(REVIEW ARTICLE)

Oleanolic acid as a potential drug molecule: A review

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Abstract

Objective: Oleanolic acid is traditionally used medicinal remedies in India. Oleanolic acid or oleanic acid is a naturally occurring pentacyclic triterpenoid related to betulinic acid. It is widely distributed in food and plants where it exists as a free acid or as an aglycone of triterpenoid saponins.

Key findings: Oleanolic acid is relatively non-toxic, hepatoprotective, and exhibits antitumor and antiviral properties. It was found to exhibit weak anti-HIV and weak anti-HCV activities in vitro, but more potent synthetic analogs are being investigated as potential drugs.

Conclusion: This review is an overall overview of the existing pharmacology of Oleanolic acid, helping to fuel further research in the various unexplored activities that are attributable to this plant.

Keywords: Oleanolic acid; Hepatoprotective; Antitumor; Antiviral; Antibacterial

1. Introduction

Oleanolic acid is used for various traditional medicinal remedies in India. Oleanolic acid belongs to the pentacyclic triterpene family. It is widely distributed in food and plants where it exists as a free acid or as an aglycone of triterpenoid saponins[1,2].Oleanolic acid can be found in olive oil, Phytolacca americana (American pokeweed), and Syzygium spp, garlic, etc. It was first studied and isolated from several plants, including Olea europaea[1,3,4] (leaves, fruit), Rosa woodsii (leaves), Prosopis glandulosa (leaves and twigs), Phoradendron juniperinum (whole plant), Syzygium claviflorum (leaves), Hyptis capitata (whole plant), Mirabilis jalapa[5] and Ternstroemia gymnanthera (aerial part). Other Syzygium species including java applet (Syzygium samarangense) and rose apples contain it. Oleanolic acid is relatively non-toxic, hepatoprotective, and exhibits antitumor and antiviral properties. [6]Oleanolic acid was found to exhibit weak anti-HIV[7] and weak anti-HCV activities in vitro, but more potent synthetic analogs are being investigated as potential drugs. [8]

2. Material and methods

Oleanolic acid is a naturally occurring pentacyclic triterpenoid related to betulinic acid.

Chemicaly *Oleanolic acid* is (4aS,6aR,6aS,6bR,8aR,10S,12aR,14bS)-10-hydroxy-2,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydropicene-4a-carboxylic acid with white appearance having chemical formula $C_{30}H_{48}O_3$. It has molecular weight equivalent to 456.711 g/mol and melting point is > 300 °C (572 °F; 573 K). [1]

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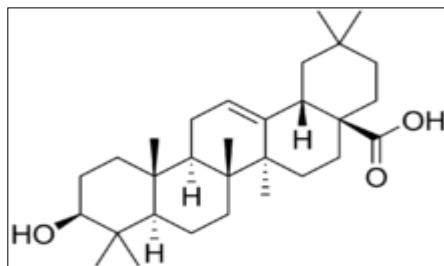
Figure 1 Chemical structure of Oleanolic acid. [1]

2.1. Biological activities

Oleanolic acid is relatively non-toxic, exhibit antimycotic, antitumoral, antibacterial, hepatoprotective,antiviral, and antiparasitic properties [9-16].Oleanolic acid was found to exhibit weak anti-HIV and weak anti-HCV activities in vitro, but more potent synthetic analogs are being investigated as potential drugs. An extremely potent synthetic triterpenoid analog of oleanolic acid was found in 2005 that is a powerful inhibitor of cellular inflammatory processes. They work by the induction by IFN-γ of inducible nitric oxide synthase (iNOS) and of cyclooxygenase 2 in mouse macrophages. They are extremely potent inducers of the phase 2 response (e.g., elevation of NADH-quinone oxidoreductase and heme oxygenase 1), which is a major protector of cells against oxidative and electrophile stress. [17]

A 2002 study in Wistar rats found that oleanolic acid reduced sperm quality and motility, causing infertility. After withdrawing exposure, male rats regained fertility and successfully impregnated female rats. [18]

3. Results and discussion

3.1. Role of Oleanolic acid in Antidiabetic

Oleanolic acid and oleanolic acid glycosides have been shown to have glucose-lowering properties in animal models in vivo. In one study, oleanolic acid glycosides purified from plants, but not oleanolic acid itself, decreased serum glucose levels in rats given an oral glucose load . More recent investigations revealed the ability of oleanolic acid to reduce plasma glucose levels in rats and mice. Although the mechanisms by which oleanolic acid reduces glycemia remain poorly understood, several hypotheses have been suggested including effects on reducing gastric emptying, enhancing acetylcholine release that in turn increases insulin release, or reducing insulin resistance. Teodoro et al. have recently demonstrated that oleanolic acid promotes insulin secretion at both basal glucose levels as well as under stimulatory conditions in the pancreatic β-cell line INS-1 832/13 and enhances acute glucose-stimulated insulin secretion in isolated rat islets. In addition to these acute effects, chronic administration of oleanolic acid increases total cellular insulin protein and mRNA levels in the INS-1 cell line. [3,4]

3.2. Oleanolic acid as a Molecular Nutrition and Diabetes

Oleanolic acid is a constituent of the leaves of Olea europaea and Viscum album .Oleanolic acid is used in Chinese medicine for the treatment of liver disorders, such as viral hepatitis, and has been shown to protect mice from various hepatotoxicants that cause oxidative and electrophilic stresses, including carbon tetrachloride, acetaminophen, bromobenzene, and thioacetamide. Oleanolic acid induces expression levels of NRF2 and its target genes in mouse liver,and administration of oleanolic acid exerts hypoglycemic effects in diabetes rodent models. Importantly, synthetic derivatives of oleanolic acid are shown to exert potent NRF2-inducing activity and have been developed as candidates for NRF2-targeting drugs, e.g., bardoxolone (oleanolic triterpenoid 1-[2-cyano-3,12-dioxooleane-1,9(11)-dien-28-oyl] methyl ester), CDDO-Im, and acetylenic tricyclic bis(cyanoeneone). Bardoxolone has been tested in the treatment of diabetic nephropathy and has been shown to successfully increase estimated glomerular filtration rate in patients with the nephropathy. Importantly, we found that administration of CDDO-Im protects pancreatic β-cell damage and lower blood glucose levels in db/db diabetes model mice by inducing NRF2. Bardoxolone has also been shown to lower blood glucose levels in the db/db mice. These findings unequivocally demonstrate that NRF2 retains activity to lower blood glucose levels. [8]

3.3. Activity of Oleanolic acid in Health and Disease Prevention

Among olive and pomace oleanolic acid has been the most widely studied and distributed in the vegetable kingdom. In fact, a wide range of biological activities has been attributed to this triterpenoid. Nevertheless, there are not many

studies focused on the cardiovascular properties ascribed to oleanolic acid and structure-related triterpenoids such as erythrodiol. Accordingly, parenteral administration of this triterpenic acid lowers blood pressure in salt-sensitive rats, an effect mainly associated with antioxidative actions. In addition, it has been recently reported that ingestion of pomace olive oil with a high proportion of oleanolic acid and erythrodiol offers a delay in the progression of lipid peroxidation in rat liver microsomes. Despite these recent findings, the effects of oleanolic acid and pomace olive oil on vascular and endothelial function have remained unknown until now. This chapter summarizes the recent and

novel advances in the vasoprotective profile provided by olive and pomace olive oil and their triterpenoids in terms of vasodilatation. [8]

3.4. Role of Oleanolic acid in Neurological Autoimmune Diseases

It was reported that treatment with either oleanolic acid or erythrodiol (50 mg/kg), before or at the early phase of EAE, ameliorated neurological signs. Moreover, oleanolic acid treatment decreased the levels of anti-MOG antibodies, blood–brain barrier leakage, and infiltration of inflammatory cells within the CNS.In line with these findings, oral administration of 80 mg/kg of olive leaf extract in rats with EAE reduced behavioral deficits, cellularity of the draining lymph nodes, and production of interferon-γ and interleukin-17. It was also reported that celastrol (1 mg/kg/day) ameliorated the behavioral deficits and inhibited the relapse in rats with EAE.

Oleanolic acid had beneficial effects in clinical trials on chronic kidney disease, diabetes mellitus type 2, and some inflammatory conditions such as arthritis. There are about 500 registered clinical trials regarding the therapeutic effects of olive. However, none of them are related to patients with MS. Similarly, no clinical trial has been performed for oleanolic acid, erythrodiol, or celastrol on patients with MS.[6]

3.5. Antibacterial Properties of Oleanolic Acids

The antibacterial properties of Oleanolic acid were assayed against different bacterial species, and the obtained results suggested the importance of these compounds as antibiotic drugs. Oleanolic acid inhibited the synthesis of insoluble glucan, catalyzed by crude glucosyltransferase (GTase) from cariogenic Streptococcus mutans. [19]. When used against Mycobacterium tuberculosis, it was found that Oleanolic acid isolated from Lantana hispida was also effective at displaying a MIC value of 25 μg/mL [20]. In addition, a MIC of 50 μg/mL was reported when Oleanolic acid was used against M. tuberculosis streptomycin-, isoniazid-, rifampin-, and ethambutol-resistant strains. Similar to Oleanolic acid purified from Chamaedorea tepejilote leaves was capable of eliminating M. tuberculosis at 100 μg/mL [21], suggesting that there is a potential for both compounds to kill this pathogen.

The diversity of the antibacterial properties of Oleanolic acid has also been illustrated against other human bacterial pathogens, such as S. pneumonia (MIC of 16 μg/mL), methicillin-sensitive and methicillin-resistant Staphylococcus aureus (MIC of 8 μg/mL and 64 μg/mL, resp.) [22], Bacillus subtilis (MIC of 8 μg/mL), B. cereus, Enterococcus faecalis (MIC of 6.25–8.00 μg/mL), E. faecium (MIC of 8 μg/mL), and Pseudomonas aeruginosa (MIC of 256 μg/mL) [23-24].

3.6. Antiviral Properties of Oleanolic Acids

The antiviral properties of Oleanolic acid have been studied since the 1990s; specifically, those used against human immunodeficiency virus (HIV) and the hepatitis virus. HIV belongs to the Retroviridae family and the genus, Lentivirus, which produces characteristically slow and progressive infection [25]. One of the first works [26] dealing with this subject showed that Oleanolic acid purified from Cynomorium songaricum (Cynomoriaceae) inhibited HIV-1 protease in a dose-dependent manner (inhibitory concentration [IC]$_{50}$ of 8 μg/mL). Oleanolic acid and its derivatives were also capable of inhibiting HIV-1 protease, with an IC$_{50}$ of 4–20 μg/mL [27]. The inhibition of this enzyme produces immature and noninfectious virions and molecules, consequently blocking the life cycle of HIV [28]; this will ultimately improve the patient's quality of life. In addition, ex vivo experiments showed that peripheral blood mononuclear cells (PBMC) from HIV-infected patients, which were incubated with different doses of Oleanolic acid, presented significant reduction of viral replication, which was comparable with the drug, azidothymidine (AZT). Similar results were found when PBMC from healthy donors were infected with HIV-1, yielding an effective concentration (EC)$_{50}$ of 22.7 μM and 24.6 μM, respectively [29]. Moreover, [30] demonstrated that Oleanolic acid could eliminate, with high selectivity, HIV (therapeutic index [TI] ratio of 12.8) when compared to the H9 cell lineage; however, the AZT drug presented with the highest TI, which was 41.667.

3.7. The Antiprotozoal Properties of Oleanolic acid

Oleanolic acid also displayed appreciable antiparasitic effects against Plasmodium falciparum, Toxoplasma gondii, Trypanosoma cruzi, and Leishmania sp.

The parasitic disease with the greatest impact is malaria; it affects around 40% of the world's population, spanning across more than 100 countries, and its etiological agent is a protozoa belonging to the genus, Plasmodium [31]. Although different drugs can eliminate this parasite, the problem with the Plasmodium sp. is that its resistance needs to be overcome [32]; this indicates that the search for new antimalarial compounds is necessary and urgent.

In this regard, one of the first works to demonstrate the antimalarial properties of triterpenes against chloroquine-resistant and chloroquine-sensitive Plasmodium falciparum was conducted by Steele et al. [33].Other studies have also demonstrated that Oleanolic acid purified from Satureia parvifolia, Mimusops caffra, M. obtusifolia, and Kleinia odora were able to eliminate P. falciparum. [34–36]

Tan et al. [37] evaluated the leishmanicidal potential of Oleanolic acid extracted from Salvia cilicica roots. The obtained results showed that Oleanolic acid was primarily active against intracellular amastigote forms of L. donovani and L. major, with an IC_{50} of 12.7 nM and 7.0 nM, respectively.

Recently, a bioguided study conducted with extracts of Baccharis uncinella leaves led to the identification of a bioactive fraction that contained Oleanolic acid triterpenes. This fraction showed moderated activity against L. (V.) braziliensis and L. (L.) amazonensis promastigotes, [11]

4. Conclusion

Conclusively, oleanolic acid is an efficient drug molecule with a potential to act against different diseases. It has widespread biological activities such as hepatoprotective , ant diabetic, viral hepatitis, hepatotoxicants, and antioxidant, anticancer and in early phase of EAE. Thus, oleanolic acid can be considered as potential drug molecule as well as adjuvant for various biological implications and thereby serving the human society.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

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