EXCLI Journal 2016;15:221-228 – ISSN 1611-2156
Received: January 21, 2016, accepted: February 17, 2016, published: March 14, 2016

Letter to the editor:

RECENT STUDIES ON URSOLIC ACID AND ITS BIOLOGICAL AND PHARMACOLOGICAL ACTIVITY

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http://dx.doi.org/10.17179/excli2016-159

Dear Editor,

Ursolic acid (3-beta-3-hydroxy-urs-12-ene-28-oic-acid; UA) is a lipophilic pentacyclic triterpenoid; it was found to be present in the epicuticular waxes of apples in 1920. It is widely found naturally in the peels of fruits, as well as in many herbs and spices such as lavender, oregano, thyme, rosemary, and thyme (Woźniak et al., 2015). UA has been confirmed to have several biological and pharmacological effects, such as anti-inflammatory (Baricevic et al., 2001), antitumor (Baglin et al., 2003), antiplatelet aggregation (Babalola et al., 2013), anti-HIV (Kashiwada et al., 2000), and anti-*Mycobacterium tuberculosis* effects (Cantrell et al., 2001).

Its many pharmaceutical and biological properties make it an interesting material for application in the pharmaceutical, food, and cosmetics industries. Herein, we review the most recent studies on UA and its biological and pharmacological activities (Table 1).

Table 1: Recent studies on ursolic acid and its biological and pharmacological activities

Key message	Reference
Ursolic acid (UA) not only inhibits cell growth but also induces apoptosis through modulation of the phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR pathway in human prostate cancer cells. This finding suggests that UA may be a new chemotherapeutic candidate against prostate cancer.	Meng et al., 2015
The antifibrotic effect of UA is partially due to its oxidative stress attenuating effect through manipulation of NADPH oxidase 4 activity and expression. This result suggests that UA may be a promising antifibrotic agent.	He et al., 2015

Table 1 (cont.): Recent studies on ursolic acid and its biological and pharmacological activities

Key message	Reference
A multi-inlet vortex mixer is a robust and pragmatic tool for tailoring the particle size of a UA nanosuspension. Particle size appears to be a critical determinant of the anticancer activity of the UA nanoparticles.	Wang et al., 2015
UA, which is reported to have antitumor activity, might be useful in sensitizing tumor cells to radiation therapy by inhibiting pathways leading to radiation therapy resistance.	Yang et al., 2015
UA increases free fatty acid (FFA) burning by enhancing skeletal muscle FFA uptake and ncing skele via uncoupling protein 3/AMP-activated protein kinase-dependent pathway, which provides a novel perspective on the biological function of UA against obesity and IR.	Chu et al., 2015
UA from *Prunella vulgaris* enhances sleep duration through GABAA receptor activation and could be a therapeutic candidate for insomnia treatment.	Jeon et al., 2015
The greater ability of the combination of UA and resveratrol to inhibit skin tumor progression was attributable to the greater inhibitory effects on growth factor and inflammatory signaling, skin inflammation, and epidermal hyperproliferation induced by 12-O-tetracanoylphorbol-13-acetate (TPA) treatment.	Cho et al., 2015
The combination of UA and artesunate can reduce both triglyceride and cholesterol, and the effects were more potent than of either agent alone, which indicates a strong synergistic effect.	Yuliang et al., 2015
UA might be considered as a potential candidate for treatment of pathological conditions associated with muscular atrophy and dysfunction, including skeletal muscle atrophy, amyotrophic lateral sclerosis, sarcopenia, and metabolic diseases of the muscles.	Bakhtiari et al., 2015
UA in concentrations of l x 10^{7} mol/L to 5 x 10^{5} mol/L induced relaxation of gastric smooth muscle (SM) tissues in a concentration-dependent manner.	Prissadova et al., 2015
UA and oleanolic acid extracted from wild loquat leaves can significantly inhibit the viability of A549 cells (human lung adenocarcinoma epithelial cell line).	Yuan et al., 2015
The beneficial effects of UA on nonalcoholic fatty liver disease (NAFLD) may be due to its ability to increase lipid heoxidation and to inhibit hepatic endoplasmic reticulum stress. Together, UA may be further considered as a natural compound for NAFLD treatment.	Li et al., 2015
UA ameliorated the symptoms of experimental autoimmune myasthenia gravis (EAMG), a rat model of MG. These findings suggest a new strategy to treat EAMG and even human MG.	Xu et al., 2015
UA and its novel prodrug derivative US597 modulate expression of cell adhesion molecules within the focal adhesion signaling pathway, leading to cancer cell motility.	Xiang et al., 2015
UA protects against wear particle-induced osteolysis by suppressing osteoclast formation and function.	Jiang et al., 2015
Folic acid-modified dendrimeric UA prodrugs have the potential for targeted delivery of UA into cancer cells to improve its anti-tumor efficacy.	Gao et al., 2015
UA induces apoptosis and inhibits the invasive phenotype of gastric cancer cells; therefore, it may have potential application as a chemopreventive agent to prevent the metastasis of gastric cancer or to alleviate metastasis.	Kim and Moon, 2015
A potential novel mechanism by which UA controls the growth of hepatocellular carcinoma (HCC) cells and suggests that DNA methyltransferase 1 could be a novel target for HCC chemoprevention and treatment.	Yie et al., 2015

Table 1 (cont.): Recent studies on ursolic acid and its biological and pharmacological activities

Key message	Reference
The combination of UA and leucine promotes muscle cell differentiation, thus suggesting that this combination of agents may prove to be beneficial in increasing muscle mass.	Kim et al., 2015
UA-induced mitochondrial reactive oxygen species (ROS) production can elicit mitochondrial uncoupling and glutathione-dependent antioxidant responses, which offer cytoprotection against oxidant injury in H9c2 cells.	Chen et al., 2015
UA significantly prevented carbon tetrachloride-induced hepatotoxicity and fibrosis, indicated by both diagnostic indicators and histopathological analysis.	Ma et al., 2015
UA exerts protective effects in cecal ligation and puncture-induced septic rats, and may be a potential therapeutic agent against sepsis.	Hu et al., 2015
UA ameliorates lipid and glucose metabolism in high-fat diet-fed mice, primarily by the activation of peroxisome proliferation-activated receptor-α and induction of the hepatic autophagy pathway. Thus, intake of UA in the diet or in an isolated form may ameliorate lipid and glucose metabolism.	Jia et al., 2015
UA activated the phagocytosis of human monocytes through MRP8 induction. These data suggest that UA firmly contributes to the intracellular killing effect of macrophages during mycobacterial infection.	Podder et al., 2015
UA may attenuate early brain injury after subarachnoid hemorrhage in rats by suppressing the toll-like receptor 4-mediated inflammatory pathway.	Zhang et al., 2014
UA and xylitol, synergistic inhibitors, could be potential agents for enhancing the antimicrobial and anti-biofilm efficacy against *S. mutans* and *S. sobrinus* in the oral environment.	Zou et al., 2014
UA exhibits significant anti-tumor effects by suppressing cell proliferation, promoting apoptosis, and inducing cell cycle arrest both in vitro and in vivo. It may be a potential agent for treating gallbladder cancer.	Weng et al., 2014
In vitro, in silico, and in vivo results indicate that UA is a promising, inexpensive, widely available natural lead, which can be designed and developed into a macrofilaricidal drug. This is the first ever report on the anti-filarial potential of UA from *E. tereticornis.*	Kalani et al., 2014
UA, a bioactive natural compound, inhibits superoxide anion generation and elastase release in human neutrophils and ameliorates trauma- and hemorrhagic shock-induced organ injury in rats.	Hwang et al., 2014
UA-induced elevation of serum irisin may be useful as a strategy for the enhancement of skeletal muscle strength during resistance training in men.	Bang et al., 2014
UA stimulates glucose uptake in 3T3-L1 adipocytes through the PI3K pathway, providing important information regarding the anti-diabetic mechanism of action of UA.	He et al., 2014
The antihyperglycemic role of UA is mediated through insulin secretion and insulinomimetic effect on glucose uptake, synthesis, and translocation of GLUT4 by a mechanism of cross-talk between calcium and protein kinases. UA is a potential anti-diabetic agent with pharmacological properties for insulin resistance and diabetes therapy.	Castro et al., 2015
UA can increase serum S100 protein expression and promote neural regeneration in BALB/c mice following sciatic nerve injury, in a dose-dependent manner.	Liu et al., 2013

Table 1 (cont.): Recent studies on ursolic acid and its biological and pharmacological activities

Key message	Reference
Combination treatment with UA and rosiglitazone down-regulated lipogenic genes and upregulated fatty acid oxidative genes in high-fat diet-fed mice. This study suggests that UA in combination with rosiglitazone reduced lipid accumulation in liver.	Sundaresan et al., 2014
UA treatment significantly ameliorates collagen-induced arthritis in mice via suppression of Th17 and differentiation. By targeting pathogenic Th17 cells and autoantibody production, UA may be useful for the treatment of autoimmune arthritis and other Th17-related diseases.	Baek et al., 2014
Low-dose UA had preventive potency for diabetic renal complications, which could be mediated by changes in hepatic glucose metabolism and the renal polyol pathway. High-dose UA was more effective anti-dyslipidemia therapy in non-obese type 2 diabetic mice.	Lee et al., 2014
UA exerts its antifilarial effect through induction of apoptosis and by downregulating and altering the level of some key antioxidants such as GSH, GST, and SOD of *Setaria cervi.*	Saini et al., 2014
UA inhibits nuclear factor-kappa B activation in both intestinal epithelial cells and macrophages, and attenuates experimental murine colitis. These results suggest that UA is a potential therapeutic agent for inflammatory bowel disease.	Chun et al., 2014
UA could be useful as an adjunct therapy for the treatment of infections involving methicillin-resistant *Staphylococcus aureus* biofilms.	Ou et al., 2014
The apoptotic mechanism of UA treatment in HeLa cells involved the mitochondrial intrinsic pathway and was closely associated with the suppression of the ERK1/2 signaling pathway.	Li et al., 2014
The inhibition of carbon tetrachloride-induced inflammation by UA is due at least in part to its antioxidant activity and its ability to modulate the S phosphorylation of transcription 3 (TAT3) and nuclear factor-kappa B signaling pathways.	Ma et al., 2014
UA as a direct negative regulator of the mechanistic target of rapamycin complex 1 signaling pathway and this suggests a novel mechanism by which UA exerts its beneficial function.	Qu et al., 2013
H_2O_2 causes the malignant transformation of WB-F344 cells. UA exerts antitumor effects by inhibiting the proliferation in malignantly transformed WB-F344 cells.	Han et al., 2014
UA exerts anticancer activity against colon cancer cells by promoting the N-terminal phosphorylation and subsequent proteasomal degradation of ainst colo.	Kim et al., 2014
UA could induce the differentiation of the human leukemia cell line U937 by activating the PI3K/Akt pathway, and it could be a potential candidate as a differentiation-inducing agent for leukemia therapy.	Deng et al., 2014
UA treatment exhibited a protective effect on kidneys in diabetic rats, implying that it could be a potential treatment for diabetic nephropathy.	Ling et al., 2013
UA and its derivatives were examined for their radical scavenging activity by using the DPPH assay, and showed significant antioxidant activity.	do Nascimento et al., 2014

Table 1 (cont.): Recent studies on ursolic acid and its biological and pharmacological activities

Key message	Reference
Signal transducer and activator of transcription 3 (STAT3) is a target for colon cancer prevention. UA, a dietary agent, might offer an effective approach for colorectal carcinoma prevention by inhibiting the persistently activated STAT3 in cancer stem cells.	Wang et al., 2013
UA induces the activation of p53, NF-e , and Bax, leading to the enhancement of p21 transcriptional activity and activation of caspase-9 and -3, thus finally inducing apoptosis of human colon adenocarcinoma cells, SW480 cells.	Nam and Kim et al., 2013
The inhibition of tumor angiogenesis via suppression of multiple signaling pathways might be one of the mechanisms whereby UA can be effective in cancer treatment.	Lin et al., 2013
UA nanocrystals may be used as a potential delivery formulation for intravenous injection with enhanced dissolution velocity and anticancer activity.	Song et al., 2014
UA inhibits the growth of cariogenic microorganisms, which suggests that it has considerable potential as an antibacterial agent for dental caries prevention.	Zhou et al., 2013

Acknowledgements

This research was supported by Agriculture, Food and Rural Affairs Research Center Support Program, Ministry of Agriculture, Food and Rural Affairs.

Conflict of interest

The authors declare no conflict of interest.

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