

Exploring the Therapeutic Potential of Ursolic Acid: Insights into Pharmacological Processes and Signaling Pathways

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Abstract

Ursolic acid (UA), a biologically active compound derived from various plant sources such as fruits, flowers, and leaves, has garnered attention for its therapeutic potential in treating a spectrum of diseases, including cancer, diabetes, obesity, cardiovascular diseases (CVDs), neurological disorders, liver ailments, and sarcopenia. Despite its promising properties, the precise mechanisms underlying its therapeutic effects remain incompletely understood. This review aims to explore the pharmacological processes and signalling pathways modulated by UA to elucidate its therapeutic potential. Through an examination of existing literature, we highlight the diverse biological activities of UA and its ability to modify key signalling pathways involved in disease pathogenesis. Ursolic acid has shown promising results in modulating the molecular pathways involved in inflammation, oxidative stress, cancer progression, metabolic disorders, neurodegenerative diseases and skin health additionally, we discuss the implications of UA in preventing the onset of chronic diseases and propose avenues for further research to fully harness its therapeutic benefits.

Key words: *Ursolic acid (UA), Neurological disorders, Anti-inflammatory, Antioxidant*

Introduction

Plants play crucial roles in ecosystem regulation and can influence diverse biological processes [1]. Derived from plants, numerous biologically active compounds exhibit efficacy in treating various diseases spanning cancer [2], diabetes [3], obesity [4], cardiovascular diseases (CVDs) [5], neurological disorders [6], liver ailments [7], and sarcopenia [8,9].

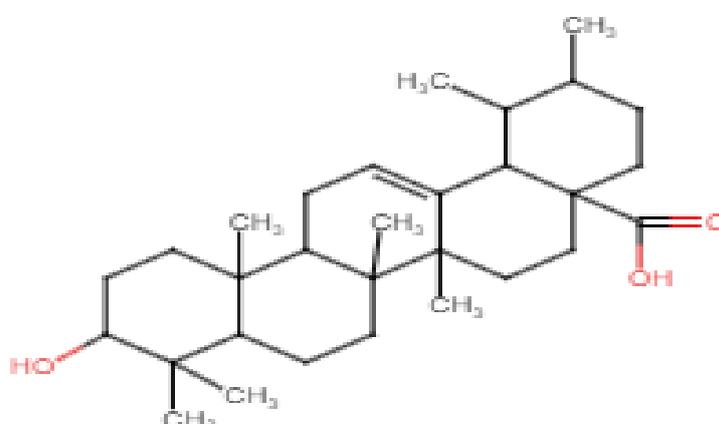
Among these compounds, Ursolic acid (UA) stands out for its therapeutic potential [10]. Nevertheless, the precise mechanisms underlying its beneficial properties remain incompletely understood.

UA is isolated from a variety of fruits (apple fruit peel), flowers, berries, and leaves (rosemary, marjoram, lavender, thyme, and organum) [11]. In order to prevent the onset of chronic diseases, UA mediates certain pharmacological processes and modifies a number of signaling pathways [12, 13].

It also demonstrates anti-inflammatory [14], anti-oxidant [15], anti-carcinogenic [16], anti-obesity [17], anti-diabetic [18], cardioprotective [19], neuroprotective [20], hepatoprotective [21], anti-skeletal muscle atrophy [22], and thermogenic effects [8].

The ways in which UA produces these advantageous effects could include controlling the following: insulin signaling in adipose tissue, nuclear factor-kappa B (NF-kB) and apoptotic signaling in cancer cells, the expression of markers of cardiac damage in the heart, inflammation and the amount of antioxidants in the brain, metabolic signaling and the amount of oxidants in the skeletal muscles. UA is soluble in hot glacial acid and ethanol sodium hydroxide [23].

Structure of Ursolic Acid



Pharmacological Properties of Ursolic Acid

Anticancer effect

UA exerts a powerful in vitro and in vitro anticancer effect (Table 1). Many studies have investigated the beneficial effects of U.A. on cancer cell metabolism in rodents and humans. The mechanisms underlying the anticancer effect of U.A. were reported to inhibit tumor development [24] and cancer cell proliferation [25], modulate apoptosis [26], prevent cell cycle repression [27], and promote autophagy [28,29]. The most recent trends in UA research have shown that the compound has a beneficial effect on autophagy and apoptosis in human breast cancer cells. Lewinska et al. [26] The 20M UA suppresses activation of Akt and promotes autophagy and apoptosis in breast cancer cells. It also reduces the level of kinase 1/2 regulated by phospho-extracellular signals and mitochondrial membrane depolarization potential. It is interesting to note that UA induces activation of Akt, increases the oxidative system, and decreases the level of adenosine triphosphate (ATP), lactic acid, and glycolytic enzymes such as hexokinase 2 and Pyruvate kinase in breast cancer cells [30,31]. In addition, it reduces the production of ATP, activates amino monophosphate (AMPK)-activated protein kinase, inhibits proliferation of T24 bladder cancer cells, and induces autophagy of U87MG cells. UA may be a powerful regulator of AMPK that inhibits glycolysis and tumor growth in vivo [31].

Xavier et al. [34] has shown that UA promotes autophagy in HCT15 colorectal and TC-1 cervical cancer cells [35]. In addition, it inhibits apoptosis and cell proliferation in human pancreatic cancer cells [36] and in ovarian cancer cells [37]. Moreover, UA reduces the activity of the Na⁺K⁺ ATPase and mitochondrial membrane potential, indicating mitochondrial dysfunction in these cancer cells.

Anti-ageing

The epidermal permeability barrier is essential for different skin functions that include physical, chemical and biological aspects. Sensitive skin, characterized by increased trans epidermal water loss and sensitivity to irritants, is often caused by weakened barrier functions and reduced ceramide levels. Conditions such as atopic dermatitis have impaired the barrier function, decreased water retention properties and reduced ceramide levels. UA emerges as a promising moisturizing agent that does not cause skin irritation [38]. In particular, the UA improves the expression of genes associated with the differentiation of terminal keratinocytes and improves the function of skin barrier [39]. Unlike retinoids that suppress the production of ceramides, UA stimulates the production of ceramide, which is essential for skin hydration and elasticity [40]. Aging-related skin problems such as wrinkling and xerosis are caused by a decline in the collagen levels of the skin and corneum layer ceramides. UA increases the ceramide content of epidermal keratinocytes and collagen production of skin fibroblasts. Furthermore, the use of topical UA enhances the recovery of the epidermal barrier and increases the level of ceramide in the epidermis, highlighting its potential as an anti-aging agent [41,42].

Immunomodulatory activity

In mice, intraperitoneal administration of UA has shown remarkable immune modulation, including an increase in total white blood cells, bone marrow cells, and alpha-esterase-positive cells. In addition, treatment with UA delayed hypersensitivity reactions and, when combined with antigens, increased the specific levels of antibodies and the number of cells that form plaques in the spleen [43]. In mice with metastatic tumors, intraperitoneal administration of UA increased the activity of natural killer cells and increased the cytotoxicity mediated by antibodies [44]. Furthermore, UA demonstrated an immune modulating function in type 1 diabetic mice with a high-fat diet [45].

Anti-inflammatory

Ursulfate is an important active ingredient in many herbal products known for its anti-inflammatory properties. These include *Pyrola rotundifolia* L. [46], *Verbena officinalis* L. *Salvia officinalis* leaves [47], *Psidium guajava* leaves *Perilla frutescens* L., and *Psidium guajava* leaves. Compared to indomethacin, UA has twice the effectiveness and has been suggested to treat diseases such as rheumatism, fever, and arthritis [48]. Its anti-inflammatory mechanism is related to the inhibition of histamine release by mast cells and the activity of lipo-oxygenase and cyclo-oxygenase [49]. Ursolic acid (UA) inhibits the expression of E-selectin, a reaction molecule induced by inflammation and initial response, in endothelial cells during inflammation through the inhibition of activation of NF-kappa B [50]. In addition, it has been shown that UA suppresses the production of intracellular reactive oxygen species, which further contributes to its anti-inflammatory effect.

Cardiovascular disease

CVDs reduce quality of life and increase social and economic costs [50]. In the first study, Somava et al. [51] shows that UA therapy (40 mg/kg) is associated with a reduction in heart rate, which means that the risk of CVD is reduced in both the *in vitro* and the *vivo*. In addition, Pozo et al. [52] reports that in rats with vascular injury model, by inhibiting light stenosis in a 10-day neo-intestinal hyperplasia (80%) by intraperitoneal administration of UA (2 and 6 mg/kg) inhibited vascular injury. UA also significantly inhibits the expression of proliferating cell nucleic antigens in damaged artery cells. Furthermore, it is reported that UA (60 mg/kg) reduces the amount of lipid peroxides by cleaning free radicals, improving the lipid profile, and reducing the serum level of membrane-bound proteins after 7 days of treatment. UA is believed to be protective against myocardial ischemia, helping to restore the normal levels of cardioprotective enzyme activity in rats. Similarly, previous research has shown that UA can restore normal heart enzymes and blood components. It has anti-apoptotic effects in cardiac muscle cells [53,54]. The effects of UA on lipid peroxidation and antioxidant capacity are also reported in alcoholic cardiomyopathy [55]. Saravanan and Pugalendi suggested that 30 days of treatment with UA (20 mg/kg/day) promoted the action of antioxidant enzymes to eliminate free radicals. Improves the activity of glutathion, ascorbic acid, and -tocopherol levels [55]. In addition, Lv et al. [56] It has been shown that UA significantly inhibits the proliferation of human umbilical vein endothelial cells induced by interleukin 6 (IL-6) and C-reactive protein (CRP) and that it inhibits parameters related to atherosclerosis depending on the dose,

Hepatoprotective activity

UA alone or in combination with other active substances is well known to protect liver tissue from acute and chronic liver damage [57]. Gutierrez-Rebolledo et al. found that a combination of UA and OA in male BALB/c mice with liver injuries caused by anti-tuberculin induced by a serum adrenase can reduce levels of aspartate transaminase, alanine aminotransferase, and increase liver histological changes [58]. UA has suppressed the progression of non-alcoholic fat liver disease, with a reduction in liver weight and liver steatosis, in addition to the accumulation of intracellular lipids, possibly due to increased -oxidation of lipids and the cessation of liver stress [59]

Neuroprotective activity

Some studies have shown that the organization of the neuroprotective effect of UA is good. It can control the inflammatory reaction of rat ischemic brain, and is shown to significantly reduce infarct size and lipid peroxidation reducing the activation of the 2nd nuclear factor (Nrf2)[60]related to the erythroid. In a study by Ding et al., UA's use for the treatment of brain injuries in murine models significantly improved brain edema and neurological problems associated with trauma and reduced oxidative stress. The study showed that UA's neuroprotective effect was associated with activation of the (Nrf2) pathway [61].

Antimicrobial activity

A study by Singh et al. UA demonstrated antimicrobial activity against mycobacterium smegmatis, mycobacterium tuberculosis, and clinically eliminated multidrug resistant M. tuberculosis at a minimum inhibitory concentration (MIC) of 62.5 mg/ml [61].

Nascimento et al. [62] UA and its derivatives evaluated the sensitivity of some pathogenic bacteria to antibiotics belonging to the amino acid-glycoside category (Neomycin, Amicamycin, Kanomimycin, and Geramycin). 3 β -Formyloxyurs-12-en-28-oic acid, which was used at 64 mg/ml in combination with Kanamycin, showed synergistic effects against *E. coli* and reduced the MIC significantly from 128 mg/ml to 8 mg/ml.

Anti-fungal Activity

The antifungal activity of Ursolic Acid has been shown in several studies. For example, Luo et al. (2014) reported that UA has a strong antifungal effect on *Candida albicans*, inhibiting its growth and the formation of biofilms [63]. Zhao et al. In 2016, it was found to inhibit the growth and production of fungus *aspergillus flavus*, suggesting that UA's antifungal activity was effective [64], thus demonstrating its potential as a natural antifungal agent. These findings highlight the promising anti-fungal properties of Ursolic acid, which may provide new treatments for fungus infections.

Anti-hyperlipidemic activity

The natural components of Ursolic acid in various plants reduced total cholesterol, triglyceride, and low-density lipoprotein (LDL) levels in animal models[65], and revealed the molecular mechanism of the anti-hyperlipid activity of Ursolic acid, revealing its ability to inhibit liver lipid accumulation and promote the expression of genes involved in lipid metabolism. Yang et al. studied the potential of ursolic acid as a drug for hyperlipidemia[66], highlighting its ability to regulate lipid metabolism pathways and improve the lipid profile of animals and humans. To establish the therapeutic effects of Ursolic Acid against hyperlipidemia, confirm its effectiveness in reducing serum lipid levels and suggest its potential as a natural treatment for hyper-lipidaemia, conduct randomized controlled trials to evaluate the effects of Ursolic acid supplementation on lipid metabolism in patients with hyperlipidemia, provide clinical evidence for its beneficial effect on lipid profiles [67].

Antiviral Activity

An Ursolic acid, the inhibition of viral reproduction, interference with viral entry into host cells and the modulation of host immune reactions [68]. Inhibition of virus replication: Research has shown that Ursolic acid can inhibit the replication of several viruses, including the Herpes Simplex virus (HSV), influenza virus, human immunodeficiency virus (HIV) and hepatitis B virus (HBV).[69] This inhibition is often caused by interference with the synthesis of viral proteins and the replication machinery. Virus entry interference: Ursolic acid has been shown [70] to interfere with the insertion of viruses into host cells by blocking the binding of viruses to cell receptors and interrupting the fusion of viral envelopes with cell membranes [71]. This prevents the onset of viral infections. Modulation of the host's immune responses: Ursolic acid can also modulate the host's immune responses to virus infections. [72]. It was reported that it increased the activity of natural killer cells (NK cells), promoted interferon production and stimulated cell secretion, all of which contributed to the host's ability to fight viral infections. [73]

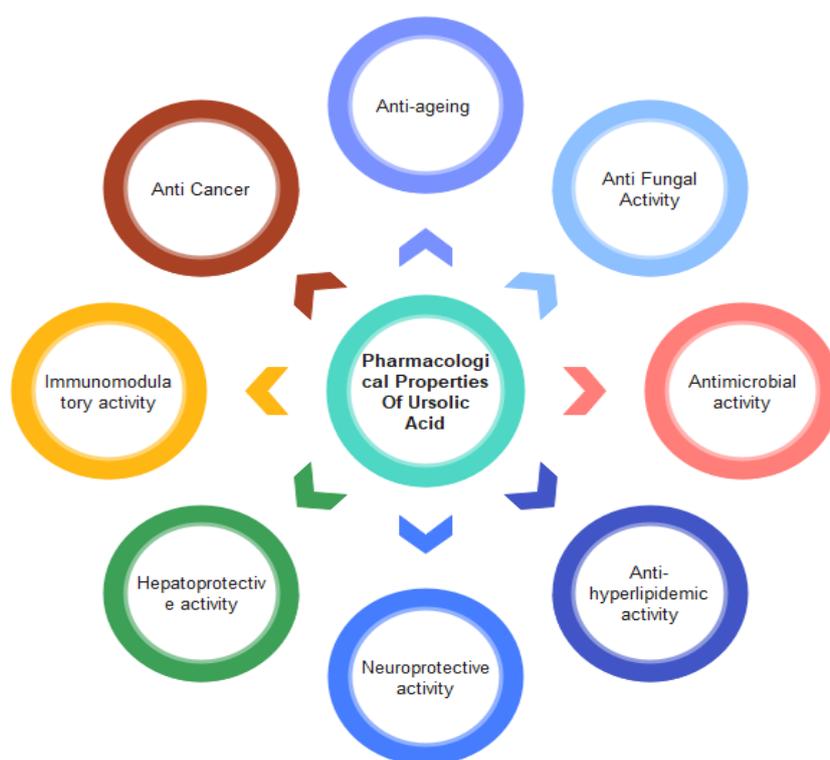
Antidiabetic activity

Improve insulin sensitivity: It has been shown that Ursolic acid increases insulin sensitivity in various tissues, including muscle, liver and fat tissue [74]. Using insulin signaling pathways, cells are able to absorb glucose more efficiently and reduce blood sugar levels.

Gluconeogenesis inhibitor: Gluconeogenesis is the process of the liver producing glucose from non-carbohydrates. Ursolides inhibit important enzymes involved in glucose generation [75], such as phosphate decoxide phosphatase (PEPCK) and glucose-6-phosphatase (G6Pase), thus reducing excess glucose production in the liver.

Stimulation of glucose absorption: Ursolic acid can increase glucose absorption in skeletal muscle and fat tissue by [76]. promoting the transfer of type 4 glucose transporter (GLUT4) to cell membranes. This helps glucose to be absorbed from the blood into cells and decreases glucose levels in the blood.

Protecting the Pancreatic cells: Pancreatic cells are responsible for producing and secreting insulin. It has been reported that ursolic acid protects pancreatic cells by reducing oxidative stress, inflammation and apoptosis and thus preserving their function and function [77].



Source of Ursolic Acid

Triterpenoids are described in the diversity of common European plants and fruits [78]. UA (3-hydroxyurs-12-en-28-oic) is a pentacyclic triterpene and plant sterol, In developed countries, the projected human use of triterpenes was 250 mg per day. In Mediterranean countries, most foods are made of olive oil, but due to the high content of olive oil, the average daily intake of triterpenes can reach 400 mg.

Triterpenes are of an unbelievable interest. Most studies focused on the cholesterol-reducing properties of triterpene. UA is particularly well-known in higher plants such as *Rosmarinus officinalis*, *Glechoma hederaceae*, *Ilex paraguariensis*, *Ichnocarpus frutescens*, *Phoradendron juniperinum*, *Syzygium claviflorum*, *Hyptis capitata*.

It is a component of many herbal medicines sold in Asia and the world to treat inflammation [79]. Among the fruits, the North American Cranberry (*Vaccinum macrocarpon*) fruit consists in particular of a considerable amount of UA in its peel. It is present in the aglycone configuration and in the esters *cis* and *trans*-*p*-hydroxycinnamate [80]. Quantitative evaluations of cranberries and products using liquid mass chromatography (LC-MS) showed that the UA content of cranberries from a variety of cultivars varies between 60 and 110 mg per 100g fresh fruit [81]. In sweetened and dried fruits, a similar content was established. On the contrary, in cranberry sauce gels or commercial cranberry juices, there is less UA due to its low water solubility [82]. Seabuckthorn (*Hippophae rhamnoides* L.) is a fruit that is produced in northern Europe. The phytochemical examination showed that UA is much larger in the buckthorn berry extract than in other berries. In addition, Fang and McLaughlin extracted UA from the red fruits of the decorative shrub winter berry (*Ilex verticillata*) [83]. Winterberries are not recommended for human consumption (USDA/NRCS Plant Information Sheet) [84]. UA, OA and their derivatives have been announced for non-fruits, including apples (*Malus pumila*). UA and OA extract aglycones and many cinnamoyl and hydroxycinnamoyl esters from apple peels [85]. Table 1 shows the content of Ursolic acid in fruits, vegetables and spices.

Various sources of Ursolic acid along with the quantity present within each [85]

Biological sources	Scientific name	Amount present in milligrams/100g
Balsam	<i>Momordica charantia</i>	42±5
Brown Mustard	<i>Brassica juncea</i>	13±4
Star Fruit	<i>Averrhoa carambola</i>	4±5
Guava	<i>Psidium guajava</i>	12±2
Mahogany	<i>Swietenia macrophylla</i>	520
Daylily	<i>Hemerocallis</i>	19.2
Damnacanthus	<i>Damnacanthus indicus</i>	57±8
Hawthorn	<i>Crataegus</i>	19±5
Apple	<i>Malus pumila</i>	152

Preclinical Studies

Preclinical research plays an important role in assessing potential drug properties and safety profiles of compounds such as Ursolic acid before going into clinical trials. Here are some preclinical studies showing the various pharmacological effects of Ursolic acid:

Anti-inflammatory effects: A study published in the journal *Biochemical Pharmacology* shows the anti-inflammatory effects of Ursolic acid in the animal model of inflammation. Researchers found that Ursolic acid inhibits proinflammatory cytokines and reduces inflammation cell invasion, indicating its potential therapeutic benefits in inflammatory diseases [86].

Antioxidant effects: Research published in *Food and Chemical Toxicology* investigates the antioxidant effect of Ursolic acid *in vitro* and *in vivo*. The study showed that ursolic acid has a powerful antioxidant activity by eliminating free radicals and increasing the activity of endogenous antioxidant enzymes. These findings suggest that Ursolic acid can protect against damage associated with oxidative stress [87].

Potential for Anti-cancers: Some preclinical studies have investigated the anticancer effects of Ursolic acid in various cancer cell lines and animal models. For example, a study published in the Journal of Cancer Reports demonstrated that Ursolic acid inhibits breast cancer cells and induces apoptosis by modulating apoptosis pathways. Furthermore, in animal cancer models, Ursolic acid suppressed tumour growth and metastasis and demonstrated its potential as a cancer treatment agent [88].

Metabolic benefits: Preclinical research has also studied the metabolic effects of Ursolic acid, especially its role in regulating glucose and lipid metabolism. In a study published in the journal Plant Therapy Research, the researchers found that Ursolic acid improved insulin sensitivity, reduced blood glucose levels, and reduced lipid accumulation in animals' models of diabetes and obesity. These results suggest that ursolic acid may be used to treat metabolic disorders [89].

Neuroprotective properties: Animal studies provide evidence of neuroprotective effects of Ursolic acid on various neurodegenerative diseases. For example, a study published in the journal Neurochemical Research showed that Ursolic acid protects against neurological damage and cognitive impairment in Alzheimer's mouse models [89].

The study suggests that Ursolic acid reduces neuroinflammation and oxidative stress, thereby promoting neuroprotection. These preliminary studies collectively provide valuable insights into the pharmacological properties of Ursolic acid and support its further studies as potential treatments for various diseases.

Clinical Studies:

Preclinical research has provided promising evidence of the pharmacological effects of Ursolic acid, but clinical research to assess its effectiveness and safety in humans is still relatively limited. However, some clinical studies have been carried out to explore the potential therapeutic advantages of Ursolic acid in various health conditions.

Metabolic syndrome and type 2 diabetes:

Randomized double-blind, placebo-controlled clinical trials investigated the effects of Ursolic acid supplements on metabolic parameters in metabolic syndrome patients. The study published in Diabetes Care shows that supplementation with Ursolic acid significantly improved insulin sensitivity and inflammation markers compared to placebo, suggesting a potential role for Ursolic acid in the treatment of metabolic diseases [90].

Muscle Atrophy and Physical Function

A clinical study published in the Journal of Muscle and Muscle Injuries evaluated the effects of Ursolic acid supplementation on muscle and body function in older adults with muscular atrophy and muscle weakness. The study revealed that Ursolic acid supplementation improved muscle mass and physical performance in comparison to placebo, suggesting a potential therapeutic strategy for preventing muscle loss due to age [91].

Skin Health: Clinical studies have also explored the skin-friendly effects of Ursolic acid. For example, randomized, double blind, placebo-controlled trials have investigated the effectiveness of a topical formulation containing Ursolic acid to improve skin elasticity and hydration in healthy volunteers. The results published in Cosmetic Dermatology showed that topical application of Ursolic acid significantly improved skin elasticity and hydration compared to placebo and suggested the possibility of use in skin care products [92].

Anticancer Potential: Most clinical studies of Ursolic acid focus on its metabolic and dermatologic effects, but interest in its potential anticancer properties is emerging. Clinical trials to evaluate the efficacy of Ursolic acid as a cancer drug are still under way, but further research is needed to establish its efficacy in humans. These clinical trials provide preliminary evidence of the potential therapeutic efficacy of Ursolic acid under various health conditions. However, larger-scale clinical trials are needed to further clarify its efficacy, safety profile and optimal dose in human populations [93].

Future Prospective of Ursolic Acid

Ursolic acid, a natural compound found in various plants like apple peels, rosemary, and basil, has shown promising potential in various fields, including medicine, cosmetics, and agriculture. Here's a glimpse into its future prospects:

Medicine:

Anti-inflammatory Properties: Ursolic acid demonstrates anti-inflammatory effects, which could be beneficial in treating inflammatory conditions like arthritis.

Anti-cancer Potential: Research suggests that Ursolic acid may have anti-cancer properties by inhibiting the growth of cancer cells. Future studies may explore its use in cancer treatment or prevention.

Metabolic Health: It has shown promise in improving metabolic health by potentially reducing obesity and improving glucose metabolism, which could lead to the development of new treatments for metabolic disorders like diabetes and obesity.

Cosmetics:

Skin Care: Ursolic acid has antioxidant and anti-inflammatory properties, making it a candidate for skincare products. It may help protect the skin from oxidative stress and inflammation, potentially reducing signs of aging and improving overall skin health.

Hair Care: Some research suggests that Ursolic acid may promote hair growth by stimulating hair follicles. This could lead to the development of hair care products targeting hair loss and promoting hair regrowth.

Agriculture:

Pesticides: Ursolic acid has shown insecticidal and antimicrobial properties, indicating its potential use as a natural pesticide in agriculture. Its biodegradability and low toxicity make it an attractive alternative to synthetic pesticides.

Plant Growth Regulator: Ursolic acid may also function as a plant growth regulator, influencing various physiological processes in plants such as growth, development, and stress responses. This could lead to the development of eco-friendly agricultural practices to improve crop yield and resilience.

Drug Delivery:

Nano-formulations: Researchers are exploring the use of nano-formulations of Ursolic acid to enhance its bioavailability and therapeutic efficacy. These formulations could improve drug delivery and tissue targeting, potentially enhancing the effectiveness of Ursolic acid-based therapies.

Overall, the future prospects of Ursolic acid appear promising across multiple fields, but further research and development are necessary to fully explore its potential benefits and applications. Additionally, regulatory approval and commercialization will play crucial roles in translating these findings into practical products and treatments.

Conclusion:

Ursolic acid is a natural compound found in various plants, has diverse pharmaceutical properties, and may be used for therapeutic purposes. Preclinical research provides evidence of its anti-inflammatory, antioxidant, anti-cancer, metabolic, neuroprotective and dermatologic effects. Ursolic acid has shown promising results in modulating the molecular pathways involved in inflammation, oxidative stress, cancer progression, metabolic disorders, neurodegenerative diseases and skin health. Clinical studies have supported some of these results, showing the beneficial effects of supplementation with Ursolic acid on improving metabolic parameters, muscle mass, physical function and skin elasticity. While research on Ursolic Acid is still in progress, these preliminary findings show its potential as a multifaceted therapeutic agent for various health conditions. Further clinical research is required to fully explain its effectiveness, safety characteristics and optimal therapeutic strategies in human populations.

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