Korean J Physiol Pharmacol 2018;22(3):235-248
https://doi.org/10.4196/kjpp.2018.22.3.235

KJPP

Review Article

Ursolic acid in health and disease

Dae Yun Seo[1], Sung Ryul Lee[1,2], Jun-Won Heo[3], Mi-Hyun No[3], Byoung Doo Rhee[1], Kyung Soo Ko[1], Hyo-Bum Kwak[3,*], and Jin Han[1,4,*]

[1]National Research Laboratory for Mitochondrial Signaling, Department of Physiology, BK21 Plus Team, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University, Busan 47392, [2]Department of Convergence Biomedical Science, Inje University, Busan 47392, [3]Department of Kinesiology, Inha University, Incheon 22212, [4]Department of Health Science and Technology, Graduate School, Inje University, Busan 47392, Korea

ARTICLE INFO

Received February 6, 2018
Revised March 16, 2018
Accepted March 19, 2018

***Correspondence**
Jin Han
E-mail: phyhanj@inje.ac.kr
Hyo-Bum Kwak
E-mail: kwakhb@inha.ac.kr

Key Words
Disease
Exercise
Health
Irisin
Ursolic acid

ABSTRACT Ursolic acid (UA) is a natural triterpene compound found in various fruits and vegetables. There is a growing interest in UA because of its beneficial effects, which include anti-inflammatory, anti-oxidant, anti-apoptotic, and anti-carcinogenic effects. It exerts these effects in various tissues and organs: by suppressing nuclear factor-kappa B signaling in cancer cells, improving insulin signaling in adipose tissues, reducing the expression of markers of cardiac damage in the heart, decreasing inflammation and increasing the level of anti-oxidants in the brain, reducing apoptotic signaling and the level of oxidants in the liver, and reducing atrophy and increasing the expression levels of adenosine monophosphate-activated protein kinase and irisin in skeletal muscles. Moreover, UA can be used as an alternative medicine for the treatment and prevention of cancer, obesity/diabetes, cardiovascular disease, brain disease, liver disease, and muscle wasting (sarcopenia). In this review, we have summarized recent data on the beneficial effects and possible uses of UA in health and disease managements.

INTRODUCTION

Plants are important regulators of ecosystems and can affect various biological functions [1]. Various plant-derived biologically active products are effective for the treatment of a wide spectrum of diseases, including cancer [2], diabetes [3], obesity [4], cardiovascular diseases (CVDs) [5], brain disease [6], liver disease [7], and sarcopenia [8,9]. Ursolic acid (UA) is a compound that has such therapeutic effects [10]. However, the precise mechanisms of its beneficial effects are not completely known.

UA is isolated from the leaves of various plants (rosemary, marjoram, lavender, thyme, and organum), fruits (apple fruit peel), flowers, and berries [11]. UA mediates some pharmacological processes and modulates several signaling pathways to prevent the development of chronic diseases [12,13]; it exhibits 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 mechanisms by which UA exerts these beneficial effects may involve regulation of the following: nuclear factor-kappa B (NF-kB) and apoptotic signaling in cancer cells, insulin signaling in adipose tissue, the expression of markers of cardiac damage in the heart, inflammation and the level of anti-oxidants in the brain, metabolic signaling and the level of oxidants in the liver, and atrophy signaling and metabolic signaling in skeletal muscles.

With this review, we attempt to outline the effect of therapeutic potential of UA, which includes its effects on cancer, obesity/diabetes, CVDs, brain diseases, and liver diseases. In addition, its beneficial effects in the prevention of sarcopenia and the improvement of exercise capacity are described to elaborate its possible role as an exercise mimetic.

Author contributions: D.Y.S., H.B.K., and J.H. contributed for conception and design of study. S.R.L., J.W.H., and M.H.N. collected the data. B.D.R. and K.S.K. contributed for critical discussion. D.Y.S., H.B.K., and J.H. wrote the manuscript.

STRUCTURE OF UA

UA (3β-3-hydroxy-urs-12-ene-28-oic-acid) is a pentacyclic triterpenoid (Fig. 1), which has the chemical formula of $C_{30}H_{48}O_3$ and a molecular mass of 456.71 g/mol [23]. UA is soluble in hot glacial acetic acid and alcoholic sodium hydroxide [23]. It is biosynthesized mainly from the dammarenyl cation through the folding and cyclization of squalene, which forms the fifth ring of UA through ring extension and the formation of an extra ring. There are three oxygen atoms in the compound, which activate double or triple neutral ligands and the donation of electron pairs to the transition metal atom [23].

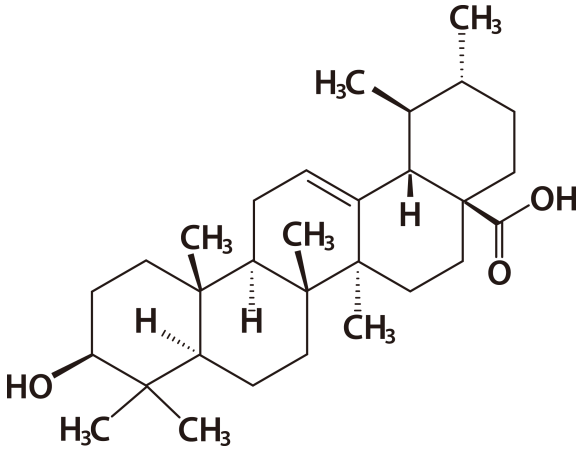

Fig. 1. Structure of ursolic acid.

Table 1. Effects of UA on cancer in health and disease

Disease type	Subject	Dose/Duration of UA	Results	Reference
Skin cancer	12-O-tetra decanoylphorbol-13-acetate-induced mouse on skin tumor	0.1, 0.3, 1, or 2 μM for 20 weeks	↓ Tumors per mouse	Huang et al. [24] 1994
Colon cancer	HCT116, HT29, and Caco2 cancer cells and male athymic nu/nu mice (4 weeks old)	20 μM for 8 hours and daily 250 mg/kg in oral for 4 weeks	↓ NF-kB, Bcl-xL, Bcl-2, and cyclin D1 protein levels ↓ MMP-9, VEGF, and ICAM-1 protein levels ↓ Ki67, CD31, STAT3, and EGFR ↑ p53 and p21 mRNA expression	Prasad et al. [25] 2012
Breast cancer	MCF-7, MDA-MB-231, and SK-BR-3 cancer cells	20 μM for 24 hours	↓ HK2, PKM2, ATP, and lactate ↓ pERK1/2, and depolarization of mitochondrial membrane potential ↑ Nitric oxide and ATM	Lewinska et al. [26] 2017
Bladder cancer	T24 cancer cells	100 and 200 μg/ml for 24 hours	↑ Caspase 3 activity ↑ AMPK activation ↑ JNK activation	Zhen et al. [32] 2012
Cervical cancer	TC-1 and HeLa cancer cells and xenograft tumor models	10, 20, and 30 μM for 5 days 0, 25 and 50 mg/kg for 10 weeks	↓ Cell proliferation ↑ Autophagy mediated PI3K signaling pathway ↓ Volume of tumor size	Leng et al. [35] 2013
Pancreas cancer	MIA, PaCa-2, and PANC-1 cancer cells and xenograft tumor models	15, 30, 45, and 60 μM for 24 h 100 and 200 mg/kg for 20 days	↓ Tumor size and weight ↑ Cleavage caspase-3 mRNA expression ↑ Caspase 3, 8, and 9 activity ↑ Cytochrome c release	Li et al. [36] 2012
Ovarian cancer	SK-OV-3 human ovarian cancer cells	20 μM for 24 h	↑ Caspase 3 and 9 protein levels ↑ phosphorylation of GSK-3β protein level ↑ β-catenin degradation	Song et al. [37] 2012
Liver cancer	HepG2, Hep3B, Huh7, and HA22T cancer cells	2, 4 or 8 μM/L for 48 h	↓ Cell adhesion, ICAM-1 level and VEGF release ↓ Mitochondrial membrane potential ↓ Na^+–K^+-ATPase activity ↑ Caspase 3 and 8 activity	Yan et al. [38] 2010

↓, Decrease; ↑, Increase; NF-kB, nuclear factor-kappa B; Bcl-xL, B-cell lymphoma-extra large; Bcl-2, B-cell lymphoma 2; MMP-9, matrix metalloproteinase; VEGF, vascular endothelial growth factor; ICAM-1, intercellular adhesion molecule-1; CD31, cluster of differentiation 31; STAT3, signal transducer and activator of transcription 3; EGFR, epidermal growth factor receptor; HK2, hexokinase 2; PKM2, pyruvate kinase muscle isozyme m2; ATP, adenosine triphosphate; ERK, extracellular signal-regulated kinase; AMPK, AMP-activated protein kinase; JNK, c-Jun N-terminal kinase; ATM, ataxia-telangiectasia mutated; PI3K, phosphoinositide 3-kinase.

ANTI-CANCER EFFECTS OF UA

UA exerts a potent substance with in vitro and in vivo anti-cancer effects (Table 1). Numerous studies have investigated the beneficial effects of UA on cancer cell metabolism in both rodents and humans. The mechanisms underlying the anti-cancer effect of UA are reported to be inhibition of tumorigenesis [24] and cancer cell proliferation [25], modulation of apoptosis [26], prevention of cell cycle arrest [27], and promotion of autophagy [28,29].

Recent trends in studies on UA have indicated the beneficial effects of the compound on autophagy and apoptosis in human breast cancer cell lines. Lewinska et al. [26] report that 20 μM UA inhibits Akt activation and promotes autophagy and apoptosis in breast cancer cells. It also decreases phospho-extracellular signal-regulated kinase 1/2 level and mitochondrial membrane depolarization potential. Interestingly, it is reported that UA induces activation of Akt, increases oxidative system, and decreases the levels of adenosine triphosphate (ATP), lactate, and glycolytic enzymes, such as hexokinase 2 and pyruvate kinase in breast cancer cells [30,31]. In addition, it decreases ATP production and activates adenosine monophosphate-activated protein kinase (AMPK), which results in inhibition of proliferation in T24 bladder cancer cells [32] and induces autophagy in U87MG glioma cells [33]. UA may be a potent regulator of AMPK, which inhibits of glycolysis and tumor growth in vivo [31]. Xavier et al. [34] demonstrated 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 ovarian cancer cells [37]. Yan et al. [38] reported that UA induces pro-apoptotic signaling in human liver cancer cell lines such as HepG2, Hep3B, Huh7, and HA22T cell lines, which are widely used to assess apoptotic mechanism of action in cancer research [39,40]. They demonstrated that UA exerts significantly improved pro-apoptotic effects by increasing the levels of caspase-3 and caspase-8, and DNA fragmentation in human liver cancer cells. Additionally, UA decreases Na^+–K^+-ATPase activity and mitochondrial membrane potential, indicating mitochondrial dysfunction in these cancer cells.

ANTI-OBESITY/ANTI-DIABETIC EFFECTS OF UA

An increase in the incidence of obesity and diabetes has heightened the need for a treatment against these conditions; the effects of UA are summarized in Table 2. Key effects of UA are inhibition of pancreatic α-amylase activity and reduction of blood glucose level in vivo and vitro [41,42]. Early work by Ramirez et al. [43] have evaluated the effects of UA on body weight and glucose tolerance in metabolic syndrome patients who received 150 mg of UA per day before breakfast for 12 weeks. Reductions in body weight, body mass index, waist circumference, and fasting blood glucose level were observed in the patients, which suggests that it significantly improves insulin sensitivity. Chu et al. [44] have also demonstrated that 0.5% UA-supplemented diet caused an decreases body weight, free fatty acids, and β-oxidation via uncoupling protein 3/AMPK-dependent pathways in high fat diet (HFD)-induced obese rats after six weeks of treatment. Similarly, mice treated with 0.14% UA-supplemented diet for six weeks exhibited a decrease in body weight gain and glucose intolerance [45]. Furthermore, Li et al. [41] demonstrated that UA (0.125, 0.25, and 0.5%) decreased body weight gain and insulin resistance in HFD-induced obese mice by improving hepatic lipid accumulation and antioxidant enzyme levels. It is also reported that 80 μM UA reduces triglyceride (TG) and cholesterol levels by increasing fatty acid oxidation and decreasing fatty acid synthesis in hepatocytes, suggesting that the upregulation of peroxisome proliferator-activated receptor alpha (PPAR-α) expression is possibly critical for the beneficial effect of UA [46]. Accordingly, UA treatment (50 and 200 mg/kg) decreases body weight, fat mass, TG level, plasma leptin concentration, and lipid accumulation and increases in high-density lipoprotein (HDL)-cholesterol, brown adipose tissue, insulin sensitivity, fatty acid uptake, and β-oxidation in HFD-induced obese rats, indicating that it increases energy expenditure [47]. Similar result was obtained by Jang et al. [48], who showed that UA (0.05%) inhibits glucose intolerance and insulin resistance by preserving pancreatic β-cells in diabetic mice.

The mechanisms underlying these effects of UA were investigated by Kunkel et al. [45], who studied that the beneficial effects of 0.14% UA supplementation in HFD-induced obese rats are due to an increase in Akt phosphorylation and an improvement in glucose uptake by skeletal muscles. In a similar, diabetic models treated with UA (1 μg/ml) did not develop insulin resistance and exhibited normal glucose transporter type 4 translocation and insulin receptors via Akt activation, suggesting that UA is a key regulator of glucose levels in diabetes [42]. Additionally, it was confirmed that 2.5-10 μM UA increases the levels of adipocyte transcription factors such as PPARγ, sterol regulatory factor-binding protein 1c transcription (SREBP-1c), fatty acid-synthase and fatty acid binding protein 4 (FABP4) in 3T3-L1 cells. These results suggest that the regulation of AMPK levels by inhibiting liver enzyme B1 is crucial for the treatment of obesity. Therefore, these findings highlight the importance of UA in the treatment of obesity and diabetes.

EFFECTS OF UA ON CARDIOVASCULAR DISEASE

CVDs are the major contributors to mortality and morbidity in the worldwide [49]. It includes coronary artery disease, myocardial infraction, stroke, heart failure, atherosclerosis, hypertensive heart disease, peripheral artery disease, and cardiomyopathy [49]. CVDs decrease quality of life and increases social and economic

Table 2. Effects of UA on obesity or diabetes in health and disease

Disease type	Subject	Dose/Duration of UA	Results	Reference
Metabolic syndrome	Diagnostics of metabolic syndrome patients	Orally 150 mg/kg for 12 weeks	↓ Body weight, BMI, and waist circumference ↓ Fasting glucose	Ramírez-Rodríguez et al. [43] 2017
Obesity	High fat diet-induced obese rat model and rat L6 and mouse C2C12 skeletal muscle cells	0.5% UA for 6 weeks and 20 and 40 μM for 4 hours	↓ Body weight ↓ FFA and TG contents in skeletal muscle ↑ Energy expenditure ↑ AMPK, CD 26, ACC, CPT, and UCP3	Chu et al. [44] 2015
Obesity	High fat diet-induced obese mice model	0.14 or 0.27% for 6 weeks	↑ Akt, grip strength, skeletal muscle mass, and mean fiber diameter ↑ Energy expenditure ↑ Run distance and UCP1 ↓ Resting heart rate, body weight, fat mass, and blood glucose ↓ Liver weight, liver TG, and Liver ACC ↓ AST and ALT in plasma	Kunkel et al. [45] 2012
Obesity	High fat diet-induced Sprague-Dawley rats	0.125, 0.25, and 0.5% for 6 weeks	↓ TG, FFA, weight in liver ↓ Body weight and fat mass ↓ Insulin and leptin ↓ TNF-α and MDA ↑ CAT and GSH-PX	Li et al. [41] 2014
Obesity	High fat diet-induced female Swiss mice	1 and 2% for 9 weeks	↓ Body weight ↓ Plasma glucose ↓ Plasma triglyceride ↓ Pancreatic lipase	Kazmi et al. [91] 2013
Obesity	High fat diet-induced Sprague-Dawley rats	250 mg/kg for 8 weeks	↓ Body weight ↓ Plasma cholesterol ↓ Plasma leptin ↑ Plasma adiponectin	Zhang et al. [92] 2016
Diabetes	3T3-L1 adipocytes 1 μg/ml for 10 min	1 μg/ml for 10 min	↑ GLUT 4, insulin receptor, and Akt ↑ Glycogen synthase kinase-3β	Jung et al. [42] 2007
Diabetes	Streptozotocin-injected male ICR mice	0.5 g/kg for 4 weeks	↓ Glucose and TNF-α ↑ Insulin (plasma, pancreatic) plasma C-peptide	Jang et al. [48] 2009
Diabetes	Streptozotocin-injected male mice	200 mg/kg per day for 6 weeks	↓ Fasting blood glucose ↓ PPAR γ and aP2 ↓ Adipocyte dysfunction ↑ Bone formation	Yu et al. [18] 2015

↓, Decrease; ↑, Increase; BMI, body mass index; AMPK, AMP-activated protein kinase; CD, cluster of differentiation 26; ACC, Acetyl-CoA carboxylase; CPT, Carnitine palmitoyltransferase, UCP, Uncoupling protein; Akt, Protein kinase B; TG, triglyceride; FFA, free fatty acid; TNF, tumor necrosis factor; AST, aspartate aminotransferase; ALT, alanine transaminase; MDA, malondialdehyde; CAT, catalase; GSH-PX, phospholipid hydroperoxide glutathione peroxidase; GLUT4, glucose transporter 4; PPAR γ, peroxisome proliferator-activated receptor gamma; aP2, activating protein 2.

costs [50]. The effects of UA in CVDs are summarized in Table 3. In the first study, Somava et al. [51] have demonstrated that treatment with UA (40 mg/kg) is associated with a lower the heart rate, which indicates an alleviation of CVD risk both in vitro and in vivo. In addition, Pozo et al. [52] reported that the intraperitoneal administration of UA (2 and 6 mg/kg) for 10 days neointimal hyperplasia (80%) by inhibiting luminal stenosis in a rat model of vascular injury. UA also potently inhibits proliferating cell nuclear antigen expression in injured artery cells. Furthermore, Senthil et al. [19] have reported that UA (60 mg/kg) reduces lipid peroxide level by scavenging free radicals, improves lipid profiles, and decreases the serum levels of membrane-bound proteins after 7 days of treatment. UA contributes to the restoration of cardioprotective enzyme activity to its normal level in rats, which suggests that it protects against myocardial ischemia. Similarly, previous findings have shown that UA is able to restore cardiac enzymes and blood constituents to their normal levels. It has an anti-apoptotic effects in cardiac muscle cells [53,54]. The effects of UA on lipid peroxidation and antioxidant capacity in alcoholic cardiomyopathy are also reported [55]. Saravanan and Pugalendi [55] have suggested that treatment with UA (20 mg/kg/day) for 30 days promotes the activities of free radical-scavenging antioxidant enzymes. It improves the activities of glutathione, ascorbic acid, and α-tocopherol levels [55]. Furthermore, Lv et al. [56] demonstrated that UA administration markedly inhibits the proliferation of human umbilical vein endothelial cells induced by

Table 3. Effects of UA on cardiovascular system in health and disease

Disease type	Subject	Dose/ Duration of UA	Results	Reference
Ischemia-reperfusion dysrhythmia	$CaCl_2$-induced arrhythmia in rats	40 mg/kg for 20 min	↓ HR and MAP ↓ Inotropic (QRS Complex) and romotropic (PQ interval)	Somova et al. [51] 2004
Atherosclerosis	Vascular injury model in rat carotid artery	2 and 6 mg/kg for 10 days	↓ Neointimal formation in the rat carotid ↓ Expression of PCNA	Pozo et al. [52] 2006
Myocardial ischemia	Isoproterenol-induced myocardial ischemia in rats	60 mg/kg for 7 days	↓ TBARS ↑ SOD, CAT, GPx, GST, GR, GSH, vitamin C and E	Senthil et al. [19] 2007
Myocardial ischemia	Isoproterenol-induced myocardial ischemia in rats	40 mg/kg for 7 days	↓ CK and CK-MB ↓ LDH-1 and 2 ↓ DNA damage	Radhiga et al. [48] 2012
Myocardial infarction	Isoproterenol hydrochloride-injected Wistar rats	40 mg/kg for 9 days	↓ cTnT and cTnI in serum ↓ TBARS, HP, and CD in plasma ↑ Vitamin C and E in plasma ↑ SOD, GST, and GR in erythrocyte ↓ TBARS, HP, CD, cytochrome C, caspase-3, -8 and caspase-9, TNF-α, and Fas in heart ↑ Vitamin C, E, GSH, SOD, CAT, GPx, GST, and GR in heart	Radhiga et al. [54] 2012

↓, Decrease; ↑, Increase; HR, heart rate; MAP, mean arterial pressure; PCNA, proliferating cell nuclear antigen; TBARS, thiobarbituric reactive substances; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GST, glutathione S-transferase; GST, glutathione-S-transferase; GR, glutathione reductase; GSH, glutathione; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; LDH, lactate dehydrogenase; cTnT, cardiac troponins T; cTnI, cardiac troponin I; HP, lipid hydroperoxides; CD, conjugated dienes; TNF-α, tumor necrosis factor-α; Fas, fatty acid synthase.

interleukin 6 (IL-6) and C-reactive protein (CRP), suggesting that it inhibits atherosclerosis related parameters in a dose-dependent manner.

EFFECTS OF UA ON BRAIN

Mild to severe defects in the nervous system typically result due to oxidative stress and excitotoxicity [10]. An imbalance in cellular homeostasis may permanently reduce cognitive function and cause brain damage [57], resulting in various brain diseases [58,59]. The effects of UA on brain diseases are summarized in Table 4. UA inhibits oxidative stress [60] and excitotoxicity [61], suggesting that it may play a protective role in various brain diseases induced by oxidative stress and excitotoxicity. In addition, UA suppresses apoptotic signaling [60] and exerts anti-inflammatory effects in the brain [62,63].

Shih et al. [61] reported that UA significantly reduces free radical levels in rat neuronal cultures. In addition, it attenuates reactive oxygen species (ROS) levels in the brain [60,63,64]. For example, Zhang et al. [60] found that UA increases the levels of antioxidant components, such as glutathione (GSH)/oxidized glutathione (GSSH) ratio, catalase (CAT) activity, and superoxide dismutase (SOD) activity in a rat model of subarachnoid hemorrhage. Lu et al. [63] showed that UA increases the levels of antioxidant enzymes, such as SOD, CAT, glutathione reductase (GR), and glutathione peroxidase (GPx). A similar work by Lu et al. [64] revealed that UA reduces ROS levels in D-galactose-treated mice. Moreover, it reduces the neuronal expression of pro-apoptotic factors, such as caspase-3 mRNA, caspase-9 mRNA, and reduces DNA fragmentation in a rat model of subarachnoid hemorrhage [60]. Specifically, Huang et al. [62] have reported that UA inhibits the activity of matrix metalloproteinase-9 (MMP-9), which is a potential cause of various cancers, in C6 glioma cells [65]. This occurs because UA could suppress the NF-kB-dependent pathways that are activated by tumor necrosis factor-alpha (TNF-α) or interleukin 1 beta (IL-1β). Similar results were obtained by Wang et al. [20], who revealed the association between UA and MMP-2/-9 expression in a rat model of cerebral ischemia and reperfusion injury. In this study, the activities of MMP-2 and MMP-9 were suppressed by UA administration. In addition, the protein levels of peroxisome proliferator-activated receptors (PPARs), particularly PPARγ, which is an effective neuroprotective agents, were elevated following UA administration to rats with cerebral ischemia and reperfusion injury. This demonstrates that UA has a protective effect against various inflammatory conditions of the brain.

EFFECTS OF UA ON LIVER DISEASE

The liver is an important organ in the body, responsible for hormone production, xenobiotics detoxification, enzymatic digestion, and the decomposition of red blood cells [10]. It has a

Table 4. Effects of UA on brain in health and disease

Disease type	Subject	Dose/Duration of UA	Results	Reference
IL-1β or TNF-α-induced C6 glioma invasion	Rat C6 glioma cells	5, 10, and 20 μM for 24 hours	↓ MMP-9 activity by IL-1β or TNF-α ↓ IκBα activity by IL-1β or TNF-α ↓ IκB kinase activity by IL-1β or TNF-α ↓ NF-κB activity	Huang et al. [62] 2009
D-Galactose-induced neurodegenerative changes	Male kunming strain mice	10 mg/kg for 8 weeks	↓ AGEs level ↓ ROS level ↓ Carbonyl protein level ↓ Number of CD11b-stained cells, GFAP-stained cells, and RAGE-positive cells ↓ COX-2, iNOS, IL-1β, IL-6, and TNF-α protein levels	Lu et al. [63] 2010
Domoic acid-induced cognitive deficits	Male ICR mice	100 mg/kg for 3 weeks	↑p-Akt ↑ p-FOXO1 ↑ HO-1 ↑ Complex I-V ↑ Electron transport chain activity ↑ ATP and APR	Wu et al. [93] 2013
Adrenocorticotrophic hormone-producing pituitary adenoma	AtT20 cells (mouse corticotrophic tumor cell line)	10, 20, and 40 μM for 24 hours	↓ POMC mRNA expression ↓ ACTH protein level ↓ ACTH release ↑ p-JNK/JNK protein level	Gong et al. [94] 2014
Subarachnoid hemorrhage (SAH)	Male Sprague Dawley experimental SAH rat model	25 and 50 mg/kg at 0.5, 24, and 47 hours after SAH	↑ Neurological score ↓ BBB permeability (EB content) ↑ Cerebral vasospasm ↓ MDA ↑ GSH/GSSH ratio, catalase activity, and SOD activity ↓ Caspase-3, -9 mRNA expression ↓ Apoptotic index	Zhang et al. [60] 2014
Parkinson's disease	Male Swiss albino mice	5, 25, and 50 mg/kg for 21 days	↑ Hanging time ↑ Rotarod test ↓ Narrow beam walking test ↓ Nitrite level ↑ Dopamine ↑ Acidhomovanilic acid	Rai et al. [95] 2016
Cerebral ischemia and reperfusion injury	Male Sprague Dawley rats	5, 10, and 20 mg/kg at 0.5, 24, and 47 hours after reperfusion	↓ Infarct volume ↓ Neurological deficit score ↑ Number of intact neuron ↑ PPARγ protein level ↓ MMP-2 and -9 protein levels	Wang et al. [20] 2016

↓, Decrease; ↑, Increase; =, No change; MMP-9, Matrix metalloproteinase-9; BBB, blood-brain barrier; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor-alpha; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; MMP-2, matrix metalloproteinase-2; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; IL-6, interleukin-6; AGEs, advanced glycation end products; ROS, reactive oxygen species; GFAP, glial fibrillary acidic protein; RAGE, receptor for advanced glycation end-products; FoxO1, Forkhead box protein O1; HO-1, heme oxygenase; ATP, adenosine triphosphate; POMC, pro-opio melanocortin; JNK, c-Jun N-terminal kinase; APR, ATP production rate; ACTH, adrenocorticotrophic hormone; MDA, malondialdehyde; GSH, glutathione; GSSH, oxidized glutathione; SOD, superoxide dismutase; PPAR, peroxisome proliferator-activated receptors; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; p-Akt, phosphorylated protein kinase B.

unique regeneration system, which can regenerate it up to 25% of its original mass; however, the liver is vulnerable to various diseases because of its various functions and strategic location [10]. As summarized in Table 5. Many studies have demonstrated that UA protects against several liver diseases, such as fatty liver disease [45], liver fibrosis [66], carcinoma [67], and liver cancer [38].

It is well known that the liver plays a pivotal role in the regulation of systemic lipid homeostasis [21]. HFD-induced obese models and non-alcoholic fatty liver disease cause abnormal lipid homeostasis, which can result in various complications. However, UA can attenuate HFD-induced fatty liver diseases, hepatocellular steatosis, and hepatic TG content [45]. In this study, plasma aspartate transaminase (AST) and alanine transaminase (ALT) levels, which are biomarkers of liver diseases, were also decreased by UA treatment, indicating that UA attenuates hepatocyte injury. Sundaresan et al. [21] found that UA down-regulated the mRNA expression of lipogenesis-related factors, such as acetyl-CoA carboxylase, and fatty acid synthase, but up-regulated the mRNA

Table 5. Effects of UA on liver in health and disease

Disease type	Subject	Dose/Duration of UA	Results	Reference
Human liver cancer	Human normal liver cell line (L-02 cell) and cancer cell lines (HepG2, Hep3B, Huh7, HA22T cells)	2, 4, and 8 μM for 48 hours	↑ DNA fragmentation ↓ Mitochondrial membrane potential ↓ Na^+-K^+-ATPase activity ↑ Caspase-3 and -8 activity ↓ Cell adhesion, ICAM-1, and VEGF level	Yan et al. [38] 2010
Fatty liver disease	C57BL/6 mice	0.14, 0.27% of HFD for 6 weeks	↓ Liver weight ↓ Liver triglycerides ↓ Plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ↓ Liver ACC protein level	Kunkel et al. [45] 2012
Hepatocellular carcinoma	Liver cancer cells (HepG2 and Hep3B)	7.5,15, and 30 μM for 24 hours	↑ Apoptotic portion ↑ Cleaved capase-3 protein level ↑ p-AMPKα (Thr 172) protein level ↑ GSK 3β (Ser9) protein level ↓ p-AKT (Ser 473) and p-mTOR (Ser 2448) protein levels	Son et al. [71] 2013
Hepatic lipid accumulation	Male C57BL/6J mice	5 mg/kg for 5 weeks	↓ SREBP-1c, ACC, FAS mRNA expression ↑ CPT-1 and ACO mRNA expression ↑ PPAR-α mRNA expression and protein level ↓ Micro- and macro-vesicular steatosis and inflammatory cell infiltration ↓ Lipid disposition	Sundaresan et al. [21] 2014
Hepatic steatosis and non-alcoholic fatty liver disease	Male Sprague-Dawley rats	0.125, 0.25, and 0.5% of HFD for 6 weeks	↓ Liver triglycerides and free fatty acid ↓ Fat/body ratio ↑ PPAR-α protein and mRNA level ↑ CPT-1 protein level ↓ FAT/CD36 protein level ↓ DGAT1, FAS and SREBP1 protein levels	Li et al. [41] 2014
Liver fibrosis	Male ICR mice	25 and 50 mg/kg for 6 weeks	↓ Hepatic fibrosis ↓ ROS and TBARS level ↑ T-SOD, CAT, GPx activity, and GSH level ↑ Nrf 2 (Nucleus/cytosol), HO-1, and GST protein levels ↓ Cleaved caspase-3 protein level ↑ Bcl-2/Bax ratio	Ma et al. [66] 2016
Hepatocellular carcinoma	Human HCC cell lines (HepG2, Bel-7402, QGY- 7703, HMCC97L, HMCC97H cells)	5, 15, 20, 25, and 30 μM for 24 hours	↑ p-p38 MAPK (Thr180/Tyr182) protein level ↑ IGFBP1 mRNA expression and protein level ↑ FOXO3 α protein level ↓ Tumor weight and volume	Yang et al. [67] 2016

↓, Decrease; ↑, Increase; =, No change; ICAM-1, intracellular adhesion molecule; VEGF, vascular endothelial growth factor; ACC, acetyl-CoA carboxylase; ACO, acyl-CoA oxidase; AMPK, AMP-activated protein kinase; GSK 3β, glycogen synthase kinase 3 beta; SREBP, sterol regulatory element-binding protein; FAS, fatty acid synthase; CPT-1, carnitine palmitoyltransferase 1; DGAT1, diacylglycerol acyltransferase 1; TBARS, thiobarbituric acid reactive substances; GST, glutathione S-transferase; Nrf2, nuclear factor E2-related factor 2; HFD, high-fat diet; IGFBP 1, insulin-like growth factor (IGF) binding protein 1; p-Akt, phosphorylated protein kinase B; p-mTOR, phosphorylated mammalian target of rapamycin; PPAR, peroxisome proliferator-activated receptors; FAT, fatty acid translocase; CD36, cluster of differentiation 36; T-SOD, total superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GSH, glutathione; HO-1, heme oxygenase; p-p38 MAPK, phosphorylated p38 mitogen-activated protein kinases; FOXO3, forkhead box O3; Bax, bcl-2-like protein 4; Bcl-2, B-cell lymphoma 2.

expression of fatty acid oxidation-related factors, such as carnitine palmitoyltransferase-1 and acyl-CoA oxidase, in a mouse model of hepatic lipid metabolism. Furthermore, UA markedly attenuated hepatic steatosis in a rat model of non-alcoholic fatty liver disease by activating PPAR-α, which is a key regulator of hepatic lipid metabolism. It also activated the PPAR-α regulated signaling pathway at both protein and mRNA levels [68,69]. In addition, it reduced the serum levels of inflammatory markers, such as TNF-α, chemokine ligand 2/monocyte chemotactic protein-1, IL-6, and oxidative stress markers, such as SOD, malondialdehyde, CAT, and GPx [41].

Excessive deposition of extracellular matrix components in the liver can cause liver fibrosis, which could be ultimately induces liver cirrhosis [70]. Ma et al. [66] demonstrated that carbon-tetra-

chloride-induced liver fibrosis is attenuated by UA via a nuclear factor E2-related factor 2/antioxidant responsive element pathway in the rodents liver. This finding suggest that UA can be a potent protective agent against liver fibrosis. Son et al. [71] reported that UA may induce apoptosis of HepG2 hepatocellular carcinoma cells through AMPK and glycogen synthase kinase-3 beta (GSK-3β) pathway. The authors also indicated that UA increase apoptotic portion and the level of cleaved caspase-3 protein, p-AMPKα (Thr 172), and GSK-3β (Ser9) in HepG2 cells. Moreover, Yang et al. [67] reported that UA suppresses the proliferation of hepatocellular carcinoma cells via p38 the mitogen-activated protein kinases (p38-MAPK)-mediated activation of the gene expression of insulin-like growth factor (IGF) binding protein 1 (IGFBP1). In addition, it increased the expression of forkhead box O3 (FOXO3a). These suggest that IGFBP1 and FOXO3a can potentially be therapeutic interventions in the management of hepatocellular carcinoma.

EFFECTS OF UA ON SARCOPENIA

The skeletal muscles accounts for approximately 40-50% of the total body mass. They are major regulator energy catabolism and postprandial glucose disposal [72,73], and are essential for whole body metabolism and locomotion [74,75]. Sarcopenia, which is defined as the loss of skeletal muscle mass and skeletal muscle function, can be induced by various conditions, especially aging [76,77]. Aging-induced sarcopenia hinders locomotion, which causes immobility and falls [78,79], resulting a behavior disabilities in the elderly [80,81]. Effects of UA on sarcopenia and exercise capacity were outlined in Table 6. UA stimulates skeletal muscle synthesis [9] and increases the strength of the skeletal muscle [45] via various signaling pathways, which suggest that it may be useful in the prevention of sarcopenia. The direct effects of UA on sarcopenia have not been exclusively studied; however, several similar studies on the effects of UA on age-related skeletal muscle dysfunction have been carried out [82,83].

Ebert et al. [83] reported that UA may be a therapeutic intervention against aging-induced muscle atrophy and dysfunction, and demonstrated that UA significantly improves skeletal muscle mass and grip strength in a rodents. A similar study conducted by Bakhtiari et al. [82] revealed that UA increases the number of satellite cells and activates myoglobin expression in aged mice, suggesting that it positively modulates skeletal muscle turnover by stimulating protein synthesis and suppressing atrophy factors. Kunkel et al. [9] have reported that UA ameliorates skeletal muscle atrophy by inhibiting of muscle-atrophy-related pathways. These include the muscle ring-finger protein-1 (MuRF-1) and atrogin-1 pathways, which are pivotal mediators of protein degradation in skeletal muscles. It was also demonstrated that UA increases skeletal muscle hypertrophy by increasing of insulin-like growth factor-1 (IGF-1) secretion. A similar investigations showed that UA increases skeletal muscle mass and strength [45]. Jeong et al. [84] also demonstrated that treatment with UA for 12 weeks improves skeletal muscle strength and skeletal muscle mass in a dose-dependent manner through the upregulation of Akt/mammalian target of rapamycin (mTOR) signaling and the downregulation of skeletal muscle atrophy parameters such as atrogin-1 and MuRF-1.

EFFECTS OF UA ON EXERCISE CAPACITY

Recently, it has been reported that UA improves exercise capacity via various molecular pathways in vitro and in vivo (Table 6). UA supplementation improves exercise capacity and decreases resting heart rate [2]. It has been found that intraperitoneal treatment with UA for seven days increases expression of sirtuin-1 and peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) in the skeletal muscles of aged rodents [82], revealing that UA may enhance physical performance.

In the above mentioned reports, UA treatment improves exercise capacity under various disease and non-disease conditions in rodents and humans [84-90]. Ogasawara et al. [85] found that UA supplementation stimulates the expression of ribosomal protein S6 kinase beta-1, and mammalian target of rapamycin complex 1 in rats after treatment with UA, which led to skeletal muscle synthesis and hypertrophy. Moreover, Jeong et al. [84] showed that UA treatment for 12 weeks improves physical performance in a dose-dependent manner (75, 150, and 300 mg/kg), as indicated by an enhancement in exercise time and distance in mice. In this study, increased skeletal muscle strength and decreased fatigue-related parameters, such as lactate, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and creatinine. Recently, Chen et al. [86] also revealed that UA stimulates mitochondrial biogenesis by activating of AMPK and PGC-1α signaling in C2C12 myotubes, leading to improved exercise endurance. Bang et al. [87,88] reported that UA supplementation increases resistance exercise capacity in men by significantly increasing the levels of IGF-1, irisin, and maximal muscle strength (peak torque) measured by a dynamometer, suggesting that UA mediated increase in irisin level may be useful to enhance the maximal skeletal muscle strength during resistance exercise [87]. They also reported that UA inhibits skeletal muscle damage markers, such as B-type natriuretic peptide (BNP), creatine kinase (CK), CK–myocardial band (CK-MB), LDH, cortisol, and myoglobin levels [88].

However, two recent studies [89,90] have been argued indicated that UA has no effect on exercise capacity. Cho et al. [89] showed that the supplementation with loquat leaf extract containing UA for 12 weeks does not enhance skeletal muscle strength, mass, and function in healthy subjects; only right-handgrip strength in female subjects treated with loquat leaf extract was significantly

Table. 6. Effects of UA on sarcopenia and exercise capacity

Disease type	Subject	Dose/Duration of UA	Results	Reference
Aging	Male C57BL/6 mice	200 mg/kg (twice a day for 7 days)	↑ SIRT1 and PGC-1α mRNA expression ↑ Pax7 gene/fiber ↑ Myoglobin & type IIa fiber	Bakhtiari et al. [82] 2015
Aging	Male C57BL/6 mice	0.27% of standard chow for 8 weeks	↑ Skeletal muscle mass (~9%) ↑ Type IIb muscle fiber diameter ↑ Grip strength (~12%) ↑ Specific force (~30%) ↓ 4E-BP1 protein level	Ebert et al. [83] 2015
HFD-induced obesity and insulin resistance	Male C57BL/6 mice	0.14% of HFD for 6 weeks and 0.27% of HFD for 17 weeks	↑ Skeletal muscle p-Akt/Akt protein level ↑ Hk2 and Vegfa mRNA level ↑ Grip strength ↑ Quadriceps and triceps mass ↑ Muscle fiber diameter ↑ Running distance ↓ Resting heart rate	Kunkel et al. [45] 2012
None	Male Sprague-Dawley rats	250 mg/kg for 11 weeks (after resistance exercise)	↑ Akt (Thr308) protein level ↑ PRAS40 (Thr246) protein level ↑ p70S6K (Thr389) and rpS6 (Ser240/244) protein levels	Ogasawara et al. [85] 2013
Aging	C2C12 Cell and male C57BL/6 mice	10 μM (7 consecutive days) and 200 mg/kg (twice a day for 7 days)	↑ SIRT1 and PGC-1α mRNA levels ↑ Pax7 gene/Fiber ↑ Myoglobin & type IIa fiber	Bakhtiari et al. [82] 2015
None	C2C12 Cell and male C57BL/6N mice	10 and 50 μg/ml for 18 h (4-5 days) and 75, 150, and 300 mg/kg for 12 weeks	↑ AMPK, IGF-1, Akt mRNA expression ↓ Atrogin-1, MuRF1 protein and mRNA expression ↑ Exercise time and running distance = Body weight and weight gain rate ↓ Fatigue serum levels (lactate, LDH, iPO, AST, ALT, ALP) ↑ Grip strength and muscle hypertrophy	Jeong et al. [84] 2015
None	C2C12 myotubes and male ICR mice	1, 2, and 5 μM for 2 days and 80 and 240 mg/kg for 3 weeks	↑ Mitochondrial ATP generation capacity ↑ p-AMPK/total-AMPK protein level ↑ Nuclear PGC-1 level ↑ mTFA expression ↑ Mitochondrial citrate synthase activity ↑ UCP 3 and COX mRNA expression ↑ Swimming duration in mice	Chen et al. [86] 2017
None	Human and male C57BL/6 mice	200 mg/kg (twice a day for 7 days) in human and 0.27% of Standard chow for 5-7 weeks in mouse	↓ Fasting blood glucose level ↓ Atrogin-1, MuRF1, and ZFAND5 mRNA expression ↑ Insulin/ IGF-1 ↑ Muscle weight and muscle fiber size ↑ Grip strength	Kunkel et al. [9] 2011
Healthy adults	Korean healthy men	450 mg/day for 8 weeks	↑ IGF-1 concentration ↑ Irisin concentration ↑ Maximal muscle strength (extension, flexion)	Bang et al. [87] 2014
Healthy adults	Korean healthy adults	Loquat leaf extract 102 mg/day for 12 weeks	= Muscle strength ↑ Right hand-grip strength for female = Muscle mass = Physical performance	Cho et al. [89] 2016
Healthy adults	Resistance-trained healthy men	3 g after exercise	= Akt/mTOR1 protein levels = Insulin concentration = IGF-1 concentration	Church et al. [90] 2016
Healthy adults	Healthy males	450 mg/day for 8 weeks	↓ Muscle damage markers (BNP, cortisol, CK-MB, CK, myoglobin, and LDH)	Bang et al. [88] 2017

↓, Decrease; ↑, Increase; =, No change; 4E-BP1, eukaryotic initiation factor 4-binding protein 1; ADP, Adenosine diphosphate; ATP, Adenosine triphosphate; PAX7, paired box protein 7; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1α; SIRT-1, sirtuin-1; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; CK, creatin kinase; CK-MB, creatin kinase-myocardial band; COX, cytochrome c oxidase; HFD, high fat diet; Hk2, hexokinase-2; IGF-1, insulin growth factor-1; iPO, inorganic phosphate; LDH, lactate dehydrogenase; MuRF1, muscle ring finger 1; mTFA, mitochondrial transcription factor A; PGC-1, peroxisome proliferator-activated receptor-γ coactivator 1; PRAS40, proline-rich Akt substrate of 40 kDa; SIRT1, sirtuin1; UCP 3, uncoupling protein 3; Vegfa, vascular endothelial growth factor-A; ZFAND5, zine finger AN1-type domain 5; p-Akt, phosphorylated protein kinase B; p70S6K, p70-s6 kinase 1; rpS6, ribosomal protein S6.

increased compared with that in placebo-treated female subjects. In addition, Church et al. [90] demonstrated that UA supplementation does not affect Akt/mTOR1 signaling and IGF-1 level following resistance exercise in resistance-trained men.

Taken together, there are several reports on dealing with the positive effects of UA in rodents and humans, which suggest that UA may be an important therapeutic agent for improving exercise capacity. However, more studies should be conducted to verify the effects of UA on exercise capacity.

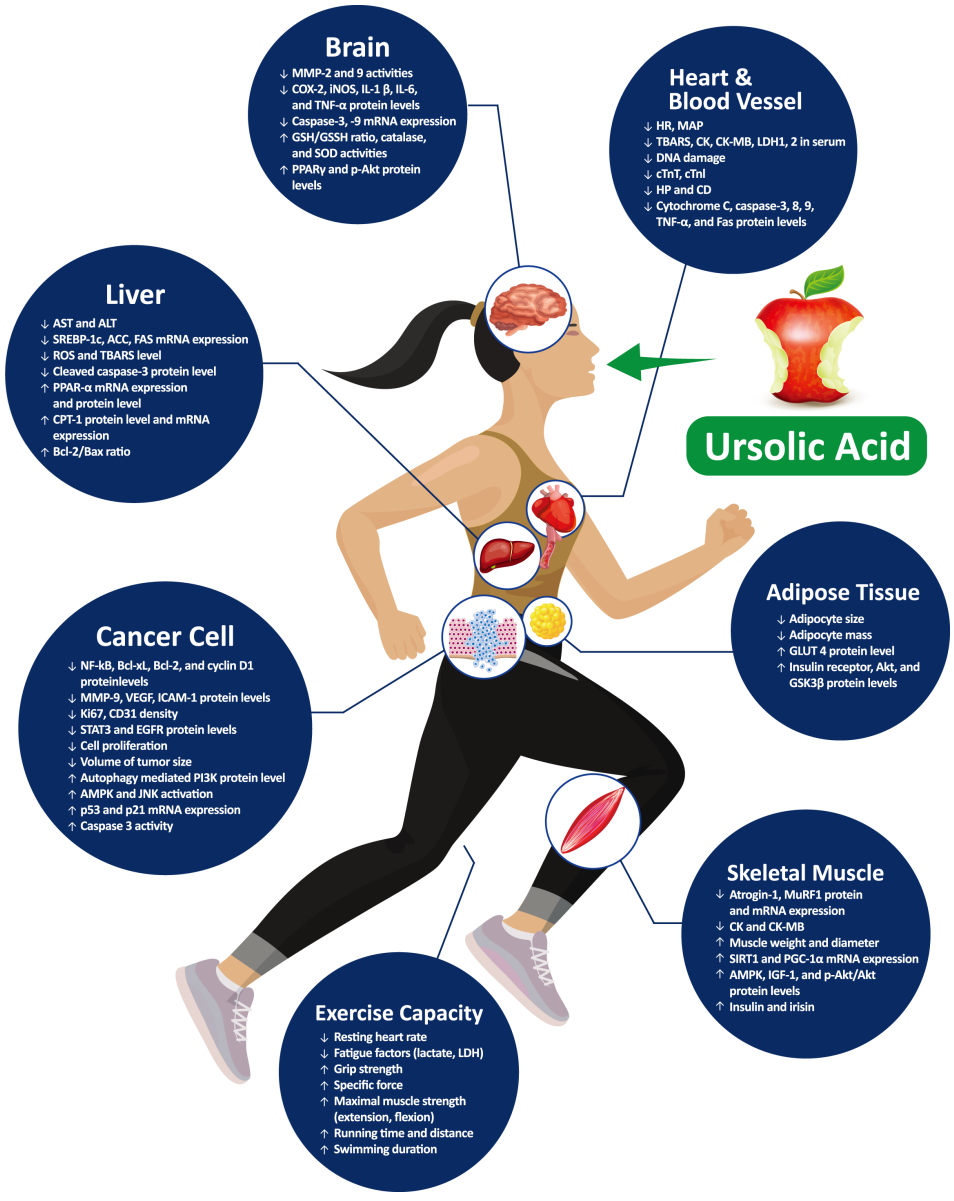

Fig. 2. Role of UA in various organs. UA supplementation or treatment can provide positive health outcomes via diverse molecular signaling and mechanisms under various diseases in multiple organs such as cancer cells, adipose tissue, heart, blood vessel, brain, liver, and skeletal muscle. NF-kB, nuclear factor-kappa B; cyclin D1; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor; ICAM-1, intercellular adhesion molecule-1; CD31, cluster of differentiation 31; STAT3, signal transducer and activator of transcription 3; EGFR, epidermal growth factor receptor; AMPK, AMP-activated protein kinase; JNK, c-Jun N-terminal kinase; GLUT 4, glucose transporter 4; GSK-3β, glycogen synthase kinase 3 beta; HR, heart rate; MAP, mean arterial pressure; TBARS, thiobarbituric reactive substances; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; LDH, lactate dehydrogenease; cTnT, cardiac troponins T; cTnI, cardiac troponin I; HP, lipid hydroperoxides; CD, conjugated dienes; TNF-α, tumor necrosis factor-α; Fas, fatty acid synthase; COX-2, cyclooxygenase; iNOS, inducible nitric oxide synthase; IL-1β, interleukin-1 beta; IL-6, interleukin-6; GSH, glutathione; GSSH, oxidized glutathione; SOD, superoxide dismutase; PPAR, peroxisome proliferator-activated receptors; AST, aspartate aminotransferase; ALT, alanine transaminase; SREBP, sterol regulatory element-binding protein; ACC, acetyl-coA carboxylase; FAS, fatty acid synthase; ROS, reactive oxygen species; PPAR-α, peroxisome proliferator-activated receptor alpha; CPT-1, carnitine palmitoyltransferase 1; MuRF1, muscle ring-finger protein-1; SIRT-1, sirtuin-1 and PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1α; IGF-1, insulin-like growth factor-1.

CONCLUSION

UA is a preventive and therapeutic intervention against various chronic diseases including cancer, metabolic syndrome, CVDs, brain disease, liver disease, and sarcopenia (Fig. 2). Although numerous findings suggest that UA improves exercise capacity and has beneficial effects on cardiopulmonary endurance and muscle strength, which indicates that it might be useful as an exercise mimetic, more investigations are needed to further elucidate how UA improves exercise capacity. Additionally, the cellular and molecular mechanisms underlying the effects of UA in various diseases must be further studied to implement UA as an exercise mimetics.

ACKNOWLEDGEMENTS

This work was supported by the Ministry of Education of the Republic of Korea and the National Research Foundation of Korea (NRF-2010-0020224) and WCSL at Inha University.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. García AC, de Souza LG, Pereira MG, Castro RN, García-Mina JM, Zonta E, et al. Structure-property-function relationship in humic substances to explain the biological activity in plants. *Sci Rep.* 2016;6:20798.
2. Sehrawat A, Roy R, Pore SK, Hahm ER, Samanta SK, Singh KB, Kim SH, Singh K, Singh SV. Mitochondrial dysfunction in cancer chemoprevention by phytochemicals from dietary and medicinal plants. *Semin Cancer Biol.* 2017;47:147-153.
3. Diarra M, El Ouahabi H, Bouxid H, Boujraf S, Khabbal Y, Ajdi F. Medicinal plants in type 2 diabetes: therapeutic and economical aspects. *Int J Prev Med.* 2016;7:56.
4. de Freitas Junior LM, de Almeida EB Jr. Medicinal plants for the treatment of obesity: ethnopharmacological approach and chemical and biological studies. *Am J Transl Res.* 2017;9:2050-2064.
5. Croft KD, Yamashita Y, O'Donoghue H, Shirasaya D, Ward NC, Ashida H. Screening plant derived dietary phenolic compounds for bioactivity related to cardiovascular disease. *Fitoterapia.* 2017. doi: 10.1016/j.fitote.2017.12.002. [Epub ahead of print]
6. Jiang T, Wang XQ, Ding C, Du XL. Genistein attenuates isoflurane-induced neurotoxicity and improves impaired spatial learning and memory by regulating cAMP/CREB and BDNF-TrkB-PI3K/Akt signaling. *Korean J Physiol Pharmacol.* 2017;21:579-589.
7. Leake I. Liver: plant sterols have a role in liver injury associated with parenteral nutrition. *Nat Rev Gastroenterol Hepatol.* 2013;10:693.
8. Katashima CK, Silva VR, Gomes TL, Pichard C, Pimentel GD. Ursolic acid and mechanisms of actions on adipose and muscle tissue: a systematic review. *Obes Rev.* 2017;18:700-711.
9. Kunkel SD, Suneja M, Ebert SM, Bongers KS, Fox DK, Malmberg SE, Alipour F, Shields RK, Adams CM. mRNA expression signatures of human skeletal muscle atrophy identify a natural compound that increases muscle mass. *Cell Metab.* 2011;13:627-638.
10. Woźniak Ł, Skąpska S, Marszałek K. Ursolic acid—a pentacyclic triterpenoid with a wide spectrum of pharmacological activities. *Molecules*. 2015;20:20614-20641.
11. Jäger S, Trojan H, Kopp T, Laszczyk MN, Scheffler A. Pentacyclic triterpene distribution in various plants - rich sources for a new group of multi-potent plant extracts. *Molecules.* 2009;14:2016-2031.
12. Hussain H, Green IR, Ali I, Khan IA, Ali Z, Al-Sadi AM, Ahmed I. Ursolic acid derivatives for pharmaceutical use: a patent review (2012-2016). *Expert Opin Ther Pat.* 2017;27:1061-1072.
13. Mancha-Ramirez AM, Slaga TJ. Ursolic acid and chronic disease: an overview of UA's effects on prevention and treatment of obesity and cancer. *Adv Exp Med Biol.* 2016;928:75-96.
14. Kashyap D, Sharma A, Tuli HS, Punia S, Sharma AK. Ursolic acid and oleanolic acid: pentacyclic terpenoids with promising anti-inflammatory activities. *Recent Pat Inflamm Allergy Drug Discov.* 2016;10:21-33.
15. Liobikas J, Majiene D, Trumbeckaite S, Kursvietiene L, Masteikova R, Kopustinskiene DM, Savickas A, Bernatoniene J. Uncoupling and antioxidant effects of ursolic acid in isolated rat heart mitochondria. *J Nat Prod*. 2011;74:1640-1644.
16. Shishodia S, Majumdar S, Banerjee S, Aggarwal BB. Ursolic acid inhibits nuclear factor-kappaB activation induced by carcinogenic agents through suppression of IkappaBalpha kinase and p65 phosphorylation: correlation with down-regulation of cyclooxygenase 2, matrix metalloproteinase 9, and cyclin D1. *Cancer Res.* 2003;63:4375-4383.
17. Jayaprakasam B, Olson LK, Schutzki RE, Tai MH, Nair MG. Amelioration of obesity and glucose intolerance in high-fat-fed C57BL/6 mice by anthocyanins and ursolic acid in Cornelian cherry (Cornus mas). *J Agric Food Chem.* 2006;54:243-248.
18. Yu SG, Zhang CJ, Xu XE, Sun JH, Zhang L, Yu PF. Ursolic acid derivative ameliorates streptozotocin-induced diabestic bone deleterious effects in mice. *Int J Clin Exp Pathol.* 2015;8:3681-3690.
19. Senthil S, Chandramohan G, Pugalendi KV. Isomers (oleanolic and ursolic acids) differ in their protective effect against isoproterenol-induced myocardial ischemia in rats. *Int J Cardiol.* 2007;119:131-133.
20. Wang Y, He Z, Deng S. Ursolic acid reduces the metalloprotease/anti-metalloprotease imbalance in cerebral ischemia and reperfusion injury. *Drug Des Devel Ther.* 2016;10:1663-1674.
21. Sundaresan A, Radhiga T, Pugalendi KV. Effect of ursolic acid and Rosiglitazone combination on hepatic lipid accumulation in high fat diet-fed C57BL/6J mice. *Eur J Pharmacol.* 2014;741:297-303.
22. Bakhtiari N, Hosseinkhani S, Soleimani M, Hemmati R, Noori-Zadeh A, Javan M, Tashakor A. Short-term ursolic acid promotes skeletal muscle rejuvenation through enhancing of SIRT1 expression and satellite cells proliferation. *Biomed Pharmacother.* 2016;78:185-196.
23. Kashyap D, Tuli HS, Sharma AK. Ursolic acid (UA): a metabolite with promising therapeutic potential. *Life Sci.* 2016;146:201-213.
24. Huang MT, Ho CT, Wang ZY, Ferraro T, Lou YR, Stauber K, Ma W, Georgiadis C, Laskin JD, Conney AH. Inhibition of skin tumori-

genesis by rosemary and its constituents carnosol and ursolic acid. *Cancer Res*. 1994;54:701-708.
25. Prasad S, Yadav VR, Sung B, Reuter S, Kannappan R, Deorukhkar A, Diagaradjane P, Wei C, Baladandayuthapani V, Krishnan S, Guha S, Aggarwal BB. Ursolic acid inhibits growth and metastasis of human colorectal cancer in an orthotopic nude mouse model by targeting multiple cell signaling pathways: chemosensitization with capecitabine. *Clin Cancer Res.* 2012;18:4942-4953.
26. Lewinska A, Adamczyk-Grochala J, Kwasniewicz E, Deregowska A, Wnuk M. Ursolic acid-mediated changes in glycolytic pathway promote cytotoxic autophagy and apoptosis in phenotypically different breast cancer cells. *Apoptosis.* 2017;22:800-815.
27. Li W, Zhang H, Nie M, Tian Y, Chen X, Chen C, Chen H, Liu R. Ursolic acid derivative FZU-03,010 inhibits STAT3 and induces cell cycle arrest and apoptosis in renal and breast cancer cells. *Acta Biochim Biophys Sin* (*Shanghai*). 2017;49:367-373.
28. Luo J, Hu YL, Wang H. Ursolic acid inhibits breast cancer growth by inhibiting proliferation, inducing autophagy and apoptosis, and suppressing inflammatory responses via the PI3K/AKT and NF-κB signaling pathways in vitro. *Exp Ther Med.* 2017;14:3623-3631.
29. Cao C, Wang W, Lu L, Wang L, Chen X, Guo R, Li S, Jiang J. Inactivation of Beclin-1-dependent autophagy promotes ursolic acid-induced apoptosis in hypertrophic scar fibroblasts. *Exp Dermatol.* 2018;27:58-63.
30. Elstrom RL, Bauer DE, Buzzai M, Karnauskas R, Harris MH, Plas DR, Zhuang H, Cinalli RM, Alavi A, Rudin CM, Thompson CB. Akt stimulates aerobic glycolysis in cancer cells. *Cancer Res.* 2004; 64:3892-3899.
31. Robey RB, Hay N. Is Akt the "Warburg kinase"?-Akt-energy metabolism interactions and oncogenesis. *Semin Cancer Biol.* 2009;19:25-31.
32. Zheng QY, Jin FS, Yao C, Zhang T, Zhang GH, Ai X. Ursolic acid-induced AMP-activated protein kinase (AMPK) activation contributes to growth inhibition and apoptosis in human bladder cancer T24 cells. *Biochem Biophys Res Commun.* 2012;419:741-747.
33. Shen S, Zhang Y, Zhang R, Tu X, Gong X. Ursolic acid induces autophagy in U87MG cells via ROS-dependent endoplasmic reticulum stress. *Chem Biol Interact.* 2014;218:28-41.
34. Xavier CP, Lima CF, Pedro DF, Wilson JM, Kristiansen K, Pereira-Wilson C. Ursolic acid induces cell death and modulates autophagy through JNK pathway in apoptosis-resistant colorectal cancer cells. *J Nutr Biochem*. 2013;24:706-712.
35. Leng S, Hao Y, Du D, Xie S, Hong L, Gu H, Zhu X, Zhang J, Fan D, Kung HF. Ursolic acid promotes cancer cell death by inducing Atg5-dependent autophagy. *Int J Cancer.* 2013;133:2781-2790.
36. Li J, Liang X, Yang X. Ursolic acid inhibits growth and induces apoptosis in gemcitabine-resistant human pancreatic cancer via the JNK and PI3K/Akt/NF-κB pathways. *Oncol Rep.* 2012;28:501-510.
37. Song YH, Jeong SJ, Kwon HY, Kim B, Kim SH, Yoo DY. Ursolic acid from Oldenlandia diffusa induces apoptosis via activation of caspases and phosphorylation of glycogen synthase kinase 3 beta in SK-OV-3 ovarian cancer cells. *Biol Pharm Bull.* 2012;35:1022-1028.
38. Yan SL, Huang CY, Wu ST, Yin MC. Oleanolic acid and ursolic acid induce apoptosis in four human liver cancer cell lines. *Toxicol In Vitro.* 2010;24:842-848.
39. Chen JC, Chung JG, Chen LD. Gypenoside induces apoptosis in human Hep3B and HA22T tumour cells. *Cytobios.* 1999;100:37-48.
40. Nagamine T, Hayakawa K, Kusakabe T, Takada H, Nakazato K, Hisanaga E, Iha M. Inhibitory effect of fucoidan on Huh7 hepatoma cells through downregulation of CXCL12. *Nutr Cancer.* 2009;61: 340-347.
41. Li S, Liao X, Meng F, Wang Y, Sun Z, Guo F, Li X, Meng M, L Y, Sun C. Therapeutic role of ursolic acid on ameliorating hepatic steatosis and improving metabolic disorders in high-fat diet-induced non-alcoholic fatty liver disease rats. *PLoS One.* 2014;9:e86724.
42. Jung SH, Ha YJ, Shim EK, Choi SY, Jin JL, Yun-Choi HS, Lee JR. Insulin-mimetic and insulin-sensitizing activities of a pentacyclic triterpenoid insulin receptor activator. *Biochem J.* 2007;403:243-250.
43. Ramírez-Rodríguez AM, González-Ortiz M, Martínez-Abundis E, Acuña Ortega N. Effect of ursolic acid on metabolic syndrome, insulin sensitivity, and inflammation. *J Med Food.* 2017;20:882-886.
44. Chu X, He X, Shi Z, Li C, Guo F, Li S, Li Y, Na L, Sun C. Ursolic acid increases energy expenditure through enhancing free fatty acid uptake and β-oxidation via an UCP3/AMPK-dependent pathway in skeletal muscle. *Mol Nutr Food Res.* 2015;59:1491-1503.
45. Kunkel SD, Elmore CJ, Bongers KS, Ebert SM, Fox DK, Dyle MC, Bullard SA, Adams CM. Ursolic acid increases skeletal muscle and brown fat and decreases diet-induced obesity, glucose intolerance and fatty liver disease. *PLoS One.* 2012;7:e39332.
46. Jia Y, Bhuiyan MJ, Jun HJ, Lee JH, Hoang MH, Lee HJ, Kim N, Lee D, Hwang KY, Hwang BY, Choi DW, Lee SJ. Ursolic acid is a PPAR-α agonist that regulates hepatic lipid metabolism. *Bioorg Med Chem Lett.* 2011;21:5876-5880.
47. Jia Y, Kim S, Kim J, Kim B, Wu C, Lee JH, Jun HJ, Kim N, Lee D, Lee SJ. Ursolic acid improves lipid and glucose metabolism in high-fat-fed C57BL/6J mice by activating peroxisome proliferator-activated receptor alpha and hepatic autophagy. *Mol Nutr Food Res.* 2015;59:344-354.
48. Jang SM, Yee ST, Choi J, Choi MS, Do GM, Jeon SM, Yeo J, Kim MJ, Seo KI, Lee MK. Ursolic acid enhances the cellular immune system and pancreatic beta-cell function in streptozotocin-induced diabetic mice fed a high-fat diet. *Int Immunopharmacol.* 2009;9:113-119.
49. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. *J Clin Epidemiol.* 1988;41:105-114.
50. Ness AR, Powles JW. Fruit and vegetables, and cardiovascular disease: a review. *Int J Epidemiol.* 1997;26:1-13.
51. Somova LI, Shode FO, Mipando M. Cardiotonic and antidysrhythmic effects of oleanolic and ursolic acids, methyl maslinate and uvaol. *Phytomedicine.* 2004;11:121-129.
52. Pozo M, Castilla V, Gutierrez C, de Nicolás R, Egido J, González-Cabrero J. Ursolic acid inhibits neointima formation in the rat carotid artery injury model. *Atherosclerosis.* 2006;184:53-62.
53. Radhiga T, Rajamanickam C, Senthil S, Pugalendi KV. Effect of ursolic acid on cardiac marker enzymes, lipid profile and macroscopic enzyme mapping assay in isoproterenol-induced myocardial ischemic rats. *Food Chem Toxicol.* 2012;50:3971-3977.
54. Radhiga T, Rajamanickam C, Sundaresan A, Ezhumalai M, Pugalendi KV. Effect of ursolic acid treatment on apoptosis and DNA damage in isoproterenol-induced myocardial infarction. *Biochimie.* 2012;94:1135-1142.
55. Saravanan R, Pugalendi V. Impact of ursolic acid on chronic ethanol-induced oxidative stress in the rat heart. *Pharmacol Rep.* 2006;

58:41-47.
56. Lv YY, Jin Y, Han GZ, Liu YX, Wu T, Liu P, Zhou Q, Liu KX, Sun HJ. Ursolic acid suppresses IL-6 induced C-reactive protein expression in HepG2 and protects HUVECs from injury induced by CRP. *Eur J Pharm Sci*. 2012;45:190-194.
57. Bondy SC1, LeBel CP. The relationship between excitotoxicity and oxidative stress in the central nervous system. *Free Radic Biol Med*. 1993;14:633-642.
58. Castegna A, Aksenov M, Aksenova M, Thongboonkerd V, Klein JB, Pierce WM, Booze R, Markesbery WR, Butterfield DA. Proteomic identification of oxidatively modified proteins in Alzheimer's disease brain. Part I: creatine kinase BB, glutamine synthase, and ubiquitin carboxy-terminal hydrolase L-1. *Free Radic Biol Med*. 2002;33:562-571.
59. De Iuliis A, Grigoletto J, Recchia A, Giusti P, Arslan P. A proteomic approach in the study of an animal model of Parkinson's disease. *Clin Chim Acta*. 2005;357:202-209.
60. Zhang T, Su J, Wang K, Zhu T, Li X. Ursolic acid reduces oxidative stress to alleviate early brain injury following experimental subarachnoid hemorrhage. *Neurosci Lett*. 2014;579:12-17.
61. Shih YH, Chein YC, Wang JY, Fu YS. Ursolic acid protects hippocampal neurons against kainate-induced excitotoxicity in rats. *Neurosci Lett*. 2004;362:136-140.
62. Huang HC, Huang CY, Lin-Shiau SY, Lin JK. Ursolic acid inhibits IL-1beta or TNF-alpha-induced C6 glioma invasion through suppressing the association ZIP/p62 with PKC-zeta and downregulating the MMP-9 expression. *Mol Carcinog*. 2009;48:517-531.
63. Lu J, Wu DM, Zheng YL, Hu B, Zhang ZF, Ye Q, Liu CM, Shan Q, Wang YJ. Ursolic acid attenuates D-galactose-induced inflammatory response in mouse prefrontal cortex through inhibiting AGEs/RAGE/NF-κB pathway activation. *Cereb Cortex*. 2010;20:2540-2548.
64. Lu J, Zheng YL, Wu DM, Luo L, Sun DX, Shan Q. Ursolic acid ameliorates cognition deficits and attenuates oxidative damage in the brain of senescent mice induced by D-galactose. *Biochem Pharmacol*. 2007;74:1078-1090.
65. Rao JS, Steck PA, Mohanam S, Stetler-Stevenson WG, Liotta LA, Sawaya R. Elevated levels of M(r) 92,000 type IV collagenase in human brain tumors. *Cancer Res*. 1993;53(10 Suppl):2208-2211.
66. Ma JQ, Ding J, Zhang L, Liu CM. Protective effects of ursolic acid in an experimental model of liver fibrosis through Nrf2/ARE pathway. *Clin Res Hepatol Gastroenterol*. 2015;39:188-197.
67. Yang LJ, Tang Q, Wu J, Chen Y, Zheng F, Dai Z, Hann SS. Inter-regulation of IGFBP1 and FOXO3a unveils novel mechanism in ursolic acid-inhibited growth of hepatocellular carcinoma cells. *J Exp Clin Cancer Res*. 2016;35:59.
68. Tailleux A, Wouters K, Staels B. Roles of PPARs in NAFLD: potential therapeutic targets. *Biochim Biophys Acta*. 2012;1821:809-818.
69. Reddy JK, Rao MS. Lipid metabolism and liver inflammation. II. Fatty liver disease and fatty acid oxidation. *Am J Physiol Gastrointest Liver Physiol*. 2006;290:G852-858.
70. Gao HY, Li GY, Lou MM, Li XY, Wei XY, Wang JH. Hepatoprotective effect of Matrine salvianolic acid B salt on Carbon Tetrachloride-Induced Hepatic Fibrosis. *J Inflamm* (*Lond*). 2012;9:16.
71. Son HS, Kwon HY, Sohn EJ, Lee JH, Woo HJ, Yun M, Kim SH, Kim YC. Activation of AMP-activated protein kinase and phosphorylation of glycogen synthase kinase3 β mediate ursolic acid induced apoptosis in HepG2 liver cancer cells. *Phytother Res*. 2013;27:1714-1722.
72. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes Care*. 2009;32 Suppl 2:S157-163.
73. Gardner DS, Rhodes P. Developmental origins of obesity: programming of food intake or physical activity? *Adv Exp Med Biol*. 2009;646:83-93.
74. Carter HN, Chen CC, Hood DA. Mitochondria, muscle health, and exercise with advancing age. *Physiology* (*Bethesda*). 2015;30:208-223.
75. Seo DY, Lee SR, Kim N, Ko KS, Rhee BD, Han J. Age-related changes in skeletal muscle mitochondria: the role of exercise. *Integr Med Res*. 2016;5:182-186.
76. Cederholm TE, Bauer JM, Boirie Y, Schneider SM, Sieber CC, Rolland Y. Toward a definition of sarcopenia. *Clin Geriatr Med*. 2011;27:341-353.
77. Cederholm T, Morley JE. Sarcopenia: the new definitions. *Curr Opin Clin Nutr Metab Care*. 2015;18:1-4.
78. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, Stamm E, Newman AB. Attenuation of skeletal muscle and strength in the elderly: the Health ABC Study. *J Appl Physiol* (*1985*). 2001;90:2157-2165.
79. Masanes F, Culla A, Navarro-Gonzalez M, Navarro-Lopez M, Sacanella E, Torres B, Lopez-Soto A. Prevalence of sarcopenia in healthy community-dwelling elderly in an urban area of Barcelona (Spain). *J Nutr Health Aging*. 2012;16:184-187.
80. Viana JU, Silva SL, Torres JL, Dias JM, Pereira LS, Dias RC. Influence of sarcopenia and functionality indicators on the frailty profile of community-dwelling elderly subjects: a cross-sectional study. *Braz J Phys Ther*. 2013;17:373-381.
81. Amigues I, Schott AM, Amine M, Gelas-Dore B, Veerabudun K, Paillaud E, Beauchet O, Rolland Y, Canouï Poitrine F, Bonnefoy M. Low skeletal muscle mass and risk of functional decline in elderly community-dwelling women: the prospective EPIDOS study. *J Am Med Dir Assoc*. 2013;14:352-357.
82. Bakhtiari N, Hosseinkhani S, Tashakor A, Hemmati R. Ursolic acid ameliorates aging-metabolic phenotype through promoting of skeletal muscle rejuvenation. *Med Hypotheses*. 2015;85:1-6.
83. Ebert SM, Dyle MC, Bullard SA, Dierdorff JM, Murry DJ, Fox DK, Bongers KS, Lira VA, Meyerholz DK, Talley JJ, Adams CM. Identification and small molecule inhibition of an activating transcription factor 4 (ATF4)-dependent pathway to age-related skeletal muscle weakness and atrophy. *J Biol Chem*. 2015;290:25497-25511.
84. Jeong JW, Shim JJ, Choi ID, Kim SH, Ra J, Ku HK, Lee DE, Kim TY, Jeung W, Lee JH, Lee KW, Huh CS, Sim JH, Ahn YT. Apple pomace extract improves endurance in exercise performance by increasing strength and weight of skeletal muscle. *J Med Food*. 2015;18:1380-1386.
85. Ogasawara R, Sato K, Higashida K, Nakazato K, Fujita S. Ursolic acid stimulates mTORC1 signaling after resistance exercise in rat skeletal muscle. *Am J Physiol Endocrinol Metab*. 2013;305:E760-765.
86. Chen J, Wong HS, Leong PK, Leung HY, Chan WM, Ko KM. Ursolic acid induces mitochondrial biogenesis through the activation of AMPK and PGC-1 in C2C12 myotubes: a possible mechanism underlying its beneficial effect on exercise endurance. *Food Funct*. 2017;8:2425-2436.

87. Bang HS, Seo DY, Chung YM, Oh KM, Park JJ, Arturo F, Jeong SH, Kim N, Han J. Ursolic Acid-induced elevation of serum irisin augments muscle strength during resistance training in men. *Korean J Physiol Pharmacol.* 2014;18:441-446.
88. Bang HS, Seo DY, Chung YM, Kim DH, Lee SJ, Lee SR, Kwak HB, Kim TN, Kim M, Oh KM, Son YJ, Kim S, Han J. Ursolic acid supplementation decreases markers of skeletal muscle damage during resistance training in resistance-trained men: a pilot study. *Korean J Physiol Pharmacol.* 2017;21:651-656.
89. Cho YH, Lee SY, Kim CM, Kim ND, Choe S, Lee CH, Shin JH. Effect of loquat leaf extract on muscle strength, muscle mass, and muscle function in healthy adults: a randomized, double-blinded, and placebo-controlled trial. *Evid Based Complement Alternat Med.* 2016;2016:4301621.
90. Church DD, Schwarz NA, Spillane MB, McKinley-Barnard SK, Andre TL, Ramirez AJ, Willoughby DS. l-Leucine increases skeletal muscle IGF-1 but does not differentially increase Akt/mTORC1 signaling and serum IGF-1 compared to ursolic acid in response to resistance exercise in resistance-trained men. *J Am Coll Nutr.* 2016;35:627-638.
91. Kazmi I, Afzal M, Rahman S, Iqbal M, Imam F, Anwar F. Antiobesity potential of ursolic acid stearoyl glucoside by inhibiting pancreatic lipase. *Eur J Pharmacol.* 2013;709:28-36.
92. Zhang Y, Song C, Li H, Hou J, Li D. Ursolic acid prevents augmented peripheral inflammation and inflammatory hyperalgesia in high-fat diet-induced obese rats by restoring downregulated spinal PPARα. *Mol Med Rep*. 2016;13:5309-5316.
93. Wu DM, Lu J, Zhang YQ, Zheng YL, Hu B, Cheng W, Zhang ZF, Li MQ. Ursolic acid improves domoic acid-induced cognitive deficits in mice. *Toxicol Appl Pharmacol.* 2013;271:127-136.
94. Gong YY, Liu YY, Yu S, Zhu XN, Cao XP, Xiao HP. Ursolic acid suppresses growth and adrenocorticotrophic hormone secretion in AtT20 cells as a potential agent targeting adrenocorticotrophic hormone-producing pituitary adenoma. *Mol Med Rep.* 2014;9:2533-2539.
95. Rai SN, Yadav SK, Singh D, Singh SP. Ursolic acid attenuates oxidative stress in nigrostriatal tissue and improves neurobehavioral activity in MPTP-induced Parkinsonian mouse model. *J Chem Neuroanat.* 2016;71:41-49.