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Review Article

A REVIEW ON URSOLIC ACID: A NATURALLY OBTAINED PENTACYCLIC TRITERPENE

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ABSTRACT

Natural products derived from plants have been used for decades in traditional medicine. Many classes of compounds exist in plants such as saponins, alkaloids, anti-oxidants, etc. Pentacyclic triterpenes are also one of the compounds occurring in plants. In this class Ursolic acid is a well-recognized compound that is available from various sources like seeds as well as fruits and possess many types of activities and is a bright contender for developing novel treatment approaches for treating diseases.

Keywords: Natural, Traditional, Triterpene, Ursolic acid

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INTRODUCTION

Secondary metabolites are natural commodities that many times possess ecological importance in maintaining the collaborations between plants and their environment. They can have many different roles such as defensive substances which include phytoalexins and phytoanticipins, antifeedants, attractants, and pheromones [1]. The significance of plant secondary metabolites in medicine, agriculture, and industry has shown the light to many research work regarding their synthesis, biosynthesis, and biological activity. It has been predicted that a not less than 40% of medicines have their sources in these active natural commodities [2]. A pivotal group of natural products consists of terpenes and their derivatives**.** A group of terpenes that are becoming popular recently is the pentacyclic triterpenoids. Ursolic acid (UA) is a pentacyclic triterpenoid having a molecular weight of 456.68 g/mol and a melting point of 283–285 °C, which falls in the class of C30 isoprenoid compounds. These compounds are extensively available in nature; hence, UA can be extracted from many plants, for example, *Calluna vulgaris*(heather), *Rosmarinus officinalis* (rosemary), Calendula officinalis (marigold), *Melaleuca leucadendron* (melaleuca), *Malusdomestica* (apple), *Origanum vulgare* (oregano), *Salvia officinalis*(sage), *Origanum majorana* (marjoram), *Lavandula angustifolia*(lavender flowers), *Thymus vulgaris* (thyme) and *Eucalyptus*(eucalyptus) [3, 4]. The existence of UA in almost all medicinal herbs and fruits makes it a part of human food [5]. The biosynthesis of UA and other isoprenoid compounds present in plant tissues begins from the cyclization of squalene into (3S)-oxidosqualene, which can synthesize over 80 different carbon skeletons through the activity of oxidosqualene cyclase enzymes that undergo the carbocation rearrangements responsible for this biological variety [6]. The common precursor (3S)-oxidosqualene is transformed into the dammarenyl ring and oleanyl cation that further proceeds towards ring expansion and other cyclization reactions to make the specific fifth ring which exists in lupeol, α-amyrin, and β-amyrin skeletons as shown in fig. 1. The α-amyrin showcases the UA skeleton, whereas its C30 isomer, β-amyrin showcases the skeleton of the oleanolic acid (OA) [7]. The crystalline solidified compound, chemically known as 3bhydroxy-urs-12-en-28-oic acid, has been employed for ages in traditional medicine for its medicinal activities [8]. Lately, the search for biologically active substances from natural sources has boosted interest in its investigation. Studies show that UA has many pharmacological activities, including anti-inflammatory, hepatoprotective, antitumor, cardioprotective, neuroprotective, antimicrobial, antihyperlipidemic, antidiabetic, antifungal, antiviral, and trypanocidal [9]. But, it is classified as a class IV drug in the Biopharmaceutics Classification System thanks to its restricted pharmacological effects because of low solubility in water and problems in permeating biological membranes [10]. Thus, novel approaches have been inaugurated to boost the biopharmaceutical properties of this compound, specifically by employing new drug delivery technologies. Several UA delivery systems have been formulated without fail, including nanoemulsions [10], mesoporous silica nanoparticles containing silica [11], solid lipid nanoparticles [12], liposomes [13], niosomal gels [14], and solid dispersions [15] which comprise of all the studies conducted. Herein, a literature survey was performed using accessible databases such as Google Scholar, PubMed, and Scopus to review research articles and thus compile a concise review regarding an introduction to ursolic aid along with its pharmacological activities and applications.

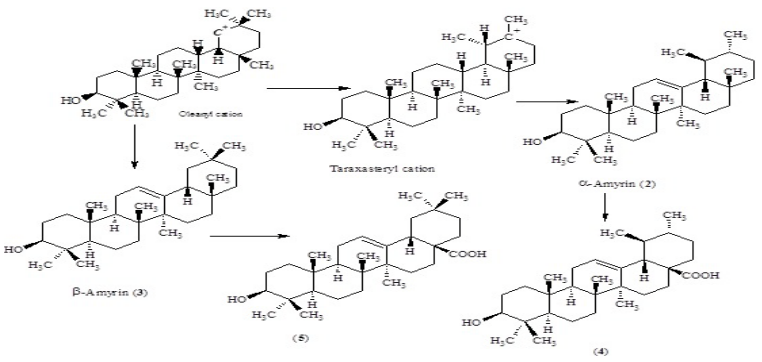

Fig. 1: Biosynthesis of ursolic Acid (4) from oleanyl cation, adapted from reference [7], Copyright Obtained by Permission

Sources

Triterpenoids have been outlined in a diversity of common European plants and fruits [16-18]. UA (3β-hydroxyurs-12-en-28-oic) is a pentacyclic triterpene and a phytosterol as shown in fig. 2. Triterpenes are largely obtained from vegetable oils, vegetarian foods, medicinal herbs, cereals, as well as fruits. A predicted human utilization of triterpenes was estimated to 250 mg per day in the developed countries. Whereas in Mediterranean countries, where most of the food consumed consists of olive oil, the mean consumption of triterpenes by a person can reach 400 mg/kg/day due to the high content of olive oil [5].

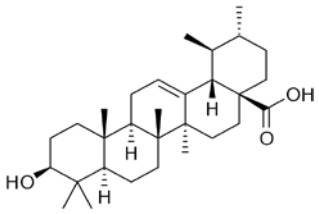

Fig. 2: Structure of ursolic acid

Lately, there is an unimaginable interest in triterpenes. The majority of the researches were concentrated on the cholesterol-lowering properties of triterpenes. UA is widely available especially in higher plants e. g. *Rosmarinus officinalis, Glechoma hederaceae, Ilex paraguariensis, Ichnocarpus frutescens, Phoradendron juniperinum, Syzygium claviflorum, Hyptis capitata* [19-22]. It is a component of many herbal medicines sold in Asia and worldwide for inflammatory conditions [23]. Among berries, North American cranberry fruit (*Vaccinum macrocarpon*), specifically consists of a considerable quantity of UA in its peel. It is present in the aglycone configuration as well as the *cis* and *trans*-p-hydroxyl cinnamate esters [24]. The quantitative examination of cranberry fruit and products by utilizing liquid chromatography-mass spectrometry (LC-MS) showed the UA content of whole cranberry fruit of a variety of cultivars to fall in between 60 to 110 mg per 100g of fresh fruit [25]. A not so different content was established in sweetened, dried fruit. As a contrast, less UA was found in the gel of cranberry sauce or commercial cranberry juice may be attributed to its low solubility in water [26]. Sea buckthorn (*Hippophae rhamnoides* L.) is an industrially grown berry in northern Europe. The phytochemical examination demonstrated that UA was present in much more quantity in buckthorn berry extract when compared against other berries [27]. Also, Fang and Mc Laughlin have extracted UA from red berries of the decorative shrub winterberry (*Ilex verticilata*) [28]**.** Winterberry is not advised for human diet (USDA/NRCS plant fact sheet) [29]. UA, OA, and their derivatives have been announced in non-berry fruits including apple (*Malus pumila*). aglycones as well as many cinnamoyl and hydroxycinnamoyl esters of UA and OA were extracted from apple peels [30]. Table 1 shows the content of ursolic acid present in various fruits, vegetables, and spices.

Table 1: Various sources of ursolic acid along with the quantity present within each

Biological sources	Scientific name	Amount present in milligrams/100g	References
Apple Peel	*Malus pumila*	152	[30]
Balsam Pear	*Momordica charantia*	42±5	[31]
Brown Mustard	*Brassica juncea*	14±5	[31]
Star Fruit	*Averrhoa carambola*	13±4	[31]
Guava	*Psidium guajava*	12±2	[31]
Mahogany	*Swietenia macrophylla*	520	[31]
Daylily	*Hemerocallis sp*	19.2-192	[31]
Damnacanthus	*Damnacanthus indicus*	57±8	[32]
Hawthorn	*Crataegus*	19±5	[33]

Pharmacological activities

Anti-inflammatory activity

Nuclear factor-kappa B (NF-kb) is a major cell signaling pathway held accountable for the maintenance of inflammatory effects genes expression [34]. The assessment of anti-inflammatory effects of UA by exposing BALB/c mice to ovalbumin for asthma induction showed that UA stops NF-kB, and thus can be adopted in the treatment of asthma [35]. Checker *et al.* saw that UA showed anti-inflammatory activity in a mouse model by halting the production of cytokines by T cells, B cells, and macrophages, via squashing of the transcription factors NF-kB, nuclear factor of activated T cells, as well as activator protein-1 [36].

Antitumor activity

In a study, UA demonstrated potential in the prevention and treatment of cancer by modulating several cell signaling enzymes and shielding against carcinogenic agents [37]. The treatment of breast cancer cells with UA at low doses (5–20 mmol) led to a G21/G1 cell cycle arrest, an elevation inp21 levels, oxidative stress, and Deoxyribosenucleicacid (DNA) damage at 20 mmol, UA brought about autophagy as well as apoptosis of breast cancer cells without damaging the normal cells [38]. Furthermore, UA boosted photo toxicity of ultraviolet to visible light broadband radiation by changing the triggering mechanism of Tumor Protein P53 and NF-kB in melanoma cells [39].

Hepatoprotective activity

The hepatoprotective effect of UA alone or in conjunction with other active ingredients on acute and chronic liver injury is well recognized [40]. Guti_errez-Rebolledo *et al.* demonstrated that the subcutaneous administration of an amalgamation of UA and OA in male BALB/c mice with hepatic injury induced by anti-tubercular agents lead to a reduction in aspartate transaminase as well as alanine aminotransferase levels and enhancement in histological changes in the liver [41]. UA stopped the advancement of non-alcoholic fatty liver disease, with attenuation in liver weight and hepatic steatosis, in addition to amassing of intracellular lipids, possibly due to a boosting of lipid β-oxidation as well as halting of hepatic stress [42]

Cardioprotective activity

Cardiovascular disorders are one of the major reasons for mortality and morbidity worldwide. UA is helpful in the treatment of cardiovascular diseases. Liobikas *et al.* assessed the effect of UA on mitochondria extracted from mouse hearts and assessed whether this compound encouraged the decoupling of oxidative phosphorylation in the mitochondria without bringing changes in the respiration rate, besides halting Hydrogen Peroxide (H2O2) production [43]. Also, the use of UA in the treatment of myocardial fibrosis and hypertrophy in experimental models *in vitro* and *in vivo* showed the reduction of fibrosis and cardiac hypertrophy, which may occur via the inhibitory mechanism of the microRNA-21 (miR21)/extracellular-signal-regulated kinase (ERK) signaling pathways in the myocardial cells [44].

Neuroprotective activity

Some studies have demonstrated the well-organized neuroprotective effect of UA. It can control inflammatory responses in the ischemic brain of rats, which was shown by a considerable deduction in infarct size as well as a reduction in lipid peroxidation

via the activation of the nuclear factor-erythroid 2-related factor 2 (Nrf2) [45]. In the study carried out by Ding *et al.* the adoption of UA for the treatment of brain lesions in a murine model considerably enhanced cerebral edema as well as neurological problems attributed to trauma along with a reduction in oxidative stress. This study showed that the neuroprotective effect of UA is connected with the activation of the Nrf2 pathway [46].

Antimicrobial activity

In a study carried out by Singh *et al.* UA demonstrated antimycobacterial activity against *Mycobacterium smegmatis*, *Mycobacterium tuberculosis*, and clinically removed multi-drug-resistant *M. tuberculosis* at a minimum inhibitory concentration (MIC) of 62.5 mg/ml [47]. Nascimento *et al.* [48] assessed the effect of UA and its derivatives on the vulnerability of certain pathogenic bacteria to antibiotics that fall in the aminoglycosides class (neomycin, amikacin, kanamycin, and gentamicin). 3b-Formyloxy-urs-12-en-28-oic acid used at a concentration of 64 mg/ml adopted in conjunction with kanamycin showed a synergistic effect against E. coli, causing a massive reduction in MIC from 128 mg/ml to 8 mg/ml.

Antihyperlipidemic activity

A few studies on the antihyperlipidemic effect of UA have been done. The adoption of UA and artesunate in the treatment of hyperlipidemia in rabbits showed that the triglycerides were decreased by the two compounds acting individually. But, when used in combination, they considerably reduced cholesterol and triglyceride levels in addition to hepatic steatosis and aortic root lesions thus providing additional benefits as contrast when using individually [49].

Antidiabetic activity

The antidiabetic property of UA has been assessed *in vivo* experimental models for type 2 diabetes. The hepatic insulin resistance was boosted by bringing changes in the fatty acid, Tumor Necrosis Factor Alpha (TNF-α), as well as adiponectin levels, which boosted Peroxisome Proliferator-Activated Receptor Alpha (PPAR-α) expression and as a result the adjustment of Phosphoenolpyruvate Carboxykinase (PEPCK) protein as well as phosphorylation of insulin receptor substrate-2 [50]. The antihyperglycemic effect of UA in hyperglycemic rats was brought about by insulin secretion and insulin imitative effect on glucose uptake by UA in addition to synthesis as well as translocation of Glucose Transporter type 4 (GLUT4) [51].

Antifungal activity

A study carried out by Mahlo *et al.* UA with MIC of 20–250 mg/ml demonstrated antifungal activity against *Aspergillus niger*, *Aspergillus parasiticus, Colletotrichum gloeosporioides, Trichoderma harzianum, Penicillium expansum, Penicillium janthinellum* as well as *Fusarium oxysporum* [52]. At varying concentrations (500, 750, and 1000 ppm), UA also considerably halted ($P<0.001$) the spore release of *Alternaria alternata, Cochliobolus lunata, Fusarium moniliforme, Fusarium pallidoroseum*, and *Helminthosporium* [53].

Anti-viral activity

Zhao *et al.* assessed the anti-viral effect of UA against cytomegalovirus and compared that to that of two other drugs, namely ganciclovir and jinyebaidu (control) [54]. The Results concluded that the antiviral activity of UA is considerably more powerful than that of ganciclovir or jinyebaidu. In another study, UA showed anti-HCV (hepatitis C virus) activity through the reduction of Hepatitis C virus nonstructural protein RNA dependent (HCV NS5B RdRp) activity by acting as a noncompetitive inhibitor [55].

Trypanocidal activity

UA showed *in vitro* trypanocidal effect which was demonstrated by an IC50 value of 25.5 mmol and 77% trypomastigote lysis at a concentration at 128 mmol. In the *in vivo* assay studies that were carried out in mice, the administration of UA at 20 mg/kg/day considerably reduced the parasitemia [10].

Applications in drug delivery systems

As discussed above UA demonstrates many pharmacological activities. However, it has less solubility in water which translates to its bioavailability and therapeutic suitability, because the solubility and polarity of a compound can determine its ability to penetrate biological membranes [56, 57]. Various methods can be utilized to bypass these shortcomings, such as particle size reduction, salt formation, chemical changes in the molecules, usage of surfactants, adjusting the pH, or addition of the drug into various delivery systems [58]. Drug delivery systems have been adopted with great accomplishments to enhance the physicochemical properties of UA as well as favor its therapeutic application. They also change the drug release besides boosting solubility and enhance the bioavailability of hydrophobic drugs such as Nanoparticles and other Nano drug delivery strategies [59-63]. In a study performed by Li *et al.* pH-sensitive mesoporous silica nanoparticles were established to be biocompatible and permitted sustained release of UA, besides improving the cytotoxic effect against human hepatocellular carcinoma cells (HepG2), when compared against free UA [11]. Vargas de Oliveira *et al.* [10] assessed the trypanocidal effect, cytotoxicity and *in vitro* dissolution profile of UA administered by the nanoemulsions (constituted by purified water, Capryol_90 and Cremophor_ EL/Transcutol_ P) and studied the enhancement in the drug dissolution profile. UA release was observed to be 3.75 times greater and 24 times more rapid when compared against a physical mixture in an alkaline dissolution medium, which showed the significance of emulsification in improving the presence of the drug in the dissolution medium. Topical formulations were also adopted due to their advantages over the oral route, such as no gastrointestinal effects, decreased renal toxicity, and higher patient compliance [64, 65]. Transdermal niosomal gels of UA formulated for the treatment of arthritis ensured in a vesicle size of 665.45 nm, drug entrapment efficiency of 92.74%, and considerably better *in vivo* results when compared against oral formulation and traditional gel system of UA.[14] Solid dispersions can also be a promising approach for the administration of UA because these, consist of molecular fusions of hydrophobic drugs with carriers that are either water-soluble or soluble in both water and organic solvents, which also provides a reduction of drug particle size thereby leading to an enhancement in the solubility and change the drug release profile [66]. An experiment done by Eloy and Marchetti to assess the impact of hydrophilic carriers (PEG 6000 and Poloxamer 407) as well as the method of preparation (fusion and solvent) of solid dispersions for aqueous solubility of UA demonstrated that Poloxamer 407 boosted the solubility as well as dissolution rate of the drug in solid dispersions more accurately than PEG 6000 owing to their surfactant properties. Also, the solvent method for preparing solid dispersions was more superior when compared against the fusion method for enhancing drug solubility [15].

CONCLUSION

All plants are useful in one or the other ways. They produce very important compounds which play a very important role either as food, nutraceuticals, or showing therapeutic activity. Triterpenes are consist of five rings fused and are synthesized within the plants from Squalene. Ursolic acid is a very versatile compound and shows a variety of activities which have been discussed. It is mostly isolated from plants and their components such as fruits and berries where it is present in different chemical forms. Ursolic acid has bioavailability and solubility problems and hence new drug delivery strategies were taken up to solve this problem with many of them exhibiting excellent results. It also represents a promising candidate for developing more effective drug delivery systems and also helping it unleash its full potential for the treatment of diseases.

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AUTHORS CONTRIBUTIONS

All authors have taken part in the design and drafting of the article and revising it critically for important intellectual content as well as approval of the final version.

CONFLICT OF INTERESTS

Declared none

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