleukin-6-inducible STAT3 activation in a dose- and time-dependent manner in multiple myeloma cells.[214]

7.28.Pharmacological modification of endogenous antioxidant enzymes by ursolic acid on tetrachloride-induced liver damage in rats and primary cultures of rat hepatocytes

The possible protective effects of ursolic acid against CCl_4-induced alterations of antioxidant defense enzymes *in vivo* as well as its effects against CCl_4-intoxication *in vitro* studied.[215]

7.29.The effect of ursolic acid on experimental liver injury in mice.[216] See supplementary material 7.29

7.30.Antiallergic and anti-inflammatory ursolic acid derevative from the herb of Prunella vulgaris.[217] See supplementary material 7.30

7.31.Inhibitory effect of triterpenes from Crataegus pinatifida on HIV-I protease

The methanol extract of *Crataegus pinnatifida* showed potent inhibitory activities against HIV-1 protease at a concentration of 100 μg/mL. The isolation of the extract gave two compounds, uvaol, and ursolic acid and inhibit HIV-1 protease with IC_{50} values of 5.5 and 8.0 μM.[218]

7.32.Treatment with ursolic acid induces apoptosis in human leukemia K562 cells and downregulates protein levels of bcl-xL. Treatment also increases phospho-Jun *N*-terminal kinase (JNK) in a dose- and time-dependent manner but does not alter phospho-Erk1/2 and phospho-P38. These results suggest that JNK may participate in ursolic acid-induced apoptosis in K562 cells.[219]

7.33.Reduction of DNA-damaging effects of anti-HIV drug 3′-azido-3′-dideoxythymidine on human cells by ursolic acid.[220] See supplementary materials 7.33

7.34.In vitro and in vivo evaluation of ursolic acid as an antimalarial

The ursolic acid isolated from the root bark of the Tanzanian tree *Uapaca nitida* Müll-Arg. It exhibited IC_{50} values of 36.5 μg/mL and 28 μg/Ml.[221]

7.35.Induction of differentiation of the cultured rat mammary epithelial cells by ursolic acid

The effects of ursolic acid and oleanolic acid, on the induction of proliferation and differentiation of normal rat mammary epithelial cells or organoids cultured in Matrigel or primary culture system was investigated.[222]

7.36.Natural-product inhibitors of human DNA ligase I.[223] See supplementary material 7.36

7.37.Anti-angiogenic activity of ursolic acid.[224] See supplementary material 7.37

7.38.Effects of ursolic acid on different steps of the angiogenic process.[225] See supplementary material 7.38

7.39.Heme oxygenase-1 inducing ursane derevatives of Prunella vulgaris in HepG2 cells.[226] See supplementary material 7.39

7.40.Endogenous reverse transcriptase as a mediator of ursolic acid's antiproliferative and differentiating effects in human cancer cell lines[227]

The effects of ursolic acid on the proliferation and differentiation of human tumor cell lines from melanoma (A375), glioblastoma (U87) and thyroid anaplastic carcinoma, and on the proliferation of a non-transformed human fibroblast cell line (WI-38) was examined.[227]

7.41.Antigenotoxic effects of ursolic acid, evaluation by the comet assay

Quercetin and ursolic acid prevented DNA damage and had antiproliferative properties in HepG2 cells suggesting an anticarcinogenic potential for these compounds.[228]

7.42.Antimicrobial activity of Ursolic acid from Salvia officinalis and related compounds on vancomycin-resistant enterococci[229]. See supplementary materials 7.42

7.43.Ursolic acid from the Chinese herb danshen [Salvia miltiorrhiza (L.)] upregulates endothelial nitric oxide synthase and downregulates Nox4 expression in human endothelial cells

Danshen, the dried root of *Salvia miltiorrhiza* Bunge, is the most commonly used traditional Chinese medicines for cardiovascular indications. Ursolic acid is responsible for this effect of the plant.[230]

7.44.Experimental study on apoptosis induced by ursolic acid isolated from asparagus in HL-60 cells[231]

7.45.Ursolic acid inhibits proliferation and stimulates apoptosis in HT-29 cells following activation of alkaline sphingomyelinase

The anticancer effects of ursolic acid on human colon cancer cells was studied. HT-29 cells were treated with ursolic acid. Cell proliferation was determined by cleavage of WST-1.[232]

7.46.Group IIA secretory PLA2 inhibition by ursolic acid

Ursolic acid inhibited secretory PLA2 enzymes purified from *Vipera russelli*, *Naja naja* venom and human pleural fluid and synovial fluid. IC_{50} values determined for these enzymes ranged from 12 to 18 μM.[233]

7.47.Aggregated ursolic acid, a natural triterpenoid, induces IL-1β release from murine peritoneal macrophages: role of CD36.[234] See supplementary material 7.47

7.48.Upregulation of matrix metalloproteinase family gene involvement in ursolic acid-induced human lung non-small carcinoma cell apoptosis.[235] See supplementary materials 7.48

7.49.Ursolic acid: a potent inhibitor of superoxides produced in the cellular system.[236] See supplementary material 7.49

7.50.Antiprotease and antimetastatic activity of ursolic acid isolated from Salvia officinalis.[237] See supplementary material 7.50

7.51.Carbenoxolone and ursolic acid inhibited mucin secretion from airway epithelial cells.[238] See supplementary material 7.51

7.52.Ursolic acid enhances COXs and tumor necrosis factor-α expression in mouse skin.[239] See supplementary materials 7.52

7.53.Ursolic acid mediates the vasorelaxant activity of Lepechinia caulescens via nitric oxide release in isolated rat thoracic aorta.[240] See supplementary material 7.53

7.54.Protection of peroxynitrite-induced DNA damage by dietary antioxidants

Dietary antioxidants such as epigallocatechin gallate, quercerin, rutin, resveratrol, and ursolic acid inhibit single strand breaks in supercoiled plasmid DNA induced by 3-morpholinosydnomine *N*-ethylcarbamide (SIN-1), a generator of peroxynitrite through the reaction between nitric oxide (NO) and superoxide anion.[241] See supplementary material S-7.54.

7.55.Anti-complementary activity of ursane-type triterpenoids from Weigela subsessilis.[242] See supplementary material 7.55

7.56.Effect of ursolic acid on caspase-3 and PARP expression of human MCF-7 cells.[243] See supplementary material 7.56

7.57.Inhibition of protein tyrosine phosphatase 1B by ursane-type triterpenes isolated from Symplocos paniculata.[244] See supplementary material 7.57

7.58.Amelioration of adjuvant-induced arthritis by ursolic acid through altered Th1/Th2 cytokine production.[245] See supplementary material 7.58

The activity of ursolic acid on pro-inflammatory and anti-inflammatory cytokines in the peripheral blood of arthritic balb/c mice was investigated.[245] See supplementary material 7.58.

7.59.The effect of ursolic acid on high glucose-induced apoptosis in U937 cells was investigated.[246] See supplementary material S-7.59

7.60.Ursolic acid promotes the release of macrophage migration inhibitory factor via ERK2 activation in resting mouse macrophages.[247] See supplementary material 7.60

7.61.Antiviral activities of extracts and selected pure constituents of O. basilicum.[248] See supplementary material 7.61

7.62.Protective effect of ursolic acid on ethanol-mediated experimental liver damage in rats.[249] See supplementary material 7.62

7.63.Differential gene expression for investigation of Escherichia coli biofilm inhibition by plant extract ursolic acid.[250] See supplementary material 7.6

7.64.Two new monoterpene glycosides and trypanocidal terpenoids from Dracocephalum kotschyi

From the whole plant of *Dracocephalum kotschyi* BOISS. ursolic acid (6.2 μM), was effective against epimastigotes of *T. cruzi*.[251]

7.65.In vitro anti-inflammatory activity of 23-hydroxyursolic acid isolated from Cussonia bancoensis in murine macrophage RAW 264.7 cells.[146] See supplementary material 7.65

7.66.Antifungal constituents of Clytostoma ramentaceum and Mansoa hirsuta

The activity-guided fractionation of *C. ramentaceum* extract afforded ursolic acid and 2-(3′,4′-dihydroxyphenyl) ethanol, both active against the test fungi (100 μg).[252]

7.67.Antitubercular constituents of Valeriana laxiflora

In a microplate alamar blue assay against *Mycobacterium tuberculosis*, compounds (+)-1-hydroxy-2, 6-bis-epi-pinoresinol, along with eleven known compounds, betulin, betulinic acid, 5,7-dihydroxy-3, 6,4′-trimethoxyflavone, 23-hydroxyursolic acid, oleanolic acid, tricin, ursolic acid exhibited MIC of 15.5–127 μg/Ml.[253]

7.68.Ursolic acid protects hippocampal neurons against kainate-induced excitotoxicity in rats.[254] See supplementary material 7.68

7.69.Anti-platelet ursolic acid from leaves of Campsis grandiflora.[255] See supplementary material 7.69

7.70.Ursolic acid, an antagonist for transforming growth factor-β1.[256] See supplementary material 7.70

7.71.Triterpene acids from the leaves of P. frutescens and their anti-inflammatory and antitumor-promoting effects

Ursolic acid, corosolic acid (**14**), 3-epicorosolic acid (**15**), pomolic acid (**16**), tormentic acid (**17**) and hyptadienic acid (**18**), were isolated from the leaves of *P. frutescens* (L.). Except 3-epicorosolic acid all compounds, were evaluated for its inhibitory effects on TPA-induced inflammation in mice. It showed a marked anti-inflammatory effect, with a 50% inhibitory dose of 0.09–0.3 mg per ear. In addition, an evaluation against the Epstein–Barr virus early antigen (Epstein–Barr virus-EA) activation induced by TPA-showed five compounds, ursolic acid, corosolic acid, 3-epicorosolic acid, tormentic acid, and 3-epimaslinic acid, with a potent inhibitory effect on Epstein–Barr virus-EA induction (91–93% inhibition at 1 × 10(3) mol ratio/TPA).[5]

7.72.Inhibition of ultraviolet-A-modulated signaling pathways by ursolic acid in HaCaT human keratinocytes

Scientists investigated the effects of ursolic acid and asiatic acid on the ultraviolet A-modulated signaling pathways using HaCaT human keratinocytes as a model cellular system.[257]

7.73.Ursolic acid inhibits nuclear factor-κβ activation induced by carcinogenic agents through suppression of Iκβα kinase and p65 phosphorylation: correlation with downregulation of COX-2, matrix metalloproteinase-9, and cyclin D1

Ursolic acid suppressed nuclear factor-κβ activation induced by various carcinogens including tumor necrosis factor, phorbol ester, okadaic acid, H_2O_2, and cigarette smoke.[258] See supplementary material 7.73.

7.74.Sterol and triterpenoid constituents of Verbena littoralis with NGF-potentiating activity

Ursolic acid and oleanolic acid were isolated from Paraguayan medicinal plant showed an enhancing activity of nerve growth factor-mediated neurite outgrowth in PC12D cells.[259]

7.75.Biological activity of some resins, gums and pigments against in vitro LDL oxidation

Amyrin, oleanolic acid, ursolic acid, lupeol, 18-α-glycyrrhetinic acid, and hydroxyl naphthoquinones (naphthazarin, shikonin, and alkannin) showed 53.5–78.8% and 27.0–64.1% low-density lipoprotein (LDL) protective activity. The combination effects (68.7–76.2% LDL protection) of ursolic, oleanolic, and ursodeoxycholic acids were almost equal to the effect (75.3%) of the Chios mastic gum extract in comparable doses.[260,261]

7.76.Cardiovascular, antihyperlipidemic, and antioxidant effects of ursolic acids in hypertension.[262] See supplementary material 7.76

7.77.Antileukemic activity of selected natural products in Taiwan

Ursolic acid possessed strong activity against human leukemia and lymphoma cell lines. Ursolic acid was effective against P3HR1 cells (IC_{50}: 2.5 μg/mL, SI: 262.6) and chronic myelogenous leukemia cells K562 (IC_{50}: 17.79 μg/mL, SI: 36.91).[263]

7.78.Suppressive effects of edible Thai plants and ursolic acid on superoxide and NO generation[264]

7.79.In vivo anti-nociceptive and anti-inflammatory effect of ursolic acid and 23-hydroxyursolic acid, from Cussonia bancoensis

Ursolic acid and 23-hydroxyursolic acid significantly inhibited 1%-carrageenan-induced edema in the rat. These results suggest that ursolic acid and 23-hydroxyursolic acid, are responsible for the anti-nociceptive and anti-inflammatory effect of *C. bancoesnsis*.[265]

Ursolic acid and 2α-hydroxyursolic exhibited strong antiallergic and anti-inflammatory inhibitory activities (IC_{50} values, 17 and 27 μM, respectively).[217]

7.80.Isolation and biological activity of ursolic acid from Vitex negundo (L.)

Ursolic acid and betulinic acid's antifeedant activity against the larvae of an agricultural pest, the castor semilooper, in a no-choice laboratory assay and their antibacterial activity against *Bacillus subtilis* and *Escherichia coli*, by the paper disc method, were tested. Ursolic acid showed more effective antifeedant activity than the betulinic acid.[266]

7.81.Brine shrimp lethality of ursolic acid from Phryma leptostachya (L.).[267] See supplementary material 7.81

7.82.Extract and identify ursolic acid from Ligustrum lucidum Ait and study its effect to periodontal pathogen.[268] See supplementary material 7.82

7.83.Ursolic acid as a trypanocidal constituent in rosemary

Ursolic acid stopped the movement of all *T. cruzi epimastigotes* at the minimum concentration (MC (100) of 40 μg/mL (88 μM) after 48 h of incubation.[269]

7.84.Triterpenes ursolic acid and phytosterols as human leukocyte elastase inhibitors[270]

7.85.Effects of ursolic acid and oleanolic acid on human colon carcinoma cell line HCT-15.[271] See supplementary material 7.85

7.86.Ursolic acid of Origanum majorana (L.) reduces αβ-induced oxidative injury.[272] See supplementary material 7.86

7.87.Inhibitory effect of ursolic acid purified from Origanum majorana (L.) on the acetylcholinesterase.[273] See supplementary material 7.87

7.88.Cytostatic, cytotoxic and protein tyrosine kinase inhibitory activity of ursolic acid in A431 human tumor cells.[274] See supplementary material 7.88

7.89.In vitro anti-inflammatory activity of triterpenoid compounds isolated from Phillyrea latifolia (L.).[275,276] See supplementary material 7.89

7.90.Novel triterpenoids inhibit both DNA polymerase and DNA topoisomerase.[277] See supplementary material 7.90

7.91.Ursolic acid was also isolated from Shandanshaoyao Decoction[278]

The crude dichloromethane bark extract of *Pilidiostigma tropicum* from north Queensland, Australia, shows antibacterial and cytotoxic activity. Bioactivity-directed separation led to the isolation of ursolic acid-3-*p*-coumarate as the biologically active materials.[279]

7.92.Cytotoxic triterpenes from stem bark of Physocarpus intermedius. See supplementary material 7.92

Ursolic acid was responsible for the cytotoxicity against five cultured human tumor cell lines, i.e., A549 (non-small cell lung), SK-OV-3, SK-MEL-2, XF498, and HCT-15 (colon), *in vitro*.[280]

7.93.Cytotoxic triterpenes from Crataegus pinnatifida.[281] See supplementary material S-7.93

7.94.Anti-AIDS agents. 30. Anti-HIV Activity of oleanolic acid, pomolic acid, and structurally related triterpenoids

Ursolic acid did show anti-HIV activity (EC_{50} 2.0 μg/mL), it was slightly toxic (IC_{50} 6.5 μg/mL, T. I. 3.3). A new triterpene (**25**) was also isolated from the $CHCl_3$-soluble fraction of *Rosa woodsii*, though it showed no anti-HIV activity. Pomolic acid (**19**) demonstrated anti-HIV activity, with EC_{50} values of 1.4 μg/mL, respectively, and inhibited uninfected H9 cell growth with IC_{50} values of 23.3 μg/mL, respectively. Ursolic acid, isolated from *Prosopis glandulosa*, *Syzygium claviflorum*, and *Hyptis capitata*, was found to show similar anti-HIV activity, with an EC_{50} value of 2.0 μg/mL and IC_{50} values of 6.5 μg/mL (T. I. value, 3.3) (Scheme 3).[282]

7.95.Ursolic acid isolated from Eucalyptus tereticornis protects against ethanol toxicity in isolated rat hepatocytes.[283] See supplementary material 7.95

7.96.Ursolic acid inhibits COX-2 transcription in human mammary epithelial cells.[284] See supplementary material 7.96

7.97.Cyclic adenosine monophosphate inhibits ursolic acid-induced apoptosis via activation of protein kinase A in human leukemic HL-60 cells.[285] See supplementary material 7.97

7.98.DNA polymerase β inhibitors from Baeckea gunniana.[286] See supplementary material 7.98

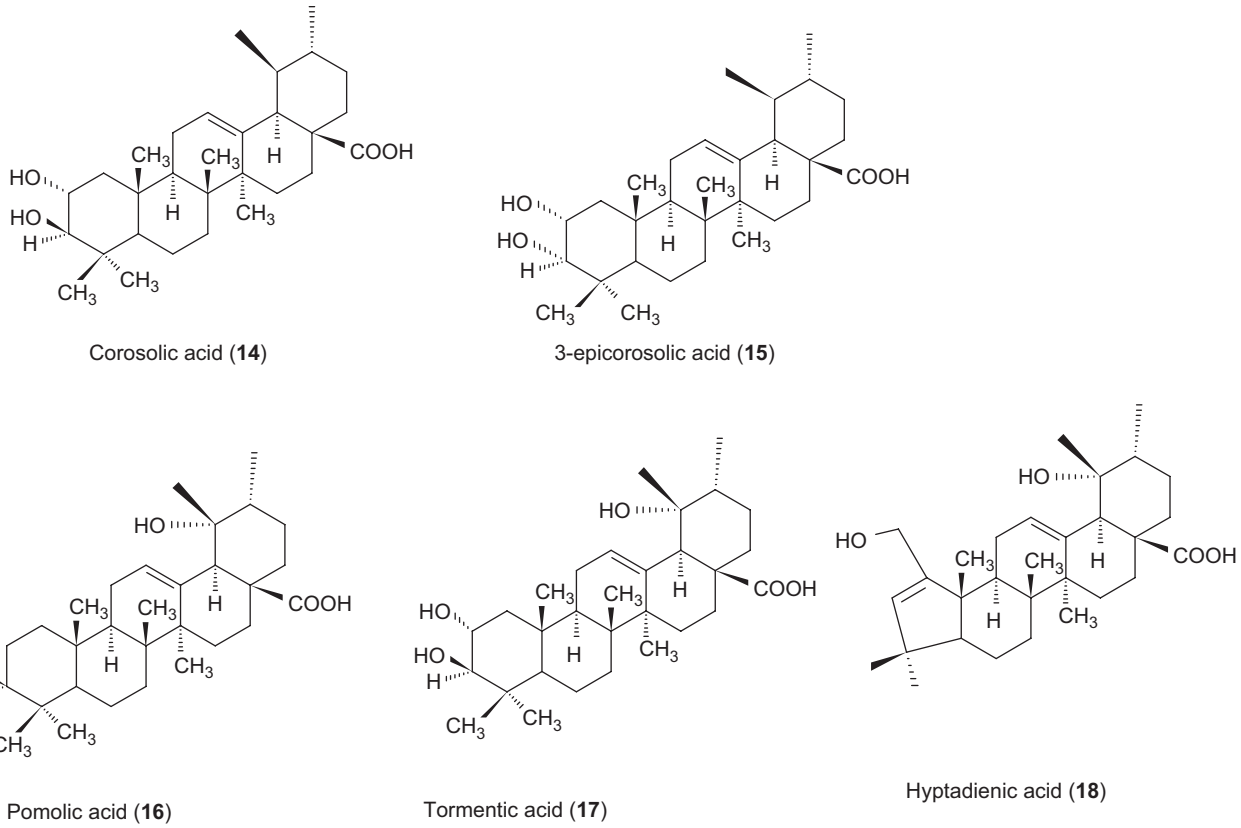
7.99.Antimalarial activity of four plants used in traditional medicine in Mali

Ursolic acid, purified from the hydromethanol extract of *Muricopsis inermis* induced a significant decrease of parasite proliferation.[287]

7.100.Chitin synthase II inhibitory activity of ursolic acid, isolated from Crataegus pinnatifida

Ursolic acid from *Crataegus pinnatifida Bunge* inhibits chitin synthase II from *Saccharomyces cerevisiae* with an IC_{50} value of 0.84 μg/mL.[288]

7.101.Ursolic acid from Plantago major, a selective inhibitor of COX-2 catalyzed prostaglandin biosynthesis.[289] See supplementary material 7.101



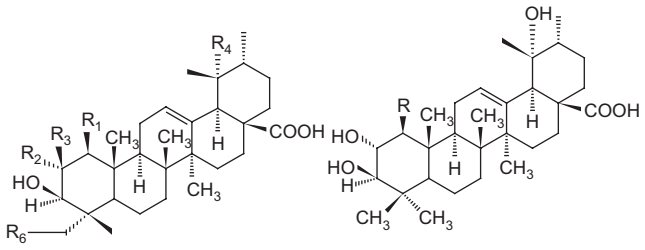
Scheme 2. Triterpene acids from the leaves of *Perilla frutescens* from apple peels.

7.102.Ursolic acid-induced downregulation of matrix metalloproteinase-9 gene is mediated through the nuclear translocation of glucocorticoid receptor in HT1080 human fibrosarcoma cells.[290] See supplementary material 7.102

7.103.Intracellular Ca2+ release mediates ursolic acid-induced apoptosis in human leukemic HL-60 cells.[291] See supplementary material S-7.103

7.104 Ursolic acid stabilize liposomal membranes[348]

Ursolic acid on the fluidity and stability of dipalmitoyl phosphatidylcholine liposomal membrane was monitored by measuring the fluorescence polarization of 1,6-diphenyl-1, 3, 5-hexatriene labeled in the liposomal membrane and the leakage of calcein from the probe-encapsulated liposomes. The experiments with the liposomes made of dipalmitoyl phosphatidylcholine and oleanolic acid or ursolic acid showed that oleanolic acid and ursolic acid exhibited a moderate fluidity-modulating effect for the liquid-crystalline liposomal membrane, and a strong condensing effect for both crystalline and liquid-crystalline liposomal membranes. These result showed that their fluidity-modulating and condensing effects might have some implications in their biological functions.[348]



	R_1	R_2	R_3	R_4	R_5
19.	H	H	H	OH	H
20.	OH	H	OH	H	H
21.	OH	OH	H	H	H
22.	H	OH	H	OH	OH
23.	H	OH	H	OH	H
24.	H	O	O	OH	H
25.	OH	O	O	OH	H
26.	OH	H	H	OH	H

Scheme 3. Ursolic acid and structurally related triterpenes for HIV activity.

7.105.Effects of oleanolic acid and ursolic acid on inhibiting tumor growth and enhancing the recovery of hematopoietic system postirradiation in mice.[292] See supplementary material 7.105

7.106.Inhibitory effect of ursolic acid on B16 proliferation through cell-cycle arrest.[293] See supplementary material 7.106

7.107.Anti-invasive activity of ursolic acid correlates with the reduced expression of matrix metalloproteinase-9 in HT1080 human fibrosarcoma cells.[294] See supplementary material 7.107

7.108.Antitumor effect in vitro and immuno-response in vivo of Fructus mume

The antitumor action of ursolic acid on HIMeg and HL-60 cells *in vitro* was tested. The immuno-response in rats was also studied. The *Fructus mume* had inhibiting effect on proliferation of HIMeg and HL-60 cells.[295]

7.109.Ursolic acid inhibits aflatoxin B1-induced mutagenicity in a Salmonella assay system

Ursolic acid significantly decreased the numbers of *Salmonella typhimurium* TA100 revertants per plate, thus showing antimutagenic activity.[296]

7.110.Inhibition of skin tumorigenesis by rosemary and its constituents carnosol and ursolic acid.[297] See supplementary material 7.110

7.111.Search for possible antitumor promoters by inhibition of TPA-induced Epstein–Barr virus activation.[6] See supplementary material 7.111

7.112.Inhibitory effects of ursolic acid on skin tumor promotion.[298] See supplementary material 7.112

7.113.The effects of 10 triterpenoid compounds on experimental liver injury in mice.[299] See supplementary material 7.113

7.114.Induction of differentiation in the cultured F9 teratocarcinoma stem cells by triterpene acids.[300] See supplementary material 7.114

7.115.Intervention of adriamycin induced free radical damage by ursolic acid.[301] See supplementary material 7.115

7.116.Effect of ursolic acid from epicuticular waxes of Jacaranda decurrens on Schizaphis graminum.[302] See supplementary material 7.116

7.117.Inhibition of lipoxygenase activity and HL-60 leukemic cell proliferation by ursolic acid

Ursolic acid from heather flowers to be an inhibitor of both potato tuber 5-lipoxygenase and soybean 15-lipoxygenase with IC_{50} values of 0.3 mM. It also inhibits lipoxygenase activity in mouse peritoneal macrophages at 1 μM and HL-60 leukemic cells growth ($IC_{50} = 0.85$ μM) as well as their DNA synthesis ($IC_{50} = 1$ μM).[303]

7.118.Characterization of ursolic acid as a lipoxygenase and COX inhibitor[304]

7.119.Inhibition of human leukocyte elastase by ursolic acid. Evidence for a binding site for pentacyclic triterpenes.[305] See supplementary material 7.119

7.120.Antibiotic action of β-ursolic acid.[306] See supplementary material 7.120

7.121.Use of ursolic acid in skin and hair care treatment

Hair growth stimulant agent: Ursolic acid and its isomer, have been used in tonics to enhance hair growth and prevent scalp irritation. It encourage hair growth by stimulating the peripheral blood flow in the scalp and activating the hair mother cells. It also furnish alopecia-preventing and dandruff-preventing effects.[307]

8.Derivatives

Ursolic acid derivatives, including ursane-type triterpenoid saponins, naturally occur as secondary metabolites through complex metabolic processes in different parts of the plant.[308,309] Synthetic derivatives obtained from ursolic acid have been reported and evaluated for their pharmacological action.

8.1.Study of the trypanocidal activity of triterpene acids isolated from Miconia species.[310] See supplementary material 8.1

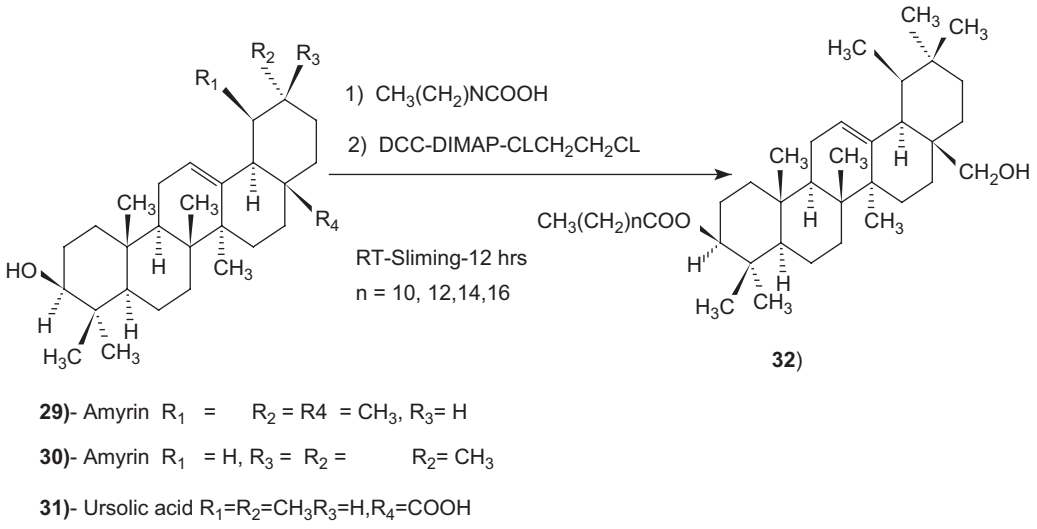
8.2.Abietane triterpenoic acids from Salvia cilicica and their antileishmanial activities

Ursolic acid was found to be potently active against amastigote IC_{50} values of 7–120 nM and moderately active against promastigote stages IC_{50} values of 51–137 *n*M) of the two *Leishmania* species.[311]

8.3.Structure-dependent inhibition of bladder and pancreatic cancer cell growth by 2-substituted glycyrrhetinic and ursolic acid derivatives[312]

8.4.Evaluation of ursolic acid and derivatives on aromatase inhibition

The inhibitory potency of ursolic acid its derivatives to inhibit aromatase activity was assessed and compared to a phytoestrogen apigenin and a steroidal aromatase inhibitor 4-hyroxyandrostenedione. Only ursolic acid showed an efficient and dose-dependent aromatase inhibition with IC_{50} value of 32 μM as did apigenin ($IC_{50} = 10$ nM), whereas IC_{50} value of 4-OHA was 0.8 nM. Results show that the incorporation of a metallocene moiety into the ursolic acid derivatives decreases the aromatase inhibition. Moreover, comparison of the structure/inhibitory potency relationship indicates that the presence of cycle A and the configuration of



Scheme 4. Synthesis of triterpenic esters with different chain lengths at C-3.

C3-OH and C17-COOH seems to be more favorable to recognize the active site of aromatase and to block its activity.[313]

8.5.Antimicrobial activity of pentacyclic triterpenes and their synthesized 3-O-lipophilic chains

The metabolites of *Diopsyros melanoxylon* viz. ursolic acid and their lipophilic 3-*O*-fatty acid ester chains (C12–C18), were evaluated for their antimicrobial activity against a series of Gram-positive and Gram-negative bacteria.

Significantly these compounds were found to exhibit potent activity against Gram-negative bacteria *Pseudomonas syringae* and fairly good activity against Gram-positive bacteria, *Bacillus sphaericus*, and *B. subtilis* (Scheme 4).[314]

8.6.Oxyfunctionalization products of terpenoids and their biological activity

Oxyfunctionalization of ursolic acid acetate and kaurenic acid, with dimethyldioxirane was investigated. Treatment of the terpenoids with dimethyldioxirane afforded a variety of oxidation and oxydegradation products to yield naturally occurring or novel compounds. The inhibitory activity of the terpenoid derivatives against α-glucosidase was investigated and ursolic acid acetate (**33**) and 11,12-dehydroursolic lactone, 3-*O*-acetyl-9,11-dehydro-12α–hydroxyoleanolic lactone (33″) were found to exhibit potent activity (Scheme 5).[315]

8.7.Inhibition by boswellic acids of human leukocyte elastase

Substantial inhibition by β-boswellic acid (**35**), amyrin (**37**, **38**), and ursolic acid, but not by 18β-glycyrrhetinic acid (**6**) was observed. The data show that the dual inhibition of 5-lipoxygenase and human leukocyte elastase is unique to boswellic acids. Other triterpenes with human leukocyte elastase inhibitory activities (ursolic acid) do not inhibit 5-lipoxygenase, and leukotriene biosynthesis inhibitors from different chemical classes do not impair human leukocyte elastase activity. Because leukotriene formation and human leukocyte elastase release are increased simultaneously by neutrophil stimulation in a variety of inflammation and hypersensitivity-based human diseases, the reported blockade of two pro-inflammatory enzymes by boswellic acids might be the rationale for the putative antiphlogistic activity of acetyl-11-keto-β-boswellic acid and derivatives (Scheme 6).[316,317]

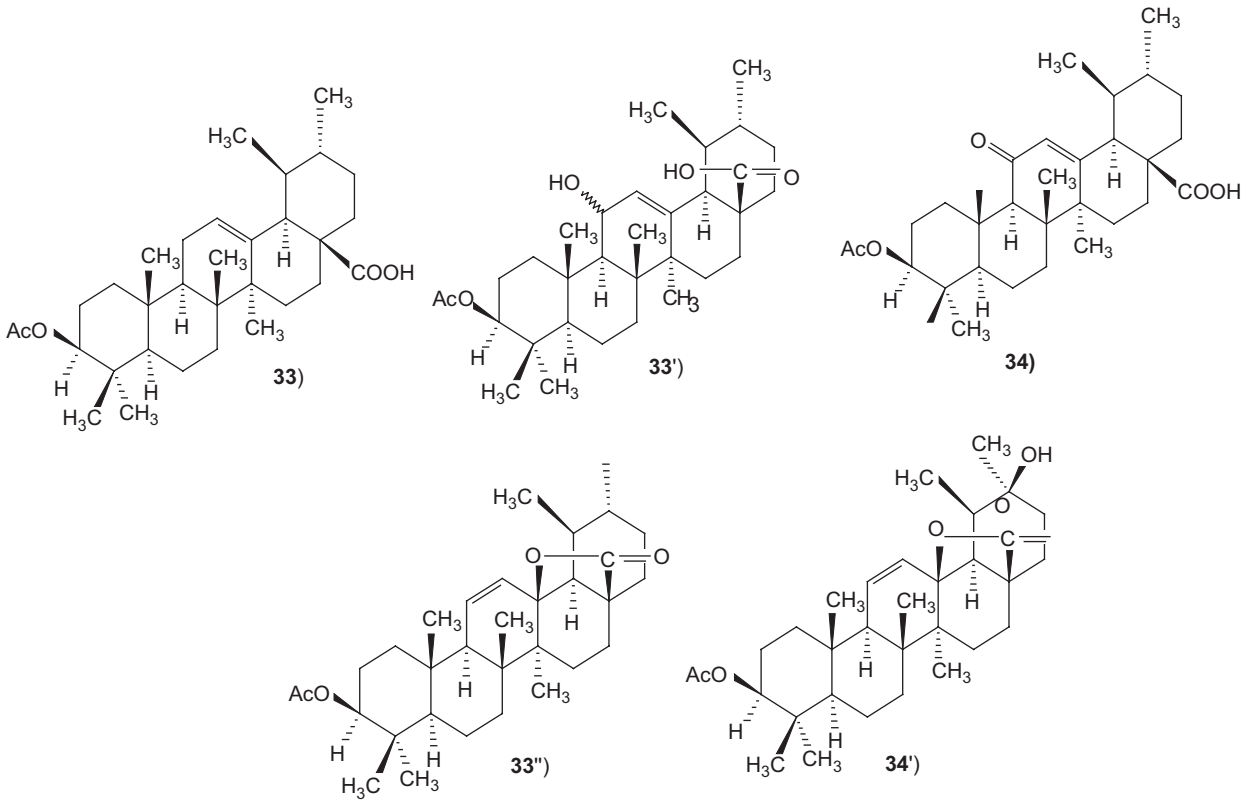
8.8.Radical-scavenging activities of new hydroxylated ursane triterpenes from cv. Annurca apples.[318] See supplementary material 8.8

8.9.Trypanocidal activity of triterpenes from Arrabidaea triplinervia and derivatives

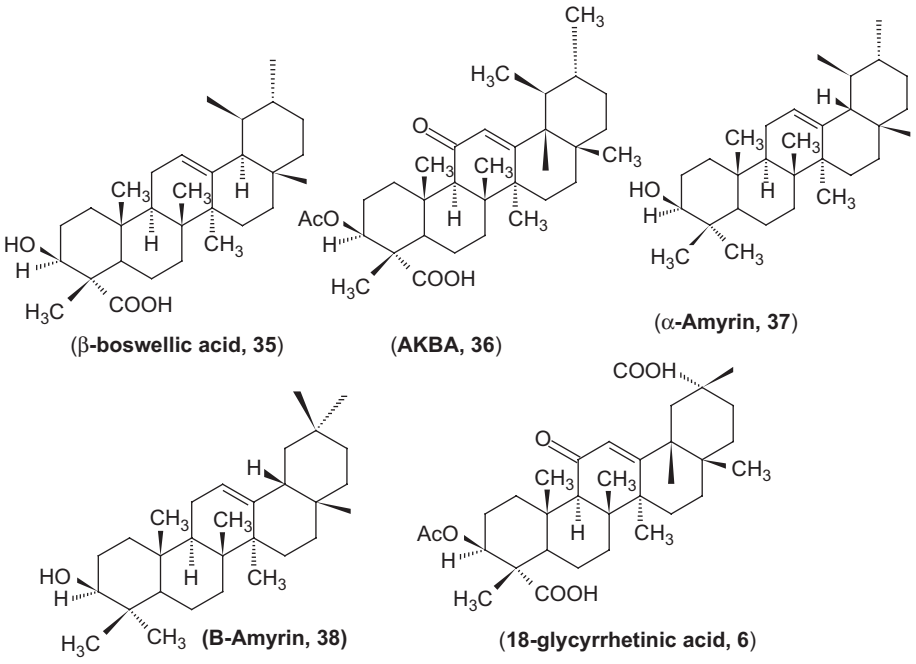
A series of derivatives of ursolic acid was assayed for structure-activity relationships studies. Ursolic acid (ED100 0.4 mg/mL) was four times more active than oleanolic acid (ED100 1.6 mg/mL). The presence of free hydroxy or carboxy groups is necessary for the trypanocidal activity as could be deduced from the effect of the acetates (**39**), methyl ester (**40**) and aldehyde derivatives (Scheme 7).[319]

8.10.Beccaridiol, an unusual 28-nortriterpenoid from the leaves of Diplectria beccariana

Beccaridiol (28-nortriterpene28-nortriterpene), 2′, 4′-dihydroxy-3-(4-methoxyphenyl)-propiophenone, 4′-hydroxy-1′, 2′-dihydro-β-ionone, 4′-*O*-methyldavidigenin and ursolic acid, isolated from *D. beccariana*. All isolates were evaluated for their potential cancer chemopreventive properties utilizing a cell culture assay to determine quinone reductase induction.[320]



Scheme 5. Oxidation of ursolic acid acetate with DMSO.



Scheme 6. Boswellic acids of human leukocyte elastase.

8.11.The cytotoxic activity of ursolic acid derivatives

Ursolic acid and 2α-hydroxyursolic acid were found to show growth inhibitory activity against four tumor cell lines, HL-60, BGC, Bel-7402, and Hela.[321] See supplementary material 8.11.

8.12.Cardiotonic and antidysrhythmic effects of ursolic acid, methyl maslinate and uvaol.[8] See supplementary material 8.12

8.13.In vitro trypanocidal activity of triterpenes from Miconia species.[322] See supplementary material 8.13

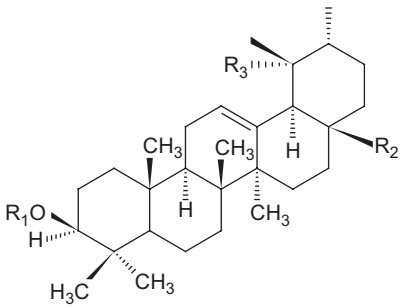
8.14.Antimycobacterial activity of cinnamate-based esters of the triterpenes betulinic, oleanolic, and ursolic acids

Ursolic acid have been modified at the C-3 position to cinnamate-based esters (43–51) and *in vitro* antimycobacterial activity against *M. tuberculosis* H (37) Ra has been determined.

The results indicated that modification of the parent structures of ursolic acid to the *p*-coumarate and, the ferulate ester analogues resulted in high antimycobacterial activity (Scheme 8). Ursolic acid exhibited antimicobacterial activity (MIC 12.5 μg/mL), whereas its cinnamoyl and *p*-chlorocinnamoyl analogues **43** and **57** were inactive. The *p*-coumarate ester **45** was highly active, with an MIC value of 6.25 μg/mL. The corresponding acetate and methyl ether derivatives, **44** and **48,** showed lower activity with MIC s of 25 and 100 μg/mL, respectively. Both the ferulate ester **49** and its acetate **48** were highly active with equal MICs of 3.13 μg/mL. However, the corresponding caffeate ester **50** and its acetate **49** were much less active, with respective MICs of 200 and 100 μg/mL.[323]

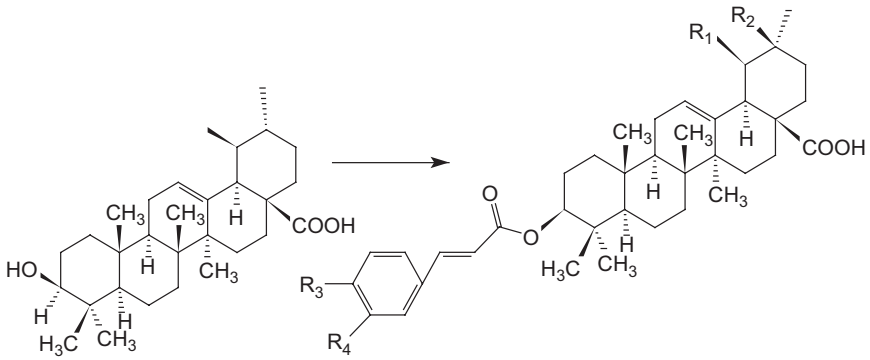
8.15.Anti-hepatoma activity and mechanism of ursolic acid and its derivatives isolated from Aralia decaisneana

Ursolic acid could significantly inhibit the proliferation of HepG2 and its drug-resistance strain, R-HepG2 cells, but had no inhibitory effect on primarily cultured normal mouse hepatocytes whereas all the six derivatives of ursolic acid (**52–57**) could not inhibit the growth of all tested cell lines. Further study on mechanism demonstrated that apoptosis and G0/G1 arrest were involved in the cytotoxicity and cleavage of poly-(ADP-ribose)-polymerase. Downregulation of COX-2 protein and upregulation of heat shock protein 105 mRNA correlated to the apoptosis of HepG2 cells treated with ursolic acid. Ursolic acid is a promising antitumor agent (Scheme 9).[324]



	R_1	R_2	R_3
39)	OH	COOH	H
40)	OH	$COOCH_3$	H
41)	$OCOCH_3$	$COOCH_3$	H
42)	OH	COOH	OH

Scheme 7. Derevatives of ursolic acid for trypanocidal activity.

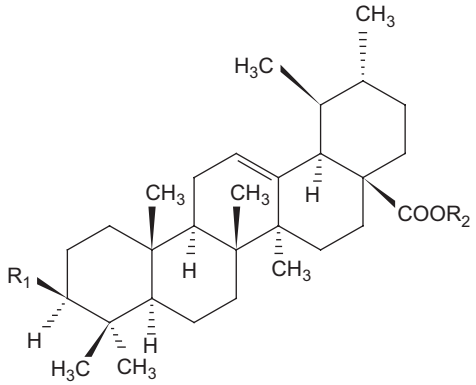


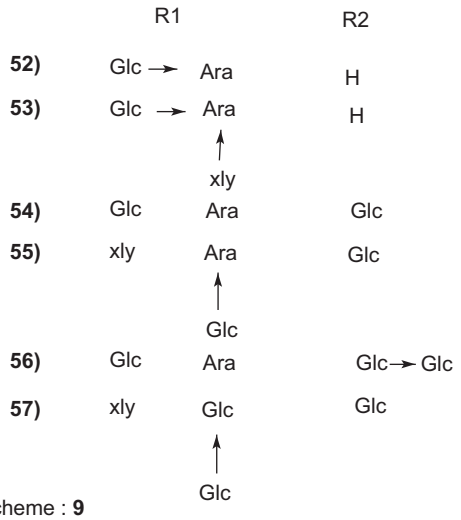
Ursolic acid

43) R1=Me R2 = R3= R4 =H
44) R1=Me R2 = R4= H R3=OAc
45) R1=Me R2 =R4 = H R3=OH
46) R1=Me R2 =R4=h R3=OMe
47) R1=Me R2= H, R3=OAc R4=OMe
48) R1=Me R2= H, R3=OH R4=OMe
49) R1=Me R2= H, R3= R4=OAc
50) R1=Me R2= H, R3= R4 =OH
51) R1= Me R2= R4=H R3=cl

Scheme 8. Synthesis of cinnamate-based esters of ursolic acid.

8.16.Inhibitory activity of minor polyphenolic and non-polyphenolic constituents of olive oil against in vitro LDL oxidation.[325] See supplementary material 8.16





Scheme : **9**

52) UA-3-*O*-β-D-glucopyranosyl (1-3)-α-L-arabinopyranoside

53) UA-3-O-β-D-xylopyranosyl (1-2)-β-D-glucopyranosyl (1-3)-α-L-arabinopyranoside

54) UA-3-O-β-D-glucopyranosyl (1-3)-α-L-arabinopyranosyl-28-O-β-D-xylopyranosyl

55) UA-3-O-β-D-glucopyranosyl (1-2)-α-L-arabinopyranosyl-28-O-β-D-xylopyranosyl -β-D-xylopyranosyl(1-3)-α-L-arabinopyranosyle -28-O-β-D-glucopyranoside

56) UA-3-*O*-β-D-glucopyranosyl (1-3)-α-L-arabinopyranoside 28-O-β-D-glucopyranosyl (1-6)-O-β-D-glucopyranoside

57) UA-3-*O*-β-D-glucopyranosyl (1-3)-β-D-xylopyranosyl-28-O-β-D-glucopyranoside

Scheme 9. (**52**) UA-3-*O*-β-D-glucopyranosyl (1-3)α-L-arabinopyranoside (**53**) UA-3-*O*-β-D-xylopyranosyl (1-2)-β-D-glucopyranosyl (1-3)α-L-arabinopyranoside (**54**) UA-3-*O*-β-D-glucopyranosyl (1-3)α-L-arabinopyranosyl-28-*O*-β-D-xylopyranosyl (**55**) UA-3-*O*-β-D-glucopyranosyl (1-2)α-L-arabinopyranosyl-28-*O*-β-D-xylopyranosyl -β-D-xylopyranosyl(1-3) α-Larabinopyranosyle-28-*O*-β-D-glucopyranoside (**56**) UA-3-*O*-β-D-glucopyranosyl (1-3)α-L-arabinopyranoside 28-*O*-β-D-glucopyranosyl (1-6)-*O*-β-D-glucopyranoside (**57**) UA-3-*O*-β-D-glucopyranosyl (1-3)β-D-xylopyranosyl-28-*O*-β-D-glucopyranoside.

8.17.Uinovic acid glycosides from Mitragyna stipulosa first examples of natural inhibitors of snake venom phosphodiesterase I

α-Amyrin, 3β-acetyl ursolic acid, and β-sitosterol glucopyranoside were isolated from the *Mitragyna stipulosa* bark extract, showed significant inhibitory activity against snake venom.[326]

8.18.Abietane triterpenoic acids from Salvia cilicica and their antileishmanial activities

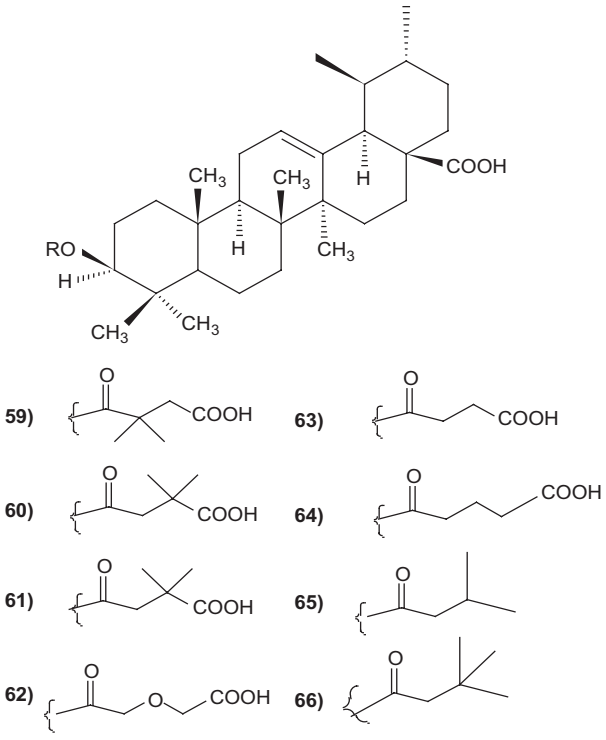
The triterpenoic acids were found to be potently active against amastigote (IC_{50} values of 7–120 nM) and moderately active against promastigote stages (IC_{50} values of 51–137 nM) of the two Leishmania species.[311]

9.Structure-activity relationship of ursolic acid

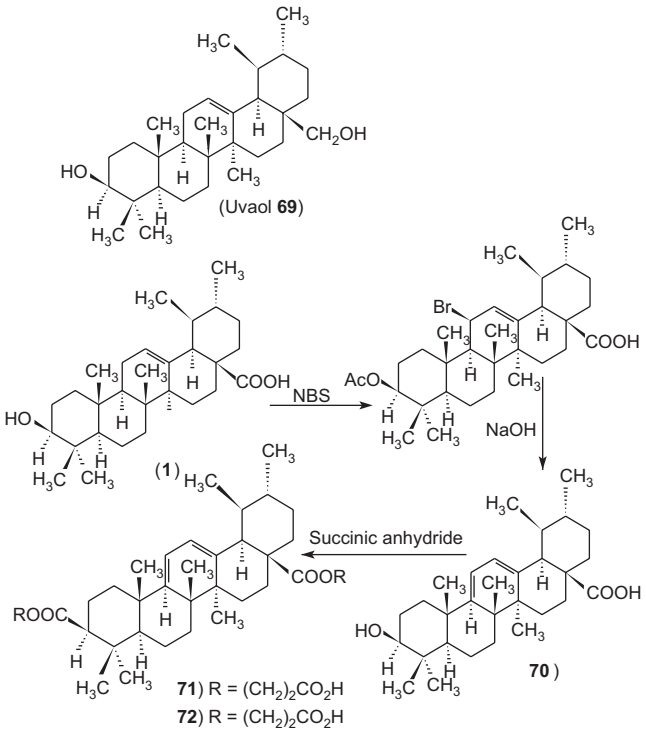
9.1.Structure-activity relationship of triterpenoids isolated from Mitragyna stipulosa on cytotoxicity.[327] See supplementary materials 9.1

9.2.Microbial transformation of cadina-4, 10 (15)-dien-3-one, aromadendr-1(10)-en-9-one and methyl ursolate by Mucor plumbeus ATCC 4740.[328] See supplementary material 9.2

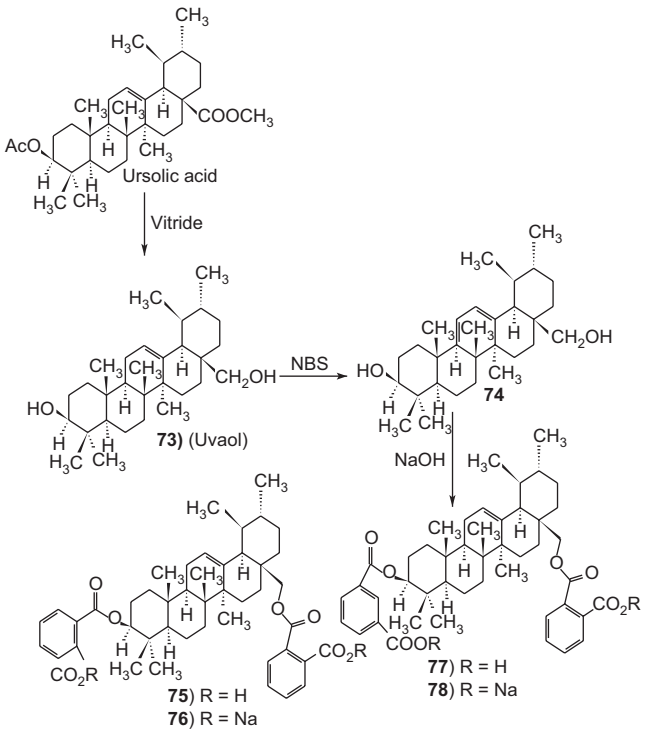
9.3.Activation of caspase-3 protease during the process of ursolic acid and its derivative-induced apoptosis.[329] See supplementary material 9.3



Scheme 10. 3-*O*-acyl ursolic acid derevatives.



Scheme 11. Synthesis of Disodium 3b-13-carboxy propyonyloxy) urea-9, 12 diene-28-oate.



Scheme 12. Synthesis of uvaol hemiphthalate derevatives

9.4.Anti-AIDS agents 38. Anti-HIV activity of 3-O-acyl ursolic acid derivatives

Several 3-*O*-acyl-ursolic acids were evaluated for anti-HIV activity. Ursolic acid was equipotent (EC_{50} 4.4 μM) with oleanolic acid (EC_{50} 3.7 μM), although it was slightly toxic (IC_{50} 14.3 μM, therapeutic index 3.3). 3-*O*-Diglycoryl-ursolic acid (**62**) demonstrated relatively potent anti-HIV activity with an EC_{50} of 0.31 μM and a therapeutic index of 155.5. In contrast, 3-*O*-(3′, 3′-dimethylsuccinyl)-ursolic acid (**60**), which is analogous to the extremely potent anti-HIV betulinic acid derivatives, displayed only weak anti-HIV activity (EC_{50} 2.1 μM) (Scheme 10).[330]

9.5.Anti-inflammatory activity

Ursolic acid not only inhibits human leukocyte elastase, but also 5-lipoxygenase and COX activity. It inhibited TPA-induced mouse ear edema by 72.4% determined that 200 g and 50 g applications of ursolic acid inhibited 12-*O*-hexadecanoyl-16-hydroxyphorbol-13-acetate-induced inflammation by 49% and 33%. It inhibited concanavalin A induced histamine release, which can cause severe inflammation, by 95% at a concentration of 0.001 M.[331]

9.6.Immunomodulating activity of ursolic acid derivatives, inhibitory effects of constituents from Cynomorium songaricum on HIV-1 protease

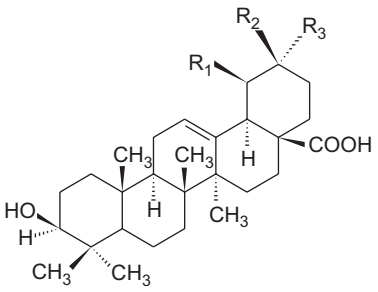
Ursolic acid and its hydrogen malonate isolated from *Cynomorium songaricum* Rupr as inhibitors of human immunodeficiency virus type 1 protease, with 50% inhibitory concentrations IC_{50} of 8 and 6 μM. Amongst various dicarboxylic acid hemiesters of related triterpenes, inhibitory activity tended to increase in the order of oxalyl, malonyl, succinyl, and glutaryl hemiesters, for ursolic acid. The most potent inhibition was observed for the glutaryl hemiesters, with an IC_{50} of 4 μM.[332]

9.7. Ursolic acid: an anti-tumorigenic and chemopreventive activity. Minireview.

Ursolic acid, is of interest to scientists in the area of oncology because of its cytotoxicity, induction of differentiation, anti-mutagenic, antiviral and anti-invasive activities. Ursolic acid is capable of inducing apoptosis in tumor cells on one side and to prevent malignant transformation of normal cells on the other side. It also interferes with numerous enzymes, including the ones serving directly to DNA synthesis. This review summarizes reports on ursolic acid biological properties and to show its main anti-tumor effects and chemopreventive properties in normal cells.[340]

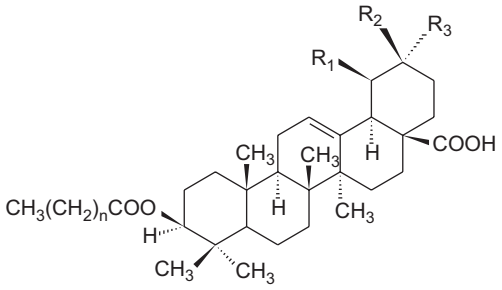
9.8.Synthesis and anti-ulcer activity of new derivatives of oleanolic and ursolic acids

Among the ursolic acid derivatives, the dihemisuccinate sodium salt **72** demonstrated a good separation between anti-ulcer and mineralocorticoid activities. Nevertheless, kidney and liver toxicity was observed in the monkey thus jeopardizing its further development. Better results were obtained with the uvaol dihemiphthalate sodium salt and the diene analogue **77**. In particular, **75** and **76** showed a potent anti-ulcer activity, 3- to 25-fold higher than carbenoxolone. Furthermore, compound **76** does not show signs of liver toxicity in the monkey (Scheme 11, 12).[333]



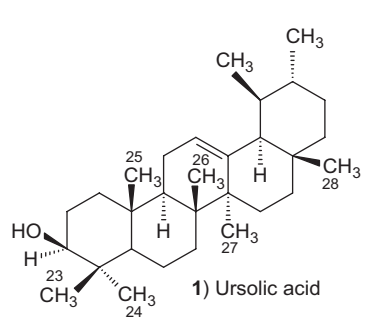
R_1 = CH_3, R_2 = H, R_3 = CH_3, ursolic acid, **1**)
R_1 = H, R_2 = R_3 = CH_3 oleanolic acid)

CH_3–(CH_2)n–COOH
n = 10 (Dodecanoic acid, **79**)
n = 12 (Tetradecanoic acid, **80**)
n = 14 (Hexadecanoic acid, **81**)
n = 16 (Octadecanoic acid, **82**)

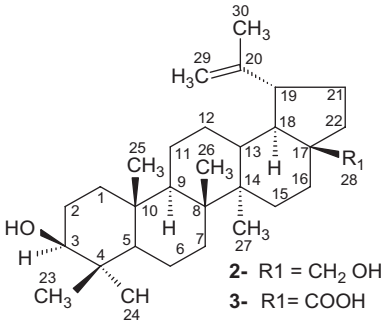


R_1= CH_3, R_2 = H, R_3 = CH_3, ursolic acid,
n =10 (Urs -12- ene-28-carboxy-3 β -*O*-dodecanoate, **83**)
R_1= CH_3, R_2 = H, R_3 = CH_3, ursolic acid,
n =12 (Urs -12- ene-28-carboxy-3 β -*O*-tetradecanoate, **84**)
R_1= CH_3, R_2 = H, R_3 = CH_3, ursolic acid,
n =14 (Urs -12- ene-28-carboxy-3 β-*O*-hexadecanoate, **85**)
R_1= CH_3, R_2 = H, R_3 = CH_3, ursolic acid,
n 16 (Urs -12- ene-28-carboxy-3 β-*O*-octadecanoate, **86**)
R_1= H, R_2 = R_3 = CH_3, ursolic acid,
n =14 (Olean -12- ene-28-carboxy- 3 β-*O*-*h*exadecanoate, **87**)
R_1= CH_3, R_2 = H, R_3 = CH_3, ursolic acid,
n =16 (Olean - 12-ene-28-carboxy-3 β-*O*-octadecanoate, **88**)

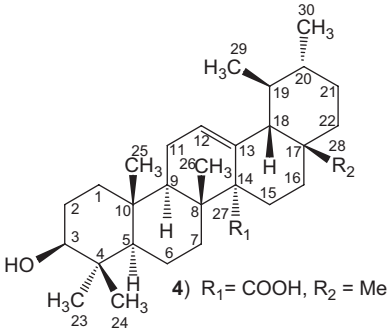
Scheme 13. 3-O-fatty acid ester derevatives of some triterpene acids.



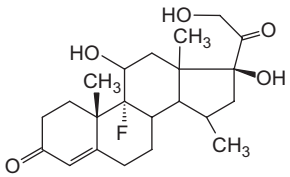
1) Ursolic acid



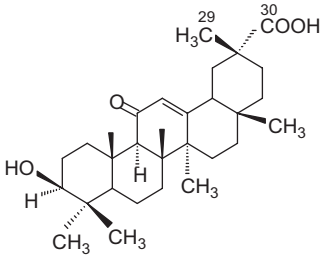
2- R1 = CH_2 OH
3- R1= COOH



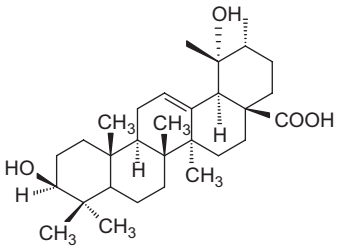
4) R_1= COOH, R_2 = Me



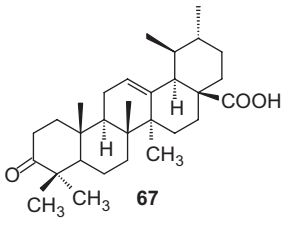
5) Dexamethasone



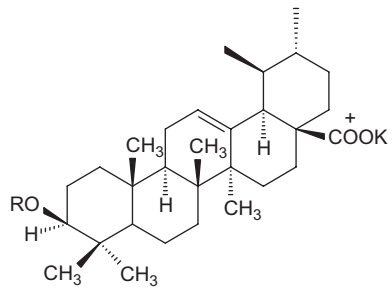
6) 18-Beta glycyrrhetinic acid



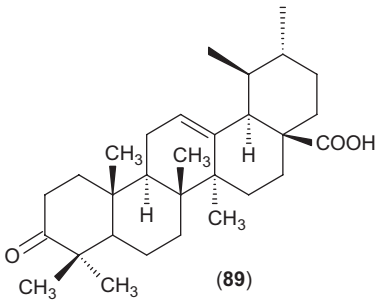
58 Pomolic acid



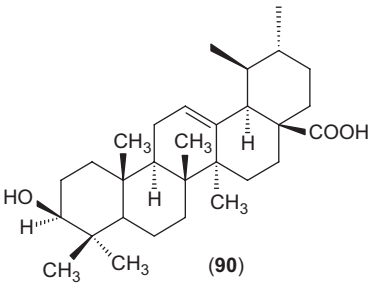
67



68) Potassium salt of ursolic acid



(**89**)



(**90**)

Figure 1.

9.9.Antifeedant activity of some triterpene acids and their fatty acid ester analogues

The 3-*O*-fatty acid ester derivatives C12–C18 of ursolic acid (**79–84**) were screened for their antifeedant activity against the agricultural pest tobacco caterpillar larvae (Spodoptera litura F) in a no-choice laboratory study. The Urs-12-ene-28-carboxy-3β-octadecanoate and olean-12-ene-28-carboxy-3β-hexadecanoate were found to exhibit exceptionally potent antifeedant activities at 50 μg/cm^2 concentration (Scheme 13).[334]

9.10.Anti-AIDS agents. Anti-HIV activity of ursolic acid and structurally related triterpenoids

Oxidation of ursolic acid (**1**) yielded a 3-oxo- derivative (**89**), which was more toxic against uninfected H9 cells than its parent compound, but inhibited HIV-1 replication, with an improved EC_{50} value of 0.11 g/mL. Treatment of **1** with a molar equivalent of potassium hydroxide furnished the potassium salt of oleanolic acid (**90**). It exhibited potent anti-HIV activity, with an EC_{50} value of 0.5 g/mL and a T.I value of 68.6. enhanced anti-HIV activity with the potassium salt.[335]

9.11.Cladocalol, and ursolic acid from Eucalyptus cladocalyx with cytotoxic activity.[336] See supplementary material 9.11

9.12.New 3-O-acyl betulinic acids and ursolic acid from Strychnos vanprukii Craib.[337] See supplementary material 9.12

9.13.Immunomodulating activity of ursolic acid derivatives, novel triterpenoids suppress inducible NO synthase and inducible COX in mouse macrophages.[338] See supplementary material 9.13

9.14.Structure-activity relationships of synthetic methyl ursolate glycosides.[339] See supplementary material 9.14

10.Conclusion

Ursolic acid has been found to be an active ingredient from *Eriobotrya japonica* and *Rubus* species. The literature survey reveals that it is a highly potent compound which shows variety of biological activities. It is known for their antimicrobial, hepatoprotective, anti-inflammatory, antiallergic, antiviral, and cytotoxic activities. It can be an active ingredient in treating urease, β-lactamase, acetyl cholinesterase, α-glucosidase, antimicrobial, hepatoprotective, anti-inflammatory, antipruritic effects, spasmolytic activity, anti-angiogenic activities, antiallergic, antiviral, and cytotoxic activities. In recent years, it was found that ursolic acid had marked antitumor effects. It was shown that it protects mice against the hepatotoxicity of carbon tetrachloride, acetaminophen, bromobenzene, thioacetamide, furosemide, phalloidin, colchicine, cadmium, D-galactosamine and endotoxin. It lower serum transaminase, lactic dehydrogenase, and γ-glutamyltransferase levels in the CCl_4-treated rats. It enhances the bioavailability of the active ingredient of the pharmaceutical compound. On the basis of its activities, it may be possible to develop triterpenoids as useful agents for chemoprevention of cancer or other chronic diseases with an inflammatory component. Ursolic acid could provide an effective and cheap treatment of most common diseases in the world.

In the end, we can suggest that *Eriobotrya japonica* which is a widely grown, in many countries, could be used as a source of ursolic acid. Further studies involving crude extracts of *Eriobotrya japonica* containing ursolic acid would be highly economic and would account for useful consumption of the problems concerned.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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