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Review Article

Antimicrobial Activity of Oleanolic and Ursolic Acids: An Update

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Triterpenoids are the most representative group of phytochemicals, as they comprise more than 20,000 recognized molecules. These compounds are biosynthesized in plants via squalene cyclization, a C_{30} hydrocarbon that is considered to be the precursor of all steroids. Due to their low hydrophilicity, triterpenes were considered to be inactive for a long period of time; however, evidence regarding their wide range of pharmacological activities is emerging, and elegant studies have highlighted these activities. Several triterpenic skeletons have been described, including some that have presented with pentacyclic features, such as oleanolic and ursolic acids. These compounds have displayed incontestable biological activity, such as antibacterial, antiviral, and antiprotozoal effects, which were not included in a single review until now. Thus, the present review investigates the potential use of these triterpenes against human pathogens, including their mechanisms of action, via *in vivo* studies, and the future perspectives about the use of compounds for human or even animal health are also discussed.

1. Introduction

The triterpenoids are the most representative group of phytochemicals; they comprise more than 20,000 recognized compounds and are biosynthesized in plants through squalene cyclization [1]. The triterpenes can be classified into groups based on their structural skeletons: cucurbitanes, cycloartanes, dammaranes, euphanes, friedelanes, holostanes, hopanes, isomalabaricanes, lanostanes, lupanes, oleananes, protostanes, tirucallanes, and ursanes, among others [2].

The diversity of triterpenes is highly associated with their broad range of pharmacological effects. In Asian countries, triterpenes are traditionally used as anti-inflammatory, analgesic, hepatoprotective, cardiotonic, and sedative agents [3]. Other studies have also demonstrated their antioxidant, antiallergic, antipruritic, antiangiogenic, and antimicrobial potential [4]. In addition, some studies have already demonstrated that several of these compounds exhibit anticancer potential, with high selectivity for cancer cells and the ability to induce apoptosis-related death in most cases [5–10]. Due to this specific action, several triterpenoids are currently being evaluated in phase I clinical trials [11].

Oleanolic acid (OA) and its isomer, ursolic acid (UA), are triterpenoid compounds that widely occur in nature in free acid form or as an aglycone precursor for triterpenoid saponins [12]. These triterpenoid acids frequently occur simultaneously because they share similar structural features. These compounds have also shown similar pharmacological activities, such as hepatoprotective, anti-inflammatory, antioxidant, and anticancer effects, which may be attributable to the different substructures in A, C, and E rings or other positions (Figure 1).

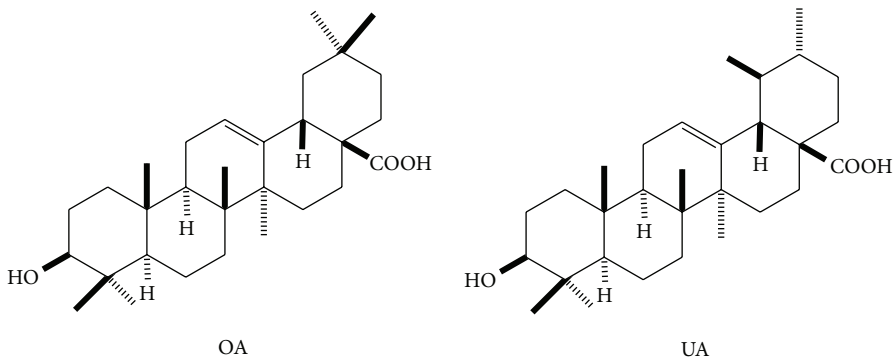

Figure 1: Skeleton of oleanolic acid (OA) and ursolic acid (UA).

2. Oleanolic Acid (OA)

OA (3β-hydroxyolean-12-en-28-oic acid) is a pentacyclic triterpenoid with widespread occurrence throughout the plant kingdom. This compound and its derivatives possess several interesting pharmacological activities, such as anti-inflammatory, antioxidant, anticancer, and hepatoprotective effects. OA was previously isolated from almost 2000 plant species [12–14], and the main source of this compound includes plants belonging to the Oleaceae family, such as *Olea europaea* (the olive) [15, 16]. In plants, the biological roles of this compound are often associated with the formation of a barrier against water loss and pathogens [17]. Moreover, allelopathic properties have already been described for this compound [18]. Several medicinal plants produce and accumulate OA and its derivatives as their main metabolites, which could be directly associated with their biological activities, as shown in Table 1.

3. Ursolic Acid (UA)

UA (3β-hydroxyurs-12-en-28-oic acid) is a pentacyclic triterpenoid compound that shares a common cooccurrence with OA in several plant species; however, it features a more restricted distribution when compared to OA [12, 84]. This compound has been found in large amounts in berries (such as cranberries) and mostly in the peel [85]. Similar to what is observed with OA, the biological role of UA in plants seems to be associated with protection against herbivores and pathogens [86]. The occurrence of UA and its derivatives as major metabolites in medicinal plants could be associated with their biological activities, as shown in Table 2.

Many comprehensive reviews of OA and UA have been published and have covered different areas of interest, such as their isolation, structural determination, and pharmacological activities [12, 87–90].

In spite of the pharmacological effects that have already been demonstrated, different reports have shown that OA and UA exhibit antimycotic, antitumoral, antibacterial, antiviral, and antiparasitic properties [4, 9, 26, 91–95], suggesting that these compounds are important classes of prototypical natural antibiotic molecules. This review aims to summarize the information regarding the microbiocidal activities of both OA and UA, highlighting the importance of these compounds as leading molecules with pharmacological and medical importance in the development of new drugs.

4. Microbicidal Effects of Oleanolic and Ursolic Acids

4.1. Antibacterial Properties of Oleanolic and Ursolic Acids. The antibacterial properties of OA and UA were assayed against different bacterial species, and the obtained results suggested the importance of these compounds as antibiotic drugs.

One of the first studies that aimed to evaluate the possible effect of OA and UA against bacteria was developed by Kozai et al. [96]. In this work, it was demonstrated that both of these triterpenes inhibited the synthesis of insoluble glucan, catalyzed by crude glucosyltransferase (GTase) from cariogenic *Streptococcus mutans*. Recently, the potential of UA against *S. mutans* and *S. sobrinus* was reinforced with a minimum inhibitory concentration $(MIC)_{50}$ of 2.0 μg/mL [97], indicating that these compounds can inhibit caries in teeth.

When used against *Mycobacterium tuberculosis*, which is a bacterium that affects around one-third of the human population and represents the infection that causes the most deaths worldwide, it was found that OA isolated from *Lantana hispida* was also effective at displaying a MIC value of 25 μg/mL [49]. In addition, a MIC of 50 μg/mL was reported when OA was used against *M. tuberculosis* streptomycin-, isoniazid-, rifampin-, and ethambutol-resistant strains. Similar to OA, UA purified from *Chamaedorea tepejilote* leaves was capable of eliminating *M. tuberculosis* at 100 μg/mL [98], suggesting that there is a potential for both compounds to kill this pathogen.

The diversity of the antibacterial properties of OA and UA 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.) [129], *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) [130–132].

Table 1: Oleanolic acid's (OA) derivatives and their biological activities.

Plant species (family)	Biological activity	Reference
Aceriphyllum rossii (Saxifragaceae)	Cytotoxic Anticomplement activity	[19] [20] [21]
Actinidia chinensis (Actinidiaceae)	Hepatoprotection	[22]
Aralia chinensis (Araliaceae)	Hepatoprotection	[23, 24]
Astilbe chinensis (Saxifragaceae)	Cytotoxic	[25]
Baccharis uncinella (Asteraceae)	Antileishmanial	[26] [27]
Baeckea gunniana (Myrtaceae)	Inhibition of β-DNA polymerase	[28]
Beta vulgaris (Chenopodiaceae)	Hepatoprotection	[29, 30]
Betula ermanii (Betulaceae)	Antitumor	[31]
Calendula officinalis (Compositae)	Antifungal activity	[32]
Chrysosplenium carnosum (Saxifragaceae)	Cytotoxic	[33]
Diospyros kaki (Ebenaceae)	Inhibition of tyrosine phosphatase	[34]
Dysoxylum hainanense (Meliaceae)	Antibacterial	[35]
Eclipta prostrata (Asteraceae)	Antifibrotic activity	[36]
Embelia schimperi (Myrsinaceae)	Antibacterial	[37]
Eugenia jambolana (Myrtaceae)	Inhibition of lipid peroxidation and protection against adriamycin toxicity; antifertility activity	[38–40]
Fagus hayatae (Fagaceae)	α-glucosidase inhibition	[41]
Fatsia polycarpa (Araliaceae)	Cytotoxic, antihepatitis B virus (HBV), and antibacterial	[42]
Ganoderma lucidum (Labiatae)	Anticariogenic activity	[43]
Glechoma hederacea (Labiatae)	Inhibition of azoxymethane-induced carcinogenesis in rats; Antitumor promotion	[44–46]
Ilex kudincha (Aquifoliaceae)	Inhibition of acyl CoA cholesteryl acyl transferase	[47]
Junellia aspera (Verbenaceae)	Cytotoxic	[48]
Lantana hispida Verbenaceae)	Antimycobacterial	[49]
Liquidambar formosana (Altingiaceae)	Inhibition of NFAT transcription factor	[50]
Ligustrum lucidum (Oleaceae)	Anti-inflammatory; antihyperglycemic; inhibition of mutagenicity by B(a)P	[51–54]
Luffa cylindrica (Cucurbitaceae)	Anti-inflammatory and inhibition of C3-convertase of the complement pathway	[55, 56]
Lysimachia heterogenea (Primulaceae)	Cytotoxic	[57]

Table 1: Continued.

Plant species (family)	Biological activity	Reference
Lysimachia parvifolia (Primulaceae)	Cytotoxic	[58]
Nardophyllum bryoides (Asteraceae)	Cytotoxic	[59]
Microtropis japonica (Celastraceae)	Cytotoxic	[60]
Nigella glandulifera (Ranunculaceae)	Cytotoxic	[61]
Oleandra neriifolia (Araliaceae)	Anti-inflammatory	[62]
Panax ginseng (Araliaceae)	Hepatoprotection	[63]
Panax stipuleanatus (Araliaceae)	Anticancer Inhibition of NF-κB	[64, 65]
Phyllanthus flexuosus (Euphorbiaceae)	Inhibition of DNA topoisomerases I and II	[66]
Platycodon grandiflorum (Campanulaceae)	Antiproliferative	[67]
Rosa laevigata (Rosaceae)	Anti-inflammatory NF-κB transcriptional activity	[68, 69]
Sapindus mukorossi (Sapindaceae)	Anti-inflammatory	[70]
Siphonodon celastrineus (Celastraceae)	Cytotoxic	[71, 72]
Swertia mileensis (Gentianaceae)	Hepatoprotection	[73–75]
Swertia japonica (Gentianaceae)	Hepatoprotection	[76]
Terminalia arjuna (Combretaceae)	Cardioprotection	[77]
Terminalia chebula (Combretaceae)	Cytotoxic	[78]
Tetrapanax papyriferum (Araliaceae)	Hepatoprotection	[79]
Tinospora sagittata (Menispermaceae)	Antihyperglycemic	[80]
Uncaria laevigata (Rubiaceae)	Inhibition of α-glucosidase	[81]
Uncaria sessilifructus (Rubiaceae)	Inhibition of activities against LPS-induced nitric oxide production in RAW264.7 macrophages	[82]
Viburnum chingii (Adoxaceae)	Cytotoxic	[83]

Although few works have examined the mode of action of these triterpenes, studies conducted with *E. coli* demonstrated that OA can moderately affect the efflux of pumps, which could directly interfere with the viability of this species [133]. Other mechanisms of action of OA can be associated with the induction of a stress response. Grudniak et al. [134] observed that *E. coli* treated with OA altered the synthesis of DnaK, thus inducing the heat-shock response in this species. Kurek et al. [135] also verified that both OA and UA inhibited peptidoglycan turnover in *Listeria monocytogenes*, affecting the amount of muropeptides and, ultimately, the cellular wall of bacteria, suggesting that this biochemical pathway can be a target for both triterpenes.

Taken together, these works suggest that OA and UA possess a broad range of antibacterial activity, mainly against gram-positive bacteria. In addition, all of these works have alerted us to the important classes of prototype drugs that can be derived from these triterpenes, including the development of drugs that can be used against infections caused by drug-resistant bacteria species.

Table 2: Ursolic acid's (UA) derivatives and their biological activities.

Plant species (family)	Biological activity	Reference
Actinidia chinensis (Actinidiaceae)	Hepatoprotective	[99]
Baeckea gunniana (Myrtaceae)	Inhibition of β-DNA polymerase	[28]
Callana vulgaris (Ericaceae)	Inhibition of lipoxygenase and cyclooxygenase in HL-60 leukemic cells	[100, 101]
Centella asiatica (Mackinlayaceae)	Inhibition of NO	[102]
Emmenopterys henryi (Rubiaceae)	Cytotoxic	[103]
Eribotrya japonica (Rosaceae)	Inhibition of mutagenesis in bacteria	[104]
Eucalyptus hybrid (Myrtaceae)	Hepatoprotection	[105]
Eucalyptus loxophleba (Myrtaceae)	Antileishmanial	[106]
Fragaria ananassa (Rosaceae)	Cytotoxic	[107]
Gentiana aristata (Gentianacea)	Cytotoxic	[108]
Glechoma hederacea (Labiatae)	Antitumor promotion	[46]
Ilex cornuta (Aquifoliaceae)	Cytotoxic	[109]
Leonurus cardiaca (Lamiaceae)	Anti-inflammatory	[110]
Melaleuca leucadendron (Myrtaceae)	Inhibition of histamine release	[111]
Microtropis japonica (Celastraceae)	Cytotoxic	[60]
Mulgedium tataricum (Asteraceae)	Cytotoxic/antibacterial	[112]
Nauclea officinalis (Rubiaceae)	Inhibition of NO production	[113]
Nardophyllum bryoides (Asteraceae)	Cytotoxic	[59]
Ocimum sanctum (Labiatae)	Inhibition of lipid peroxidation and protection against adriamycin toxicity	[38, 39]
Petasites tricholobus (Asteraceae)	Antibacterial	[114]
Potentilla fulgens (Rosaceae)	Antioxidant	[115]
Pyrola rotundifolia (Pyrolaceae)	Anti-inflammatory	[116]
Psychotria serpens (Rubiaceae)	Cytotoxic to leukemia cells	[117]
Rhododendron brachycarpum (Ericaceae)	Inhibition of PTP1B	[118]
Rosa laevigata (Rosaceae)	Anti-inflammatory	[68]
Rosmarinus officinalis (Labiatae)	Antimicrobial activity; inhibition of mouse skin tumorigenesis; anti-inflammatory	[85, 119]

Table 2: Continued.

Plant species (family)	Biological activity	Reference
Salvia miltiorrhiza (Lamiaceae)	Inhibition of atherosclerosis	[120]
Saprosma merrillii (Rubiaceae)	Cytotoxic	[121]
Siphonodon celastrineus (Celastraceae)	Cytotoxic	[71]
Solanum incanum (Solanaceae)	Hepatoprotection	[122]
Symplocos lancifolia (Symplocaceae)	Antibacterial	[123]
Teucrium viscidum (Lamiaceae)	Inhibition of activities against 11β-HSD1	[124]
Triplerospermum taiwanense (Gentianaceae)	Hepatoprotection	[125]
Uncaria laevigata (Rubiaceae)	Inhibition of α-glucosidase	[81]
Uncaria sessilifructus (Rubiaceae)	Inhibition of activities against LPS-induced nitric oxide production in RAW264.7 macrophages	[82]
Vladimiria muliensis (Asteraceae)	Antimicrobial	[126]
Weigela subsessilis (Caprifoliaceae)	Diabetes treatment	[127]
	Anticomplementary	[128]

4.2. Antiviral Properties of Oleanolic and Ursolic Acids. The antiviral properties of OA and UA 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 [136]. One of the first works [137] dealing with this subject showed that UA purified from *Cynomorium songaricum* (Cynomoriaceae) inhibited HIV-1 protease in a dose-dependent manner (inhibitory concentration $[IC]_{50}$ of 8 μg/mL). OA and its derivatives were also capable of inhibiting HIV-1 protease, with an IC_{50} of 4–20 μg/mL [138]. The inhibition of this enzyme produces immature and noninfectious virions and molecules, consequently blocking the life cycle of HIV [139]; 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 OA, 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 [140]. Moreover, [141] demonstrated that OA was capable of eliminating, 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.

The potential of OA and UA was also determined against hepatitis B and C viruses (HBV and HCV, resp.). These viruses are of serious concern for human populations, since approximately 500 million people are chronically infected with one or both viruses, resulting in fibrosis and cirrhosis of the liver, and ultimately leading to the development of hepatocellular carcinoma [142, 143]. Although vaccines and therapeutic strategies against these viruses already exist, new drug prototypes are under development, such as OA and UA. In this regard, it was demonstrated that UA primarily decreased the migratory process and matrix metalloproteinase-3 secretion in HBV X protein-transactivated cell lineages. In addition, UA-treated cells were more sensitive to transforming growth factor- (TGF-) β-mediated apoptosis than were the control cells. *In vivo* experiments showed that HBV-induced tumors were significantly lower in UA-treated animals when compared to controls [144]. These interesting studies showed that UA could block the pathological effects of HBV in cell lineages, suggesting that new classes of antiviral drugs could be developed using UA. In contrast, OA isolated from *Ligustri lucidi* seems to be very effective at eliminating intracellular HCV with an IC_{50} of 5.5 μg/mL and a high selectivity index (SI) of 30.8. Otherwise, the IC_{50} found for UA activity was higher than that determined for OA (IC_{50} of 33.8 μg/mL), and the latter featured a lower SI (6.7). In addition, one possible mechanism of action of OA was related to the suppression of the viral NS5B RdRp enzyme, which is a central enzyme responsible for HCV RNA replication [145].

UA and OA were also assayed against the proliferation of herpes viruses in host cells. Herpes simplex viruses (HSV) cause herpes labiles, herpes genitalis, keratitis, and encephalitis. The HSV infection caused by type-1 and type-2 viruses is mainly transmitted through close personal contact. The therapy that is used against the infection has severe side effects, and drug-resistant viruses have been detected

[146], justifying the rationale to search for new drugs. In this regard, ethnomedicinal studies conducted in India showed that some plants used to treat skin problems, such as *Mallotus peltatus* and *Achyranthes aspera* [147, 148], produce appreciable amounts of UA and OA [149]. Considering that herpes infections affect the skin and mucosa, Bag et al. [146] and Mukherjee et al. [150] assayed crude extracts of, and active fractions derived from, *M. peltatus* and *A. aspera*, which contained UA and OA. The researchers found that both fractions presented with strong inhibitory activity against HSV-1 and HSV-2, which was comparable to the standard drug, Aciclovir. In addition, the OA-containing fraction from *A. aspera* triggered interleukin- (IL-) 12 production in treated peritoneal macrophages [150], which is an important cytokine that is responsible for activating the $CD4^+$Th1 cell population and for eliminating intracellular pathogens [151, 152].

These works indicate that OA and UA inhibit viral spreading in different host cell lineages with high levels of sensitivity and selectivity; this mainly depends upon the virus type and the host cell. In addition, the mechanism of action of both triterpenes was related to the control of virus replication and also to the immunomodulatory effect on the host cells, suggesting that new drugs can be developed from these structures.

4.3. The Antiprotozoal Properties of OA and UA. OA and UA 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* [153]. Although different drugs can eliminate this parasite, the problem with the *Plasmodium* sp. is that its resistance needs to be overcome [154]; 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. [155]. In this study, OA and UA were purified from ethanolic extract, which was prepared from the root barks of *Uapaca nitida* (Euphorbiaceae). UA showed antimalarial effects with an IC_{50} of 36.5 μg/mL and 28 μg/mL against chloroquine-resistant and chloroquine-sensitive strains, respectively. Otherwise, the IC_{50} that was found for OA was 88.8 μg/mL and 70.6 μg/mL for chloroquine-resistant and chloroquine-sensitive strains, respectively. Other studies have also corroborated the potential of UA, purified from *Mitragyna inermis*, against chloroquine-sensitive and chloroquine-resistant strains, showing an IC_{50} between 15 μg/mL and 18 μg/mL. In addition, infected blood cells treated with UA presented with lower parasitism than did infected controls [94]. Other studies have also demonstrated that OA and UA purified from *Satureia parvifolia*, *Mimusops caffra*, *M. obtusifolia*, and *Kleinia odora* were able to eliminate *P. falciparum* [156–158].

Drugs based on pentavalent antimonials, Amphotericin B, nifurtimox, and benznidazole, are employed to treat patients with leishmaniasis and American trypanosomiasis but, unfortunately, these drugs are toxic and reports of parasite resistance to them have been constantly published, justifying the search for new active compounds. In infections caused by trypanosomatids, OA and UA were also tested, first in the use against *Leishmania* sp. parasites, and then against *Trypanosoma cruzi*, the etiological agents of leishmaniasis and American trypanosomiasis, respectively. Leishmaniasis is a complex disease, and its symptoms range from the presence of severe cutaneous lesions to the more visceral form of the disease, which affects the spleen, liver, and bone marrow [159].

Tan et al. [160] evaluated the leishmanicidal potential of OA and UA extracted from *Salvia cilicica* roots. The obtained results showed that UA 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. These values were comparable to the standard drug, Pentostam, whose IC_{50} was 10.6 nM and 9.8 nM against the same parasite species, respectively. *L. (L.) amazonensis* promastigotes were shown to be highly sensitive to OA and UA, presenting an IC_{50} of 10 μg/mL and 5 μg/mL, respectively. In addition, both of these compounds were active against the intracellular form of *L. (L.) amazonensis*, showing an IC_{50} of 27 μg/mL and 11 μg/mL, respectively. On the other hand, an IC_{50} of 83 μg/mL was obtained for experimental treatment with meglumine antimoniate [95], suggesting that these triterpenes are more effective than one of the standard drugs that is currently used to treat patients. The effect of these triterpenes on amastigote forms was not related to nitric oxide production, since elevation of this effector molecule was not verified in infected macrophages. Further studies also demonstrated that UA was active against promastigote forms of *L. (L.) amazonensis*, *L. (L.) infantum* [161], and *L. (L.) donovani* [162].

Recently, a bioguided study conducted with extracts of *Baccharis uncinella* leaves led to the identification of a bioactive fraction that contained OA and UA triterpenes. This fraction showed moderated activity against *L. (V.) braziliensis* and *L. (L.) amazonensis* promastigotes, although it was very active against amastigote forms of both parasite species; moreover, the leishmanicidal effect could be related to a direct effect on the amastigote forms. Additionally, these compounds triggered nitric oxide production in the macrophages, since infected cells incubated with the highest concentration of this fraction produced significant amounts of this effector molecule [26]. Due to this leishmanicidal potential, this fraction (OA + UA) was assayed as a prototype drug in *L. (L.) amazonensis*-infected mice. Animals that were treated with 1.0 mg/kg and 5.0 mg/kg of triterpene fraction presented with reduced lesion sizes and skin parasitism, which was accompanied by a significant elevation of IL-12 and interferon- (IFN-) γ cytokines. Furthermore, the treatment did not alter the histological profile of the spleen, liver, heart, lungs, and kidneys of mice [27]. Interestingly, a total dose of 1.25 mg of amphotericin B was required to eliminate 86% of parasites, while only 0.625 mg of the triterpene fraction was required to inhibit approximately 93% of skin parasitism,

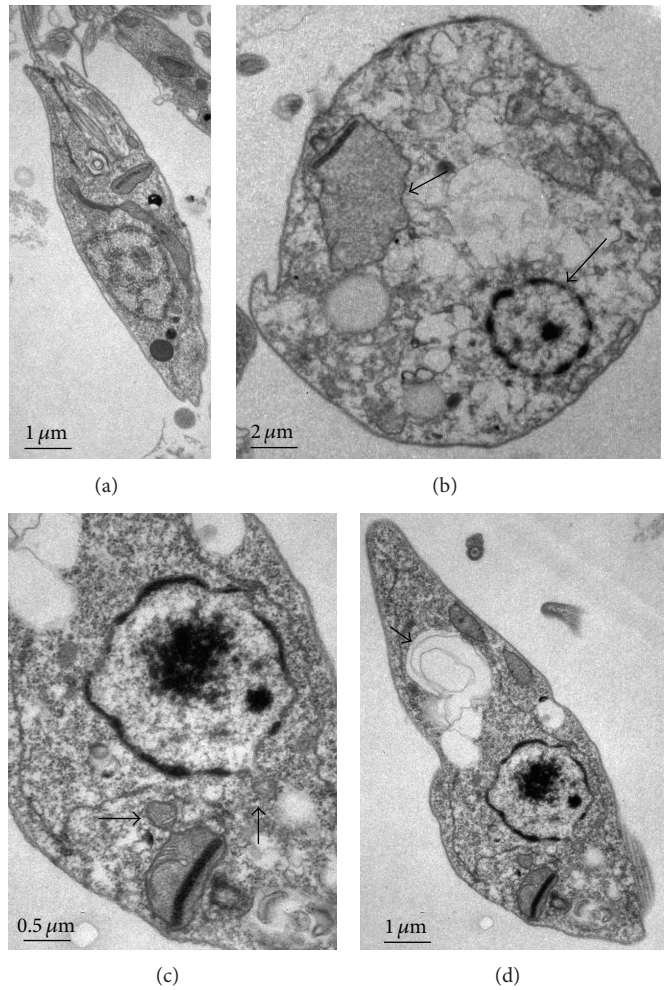

Figure 2: Ultrastructural alterations induced by 10.96 μg of UA on promastigote forms of *L. (L.) amazonensis*. (a) Control parasites showed a normal morphology of the cell membranes, nucleus, and kinetoplast (20.000x). (b) Parasites treated with UA presented with evident external and internal alterations, such as mitochondrial swelling (arrowhead) and a pyknotic nucleus (short arrow) (10.000x); (c) Blebs (arrows) were detected in the nucleus and kinetoplast (40.000x); and (d) membranes were detected inside vacuoles, as indicated by the arrow (20.000x).

suggesting the elevated leishmanicidal potential of OA and UA.

In addition, our group demonstrated, through ultrastructural studies, that *L. (L.) amazonensis* promastigote forms treated with 10.96 μg of UA presented with irreversible morphological changes after 18 hours of incubation. Control parasites presented with normal membrane morphology, cytoplasm, nucleus, mitochondrion, and flagellum (Figure 2(a)). Otherwise, treated parasites presented with rounded-shape morphology, and the intracellular environment presented with vacuoles, suggesting organelle degradation (Figure 2(b)) and swelling of the mitochondrion, and a pyknotic nucleus was detected (Figure 2(b)); blebs were also visualized in the nucleus and in the kinetoplast (Figure 2(c)). In addition, intracellular vacuoles presented with fragments of membranes (Figure 2(d)), suggesting degradation of the organelles. Taken together, these results suggest that, in promastigote forms of *L. (L.) amazonensis*, UA induces a mechanism of death associated to apoptosis or even autophagy. This is the first study that depicted the possible mechanism of action of UA on *L. (L.) amazonensis* promastigote forms.

Based on previous works, these triterpenes can be regarded as antileishmanial agents since these studies demonstrated that these agents can be more effective than conventional drugs. In addition, more attention needs to be paid to UA, which is the primary antileishmanial agent when compared to its isomeric derivative, OA.

In American trypanosomiasis, the parasite *T. cruzi* infects a broad range of cell types, preferentially, muscle cells from the gut and heart, leading to a loss of organ function [163, 164]. Unfortunately, there are only two drugs that can be used to treat patients (nifurtimox and benznidazole), which are associated with serious side effects and are effective only in the acute phase of the disease [165], indicating that a search for a new trypanocidal compound is necessary. OA and UA purified from *Miconia* species were shown to be active against the blood form of *T. cruzi*; they showed an IC_{50} of 80.4 μM and 21.3 μM, respectively, while the IC_{50} for gentamicin violet

was 71.6 μM [92], reinforcing the antiparasitic potential of UA. These interesting results led to the evaluation of the therapeutic potential of OA and UA triterpenes in a murine model of American trypanosomiasis. Animals treated with 2.0 mg/kg of OA, UA, and a mixture of OA plus UA presented with low parasitemia when compared to animals treated with benznidazole [166]. Ferreira et al. [167] also demonstrated that OA and UA were capable of controlling the peak of parasitemia in infected mice and, interestingly, treated mice did not show any alterations in their biochemical parameters, reinforcing the idea that these triterpenes are not toxic for animals. Considering the low or absent level of toxicity of triterpenes for mice, as well as their high trypanocidal activity, these results suggest that both compounds can be used for the development of new drugs against *T. cruzi*.

5. Conclusion

Several triterpenes, which displayed interesting structural features, have been considered inactive for a long period of time. However, different works have since demonstrated the wide array of pharmacological activities inherent in this class of natural compounds.

Specifically, UA and OA present remarkable antimicrobial activities, and they act against important human pathogens such as mycobacteria, HIV, and different protozoal species. The present review described interesting works about the antimicrobial action of UA and OA that, in fact, could be considered drug prototypes. In spite of this, the present review also alerted us to some concerns, insofar as the majority of the works presented here have not depicted the possible mechanism of action of these triterpenoids in microorganisms. Moreover, studies have not associated the *in vitro* potency of these agents with studies dealing with their therapeutic action (*in vivo*); this should be a priority in this field. In addition, these types of strategies will be crucial in the development of new drugs that can be used for populations that are at risk for contracting certain diseases.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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