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A Review of the Pharmacological Properties of Ursolic Acid

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Abstract

Plants are known to produce a variety of bioactive metabolites which are being used to cure various life threatening and chronic diseases. The molecular mechanism of action of such bioactive molecules may open up new avenues for the scientific community to develop or improve novel therapeutic approaches to tackle dreadful diseases such as cancer, cardiovascular and neurodegenerative disorders etc. Ursolic acid (UA) is one among the categories of such plant-based therapeutic metabolites having multiple intracellular and extracellular targets that play role in apoptosis, metastasis, angiogenesis and inflammatory processes. Ursolic acid (UA) is a pentacyclic triterpenoid widely found in herbs, leaves, flowers and fruits. Moreover, the synthetic derivatives of UA have also been seen to be involved in a range of pharmacological applications, the great interest in this bioactive compound is related to the beneficial effects in human health due to antioxidant, antimicrobial, anti-inflammatory, hepatoprotective, immunomodulatory, anti-tumor, chemopreventive, cardioprotective, antihyperlipidemic and hypoglycemic activities, and others. UA may augment the resistance of the skin barrier to irritants, prevent dry skin and could be suitable to develop antiaging products. Evidences suggest that UA could be used as a potential candidate to develop a comprehensive competent strategy towards the treatment and prevention of health disorders. The review article herein describes the possible therapeutic effects of UA along with putative mechanism of action.

Keywords: Ursolic acid; Apoptosis; Antioxidant; Antimicrobial; Hepatoprotective; Immunomodulatory; Chemopreventive; Cardioprotective; Antihyperlipidemic; Hypoglycemic; Antimetastasis

Introduction

Plants are the only producers in the ecosystems which have been deliberated to influence mankind throughout life. The bioactive products derived from plants are being considered to be an unparalleled source to design novel and effective therapeutic agents for the treatment of dreadful diseases including cancer, cardiovascular and neural disorders (Tuli et al; 2013). Various plant-derived biologically active products are effective for the treatment of a wide spectrum of diseases, including cancer (Sehrawat et al; 2017), diabetes (Diarra et al; 2016), obesity (de Freitas Junior et al;

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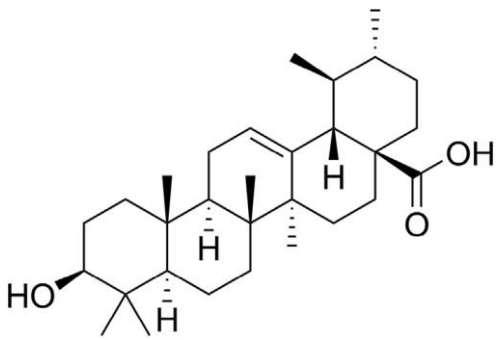
2017), cardiovascular diseases (CVDs) (Croft et al; 2017), brain disease (Jiang et al; 2017), liver disease (Leake et al; 2013), and sarcopenia (Katashima et al; 2017, Kunkel et al; 2011). Ursolic acid (UA) is a compound that has such therapeutic effects (Wozniak; 2015). neurodegenerative, and other diseases (Seo et al; 2018)

Ursolic acid (UA) (3β-hydroxy-urs-12-en-28-oic-acid) (Fig. 1) is a pentacyclic triterpenoid carboxylic compound (C30H48O3) which may occur in the free acid form or as aglycones for triterpenoid saponins. Its isomer, oleanolic acid (OA) (3β-hydroxy-olea-12-en-28-oic-acid), presents different substitution of the methyl group, but they have similar molecular structures and pharmacological activity (Lim et al., 2007). Oleanolic acid and ursolic acid are ubiquitous triterpenoids in plant kingdom, medicinal herbs, and are integral part of the human diet, once they are found in fruits and medicinal herbs. In recent years they became the subject of many publications because of their various activities and low toxicity. Many beneficial effects such as antioxidative, antimicrobial, anti-inflammatory, anticancer, anti-hyperlipidemic, analgesic, hepatoprotectory, gastroprotective, anti-ulcer, anti-HIV, cardiovascular, antiatherosclerotic and immunomodulatory effects have been reported (Kashyap, Tuli, & Sharma, 2016; Liu, 1995; Woźniak, Skąpska, & Marszałek, 2015). Several works have shown that the ursolic acid can also stimulate muscle growth, reduce fat gain and enhance the epidermal permeability barrier recovery in the skin (Kunkel et al., 2012), therefore it has been proposed as a skin therapeutic agent and it could be introduced in sport supplements (Close, Hamilton, Philp, Burke, & Morton, 2016; Deane et al., 2017), cosmetics (De Almeida et al., 2014) and health products (Navina, Lee, & Kim, 2017). During the last decade articles published reported on the isolation and purification of these triterpenoids from various fruits, plants and herbs, the chemical modifications to prepare more effective and water soluble derivatives, the pharmacological research on their beneficial effects, the toxicity studies, and the clinical use of these triterpenoids in various diseases including anticancer chemotherapies (Chen, Gao, et al., 2015; Jin et al., 2016; Liu, 2005; Sultana, 2011). The effects of pentacyclic triterpenes on proinflammatory mediator signaling pathways and data from experimental animal models and clinical trials (Safayhi & Sailer, 1997) and the antitumor and chemopreventive activity and its main anti-tumor effects and chemopreventive properties have been reviewed (Novotny, Vachalkova, & Biggs, 2001; Ovesna, Vachalkova, Horvathova, & Tothova, 2004; Woźniak et al., 2015). More recently, the therapeutic effects of UA, both in prevention and treatment of health disorders, and its mechanisms of action were compiled (Kashyap et al., 2016).

Despite its common occurrence in nature including in herbs such as basil, rosemary, and sage or common fruits including apple and pears, UA has diverse pharmacological effects. Some of these effects are reviewed in recent years and include brief overviews of pharmacology related to anticancer (Iqbal et al. 2018; Yin et al., 2018), antiobesity (Katashima et al., 2017; Mancha-Ramirez et al., 2016), neurodegenerative, and other diseases (Seo et al., 2018) While the anti-inflammatory effect of UA and other triterpenes is widely known (Kashyap et al., 2016), it does not possess direct reactive oxygen species (ROS) scavenging effect. This is understandable considering its structure (Figure 1) that lacks the phenolic structural moiety which is often linked to radical scavenging and metal ion chelation pharmacology. A plethora of studies, however, suggest that UA has antioxidant effects in vivo through upregulation of antioxidant defenses. Hence, through the combined antioxidant and anti-inflammatory mechanisms, the compound is endowed with a unique potential to ameliorate a range of neuronal diseases. The present review aims at presenting the chemical and biological properties of ursolic acid, their occurrence, natural sources and applications of this compound.



Figgure 1: Chemical structure of ursolic acid

Sources

Ursolic acid can be isolated from various medicinal plants, *Lamiaceae* family being one of the most known source of triterpenes (Razborsek, Voncina, Dolecek, & Voncina, 2008; Wójciak-Kosior, Sowaa, Kocjan, & Nowak, 2013), with contents up to 2.95% d.w. (Jäger, Trojan, Kopp, Laszczyk, & Scheffler, 2009; Razborsek et al., 2008) in *Rosmarinus officinalis* leaves, one of the traditional commercial sources (Silva et al., 2008). UA has also been

identified in a variety of sources, particularly in leaves and flowers (Han et al., 2014; Kowalski, 2007; Takada, Nakane, Masuda, & Ishii, 2010; Xing, Bi, Zhao, & Xia, 2013). The triterpenic acids oleanolic and ursolic were recently detected for the first time in wild edible mushrooms (Kalogeropoulos, Yanni, Koutrotsios, & Aloupi, 2013) and in some commercial dried fruits (Zhang, Daimaru, Ohnishi, Kinoshita, & Tokuji, 2013). Other sources are indicated in Table 1. Cuticular waxes are excellent sources of triterpenoids with a role in protection against biotic stresses, such as herbivores and pathogens, on the mechanical properties of the fruit surface, and these compounds are partially responsible for allelopathic potential (Szakiel & Mroczek, 2007). Triterpene distribution within various plant materials (Jäger et al., 2009) and the triterpenoid profile of cuticular waxes of some edible fruits is compiled (Szakiel & Mroczek, 2007; Szakiel, Pączkowski, Pensec, & Bertsch, 2012). Agro-industrial wastes are advantageous alternative sources. Ursolic acid is the major triterpene in the leaf and fruit of argan, this latter as a by-product of the argan oil industry (Guinda, Rada, Delgado, & Castellano, 2011), and is found in wastes such as those from juice production (Popov et al., 2011; Sorokina et al., 2010), apple peels (Fan et al., 2013; He & Liu, 2007; Lv, Tahir, & Olsson, 2016; Yamaguchi et al., 2008), the discarded by-products from apple or persimmon processing, especially peels (Cargnin & Gnoatto, 2017; Chun, Park, Choung, Kim, & Lee, 2014), unripe and overripe fruits produced on harvesting, i.e. elderberries (Salvador, Rocha, & Silvestre, 2015), and raffinates, such as rosemary leftovers obtained after the extraction of carnosic acid (Liang et al., 2015). Forestry wastes could be another source, i.e. the barks of Eucalyptus sp. (de Melo, Oliveira, Silvestre, & Silva, 2012; Domingues et al., 2013; Patinha et al., 2013).

The developmental stage and the environmental conditions modulate the UA biosynthesis (Guinda et al., 2011) and seasonal variations were observed during ripening in fruits and leaves of olive tree cultivars (Peragón, 2013), in *Silphium sp.* (Kowalski, 2007), in apple peels (Lv et al., 2016), in *S. integrifolium and S. trifoliatum* leaves before and at the beginning of flowering (Kowalski, 2007). The levels of sugars and most triterpenic acids increased with ripening in jujube (*Ziziphus jujuba*) fruit (Guo et al., 2015). Ursolic and oleanolic acids, the most abundant compounds in lipophilic extractives of *Sambucus nigra* L., followed by smaller amounts of long chain aliphatic alcohols and sterols, showed an initial growth during ripening and a systematic decrease until maturity (Salvador et al., 2015). The relative levels of triterpenoid individual compounds can vary in consecutive years due to the influence of external abiotic and biotic stimuli (e.g., meteorological conditions, pathogen infections). A considerable decrease in the level of oleanolic acid was observed during fruit development, probably due to an increase in the level of aliphatic constituents of cuticular waxes. During fruit development, the total triterpenoid content decreased, and in mature grapes, the total triterpenoid content ranged from 34 to 49% of the wax extract mass (Pensec et al., 2014). The variation of triterpenoids in fruits and leaves of olive tree cultivars during processing was also reported (Peragón, 2013).

Oleanolic acid, oleanolic and ursolic acid methyl esters, and oleanolic aldehyde are among the common compounds identified in eight grape cultivars grown in the Upper Rhine Valley. The total triterpenoid content significantly differed among cultivars, ranging from 42 to 80% (Pensec et al., 2014). The UA content varied in different parts of the plant and this pattern of distribution may have an important physiological and ecological meaning (Szakiel & Mroczek, 2007). Higher contents in the inflorescences and leaves than in roots were observed (Kowalski, 2007), in the leaf of argania were four times higher than in the fruit (Guinda et al., 2011). Free triterpene acids and small amounts of the oleanolic and UAs bound forms (presumable glycosides and glycoside esters) occur in fruits and the vegetative part of *Vaccinium vitis-idaea* L. (Szakiel & Mroczek, 2007). The total content of both acids was the highest in fruits and leaves, lower in stems and rhizomes, these latter contained more bound forms of both acids. UA content in the samples from different sources were significantly different (Yang, Wei, Chiu, & Huang, 2013), and the geographic variation was also observed in *Paulownia* fortune (Li et al., 2011), *Ocimum* species (Silva et al., 2008), *Argania spinosa* (Guinda et al., 2011). The outer barks of *Eucalyptus* trees from temperate and Mediterranean zones are richer in triterpenic acids than the species from sub-tropical and tropical regions (Domingues et al., 2011).

Properties

Ursolic acid displayed lower toxicity than OA, 0.95 up from 0.10 mg/mL, respectively (Somova, Nadar, Rammanan, & Shode, 2003), but the data ranged depending on the raw material source, the extraction solvent, the type of activity, the disease, the clinical, cosmetical or pharmacological study, the study in animal or human, etc. Bioavailability studies confirmed a low plasma concentrations of UA in plasma of mice orally administered with high dose of UA, suggested either high binding activity in organs or low bioavailability or metabolism by the gut wall of the intestine and liver (Wójciak-Kosior et al., 2013). Recent compilations of the biological activities are available (Kashyap et al., 2016; Woźniak et al., 2015). Despite many aspects of the biological activities of UA are not

completely understood, the pharmacological effects could be attributed, in part, to their action against free radicals. The description of some biologic effects of the ursolic acid is summarized in Table 1.

Hepatoprotection

UA can be used alone or in combination with other compounds with hepatoprotective effects (such as α-hederin, oleanolic acid, uvaol, etc.) as oral medications (Liu, 2005), and it is among the natural products with demonstrated activity against liver fibrosis through different mechanisms of action, including anti-hepatitis B and C virus activity, antiinflammation, inhibition of cytokine production and nuclear receptor activation, and free radical scavenging (Chen, Chen, Lu, Wang, & Wang, 2015; Shyu, Kao, & Yen, 2010). UA is more potent than OA in decreasing chemically induced liver injury in mice (Liu, 1995; Liu, Liu, Mao, & Klaassen, 1994). However, the appropriate dose should be selected, since low-doses of oleanolic acid are hepatoprotective, whereas the high-dose, depending of the disease, could produce cholestasis and hepatotoxicity (Liu, 2005); e.g. for the liver injury in rats from ethanol administration (7.9 g/kg/day) for 60 days and coadministration of ursolic acid (10, 20 and 40 mg/kg body weight) for 30 days along with the daily dose of ethanol, shows that the 20 mg/kg dose was comparable with a known hepatoprotective drug (silymarin) (Saravanan, Viswanathan, & Pugalendi, 2006).

Cardiovascular Protection and Anti-Hyperlipidemic Effects

Cardiovascular protection, antihyperlipidemic (triglycerides, total cholesterol and lipoprotein fractions), antioxidant (glutathione peroxidase and superoxide dismutase activities), hypoglycemic effects and prevention of hypertension were observed in rats (Somova et al., 2003), displaying UA a low toxicity (LC50 0.95 mg/mL). Somova, Shode, and Mipando (2004) presented, for the first time, a cardiotonic and antidysrhythmic effect of three triterpenoid derivatives (ursolic and oleanolic acids and uvaol) isolated from the leaves of *Olea europaea* subsp. *africana*. The two acids displayed antidysrhythmic effects on adrenaline-induced chemical arrhythmias, probably due to β- adrenergic antagonistic effect, and on ischemia-reperfusion arrhythmia, which can be can be attributed to β-blocking activity and antioxidant activity.

Ursolic acid fed to rabbits and rats prevented the experimental atherosclerosis and lowered blood cholesterol (Liu, 1995). A strong synergistic effect derived from the combination of ursolic acid and artesunate can reduce both triglyceride and cholesterol, showing more potent effects than either agent alone (Wang, Wang, Shen, Yin, & Tang, 2015). Ethanolic extract from the stems and roots of *Celastrus orbiculatus* Thunb. decreases athero-susceptibility in lipoproteins and the aorta of guinea pigs fed a high-fat diet, and increases high-density lipoprotein; likewise, it reduce lipid accumulation and promote reverse cholesterol transport *in vivo* and *in vitro* (Zhang, Si, et al., 2016).

Antitumor and Chemopreventive Activities

Beneficial action of ursolic acid and its derivatives was reported based on their anti-tumor, including inhibition of angiogenesis, invasion of tumor cells and metastasis, induction of apoptosis in tumor cells and prevention of malignant transformation of normal cells, and it also interferes with numerous enzymes (Dong et al., 2015; Kashyap et al., 2016; Liu, 1995; Novotny et al., 2001; Shanmugam et al., 2013). Clinical tests suggesting the possibility of practical use of UA have already been conducted (Woźniak et al., 2015). Ursolic acid was identified as active components of different plants for inhibiting mutagenicity and tumor-promotion (He & Liu, 2007; Kadioglu & Efferth, 2015; Kondo et al., 2011). Ursolic acid exert anticancer effects in various cancer cell systems (Woźniak et al., 2015), it may have a potential application as a chemopreventive agent in gastric cancer (Kim & Moon, 2015), colorectal carcinogenesis and tumors of the colon (Andersson, Liu, Nilsson, & Duan, 2003; Furtado et al., 2008), lymphoma (Lauthier, Taillet, Trouillas, Delage, & Simon, 2000), lung cancer (Li, Xing, Chen, & Chen, 2010), prostate cancer (Shanmugam et al., 2012), UA pretreatment potentiated cell cycle arrest and UV radiation-induced apoptosis selectively in skin melanoma cells (Lee, Wang, Kumar, & Glickman, 2014). UA was a more potent tumorigenic inhibitor than OA (Hsu, Yang, & Lin, 1997) and both compounds are relatively non-toxic (Ovesna et al., 2004; Yamaguchi et al., 2008).

Antimicrobial

Ursolic acid and its derivatives have shown growth inhibition of gram-positive and gram-negative bacteria and fungi (Zaletova et al., 1986), and UA showed ability to control bacterial growth, biofilm formation, and elastase activity (Gilabert et al., 2015). Synergistic effect of UA and two semi-synthetic derivatives and the aminoglycosides antibiotics neomycin, amikacin, kanamycin and gentamicin towards twelve bacterial pathogens strains was observed

(Do Nascimento et al., 2014), with the minimal inhibitory concentration (MIC) from 32 to 526 µg/mL. Ursolic acid is the active components in natural extracts to inhibit the growth of some food-associated bacteria and yeast (Collins & Charles, 1987), protozoa (*Trypanosoma cruzi*) (Abe et al., 2002; da Silva Ferreira et al., 2013), promoting an anti-inflammatory response during *Leishmania* infection (Rodrigues et al., 2015). Antibacterial, antifungal, antiparasitic and antiviral activity of UA was recently reviewed (Kashyap et al., 2016; Woźniak et al., 2015).

Immunomodulatory Activity

Intraperitoneal administration of UA in Balb/c mice enhanced the total white blood cells count, bone marrow cellularity and alpha-esterase positive cells, delayed hypersensitivity reactions, and the treatment with various triterpenoids in combination with antigen also enhanced the specific antibody titre and the number of plaque forming cells in the spleen (Raphael & Kuttan, 2003). Intraperitoneal administration of UA to metastatic tumor-bearing mice increased natural killer cell activity and antibody-dependent complement-mediated cytotoxicity (Raphael & Kuttan, 2008). UA exhibited immunomodulatory action in type 1 diabetic mice fed a high-fat diet (Jang et al., 2009).

Table 1: Biological activities of UA and its derivatives and some representative references.

Activity	Observed effects	Reference
Antiaging, photodamage, skin wrinkling and xerosis	Improved epidermal barrier function; induced collagen and ceramides production; decreased transepidermal water loss, improved skin moisturization, reduced scaliness, improved skin elasticity, improved blood microflow, skin sebum content and skin thickness; induced epidermal keratinocyte differentiation	Yarosh et al. (2000), Both et al. (2002), Lee et al. (2006), Lim et al. (2007), Farwick et al.(2014)
Antidiabetic	Increase of insulin levels with preservation of pancreatic β-cells and modulation of blood glucose levels; improved blood glucose levels, glucose intolerance, and insulin sensitivity	Jang et al. (2009), Zhu et al. (2014)
Anti-inflammatory	Suppression of the formation of inducible nitric oxide synthase and inducible cyclooxygenase in macrophages; inhibition of histamine release from mast cells, prostaglandin E2, lipoxygenases, cyclooxygenases activity and elastase; suppression of the production of intracellular reactive oxygen species; suppress the inflammatory cytokine-induced expression of E-selectin in endothelial cells; antiinflammatory activity in carrageenan ear and paw oedema model; treatment of rheumatism, fever and arthritis	Liu (1995), Recio, Giner, Manez, and Ríos (1995), Suh et al. (1998), Deepak and Handa (2000), Baricevic et al. (2001), Banno et al. (2004), Takada et al. (2010), Kim et al. (2015)
Antimicrobial and antiviral	Growth inhibition of gram-negative organisms, food-associated bacteria and yeast; control of bacterial growth, biofilm formation; antiviral effects; synergistic action with some antibiotics; antileishmanial; antitrypanosomal	Collins and Charles (1987), Abe et al. (2002), da Silva Ferreira et al. (2013), Do Nascimento et al. (2014), Gilabert et al. (2015), Rodrigues et al. (2015)
Antioxidant	Antiradical activity; protection from lipid oxidation; DNA protection against oxidation; increase of antioxidant enzymes activity (catalase, superoxide dismutases, glutathione peroxidase and glutathione reductase)	Balanehru and Nagarajan (1991), Lu et al. (2007), Ramos, Pereira-Wilson, and Collins (2010), Wójciak-Kosior et al. (2011), Xiaosi (2012)
Antitumoral	Induction of apoptosis, inhibition of growth; antiproliferative action; cytotoxicity; Inhibition of glucose metabolism of cancer cells; enhancement of chemotherapeutic effect; suppression of metastasis; antiangiogenesis	Farina et al. (1999), Lauthier et al. (2000), Ma et al. (2005), Li et al. (2010), Shanmugam et al. (2012), Mallavadhani et al. (2013), Dong et al. (2015), Jin et al. (2016)
Cardiovascular	Antihyperlipidemic, antioxidant, vasorelaxant, diuretic/saluretic and hypoglycemic activity; prevention of severe hypertension in rats; prevention of injuries to blood vessels	Somova et al. (2003), Aguirre-Crespo et al. (2006), Pozo et al. (2006), Woźniak et al. (2015)
Hepatoprotection	Active against acute chemically induced liver injury; protection against chronic liver fibrosis and cirrhosis and against a wide range of liver threatening compounds; ameliorated high fat diet-induced hepatic steatosis improving key enzymes controlling lipid metabolism; enhanced liver regeneration after partial hepatectomy in mice.	Jin, Jin, Li, Piao, and Jin (2012), Li et al. (2014), Woźniak et al. (2015)
Hypolipidemic	Prevention of atherosclerosis, lowered blood cholesterol. In hyperlipidemic rats decreased the plasma triglycerides; synergistic effect with artesunate	Kazmi et al. (2013), Wang, Wang, Shen, Yin, and Tang (2013), Wu, He, Huang, Lu, and Zhang (2014), Wang et al. (2015)
Immunomodulatory	Enhancement of the total white blood cells count, of bone marrow cellularity and alpha-esterase positive cells; enhancement in the specific antibody titre and the number of plaque forming cells in the spleen; inhibition hypersensitivity reaction; modulation of T-cell proliferation and cytokines production by lymphocytes	Raphael and Kuttan (2003), Jang et al. (2009)
Others	Treatment of muscle atrophy; reduction of white fat and increase in brown fat; antiulcer activity; neuroprotection against β-amyloid peptide; anti-acetylcholinesterase effects; anxiolytic-like action	Kunkel et al. (2011), Colla, Rosa, Cunha, an Rodrigues (2015), García-Morales et al. (2015)

Anti-diabetic

Ursolic acid exhibits potential anti-diabetic (Jayaprakasam, Olson, Schutzki, Tai, & Nair, 2006), and immunomodulatory properties by increasing insulin levels with preservation of pancreatic beta-cells and modulating blood glucose levels, T-cell proliferation and cytokines production by lymphocytes in type 1 diabetic mice fed a high-fat diet, compared to the diabetic group (Jang et al., 2009). Type 2 diabetes is associated with obesity and ursolic acid may prevent or treat this disorder and its related comorbidities by acting as hypoglycemic and antiobesity agent with five effects: reduction of the absorption of glucose, decrease the endogenous glucose production and increase the glycogen synthesis, increase the insulin sensitivity, improvement of lipid homeostasis, and promotion of the body weight regulation (Silva, Oliveira, & Duarte, 2016).

Antioxidant and Anti-inflammatory

Ursolic acid could be the active component of some medicinal plants with anti-inflammatory action, such as *Pyrola rotundifolia* L. (Kosuge, Yokota, Sugiyama, Yamazawa, & Yamamoto, 1985), *Rosmarinus officinalis* L. (Huang et al., 1994), *Verbena officinalis* L. (Deepak & Handa, 2000), *Salvia officinalis* L. leaves (Baricevic et al., 2001), *Perilla frutescens* L., *Psidium guajava* (Kim, Kim, Han, & Kim, 2015). UA was twice as potent as indomethacin, and has been proposed for the treatment of rheumatism, fever and arthritis. The mechanisms of the anti-inflammatory action of ursolic acid and novel derivatives may be ascribed to inhibition of histamine release from mast cells, lipoxygenases, cyclooxygenases activity, inducible nitric oxide synthase and elastase (Liu, 1995; Suh et al., 1998), suppress the inflammatory cytokine-induced expression of E-selectin (an early response adhesion molecule expressed on the surface of endothelial cells during inflammation) in endothelial cells via inhibition of NF-kappa B activation (Takada et al., 2010) and suppressed the production of intracellular reactive oxygen species (Kim et al., 2015).

Direct ROS scavenging or their formation through metal chelation is a structural attribute endowed by phenolic compounds.\ Accordingly, compounds that possess the catechol functional group such as caffeic acids (Habtemariam, 2017) and their derivatives including rosmarinic and salvianolic acids (Habtemariam, 2018) or flavonoids such as rutin (Habtemariam, 2016) and others (Elufioye et al., 2017) have been reported for their therapeutic potential in AD. Terpenoids could also share this function if they are to become aromatized and carry the phenolic structural moieties as shown for rosemary diterpenoids (Habtemariam, 2016). On the other hand, terpenoids even as small molecular size as monoterpenes could have antioxidant effects in vivo by inducing antioxidant defenses such as SOD, CAT, GPx, and GR as demonstrated for their therapeutic potential in AD through a variety of assay systems (Habtemariam, 2018). These terpenoids and even the polyphenolic compounds that display antioxidant effects do also possess anti-inflammatory properties. Hence, they are working to tackle complex diseases through what has been described as one drug→ multitargets→ one/many disease(s) therapeutic principle (Habtemariam, 2017). In this context, the therapeutic potential of UA as a prototype lead is shown in various CNS diseases primarily through antioxidant and anti-inflammatory mechanisms and also specific actions in various receptor/enzyme systems outlined in the preceding sections. Similarly, the antioxidant-anti-inflammatory axis has been shown to play a role in the antidiabetic effect of UA as demonstrated in the streptozotocin-induced rats (Xu et al., 2018; Wang et al., 2018) in the db/db diabetic mouse model (Li et al., 2015), other models of diabetes nephropathies (Li et al., 2018; Wang et al., 2018), diabeticinduced monocyte dysfunction and atherosclerosis in mice (Ullevig et al., 2011), aortic injury in STZ-induced diabetic rats (Xiang et al., 2011), or clinical trial in human (Ramírez-Rodríguez et al., 2011). The anti-inflammatory effect of UA in HFD-induced obese rats (Zhang et al., 2016; Li et al., 2014), inhibition of lipoxygenase-1- (LOX-1-) mediated ROS generation and NF-κB activation as well as atherosclerosis development in mice (Li et al., 2018), inhibition of matric metalloproteases in the aortic smooth muscle cells (Zhai et al., 2018), cytokine-induced glioma cell invasion in the transwell cell migration assay (Huang et al., 2009), or cytokine expression in a macrophage and inhibition of atherosclerosis in mice (Leng et al., 2016) have also been shown.

The antioxidant and anti-inflammatory effects of UA were demonstrated in hepatoprotection through multiple pathways including antihyperlipidemic effect (Wang et al., 2013), the carbon tetrachloride- (CCl4-) induced liver damage in mice (Ma et al., 2015; Ma et al., 2014; Ma et al., 2014), high choline diet-induced liver toxicity and endothelial dysfunction (Li et al., 2016), ethanol-mediated experimental liver damage in rats (Saravanan and Pugalendi, 2006), liver transplantation model in pigs (Zhou et al., 2017), and LPS-induced hepatocyte damage (Yang et al., 2015). The renoand cardioprotection of UA were similarly evident as demonstrated in the hypoxia-reoxygenation-induced

myocardial injury cellular model in H9c2 cells (Chen et al., 2018), ischemia/reperfusion- induced acute kidney injury in rats (Peng et al., 2016), and chronic ethanol-induced oxidative stress in the rat heart (Saravanan et al., 2006). UA ameliorates autoimmune arthritis (Baek et al., 2014), acute inflammation and adjuvant-induced chronic arthritis induced by zymosan in mice (Kang et al., 2008), or chronic constriction injury-induced neuropathic pain in rats (Bhat et al., 2016). Other antiinflammatory and antioxidant actions of UA were in the mouse model of allergic asthma (Kim et al., 2013), cigarette smoke induced emphysema in rats as chronic obstructive pulmonary disease (COPD) (Lin et al., 2017), and the LPS-induced lung injury in mice (Chen et al., 2013). The 2,4,6-trinitrobenzenesulfonic acid- (TNBS-) induced colitis (colon shortening and myeloperoxidase (MPO) activity) model in the mouse model (Jang et al., 2014); sepsis-induced acute kidney injury via inhibition of ROS and inflammatory cytokines, including TNF-α, IL-1β, and IL-6 in the kidney from septic mice (Zhang et al., 2018); sepsis induced in rats by cecal ligation and puncture (Hu et al., 2015); LPS-induced acute inflammation model (Zhang et al., 2017); and various other multiple mechanisms including NF-κB and STAT3 inhibition (Ma et al., 2017) have been demonstrated. All these data support the antiinflammatory mechanisms through inhibition of key inflammatory cytokines, COX and iNOS expressions, and antioxidant mechanisms including the activation of the Nrf2 pathway. Hence, the argument for the inflammatory and antioxidant mechanisms of neuroprotection by UA is also supported through the plethora of other systemic effects of UA in various experimental models. An overview of UA's action in CNS disorders is depicted in Figure 2.

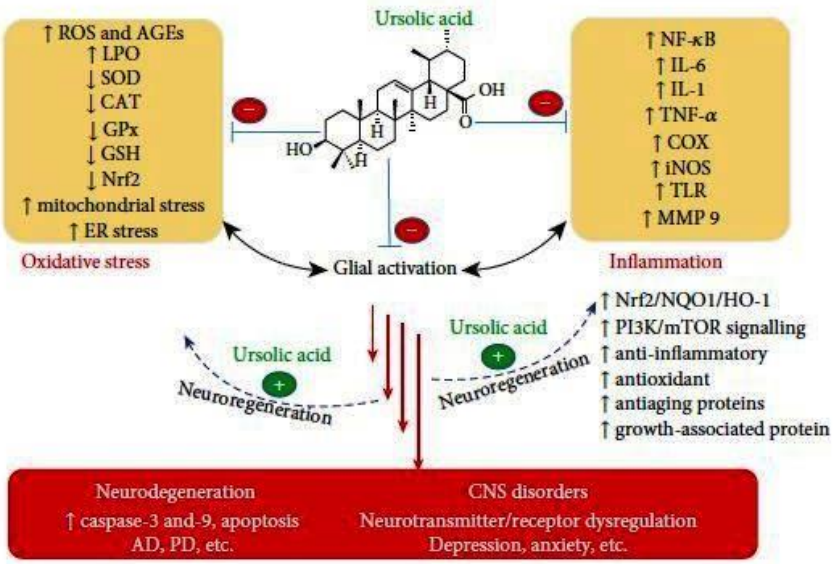


Figure 2: Anti-inflammatory and antioxidant mechanisms of neuroprotection and neuronal function by ursolic acid. Glial cells play a pivotal role in oxidative stress and neuroinflammation that are prevalent in various neurodegenerative disease, traumatic brain/spinal cord injuries, and psychological disorders. By suppressing the generation of ROS, AGEs, and lipid peroxidation (LPO) products as well as increasing antioxidant defenses including through upregulation of the Nrf2 pathway, UA display neuroprotective effects in neuronal cells. The anti-inflammatory action of UA such inhibition of key inflammatory cytokines via the NF-*κ*B signalling pathways is also inhibited by UA. By acting on multiple targets and promotion of neuronal regenerations, UA has diverse function in the CNS. Symbols indicate the following: (-) inhibition and (+) promotion.

Antiaging effects

The epidermal permeability barrier plays a crucial role in human physical, chemical and biological cutaneous functions. Sensitive skin, associated with increased transepidermal water loss, penetrability and susceptibility to irritants, is related with impaired barrier function and reduction in ceramides. The atopic dermatitis displays impaired epidermal permeability barrier function, diminished water-holding properties and decreased ceramide levels. UA are great moisturizing candidates that do not create any cutaneous irritations (Both, Goodtzova, Yarosh, & Brown, 2002). Induction of ceramide synthesis is usually associated with keratinocyte differentiation. The ursolic acid increases the expression of genes required for terminal keratinocyte differentiation (involucrin, loricrin and filaggrin), improving the recovery of skin barrier function. UA exerts effects on human keratinocytes similar to those of retinoids, unlike retinoids, which decrease ceramide synthesis, UA stimulates ceramide synthesis. Skin wrinkling and xerosis associated with aging result from decreases of dermal collagen and stratum corneum ceramide content. UA increases both the ceramide content of cultured normal human epidermal keratinocytes and the collagen content of cultured normal human dermal fibroblasts (Both et al., 2002; Yarosh, Both, & Brown, 2000).

Intercellular lipids, especially ceramide, play a critical role in the water-holding properties of the stratum corneum. Topical application of UA enhanced the recovery of epidermal permeability barrier function as well as increased

ceramides in epidermis (Lim et al., 2007). UA could be the good candidates to develop antiaging reagents for skin (Lee, Nam, Kim, & Lee, 2006). Pentacyclic triterpenoids showed in vitro and in vivo antiaging properties, by improving epidermal barrier function and inducing collagen production. Clinical studies confirmed decreased transepidermal water loss, improved skin moisturization, reduced scaliness and improved skin elasticity, and in postmenopausal volunteers improved blood microflow, skin sebum content and skin thickness (Farwick et al., 2014).

Other Pharmacological Effects

Triterpenes, polyphenols and coumarins induced significant neuroprotection against β-amyloid peptide, anti-inflammatory, antioxidant and anti-acetylcholinesterase effects and could be proposed as therapeutic agent in treatment of Alzheimer's disease (García-Morales et al., 2015). Anti-ulcer effects of ursolic acid and its derivatives have been reported (Farina, Pinza, & Pifferi, 1999). Ursolic acid can be proposed for treating muscle atrophy, decreasing white fat and body fat percentage (Kunkel et al., 2012).

Ursolic Acid Side Effects

Despite UA shows important beneficial properties, the risk of some negative effects on human health have been warned (Kashyap et al., 2016; Woźniak et al., 2015), including pro-inflammatory effects in macrophages (You et al., 2001); disruption of spermatogenesis in animals (Akbarsha, Palanisamy, Murugaian, & Lakshmi Latha, 1998) and UA was toxic for normal human skin fibroblasts in concentrations exceeding 5 μM. This effect was not observed in the case of oleanolic acid (Wójciak-Kosior, Paduch, Matysik-Woźniak, Niedziela, & Donica, 2011).

The utilization of nanoparticle-based drugs could reduce the side effects of high doses of UA in organisms (Jin et al., 2016). The limited solubility, rapid metabolism and poor bioavailability of UA limit the potential of this bioactive and the further applications. Numerous UA derivatives were synthetized (Chen, Gao, et al., 2015), but the nanotechnology will play a decisive role in drug design and delivery, because the nano-sized drugs could selective enter or target to tumor cells. The negative characteristics and the toxicity of UA can be reduced by using novel drug systems, microsphere, nanocrystals or nanoparticlesbased drug delivery system (Song et al., 2014) which allow to increase the drug water solubility. Nanoparticles penetrate best in cancer cell membrane and increase the area and duration of contact between the drug and cells, increasing stability and specificity and enhancing the delivery efficiency (Zhang, Li, et al., 2013). Furthermore this prolonged half-life and passive accumulation in specific tissues allow to reduce the dose and administration frequency, decreasing the dose effect induced by high dose of UA in body.

Applications

Ursolic acid is relatively non-toxic and has been used in cosmetics and health products either as the active compound, in a mixture with other actives or as a natural scaffold for the synthesis of a wide range of novel and potent bioactive molecules (Gribble, Fu, Sporn, & Liby, 2015; Mallavadhani & Pattnaik, 2011; Xue et al., 2012). Ursolic acid is a pentacyclic structure with very low water solubility, a significant disadvantage in terms of bioavailability. Several strategies suitable for industrial mass production have been tried to increase solubility, biological potential and bioavailability, maintaining physical and chemical stability, reducing toxicity and representing an excellent prospect in clinical applications, including the design of inclusion complexes between these acids and cyclodextrins (Campbell, 2015; Soica et al., 2014), mixture of polyethylene or propylene glycol and poloxamer (Yang, Wei, & Huang, 2012), or microcrystalline cellulose, silica powder, sodium carboxymethyl starch (Yan et al., 2013) to prepare granules and capsules, or the use of nanoparticles and nanosuspensions (Chen, Liu, Yang, Zhao, & Xu, 2005; De Almeida et al., 2014), or incorporated into liposomes (Yarosh et al., 2000), salt formation (Bin & Zhiming, 2010; Liang et al., 2015; Olariu et al., 2012), preparation of modified products by reaction (Gao, Lu, & Wang, 2014), introduction of monosaccharyls or oligosaccharyls (Bing et al., 2010), granulation with dextrin and additives (Chenshi, Lan, Wenlu, & Chaofeng, 2013) or with granulesten and polyethylene ketopyrrolidine K30 (Tangyu & Yimu, 2010).

Cosmetics, Cosmeceuticals and Nutraceuticals

UA can confer antioxidant, antimicrobial, and anti-irritant functions to cosmetic formulations. Ursolic acid and/or its derivatives can be one of the active compounds in different cosmetic products, such as external creams or lip care cosmetics with wrinkles hiding and ameliorating effect (Asami & Lida, 2014; Kiyono, 2015). UA was used for protecting ultraviolet absorbers (Oikawa, 2014), to prevent pigmentation induced by UV irradiation (Fukuda, 2010a, 2010b), in skin care emulsions for wrinkle treatment (Sugiyama, Imamura, & Tada, 2006a, 2006b), in moisturization and antiaging hydrogels (Kim & Kim, 2000; Lee, Seo, Lee, & Kim, 2009), for lowering the transepidermal water loss

(Akamatsu, Suzuki, & Sakai, 2007a, 2007b), in formulation for skin hydration and sedation (Jung, Kim, & Lee, 2009), in skin care preparation exhibiting an excellent percutaneous absorption promoting action of an anti-inflammatory component (Kobayashi, Imamura, & Seto, 2008), It has also been incorporated in preparations for improving and preventing skin roughness (Suenobe & Hitani, 2007) or in formulations against acne (Kallimanis, Kallimanis, & Kallimanis, 2009), scar-removing hand cream (Chen & Wang, 2013c), bleaching agent for tyrosinase production inhibition (Kanjo & Okano, 2007), in personal care compositions to regulate hair growth and the condition of mammalian skin (Oblong, McPhail, Weitz, & Harris, 2005; Oblong, McPhail, Weitz, Harris, & McIver, 2005), into cleansing preparations (Tan & Kobayashi, 2009a, 2009b), toilet soap with skin care and disinfection functions (Chen & Wang, 2013a, 2013b), dentrifice compositions (Trivedi, Xu, Worrell, & Panaligan, 2013) or even preparations for the prevention of skin cancer for topical use (Ishida et al., 1990; Liu, 1995).

Different patents claimed the development of techniques to stabilize ursolic acid and other bioactives in external skin preparations, such as in a water-in-oil type emulsion using an organic-modified clay mineral (Akatsuka & Seto, 2007), ceramide and/or an acylated acidic amino acid diester (Sugiyama, Hatanao, Suenobe, & Fukuda, 2009), microspheres (Tan & Kobayashi, 2009a, 2009b), nanostructured forms incorporated into a cosmetic, which remained stable to a temperature of 250 °C (De Almeida et al., 2014), or polymer nanocapsules, which offered enhanced skin penetration properties (Ryu et al., 2007).

Other alternative is the incorporation of the natural extracts (Akamatsu et al., 2007b) or the essential oils providing both fragrance and potent inhibition of hyaluronidase (Kawada, 2006), and then UA can be incorporated into cosmeceutical anti-aging products, i.e. a tablet containing different natural extracts, vitamins, peptides, lycopene, sodium hyaluronate, ursolic acid and niacin (Li, 2013) and in nutraceuticals compositions with the extract of Cocos nucifera, Garcinia sp., seed coat of Tamarindus indicus, seed of Nelumbo sp., Murraya koenigii leafs, chlorogenic acid from Coffea arabica beans, and the triterpenes pentapeptides of oleanolic acid and ursolic acid, to ensure the maintenance of the viability and constant renewal of the cells of the skin, and to offer a solution to the pathological states associated with skin (Majeed, 2009). Extract from flowers of Prunella vulgaris L. containing ursolic acid, β-amyrin, quercetin, α-spinasterol, stigmasterol, β-sitosterol and daucosterol permet skin nourishing and block adipocyte differentiation (Dorni, Amalraj, Gopi, Varma, & Anjana, 2017). Deane et al. (2017) shown that nutraceuticals containing leucine, hydroxyl β- methylbutyrate, creatine, vitamin-D, ursolic acid or phosphatidic acid have effects in relation to muscle mass/protein metabolism.

Pharmaceutical

A number of compositions based on UA or its pharmaceutically acceptable derivatives have been prepared for preventing or treating diabetes or diabetes complications (Kun, Ling, & Yi, 2010; Ryu et al., 2013), for improving insulin resistance (Zhu et al., 2014), and for resisting diabetes and complications, reducing blood sugar and hyperglycemia (Jia, Liu, Hongbin, Luyong, & Pu, 2010). A hypoglycemic composition from sweet osmanthus, inhibiting alpha-glucosaccharase, was more efficient than the hypoglycemic medicine acarbose (Wenyi, Yanli, & Jinmei, 2009). Ursolic acid or a plant extract containing this compound can be used in the formulation of a digestive enzyme activity inhibitor to be incorporated in medicines, drinks, foods and health products for controlling or curing diabetes or adiposity (Colceru-Mihul et al., 2009; Guiyun & Bin, 2009a).

UA is one of the bioactives in fruit extracts for hypercholesterolemia treatment (In et al., 2011). A colorless or yellowish wine, sweet smell and stable quality containing Chinese medicine with puerarin and ursolic acid as active substances can play a role of inhibiting too high blood fat and to control atherosclerosis (Changqing et al., 2010). Pharmaceutical compositions with natural extracts containing UA as a predominant compound were claimed for treating anxiety disorders as well as high blood pressure and comorbidity in both (García, Ferrer, Ruiz, & Cortázar, 2012).

The UA from natural extracts showed low toxicity and has shown anti-tumor activity, such as those from Oldenlandia diffusa on human liver cancer multi-drug-resistance cells (Guopei et al., 2010), selfheal and/or garden orache extracts comprising phenolic acids and triterpenes components showed lung cancer preventing properties (Yan et al., 2012). UA can be proposed for the preparation of analgesic drugs for the process of tumor cure, reducing the side effects of the other drugs (Junming, Yan, & Yimu, 2012). Several patents claim the use of chemical modification of UA to obtain products with antitumor and anticancer properties (Hadzhieva & Chobanov, 2013; Huang & Wu, 2013; Kaikai, Fenling, Xianai, Chun, & Yanghao, 2010a, 2010b; Kaikai, Yanghao, Yunquan, & Xianai, 2012; Kondo et al.,

2011; Li et al., 2009; Lin et al., 2011; Meng et al., 2013; Shao, Li, & Wang, 2013; Shao, Xiang, Yang, & Jia, 2016; Yanqiu, Zhongwei, Yan, Jie, & Zhaokai, 2013; Zhang, Gao, et al., 2013). Different derivatives of ursolic acid, such as diethanol amine (Jingwei & Fengping, 2010a, 2010b), piperazine (Jingwei & Fengping, 2010a), or indole (Gu et al., 2014) derivatives, among others, have been proposed.

Ursolic acid derivatives showed anti-inflammatory properties (Caihu et al., 2013; Sorokina et al., 2010) and are useful in the preparation of medicines for treating rheumatoid arthritis (Anonymous, 2013). Ursolic acid is used also as an immunomodifier (Ping, Yong, & Chengbiao, 2011), is safe and non-toxic for the preparation of an immunologic adjuvant vaccine that inhibited tumor growth, and protected immune organs (Herrera, Pérez, López, & Sánchez, 2012; Li, Li, Lu, & Xiao, 2013; Li, Li, Xiao, & Lu, 2013). The use of UA saponins and oleanolic acid saponin in preparing medicaments for increasing leucocytes and/or platelets was also claimed (Bing et al., 2010). A new UA-based ointment was proposed for the treatment of wounds suppressing different symptoms, aiding in regeneration-recovering of the skin without side-effects (Kallimanis, 2009), and the inclusion of terpenoids and flavonoids of coniferous pine twigs in a suitable pharmaceutical carrier can be useful in the treatment of radiation changes of the mucous membranes, traumatic injuries after burns and secondary healing surgery wounds (Hadzhieva & Chobanov, 2013).

Other formulated products include a variety of beneficial effects, such as hepatoprotective function (Sorokina et al., 2010; Xiaosheng, Lin, Haiyan, Jingzhen, & Xiaojiang, 2013; Xiaosheng, Lin, Lei, Jingzhen, & Xiaojiang, 2014), resistance to tumors, reduction of blood lipid and regulation of immunity (Li & Liu, 2013). UA in natural extracts (Xiaosi, 2012) and in derivatives is an antioxidant (Sorokina et al., 2010). UA can be the active compound in a formulation of an inhibitor capable of increasing the bio-availability of a drug and clearance rate of morphine-like analgesic agents (Oliver, Hsiong, Wang, & Pao, 2009). A pharmaceutical composition was proposed to prevent and treat osteoporosis, fracture, periodontal diseases and bone growth disability (Min, Ryu, Kim, & Lee, 2009).

Ursolic acid is used in the formulation of different products, i.e. geriatric medicament of stomatologic use (Tamas, Manzatu, & Dobos, 2003), phytotherapeutic composition with sedative, myorelaxant, antispasmodic action (Colceru-Mihul et al., 2009), sugar-free compound fructus momordicae antitussive particles (Huang, Liang, & Wei, 2013). Ursolic acid can be included in compositions for delaying the onset of the symptoms of Alzheimer's disease in humans (Stephen, 2012), for inhibiting cytochrome P450 isozyme, CYP2C9 (Hu, Wang, Hsiong, & Bau, 2005), for inhibiting or preventing muscle atrophy or increasing muscle mass (Adams & Kunkel, 2013) and in formulations for the prevention or treatment of hypersensitivity and/or hyper-reactivity (Cain, Stam, Schmid, & Collins, 2011).

Antimicrobial and Antiviral Compositions

Antimicrobial and antiviral compositions formulated with natural extracts, pure UA or its derivatives, can be utilized as alternative antibiotics against Salmonella enterica (Zadeh & Leij, 2016), to disinfect swimming pools (Hadzhieva & Chobanov, 2013), in all stages of handling agricultural products, in hospitals, and in commercial and household applications (Lemmons, 2008); also in pharmaceutical compositions (Marinescu, 2009), with anti-HCV effect (Kong, Li, Zhang, Wu, & Wang, 2013), or against influenza virus (Qiaofeng et al., 2009). Combinations of terpenoids and antimicrobial agents can prevent and treat microbial infections (Chun et al., 2014). Application of ursolic acid combined with penicillin on resisting drug resistant Staphylococcus aureus confirmed in vitro synergic action and better antibacterial activity than the individual compound (Wenyi, Yanli, Zhiqiang, & Jinmei, 2010). A plant-virus-resisting agent composition containing glycyrrhizin and ursolic acid can be used for controlling tobacco mosaic virus safe to the environment and humans (Ma, Feng, Han, Wang, & Zhang, 2013). Extracts with > 90% ursolic acid from rosemary showed bacteriostatic action, tumor resistance and anti-inflammatory action (Yao, 2015).

Conclusions and Future Perspectives

Ursolic acid is a ubiquitous pentacyclic triterpene, widely found in food, medicinal herbs and other plants. This class of natural isoprenoid exhibits a wide range of biological activities, including antioxidant, antifungal, insecticidal, liver protective, anti-inflammatory, antitumor, antiangiogenic, and proapoptotic effects, and hence is of growing research interest. Future researches should be targeted to improve the efficiency of extraction of UA from new raw material or wastes by employing faster and green methodology, although the synthesis of UA derivatives could be used as a promising technology. Besides an extensive research to elucidate the total knowledge of the action mechanisms of UA and/or their natural or synthetic derivatives as cosmetic, nutraceutic and therapeutic agents is required. This compound has low cytotoxicity, but several strategies, as the nanobiotechnology, can improve its biological potential and minimize the required active dose. Moreover, more research is needed to develop a therapy for patients and assay

the combination with other therapeutic molecules. The development of novel products useful in the cosmetic, food or sport industry and/or clinical practice is growing.

Both as a component of common fruits, herbs, and medicinal plants as well as dietary supplements, UA is a natural product that has been safely used by humans in various forms. Among the plethora of pharmacological effects shown for UA is an anti-inflammatory and antioxidant mechanism in cellular and animal models. In parallel with its effects as antidiabetic, antiobesity, antihyperlipidemic, and hepato-, cardio-, and renoprotective agent and in chronic inflammation (arthritis, long injury, sepsis, and colitis) models, the CNS effect of UA has also been demonstrated. The brain injury, cerebral ischemia, cognition deficit, anxiety, and depression are used in this communication to appraise the therapeutic potential of UA. The antioxidant and anti-inflammatory mechanisms play a pivotal role for UA's effect while other mechanisms include specific effect on neurotransmitter uptake, receptor modulation, and enzyme inhibition, primarily MAO and AChE. In view of such a diverse pharmacological effect/efficacy, a further lead optimization study by using UA as a prototype drug candidate is well merited.

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