New applications of oleanolic acid and its derivatives as cardioprotective agents: A review of their therapeutic perspectives

Ning Sun [a], Dongli Li [b], Xiaoqing Chen [c], Panpan Wu [b], Yu-Jing Lu [d], Ning Hou [c,*], Wen-Hua Chen [b,*], Wing-Leung Wong [a,b,*]

[a] The State Key Laboratory of Chemical Biology and Drug Discovery, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, P. R. China.
[b] School of Biotechnology and Health Sciences, Wuyi University, Jiangmen 529020, P. R. China; International Healthcare Innovation Institute (Jiangmen), Jiangmen 529040, P. R. China.
[c] Key Laboratory of Molecular Target & Clinical Pharmacology, School of Pharmaceutical Sciences and the Fifth Affiliated Hospital, Guangzhou Medical University, Guangzhou 511436, P. R. China.
[d] Goldenhealth Biotechnology Co. Ltd, Foshan 528000, P. R. China.

* Corresponding authors
E-mail (NH): houning@gzhmu.edu.cn
Email (WHC): whchen@smu.edu.cn
E-mail (WLW): wing.leung.wong@polyu.edu.hk

Abstract

Oleanolic acid is an analogue of pentacyclic triterpenoids. It has been used as a hepatic drug for over 20 years in China. Currently, there are only five approved drugs derived from pentacyclic triterpenoids including oleanolic acid (liver diseases), asiaticoside (wound healing), glycyrrhizinate (liver diseases), isoglycyrrhizinate (liver disease) and sodium aescinate (hydrocephalus). To understand more about the bioactivity and functional mechanisms of oleanolic acid is able to develop potent therapeutic agents, in particular for the prevention and treatment of heart diseases, which are the leading cause of death for people worldwide. The primary aim of this mini-review is to summarize concisely the new applications of oleanolic acid and its derivatives as cardioprotective agents reported in recent years and to highlight their therapeutic perspectives in cardiovascular diseases.

1. Introduction

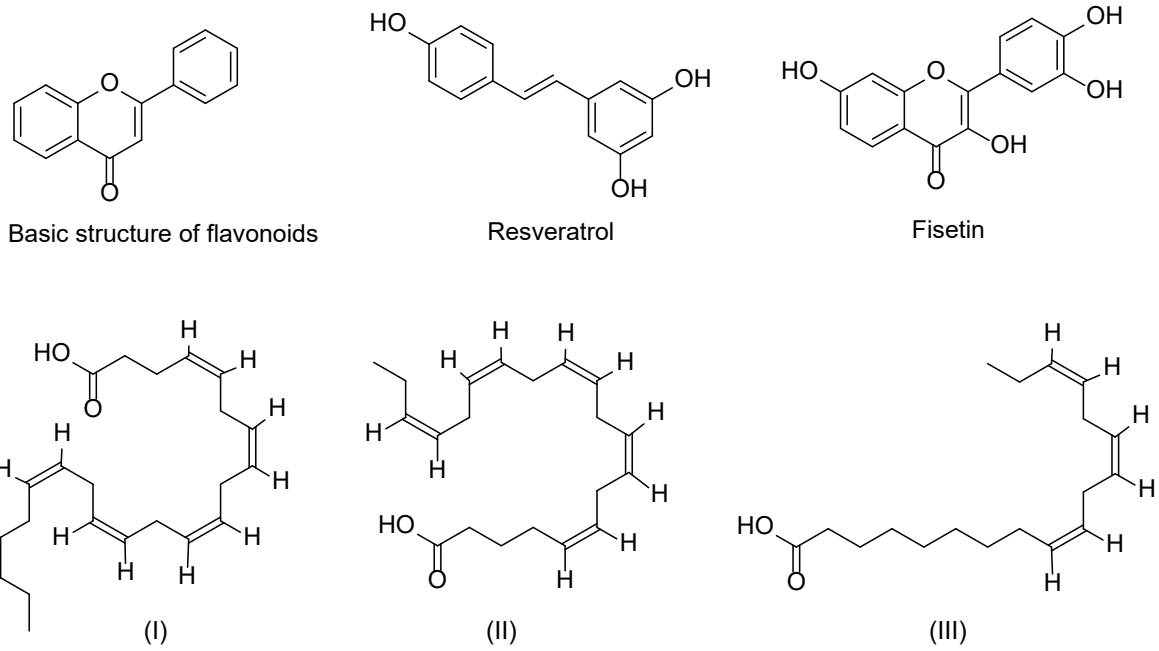
Cardiovascular diseases (CVDs) generally refer to a group of disorders of heart and blood vessels. CVDs are usually caused by a combination of risk factors [1]. With respect to the fact sheets on CVDs released by World Health Organization (WHO) in 2017, CVDs were the number one cause of death worldwide. In 2016, an estimated number of 17.9 million people died from CVDs (85% are due to heart attack and stroke), which represents 31% of all global deaths. It is estimated that up to 23.6 million people may probably die from CVDs by 2030, most of which are from heart disease and stroke [2]. However, most CVDs can be prevented by addressing behavioral risk factors. The key recommendations from WHO to protect heart health are to engage in physical activity for at least 30 minutes every day of the week, eat at least five servings of fruit and vegetables a day, and limit salt intake to less than one teaspoon a day [2]. All these habits help prevent heart attacks and strokes.

Cardioprotective drugs or therapeutics are important in the treatment of patients with cardiovascular disease. The clinical use of pharmacologic agents and drugs such as aspirin, statins, adrenergic β-blockers, renin-angiotensin system (RAS) blockers, antiarrhythmic drugs, anticoagulants, thrombolytic therapy, digoxin, diuretics, antiplatelet drugs, and calcium antagonists are vital in combating and preventing CVDs over the last few decades [3, 4]. Moreover, estrogen (a steroid hormone) is also demonstrated to exert cardioprotective effects against atherosclerosis [5]. In recent years, both exercise and pharmacotherapies have been applied as modern medical approaches to treat CVDs [6, 7]. Despite a large number of cardioprotective therapies have been investigated regarding the methods and mechanisms of cardioprotective interventions, the effective therapy has yet to be successfully implemented clinically.

From the COST Action (termed EU-CARDIOPROTECTION) [8], the main challenge to develop effective therapies is to improve the translation of novel and effective pre-clinical cardioprotective therapies into the clinical field for patient benefit. The crucial reasons for the failure in the translation of new cardioprotective therapies into the clinical setting are multiple and complex and a number of recent review papers have discussed on these technical issues [9-12]. Some of the most

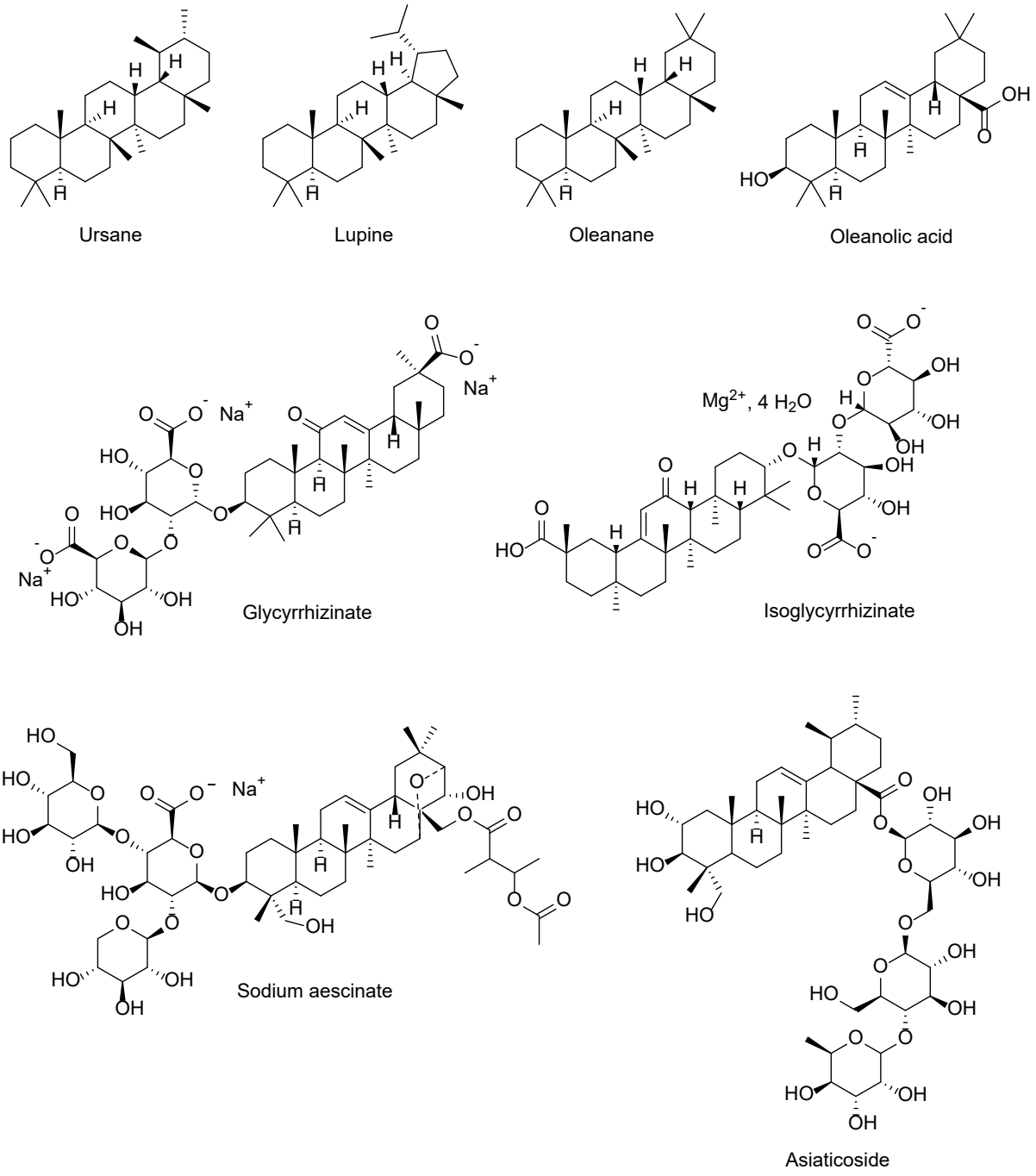
important issues mentioned to be addressed in the near future are as follows: (i) to discover novel signaling pathways and therapeutic targets within and outside the cardiomyocyte and to identify innovative strategies for cardioprotection; (ii) to investigate combination therapy, instead of single targeted cardioprotective therapies, directed to multiple cardioprotective pathways and targets both within and outside the cardiomyocyte as an innovative treatment strategy for cardioprotection; (iii) to improve the translational value of the animal myocardial infarct models and (iv) to improve the therapies with inconsistent cardioprotective efficacy [8].

Natural product-based drug discovery over the past few years has become another important part of the study targeted at cardioprotective therapy to develop new compounds as drugs to treat CVDs [13]. Recent epidemiological and clinical studies indicate that some dietary nutrients including flavonoids from citrus fruits, pulses, red wine, tea and cocoa; omega-3 fatty acids from fish oil and fish-based products; lycopene from tomato and its related products; resveratrol from grapes and red wine; fisetin and its analogues from strawberry, blueberries, mangoes, apples, persimmon, kiwi, onions, grapes and cucumber; olive oil, coffee, soy and so on, show profound cardioprotective effects in both primary and secondary prevention of coronary heart diseases (Scheme 1). The mechanism of action on cardioprotection (prevention and treatment of cardiovascular disorders) derived from these dietary nutritional supplements have also been studied and reviewed [14]. Therefore, the phytochemicals of plant-derived small molecules appear to provide great advantages in the treatment of various diseases. For examples, anticancer drug paclitaxel and antimalarial agent artemisinin are phytochemicals originally extracted from plants [15, 16]. The cardioprotective effects of plant-derived small molecules and their mechanism of actions against doxorubicin-induced cardiotoxicity were also reviewed in 2016 [17].



Scheme 1. Natural product-based cardioprotective therapy: some bioactive compounds from some dietary nutrients.

Pentacyclic triterpenoids including ursane, lupane and oleanane (Scheme 2) are a class of naturally occurring bioactive compounds and are widely distributed in many medicinal herbs, such as Glycyrrhiza species, Gymnema species, Centella asiatica, Camellia sinensis, Crataegus species and Olea europaea [18]. These natural products are commonly used in traditional medicine for the treatment of diabetes and diabetic complications [19]. Nowadays, five drugs have been approved from the analogues of pentacyclic triterpenoids including oleanolic acid (liver diseases), asiaticoside (wound healing), glycyrrhizinate (liver diseases), isoglycyrrhizinate (liver diseases) and sodium aescinate (hydrocephalus) [20-22].



Scheme 2. Chemical structures of pentacyclic triterpenoids (Ursane, Lupine, Oleanane) and five approved drugs from their analogues.

Among the pentacyclic triterpenes analogues, oleanolic acid is one of the most well-known natural compounds. It has been clinically used as a hepatoprotective drug in China for decades [23]. The natural occurrence of oleanolic acid is either in free acid or in the form of triterpenoid saponin linked with one or more sugar chains [24]. This compound is widely found in several dietary and medicinal plants and can be

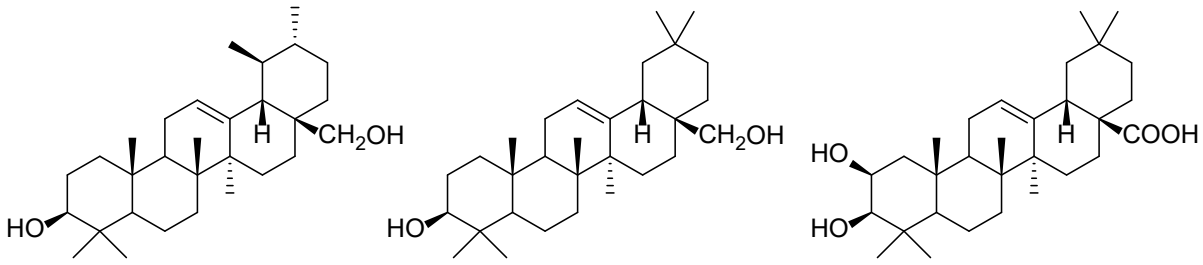
isolated from over 1600 plant species. Its major abundance is found in ginseng roots [25] and in olive plant (Olea europaea) [26] that is the main commercial source for the mass production of this compound. In recent years, the diverse biological activities of oleanolic acid including anticancer, anti-osteoporosis, anti-obesity, anti-diabetic, anti-inflammatory, immune-regulatory, and antioxidant effects have been intensively investigated and documented [22, 27-31]. Because oleanolic acid possesses many merit properties and biological functions, it is therefore able to provide a readily available and cheap traditional medicine source for the treatment of myocardial ischemia in many developing countries. This is also an important advantage of developing oleanolic acid to prevent and treat cardiovascular disease compared to other traditional cardioprotective drugs. In this review, we summarized the biological functions, pharmaceutical and medical uses of oleanolic acid and its derivatives as the cardioprotective agents for CVDs treatment and highlighted their therapeutic perspectives.

2. Antiatherogenic activity and hypolipidemic effect

To obtain pentacyclic triterpenes from dietary fruits and vegetables is an important tool for the prevention of cardiovascular diseases [32]. Some studies pointed out that thrombosis is one of the latest fatal clinical consequences of atherosclerosis and the oxidation of low-density lipoprotein (LDL) cholesterol may play a critical role in the early state of atherosclerosis [33]. A recent report examined oleanolic acid and its derivatives including uvaol, erythrodiol, and maslinic acid as antioxidant and antithrombotic agents in the potential cardioprotective activity (Scheme 3). Their antioxidant and antithrombotic activities related to LDL particles were evaluated *in vitro* [34]. The results revealed that maslinic acid, uvaol and erythrodiol show antiatherogenic effect. Both uvaol and erythrodiol exhibited antioxidant and antithrombotic activities while maslinic acid demonstrated the most potent dose-dependent antioxidant effect but no antithrombotic properties. The study illustrated that the cardioprotective effect attributed from the dietary triterpenes may

function by different mechanisms of action that are related to antioxidant and antithrombotic activities.

The effect of oleanolic acid on atherosclerosis development and vascular function in apolipoprotein E knockout ($ApoE^{-/-}$) mice was also reported. The oral treatment with the compound is able reduce atherosclerosis development in the aortic arch and descending aorta of $ApoE^{-/-}$ mice. The mechanism is found independent of plasma total cholesterol and triglyceride levels and is associated with the alterations in vascular contractile reactivity without significant changes in eNOS-mediated acetylcholine relaxation. However, oleanolic acid is believed to reduce iNOS expression that may alter the vascular reactivity to phenylephrine [35].



Scheme 3. Structures of Uvaol, Erythrodiol, and Maslinic acid.

3. Cardiovascular homeostasis effects

Homeostasis is a very important process that helps human body control and maintain at the state of balance or internal equilibrium. The circulatory system, which is responsible for transporting blood throughout our body, is one of the systems in the homeostasis process. Cardiovascular homeostasis is to regulate of the delivery of hormones and nutrients and also the removal of wastes through the blood stream. Therefore, in our body, cardiovascular homeostasis is one of the interconnecting systems accountable for maintaining stability corresponding to the changes from both the environmental pressures such as external temperature change and the internal issues such as hormone imbalance. The body uses these systems of homeostasis process to retain the body function and to keep organs, muscles, nerves, and all other tissues working properly. The circulatory systems include the heart and connected

system of blood vessels. The cardiovascular system is responsible to regulate and control heart rate, blood pressure, and other characteristics, and to ensure our body is supplied with the required hormones, oxygen, and nutrients. The our body is via this system to retain the whole body function including to keep all organs, muscles, nerves, and tissues as well to work properly.

Oleanolic acid has been demonstrated possessing beneficial effects on the regulation of cardiovascular homeostasis. Plasma levels, atrial synthesis, and the secretion of atrial natriuretic peptide (ANP) are the key parameters that verify the effects of oleanolic acid. *In vivo* study in rats showed that the administration of oleanolic acid is able to increase plasma ANP levels, atrial ANP content, and ANP mRNA expression in a dose-related manner [36]. By the chronical treatment with oleanolic acid (administered orally at 10–30 mg/kg/day for two weeks), the effects on ANP secretion, atrial stretch, and muscarinic acetylcholine receptor activation to the atria from rats were evaluated. The results compared to those treated with vehicle show that the baseline levels of ANP secretion were higher in the atria treated with oleanolic acid. The results indicate that oleanolic acid increases plasma ANP levels through the enhancement of ANP synthesis and secretion in rats. It is therefore suggested that oleanolic acid has beneficial effects on the regulation of cardiovascular homeostasis.

An invention based on the composition containing oleanolic acid as the active ingredient for preventing, improving or treating body fluid and cardiovascular system homeostasis impairment disorders was disclosed in 2014 [37]. For the rats reference to 10–30 mg/kg/daily oral administration, the atrial diuretic hormone (ANP) mRNA levels of atrial tissue, the promotion of the synthesis and secretion of atrial diuretic hormone, and the atrial night power were increased. Although some recent evidences suggested that oleanolic acid possesses beneficial effects on the regulation of the cardiovascular homeostasis, its exact role in the regulation of body fluid balance and blood pressure homeostasis and its mechanisms involved are not very clear to-date.

In 2017, some experimental results were reported on the identification of the

effects of using oleanolic acid on the renin-angiotensin system, cardiac natriuretic hormone (ANP) system, renal function, and blood pressure in normotensive and renovascular hypertensive rats [38]. The parameters that change in the plasma levels of hormones and the expressions of renin, angiotensin II receptors, ANP, natriuretic peptide receptor-C, M2 muscarinic receptor, and GIRK4 were determined in the kidney, heart and aorta in the rats. It was found that oleanolic acid is able to (i) suppress plasma levels of renin activity and aldosterone; (ii) block intrarenal levels of renin and angiotensin II type-1 receptor expression; (iii) increase angiotensin II type-2 receptor; and (iv) increase plasma levels of ANP.

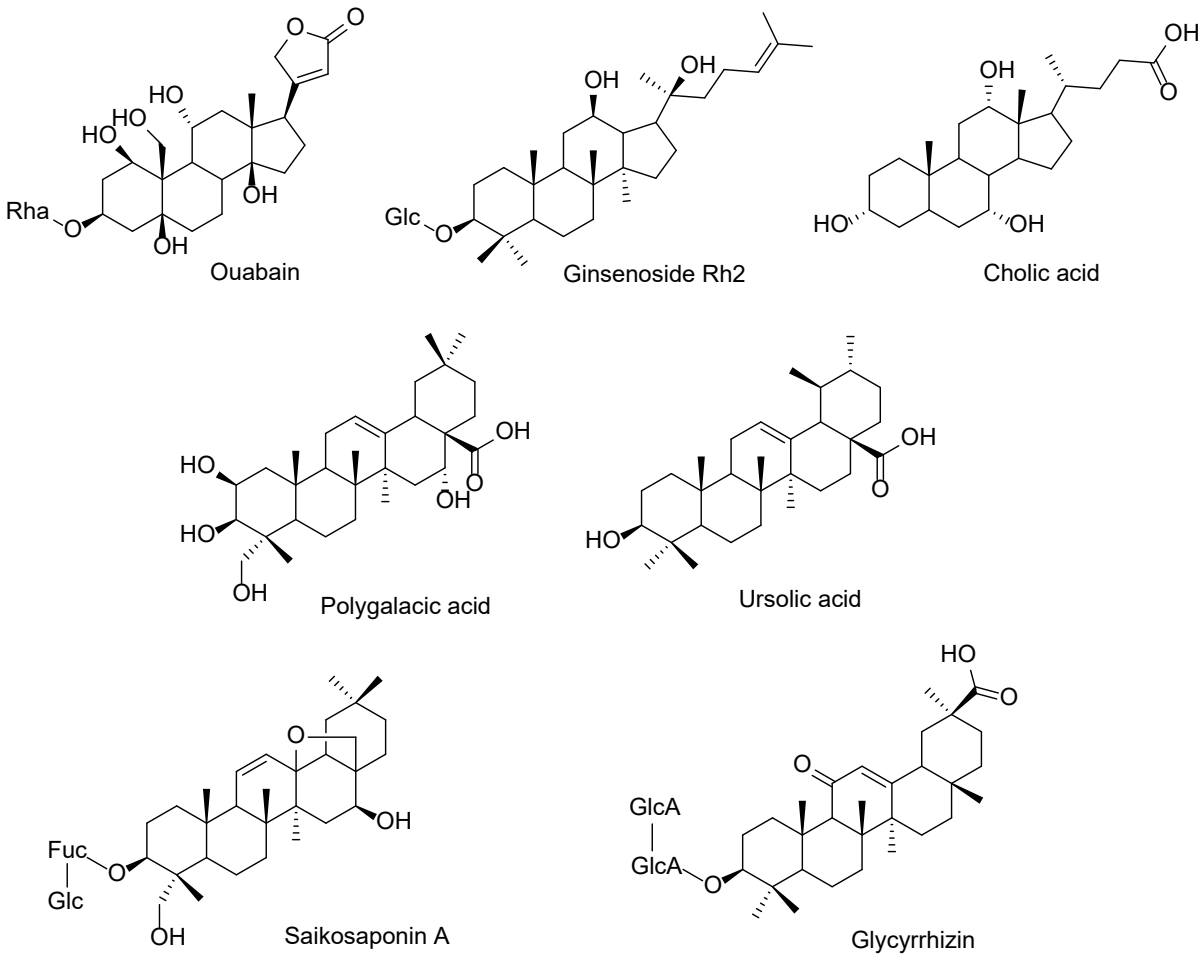
The study also indicated that oleanolic acid suppressed angiotensin II type 1 receptor and natriuretic peptide receptor-C expression and increased angiotensin II type 2 receptor and ANP expression in the heart and aorta. These results suggested that oleanolic acid makes urinary volume, electrolyte excretion and glomerular filtration rate in normotensive rats more prominent and also suppresses arterial blood pressure in hypertensive rats. Therefore, the beneficial effects of oleanolic acid on the cardiorenal system may be closely related with its roles in the renin-angiotensin system and cardiac natriuretic hormone system, which is rarely investigated in literature.

4. Enhancing cardiac function by inhibiting Na^+/K^+-ATPase

Some Chinese medicinal herbs are able to promote blood circulation, such as the improvement of hemodynamic, hemorheology, and removing blood stasis, to achieve therapeutic effects for heart diseases [39]. However, there are only a few studies on the mechanisms of using these medicinal herbs to promote or stimulate blood circulation. The steroid-like compounds (some examples are listed in Scheme 4), in particular cardiac glycosides such as ouabain and digoxin, have been applied in the treatment of congestive heart failure and supraventricular arrhythmias. The therapeutic effect of these compounds are probably attributed to their reversible inhibition on the membrane-bound Na^+/K^+-ATPase located in human myocardium.

The inhibition results in the increase of intracellular Na^+ concentration that activates a Na^+/Ca^{2+} exchanger and subsequently in enriching the intracellular Ca^{2+} concentration. The raised-up intracellular Ca^{2+} concentration leads to an increased inotropism that accentuates the force of myocardial contraction by increasing the velocity and extent of sarcomere shortening [40].

Ginsenosides with sugar moieties attached at the C-3 position of their core four-membered ring structure are demonstrated possessing good inhibitory potency on Na^+/K^+-ATPase activity [41]. Their cardiac therapeutic effects could be due to the promotion of blood circulation. A few years ago, a study examined the use of oleanolic acid and ursolic acid as moderate inhibitors of Na^+/K^+-ATPase and their effects in the promotion of blood circulation. It was found that the polygalacic acid, glycyrrhizin, and saikosaponin A showed weak inhibition. However, the IC_{50} values of oleanolic acid (94.3 μmol/L) and ursolic acid (76.7 μmol/L) were comparable to that of ginsenoside Rh2 (37.5 μmol/L). The relatively high inhibitory potency observed with ursolic acid and oleanolic acid is probably attributed to the formation of hydrogen bonding between its carboxyl group at C-17 and the Ile322 residue in the deep cavity close to the K^+ binding sites of Na^+/K^+-ATPase, as revealed by molecular docking study [42]. Interestingly, this hydrogen-bonding interaction is not observed in saikosaponin A, polygalacic acid, or glycyrrhizin. In addition, recent findings give more evidences to support that Na^+/K^+-ATPase may be a good drug target for the treatment of CVDs such as congestive heart failure and ischemic stroke [43].

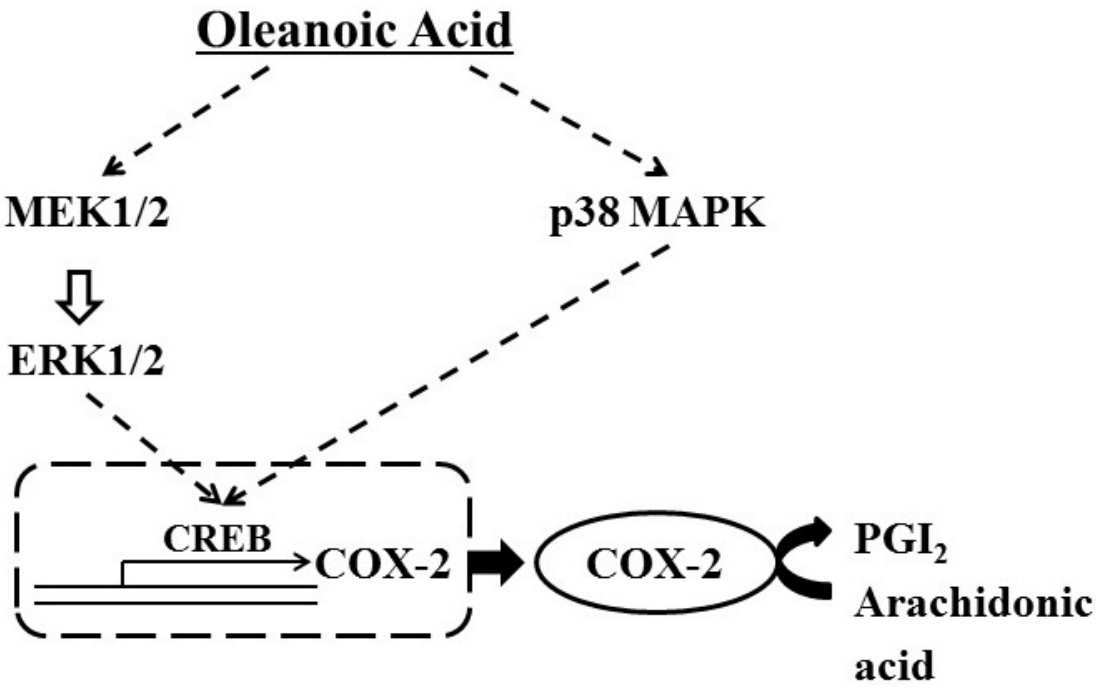


Scheme 4. The steroid-like compounds and cardiac glycosides used in heart diseases treatments.

5. Vasorelaxant effects

Oleanolic acid is also found inducing prostaglandin I_2 (PGI_2) release by human coronary vascular smooth muscle cells (SMC) in a Cyclooxygenase (Cox-2) dependent manner [44]. The activation mechanism generally involves HDL-induced upregulation of Cox-2, in which Mitogen-activated protein kinase (MAPK) signaling and cAMP regulatory element-binding protein (CREB) activation are included. In recent years, the role of Cox-2 in the vascular system has become clear. It is found associated with the pro-inflammatory or pro-atherogenic stages due to its inducible characters and upregulation in monocyte-derived macrophages present in atherosclerotic lesions. The experimental data obtained from both genetically modified mice and wild-type animal models highlight that Cox-2 derived PGI_2 prevents local thrombosis and neointima formation and also contributes to defensive

mechanisms of the myocardium [45]. The study indicated that some synthetic triterpenoid analogues of oleanolic acid exhibited anti-inflammatory properties preventing the upregulation of both inducible nitric oxide synthase and cyclooxygenase Cox-2 in the cultures of human macrophages and mouse cells with interferon-γ stimulation [46].



Scheme 5. The proposed mechanisms involving Cox-2 upregulation and PGI_2 release by oleanolic acid in human coronary smooth muscle cells. Figure modified from ref. [44].

The upregulation of Cox-2 with oleanolic acid through the activation of MAPK pathways was investigated. Oleanolic acid induced the early activation of p38 MAPK and MAPK (ERK1/2). The activation of p38 MAPK was found increased over time. However, the activation of ERK1/2 was more transient and then decreased after stimulation. The findings may conclude that both p38 MAPK and ERK1/2 are possibly involved in the upregulation of Cox-2 stimulated by oleanolic acid. The experimental results indicated that oleanolic acid is a strong inducer of PGI_2 synthesis in human coronary SMC. The activation of CREB-P (phosphorylation in Ser133)

reached a maximal induction at 15 min with 50 mmol/L oleanolic acid. Scheme 5 outlined the pathways involved in the Cox-2 expression/PGI_2 release that induced by oleanolic acid [44]. It seems that the activation of CREB is the key factor associated with the Cox-2 transcriptional regulation.

Nitric oxide (NO) has been identified as a very critical regulator of vascular functions in recent years and it controls blood vessel tone and blood cell interactions with the vascular wall [47]. Clinical studies support that endothelium-derived NO is involved in normal and pathological blood pressure regulation in humans. Therefore, the NO/cGMP signaling relationship plays an important role in vascular smooth muscle relaxation. The *in vitro* investigations into oleanolic acid and erythrodiol (Scheme 4) as vasodilatory agents suggested an endothelium-dependent vasorelaxation in rat aorta. The results reveal that the mechanism of relaxation is mediated most likely by the endothelial production of nitric oxide (NO) and also suggest that both oleanolic acid and erythrodiol may have interesting therapeutic potentials as new vasodilator drugs to protect the cardiovascular system [48]. In addition, ursolic acid was found to produce a significant vasodilator effect in a concentration-dependent and endothelium-dependent manner. The mode of action is also found related with the activation of nitric oxide synthase (NOS), followed by an increase in NO production and release. Consequently, the guanylate cyclase (sGC), a signal transduction enzyme that is vascular smooth muscle soluble, was activated to form the second messenger cGMP [49].

6. Autoimmune myocarditis

Myocarditis is a serious disease, which represents the most common cause of chronic heart failure or sudden death in people. The pathogenesis of this heart disease is not very clear to-date. However, there are substantial evidences pointing out that the autoimmune response to heart antigens, in particular cardiac myosin may contribute to the disease process after viral infection [50]. The current therapeutic strategies in myocarditis are limited and depend on the different stages of the disease, which

include the elimination of the infecting agent, inhibition of the heart-specific autoimmune response, reduction of inflammation and so on. The use of new immunosuppressive agents commonly encountered serious disadvantages such as high toxicity, high cost and limited efficacy. The identification of new compounds for the treatment of myocarditis and dilated cardiomyopathy (DCM) with low toxicity and cost is a big challenge.

The beneficial actions of using oleanolic acid as a potent immune-regulatory drug in myocarditis treatment have been known for several years [51]. However, only a few reports on this aspect can be found in literature. A comprehensive study reported the evaluation of the effectiveness of oleanolic acid *in vivo* in the prevention and treatment of experimental autoimmune myocarditis (EAM) through (i) the administration of the compound to the cardiac α-myosin (MyHc-$\alpha_{614–629}$)-immunized BALB/c mice from day 0 or day 21 post-immunization and (ii) the addition of the compound to stimulated-cardiac cells *in vitro*. The results compared with the control groups showed that the heart-weight per body-weight ratio and plasma levels of brain natriuretic peptide and myosin-specific autoantibodies production were found significantly reduced in oleanolic acid treated EAM animals. In addition, the histological heart analysis revealed that the treatment diminished cell infiltration, fibrosis and dystrophic calcifications. Induced by the relevant cytokines of active myocarditis, oleanolic acid reduced the proliferation of cardiac fibroblast *in vitro* and also weakened calcium and collagen deposition. Observed from the treated EAM mice serum, both T_{reg} cells number and IL-10 and IL-35 levels were found increased. On the other hand, the pro-inflammatory and profibrotic cytokines were reduced. Therefore, these results suggest that the treatment with oleanolic acid can affect the aspects of humoral and cellular immunity against MyHCα in EAM mice. Oleanolic acid could be utilized as a useful agent for the intervention in inflammatory cardiomyopathies including myocarditis.

It is also known that hemodynamic overload on the myocardium triggers compensatory hypertrophy at its early stages. The persistent severe overload could

eventually cause malignant hypertrophy, which involves systolic and diastolic dysfunction, heart failure, and even death [52]. The effects of using oleanolic acid to alleviate pressure overload-induced cardiac remodeling are not very clear. A recent study investigated the effects and addressed the underlying mechanism with mice subjected to aortic banding [53]. After these mice had been administered with oleanolic acid premixed in diets for eight weeks, the echocardiography and catheter-based measurements of hemodynamic parameters were conducted to evaluate the cardiac hypertrophy and tissue fibrosis. Evidenced by echocardiography and catheter-based measurements, oleanolic acid is found to ameliorate the systolic and diastolic dysfunction induced by pressure overload. In addition, oleanolic acid decreased the mRNA expression of cardiac hypertrophy and fibrosis markers, which is also verified by RT-PCR. It is noteworthy to mention that pressure overload may activate the phosphorylation reaction of Akt, mTOR, p70s6k, S6, GSK3β, and FoxO3α. Nonetheless, the treatment of oleanolic acid is able to weaken the phosphorylation of all these proteins. Furthermore, *in vitro* treatment of oleanolic acid can also inhibit hypertrophy of cardiomyocytes and fibrosis markers that are induced by AngII [53].

7. Ischemic heart diseases

It is a hot research area in the development of new and effective therapeutic interventions targeted at enhancing myocardial consequences arising from ischemia-reperfusion. Ischemic preconditioning is able to provide an endogenous adaptive response to protect the heart against a prolonged ischemic injury [54]. Some recent studies showed that the pretreatments with emodin and oleanolic acid protected against ischemia-reperfusion injury in isolated rat hearts (Scheme 6) [55]. The cardioprotection was found associated mainly with the enhancements in mitochondrial anti-oxidant components when under ischemia-reperfusion condition. Mitochondria are the major source of oxy-radical production in the myocardium. Ischemic damage increases the generation of oxy-radicals during reperfusion and

results in additional mitochondrial production and cardiomyocyte injury. Therefore, maintaining a good anti-oxidant capacity of mitochondrial is critical to reduce or limit the degree of ischemia-reperfusion injury [56]. By using an *ex vivo* rat heart model of ischemia-reperfusion injury, the pharmacological preconditioning effect using a chronic treatment with the combination of emodin and oleanolic acid at low dose (25 μmol/kg/day × 15) and/or ischemic preconditioning (4 cycles of 5 min ischemia followed by 5 min of reperfusion) on myocardial injury was investigated. The results indicated that the pretreatment is able to produce cardioprotective action in a semi-additive manner via the biochemical mechanism of enhancing mitochondrial anti-oxidant capacity [55, 57].

The isoproterenol-induced myocardial ischemia is a widely used experimental model to evaluate the beneficial effects of drugs and cardiac function. The protective effect of oleanolic acid was also investigated with this model in rat myocardium. The study showed that the changed activity of the membrane-bound phosphatases by isoproterenol was protected by the pretreatment with oleanolic acid probably due to its multiple functions including anti-oxidative effect, anti-hyperlipedemic and anti-arrhythmic properties, and the membrane-stabilizing action against the reactive oxygen species induced by isoproterenol [58]. The results suggested that oleanolic acid is effective in reducing the level of myocardial damage by decreasing lipid peroxidation, preventing the overloading of myocardium with lipids and its *β*-blocking activity.

Echinocystic acid is an analogue of oleanolic acid and also shows cardioprotective effects in rat models with acute myocardial ischemia induced by isoproterenol and vasopressin. It was found that echinocystic acid prohibited the ST-segment depression that was induced by isoproterenol or vasopressin in a dose-dependently manner. The mRNA expression of Bcl-2 in rats analyzed by real-time PCR disclosed an elevation of Bcl-2 mRNA level in infarcted tissue induced by isoproterenol. These results demonstrated that cardioprotective effect of echinocystic acid is associated with a reduction in apoptotic cell death in myocardial

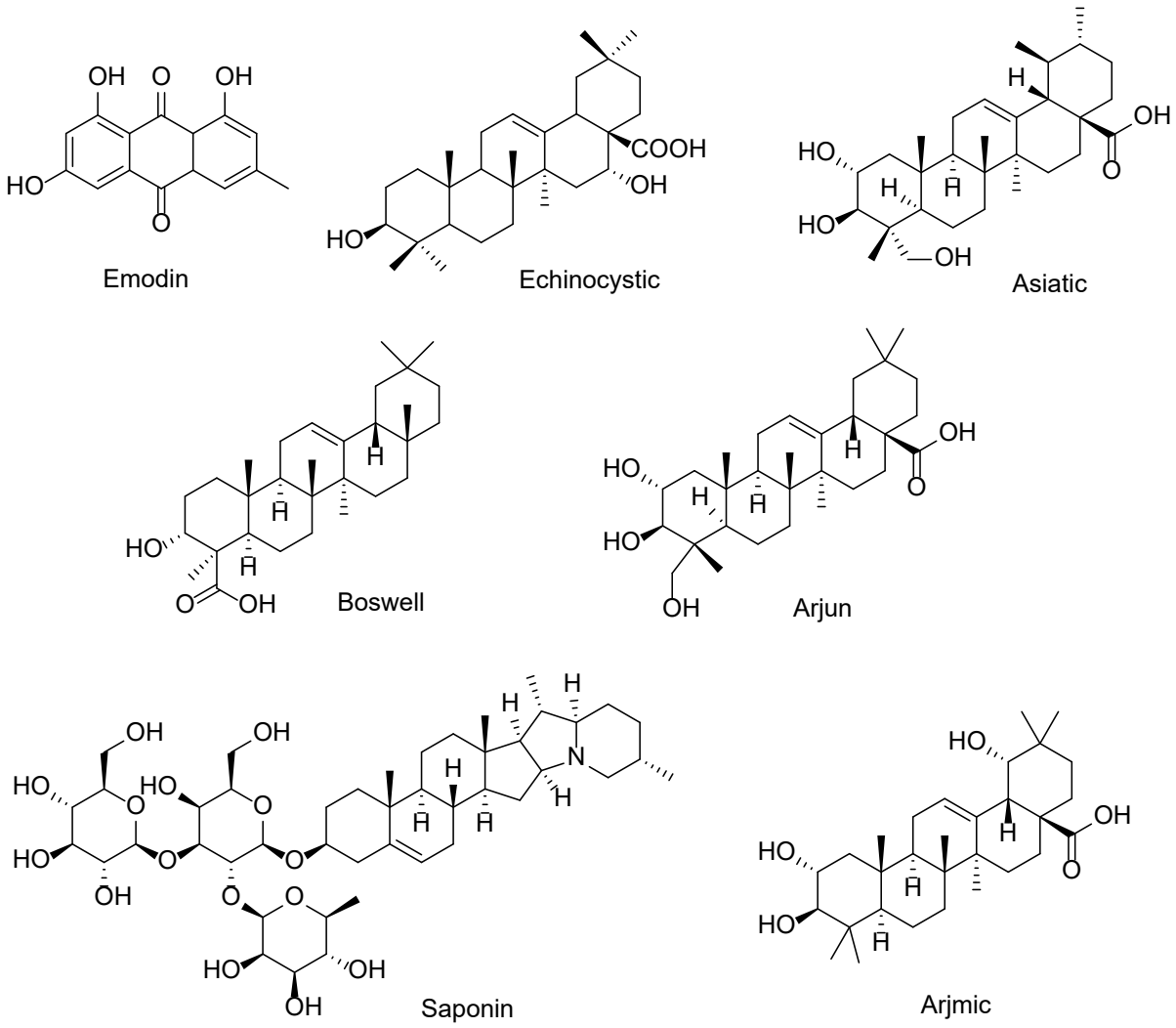
tissue [59].

Several studies indicated that hyperglycemia-induced cardiac injury is the major cause of mortality in people with diabetes and hyperglycemia boosts cardiac production of reactive oxygen species and inflammatory cytokines, which harm cardiac contractile function and induce the development of myocardial infarction, cardiac hypertrophy and heart failure [60]. Oleanolic acid, asiatic acid and boswellic acid (Scheme 6) are reported to retard NF-κB and MAPK activity/expression and also reduce apoptotic stress via lowering caspase-3 activity and Bax formation [61]. The study with these natural compounds as therapeutic agents in high glucose-treated H9c2 cells to attenuate oxidative damage and improve cell viability, showed that the pre-treatment of these compounds are able to (i) reserve glutathione, maintaining the activity and expression of GPX, GR, and catalase; (ii) reduce reactive oxygen species, oxidized glutathione, and inflammatory cytokines generation; (iii) retain Na^+/K^+-ATPase activity, (iv) suppress protein expression of NF-κB, p-P38, Bax; and (v) decline caspase-3 activities [62]. Some more triterpenoid saponins derivatives isolated from *Ilex cornuta* (or *Clinopodium polycephalum* [63]) and their protective effects against H_2O_2-induced myocardial cell injury were also demonstrated [64]. These results suggest that these triterpenes could be utilized as potent cardiac-protective agents.

Some experimental evidences showed that AMP-activated protein kinase (AMPK) has cardioprotective effect against ischemic injury. Recently, forkhead transcription factor 3 (FOXO3) has also been identified as a downstream target of AMPK. Oleanolic acid was demonstrated with the male C57BL/6 mice (subjected to *in vivo* regional cardiac ischemia stimulated AMPK Thr172 phosphorylation) on the protection against ischemic dysfunction of cardiomyocytes via activation of AMPK signaling pathway [65]. The compound was found to significantly stimulate the activation of cardiac AMPK in cardiomyocyes both in time- and dose-dependent manners. The AMPK activation mechanism may be attributed to the loss of mitochondrial membrane potential. Oleanolic acid also triggered FOXO3 (Ser413)

phosphorylation in cardiomyocytes and thus protect the cells from contractile dysfunction induced by hypoxia.

Arjunolic acid and arjunic acid are the analogues of oleanolic acid and their effects as a non-zinc binding inhibitor of the catalytic activity of carbonic anhydrase II (CA II) were investigated because high levels of CA II are found associated with cardiac hypertrophy and heart failure [66]. The study demonstrated that arjunolic acid is not cytotoxic towards cardiac myocytes at the concentration showing inhibition potency on CA II activity (the most potent *in vitro* with the IC_{50} of 9 μM). Molecular docking results indicated that the mechanism of inhibition is most likely through the following two pathways: (i) hydrogen-bonding interaction of the hydroxyl group (at C2 of A-ring) of the compound with the key catalytic site residues (His64, Asn62 and Asn67) of the enzyme involving proton transfer; and (ii) the interaction of the *gem*-dimethyl group at C20 of E-ring that greatly influences the inhibitory activity. Furthermore, arjunolic acid showed inhibitory effects on the cytosolic activity of CA in H9c2 cardiomyocytes as the intracellular pH was found decreased.



Scheme 6. Natural compounds with similar therapeutic effects with oleanolic acid for the treatment of myocardial ischemia and related heart diseases.

8. Hyperglycemia-induced contractile dysfunction

Stress-induced hyperglycemia in non-diabetic patients with acute myocardial infarction is also associated with high in-hospital mortality. A recent study investigated the glucose-insulin treatment in patients undergoing coronary artery bypass grafting under normoglycemia and the results indicated that glucose-insulin-potassium is cardioprotective and improves myocardial function as the high blood glucose levels actually damage the cardiovascular system [67]. Oleanolic acid is found effective in the reduction of both acute and chronic hyperglycemia-mediated pathophysiologic molecular events including oxidative stress,

apoptosis, hexosamine biosynthetic pathway, ubiquitin-proteasome system. Consequently, contractile function in response to ischemia-reperfusion can be improved [68]. The long-term treatment with oleanolic acid also improved heart functions in streptozotocin-diabetic rats. These results may indicate that oleanolic acid could be promising in the novel therapeutic interventions to treat acute hyperglycemia both in the non-diabetic patients and diabetic patients with associated cardiovascular complications. In addition, these advantages of oleanolic acid show higher application potential as a new cardioprotective agent compared to some other traditional drugs because of its low toxicity and effectiveness.

Effects of oleanolic acid treatment on *ex vivo* myocardial reactive oxygen species levels and apoptosis were investigated. Oleanolic acid is proposed to function as an anti-oxidant with anti-apoptotic properties within an *ex vivo* situation. Under the pre-ischemic conditions, the treatment with oleanolic acid did not significantly affect myocardial superoxide dismutase activity or apoptosis. However, succeeding ischemia oleanolic acid administration was able to reduce high glucose-induced myocardial superoxide levels and concurrently upregulated the superoxide dismutase activity. In addition, within the first 20 min after ischemia, oleanolic acid was found to exert its anti-oxidant effects. From the assessment on the anti-apoptotic effects of oleanolic acid in *ex vivo* perfused heart tissues, the treatment significantly increased cardiac *p*-BAD/BAD and decreased caspase-3 peptide levels under high glucose perfusion conditions. The anti-apoptotic effects began at 40 min, which suggested that the effects happened as a result of the earlier upstream reduction of oxidative stress [68].

9. Doxorubicin induced cardiotoxicity

Oxidative stress is one of the key factors causing myocardial infarction and other cardiovascular diseases [69]. It is known that doxorubicin boosts the activity of xanthine oxidase that is responsible for free radicals generation [70]. The proposed mechanisms in doxorubicin-induced cardiotoxicity are closely related to the formation

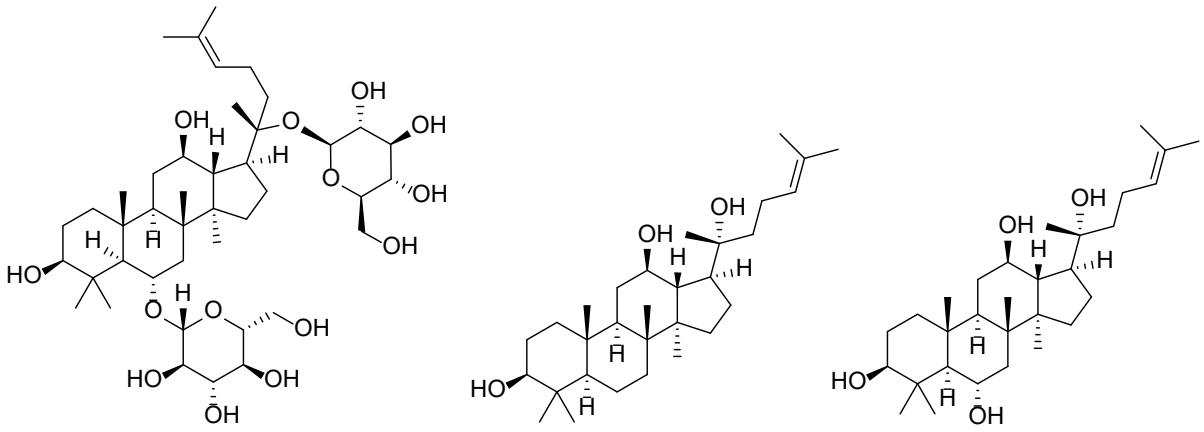
of mitochondrial reactive oxygen species, Ca^{2+} overloading, oxidative damage to membrane lipids, and activation of apoptotic factor [71]. With respect to recent findings, more and more evidences suggest that doxorubicin can be catalyzed into a secondary alcohol metabolite (doxorubicinol) through a two-electron carbonyl reduction reaction [72]. In addition, the blood pressure and heart rate may be changed by doxorubicin, which cause loss of contractility of myocardium [73]. Overexpression of the natural antioxidant proteins, catalase, and superoxide dismutase are the new approaches to avoid doxorubicin-induced cardiotoxicity.

The protective effect of oleanolic acid as an antioxidant agent on the oxidative injury and cellular abnormalities in doxorubicin induced cardiac toxicity in rats has been reported recently [74]. In the study, the cardiotoxicity was induced in Wistar rats with single intravenous injection of doxorubicin (Dosage at 67.75 mg/kg IV for 48 h). Doxorubicin administration caused remarkable alterations in biochemical parameters and endogenous antioxidants. The induction of cardiotoxicity was confirmed by the increase in systolic, diastolic, mean arterial pressures, maximal positive rate of developed left ventricular pressure, maximal negative rate of developed left ventricular pressure and an increase in left ventricular end-diastolic pressure. The administration of oleanolic acid revealed maximal protection against doxorubicin induced cardiac toxicity as indicated by the results obtained from the reduction in blood pressure, prevention of left ventricular function and weakening of biochemical and antioxidant parameters. From these experimental results, it is suggested that oleanolic acid can be used as a natural and effective therapeutic agent in treating doxorubicin induced cardiotoxicity or cancers. Moreover, doxorubicin in combination with other cytotoxic drugs such as amifostine and oleanolic acid shows noticeable clinical advantages [75].

10. Chronic heart failure

Heart failure is a major public health problem and is a leading cause of morbidity and mortality in old people [76]. An estimated lifetime risk of developing heart failure for both men and women at age 80 is 20 %. Many challenges and technical issues on

the assessment, diagnosis and treatment of heart failure are encountered to-date. Nonetheless, it is important to call attention that the incidence of heart failure is found dependent on age. Some studies pointed out that the main pathogenic mechanisms of chronic heart failure involve in agerelated myocardial hypertrophy, changes in salt and fluid retention, and deregulation of the neurohormonal system [77]. Moreover, over the past 20 years, many studies have proved that the inflammatory activation is an important pathway in pathogenesis and in the progression of chronic heart failure [78, 79]. A large number of reports also commented that the inflammation-sensitive transcription factor (NF-κB) is activated during chronic heart failure [80].



Scheme 7. Bioactive analogues of oleanolic acid used in the treatment of chronic heart failure.

Some studies explored the use of bioactive compounds (Scheme 7) such as Yi-qi-fu-mai (a traditional Chinese medicine; bioactive components mainly are ginsenosides), protopanaxadiol, protopanaxatriol, and oleanolic acid in the treatment of chronic heart failure in rats through the anti-inflammation mechanism [81-83]. A lot of evidence suggested that NF-κB regulates a group of inflammatory genes including TNF-α, IL-1β, IL-6 and IL-8 and is important for the initiation and progression of numerous pathological states [84, 85]. The four above-mentioned natural compounds at a dose 100 mmol/L were added to TNF-α-stimulated rat cardiac

microvascular endothelial cells. All these compounds showed inhibitory effects in the expression of NF-κB, IL-1β, and IL-6.

Conclusion

In summary, oleanolic acid and its bioactive analogues exhibit potent cardioprotective effects with experimental evidences against a number of heart diseases including but not limited to anti-atherogenic activity and hypolipidemic effect, cardiovascular homeostasis effects, inhibition on Na^+/K^+-ATPase and promotion of blood circulation, vasorelaxant effects, autoimmune myocarditis, ischemic heart diseases, hyperglycemia-induced contractile dysfunction, doxorubicin-induced cardiotoxicity and heart failure. The mechanisms of action for some inhibitory effects are well investigated. In addition, oleanolic acid as a pentacyclic triterpenoid is abundant in plants of the Oleaceae family such as olive plants. In China, oleanolic acid has been used as a hepatic drug for over 20 years. To understand more about its bioactivity is able to develop potent therapeutic agents for the treatment and management of human diseases, in particular for heart diseases. Furthermore, recent studies utilizing oleanolic acid as a natural molecular scaffold have been carried out for the development of novel semi-synthetic triterpenoids and derivatives to enhance its solubility, bioavailability and potency and reduce toxicity for clinical applications. Some of its derivatives have been identified in clinical trials. Bardoxolone methyl is one of the examples. It is most likely that oleanolic acid and its derivatives may possess certain advantages compared to other traditional cardioprotective drugs. Therefore, it is realistic to conclude that oleanolic acid and its derivatives are a class of important and useful natural compounds to establish alternative therapies for the treatment of cardiovascular diseases and other related diseases with high efficacy and low toxicity.

Acknowledgment

We acknowledge the supports received from Jiangmen Program for Innovative Research Team (No. 2018630100180019806), the Science and Technology Program of Guangdong Province (2012B020306007), the Department of Education Guangdong Province (No. 2016KCXTD005, 2017KSYS010), the National Natural Science Foundation of China (21102021, 81473082, 81703333 and 81773720), the Natural Science Foundation of Guangdong Province, China (2017A030313078), the National Natural Science Foundation of China (81703333) and the State Key Laboratory of Chemical Biology and Drug Discovery, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University.

References

[1] Hajar R. Framingham Contribution to Cardiovascular Disease. Heart Views 2016; 17: 78-81.

[2] Soliman EZ, Mendis S, Dissanayake WP, et al. A Polypill for primary prevention of cardiovascular disease: a feasibility study of the World Health Organization. Trials 2011; 12: 3.

[3] Volpe M, Francia P. Synergistic effects of cardiac resynchronization therapy and drug up-titration in heart failure: is this enough? Eur Heart J Cardiovasc Pharmacother 2015; 1: 189-90.

[4] Kendall MJ, Rajman I, Maxwell SR. Cardioprotective therapeutics--drugs used in hypertension, hyperlipidaemia, thromboembolism, arrhythmias, the postmenopausal state and as anti-oxidants. Postgrad Med J 1994; 70: 329-43.

[5] Moolman JA. Unravelling the cardioprotective mechanism of action of estrogens. Cardiovasc Res 2006; 69: 777-80.

[6] Quindry JC, Franklin BA. Cardioprotective Exercise and Pharmacologic Interventions as Complementary Antidotes to Cardiovascular Disease. Exerc Sport Sci Rev 2018; 46: 5-17.

[7] Schuler G, Adams V, Goto Y. Role of exercise in the prevention of cardiovascular disease: results, mechanisms, and new perspectives. Eur Heart J 2013; 34: 1790-9.

[8] Andreadou I, Adamovski P, Bartekova M, *et al*. Realizing the therapeutic potential of novel cardioprotective therapies: The EU-CARDIOPROTECTION COST Action-CA16225. Cond Med 2018; 1: 116-123.

[9] Ovize M, Baxter GF, Di Lisa F, *et al*. Postconditioning and protection from reperfusion injury: where do we stand? Position paper from the Working Group of Cellular Biology of the Heart of the European Society of Cardiology. Cardiovasc Res 2010; 87: 406-23.

[10] Hausenloy DJ, Erik Botker H, Condorelli G, et al. Translating cardioprotection for patient benefit: position paper from the Working Group of Cellular Biology of the Heart of the European Society of Cardiology. Cardiovasc Res 2013; 98: 7-27.

[11] Lecour S, Botker HE, Condorelli G, *et al*. ESC working group cellular biology of the heart: position paper: improving the preclinical assessment of novel cardioprotective therapies. Cardiovasc Res 2014; 104: 399-411.

[12] Ibanez B, Heusch G, Ovize M, *et al*. Evolving therapies for myocardial ischemia/reperfusion injury. J Am Coll Cardiol 2015; 65: 1454-71.

[13] Mlakar P, Salobir B, Cobo N, *et al*. The effect of cardioprotective diet rich with natural antioxidants on chronic inflammation and oxidized LDL during cardiac rehabilitation in patients after acute myocardial infarction. Int J Cardiol Heart Vasc 2015; 7: 40-48.

[14] Shukla SK, Gupta S, Ojha SK, *et al*. Cardiovascular friendly natural products: a promising approach in the management of CVD. Nat Prod Res 2010; 24: 873-98.

[15] Weng CJ, Yen GC. Chemopreventive effects of dietary phytochemicals against cancer invasion and metastasis: phenolic acids, monophenol, polyphenol, and their derivatives. Cancer Treat Rev 2012; 38: 76-87.

[16] Wang TY, Li Q, Bi KS. Bioactive flavonoids in medicinal plants: Structure, activity and biological fate. Asian Journal of Pharmaceutical Sciences 2018; 13: 12-23.

[17] Ojha S, Al Taee H, Goyal S, *et al*. Cardioprotective Potentials of Plant-Derived Small Molecules against Doxorubicin Associated Cardiotoxicity. Oxid Med Cell Longev 2016; 2016: 5724973.

[18] Sheng H, Sun H. Synthesis, biology and clinical significance of pentacyclic triterpenes: a multi-target approach to prevention and treatment of metabolic and vascular diseases. Nat Prod Rep 2011; 28: 543-93.

[19] Alqahtani A, Hamid K, Kam A, *et al*. The pentacyclic triterpenoids in herbal medicines and their pharmacological activities in diabetes and diabetic complications. Curr Med Chem 2013; 20: 908-31.

[20] Corey EJ, Lee J. Enantioselective total synthesis of oleanolic acid, erythrodiol, .beta.-amyrin, and other pentacyclic triterpenes from a common intermediate. Journal of the American Chemical Society 1993; 115: 8873-8874.

[21] Wang YK, Han J, Xiong WJ, *et al*. Evaluation of in vivo antioxidant and immunity enhancing activities of sodium aescinate injection liquid. Molecules 2012; 17: 10267-75.

[22] Lin C, Wen X, Sun H. Oleanolic acid derivatives for pharmaceutical use: a patent review. Expert Opin Ther Pat 2016; 26: 643-55.

[23] Gutierrez-Rebolledo GA, Siordia-Reyes AG, Meckes-Fischer M, *et al*. Hepatoprotective properties of oleanolic and ursolic acids in antitubercular drug-induced liver damage. Asian Pac J Trop Med 2016; 9: 644-51.

[24] Raphael TJ, Kuttan G. Effect of naturally occurring triterpenoids glycyrrhizic

acid, ursolic acid, oleanolic acid and nomilin on the immune system. Phytomedicine 2003; 10: 483-9.
[25] Fu L. Isolated and Identified of New Gisenoside of Oleanolic Acid Type from Fresh Panax ginseng Roots. Journal of Jilin Agricultural University 1998;02.
[26] Saimaru H, Orihara Y, Tansakul P, *et al*. Production of triterpene acids by cell suspension cultures of Olea europaea. Chem Pharm Bull (Tokyo) 2007; 55: 784-8.
[27] Ayeleso TB, Matumba MG, Mukwevho E. Oleanolic Acid and Its Derivatives: Biological Activities and Therapeutic Potential in Chronic Diseases. Molecules 2017; 22.
[28] M.A. Domingues R, R. Guerra A, Duarte M, *et al*. Bioactive Triterpenic Acids: From Agroforestry Biomass Residues to Promising Therapeutic Tools. Mini Rev Org Chem 2014; 11: 382-399.
[29] Luo QF, Liu JH, Chen L. Recent Advances in Enone and NO-Releasing Derivatives of Oleanolic Acid with Anti-cancer Activity. Mini Rev Org Chem 2014; 11: 355-361.
[30] Paszel-Jaworska A, Romaniuk A, Rybczynska M. Molecular Mechanisms of Biological Activity of Oleanolic Acid - A Source of Inspiration for A New Drugs Design. Mini Rev Org Chem 2014; 11: 330-342.
[31] Xu K, Chu F, Li G, *et al*. Oleanolic acid synthetic oligoglycosides: a review on recent progress in biological activities. Pharmazie 2014; 69: 483-95.
[32] Ferdowsian HR, Barnard ND. Effects of plant-based diets on plasma lipids. Am J Cardiol 2009; 104: 947-56.
[33] Lusis AJ. Atherosclerosis. Nature 2000; 407: 233-41.
[34] Allouche Y, Beltran G, Gaforio JJ, *et al*. Antioxidant and antiatherogenic activities of pentacyclic triterpenic diols and acids. Food Chem Toxicol 2010; 48: 2885-90.
[35] Buus NH, Hansson NC, Rodriguez-Rodriguez R, *et al*. Antiatherogenic effects of oleanolic acid in apolipoprotein E knockout mice. Eur J Pharmacol 2011; 670: 519-26.
[36] Kim HY, Cho KW, Kang DG, *et al*. Oleanolic acid increases plasma ANP levels via an accentuation of cardiac ANP synthesis and secretion in rats. Eur J Pharmacol 2013; 710: 73-9.
[37] Maiwald M, Widmer AF, Rotter ML. Lack of evidence for attributing chlorhexidine as the main active ingredient in skin antiseptics preventing surgical site infections. Infect Control Hosp Epidemiol 2011; 32: 404-5.
[38] Ahn YM, Choi YH, Yoon JJ, *et al*. Oleanolic acid modulates the renin-angiotensin system and cardiac natriuretic hormone concomitantly with volume and pressure balance in rats. Eur J Pharmacol 2017; 809: 231-241.
[39] Sengupta S, Toh SA, Sellers LA, *et al*. Modulating angiogenesis: the yin and the yang in ginseng. Circulation 2004; 110: 1219-25.
[40] Li-Saw-Hee FL, Lip GY. Digoxin revisited. QJM: An International Journal of Medicine 1998; 91: 259-264.
[41] Chen RJ, Chung TY, Li FY, *et al*. Effect of sugar positions in ginsenosides and

their inhibitory potency on Na+/K+-ATPase activity. Acta Pharmacol Sin 2009; 30: 61-9.

[42] Chen RJ, Chung TY, Li FY, *et al*. Steroid-like compounds in Chinese medicines promote blood circulation via inhibition of Na+/K+ -ATPase. Acta Pharmacol Sin 2010; 31: 696-702.

[43] Prassas I, Diamandis EP. Novel therapeutic applications of cardiac glycosides. Nat Rev Drug Discov 2008; 7: 926-35.

[44] Martinez-Gonzalez J, Rodriguez-Rodriguez R, Gonzalez-Diez M, *et al*. Oleanolic acid induces prostacyclin release in human vascular smooth muscle cells through a cyclooxygenase-2-dependent mechanism. J Nutr 2008; 138: 443-8.

[45] Martinez-Gonzalez J, Badimon L. Mechanisms underlying the cardiovascular effects of COX-inhibition: benefits and risks. Curr Pharm Des 2007; 13: 2215-27.

[46] Suh N, Honda T, Finlay HJ, *et al*. Novel triterpenoids suppress inducible nitric oxide synthase (iNOS) and inducible cyclooxygenase (COX-2) in mouse macrophages. Cancer Res 1998; 58: 717-23.

[47] Lo YC, Tsou HH, Lin RJ, *et al*. Endothelium-dependent and -independent vasorelaxation by a theophylline derivative MCPT: roles of cyclic nucleotides, potassium channel opening and phosphodiesterase inhibition. Life Sci 2005; 76: 931-44.

[48] Rodriguez-Rodriguez R, Herrera MD, Perona JS, *et al*. Potential vasorelaxant effects of oleanolic acid and erythrodiol, two triterpenoids contained in 'orujo' olive oil, on rat aorta. Br J Nutr 2004; 92: 635-42.

[49] Aguirre-Crespo F, Vergara-Galicia J, Villalobos-Molina R, *et al*. Ursolic acid mediates the vasorelaxant activity of Lepechinia caulescens via NO release in isolated rat thoracic aorta. Life Sci 2006; 79: 1062-8.

[50] Cihakova D, Rose NR. Pathogenesis of myocarditis and dilated cardiomyopathy. Adv Immunol 2008; 99: 95-114.

[51] Martin R, Cordova C, San Roman JA, *et al*. Oleanolic acid modulates the immune-inflammatory response in mice with experimental autoimmune myocarditis and protects from cardiac injury. Therapeutic implications for the human disease. J Mol Cell Cardiol 2014; 72: 250-62.

[52] Maillet M, van Berlo JH, Molkentin JD. Molecular basis of physiological heart growth: fundamental concepts and new players. Nat Rev Mol Cell Biol 2013; 14: 38-48.

[53] Liao HH, Zhang N, Feng H, *et al*. Oleanolic acid alleviated pressure overload-induced cardiac remodeling. Mol Cell Biochem 2015; 409: 145-54.

[54] Baines CP, Zhang J, Wang GW, *et al*. Mitochondrial PKCepsilon and MAPK form signaling modules in the murine heart: enhanced mitochondrial PKCepsilon-MAPK interactions and differential MAPK activation in PKCepsilon-induced cardioprotection. Circ Res 2002; 90: 390-7.

[55] Du Y, Ko KM. Effects of pharmacological preconditioning by emodin/oleanolic acid treatment and/or ischemic preconditioning on

mitochondrial antioxidant components as well as the susceptibility to ischemia-reperfusion injury in rat hearts. Mol Cell Biochem 2006; 288: 135-42.

[56] Otani H, Tanaka H, Inoue T, *et al*. In vitro study on contribution of oxidative metabolism of isolated rabbit heart mitochondria to myocardial reperfusion injury. Circ Res 1984; 55: 168-75.

[57] Du Y, Ko KM. Oleanolic acid protects against myocardial ischemia-reperfusion injury by enhancing mitochondrial antioxidant mechanism mediated by glutathione and alpha-tocopherol in rats. Planta Med 2006; 72: 222-7.

[58] Senthil S, Sridevi M, Pugalendi KV. Cardioprotective effect of oleanolic acid on isoproterenol-induced myocardial ischemia in rats. Toxicol Pathol 2007; 35: 418-23.

[59] Wu J, Li J, Zhu Z, *et al*. Protective effects of echinocystic acid isolated from Gleditsia sinensis Lam. against acute myocardial ischemia. Fitoterapia 2010; 81: 8-10.

[60] Rajamani U, Essop MF. Hyperglycemia-mediated activation of the hexosamine biosynthetic pathway results in myocardial apoptosis. Am J Physiol Cell Physiol 2010; 299: C139-47.

[61] Tsai SJ, Yin MC. Anti-oxidative, anti-glycative and anti-apoptotic effects of oleanolic acid in brain of mice treated by D-galactose. Eur J Pharmacol 2012; 689: 81-8.

[62] Chan CY, Mong MC, Liu WH, *et al*. Three pentacyclic triterpenes protect H9c2 cardiomyoblast cells against high-glucose-induced injury. Free Radic Res 2014; 48: 402-11.

[63] Hu YX, Zhang W, Zhang W, *et al*. Oleanane triterpene saponins with cardioprotective activity from Clinopodium polycephalum. J Asian Nat Prod Res 2017; 19: 697-703.

[64] Li S, Zhao J, Liu Y, *et al*. New triterpenoid saponins from Ilex cornuta and their protective effects against H2O2-induced myocardial cell injury. J Agric Food Chem 2014; 62: 488-96.

[65] Wang J, Ma H, Zhang X, *et al*. A novel AMPK activator from Chinese herb medicine and ischemia phosphorylate the cardiac transcription factor FOXO3. Int J Physiol Pathophysiol Pharmacol 2009; 1: 116-126.

[66] Kalyanavenkataraman S, Nanjan P, Banerji A, *et al*. Discovery of arjunolic acid as a novel non-zinc binding carbonic anhydrase II inhibitor. Bioorg Chem 2016; 66: 72-9.

[67] Carvalho G, Pelletier P, Albacker T, *et al.* Cardioprotective effects of glucose and insulin administration while maintaining normoglycemia (GIN therapy) in patients undergoing coronary artery bypass grafting. J Clin Endocrinol Metab 2011; 96: 1469-77.

[68] Mapanga RF, Rajamani U, Dlamini N, *et al*. Oleanolic acid: a novel cardioprotective agent that blunts hyperglycemia-induced contractile dysfunction. PLoS One 2012; 7: e47322.

[69] Ziaee M, Khorrami A, Ebrahimi M, *et al*. Cardioprotective Effects of Essential Oil of Lavandula angustifolia on Isoproterenol-induced Acute Myocardial Infarction in Rat. Iran J Pharm Res 2015; 14: 279-89.

[70] Saad SY, Najjar TA, Al-Rikabi AC. The preventive role of deferoxamine against acute doxorubicin-induced cardiac, renal and hepatic toxicity in rats. Pharmacol Res 2001; 43: 211-8.

[71] Menna P, Recalcati S, Cairo G, *et al*. An introduction to the metabolic determinants of anthracycline cardiotoxicity. Cardiovasc Toxicol 2007; 7: 80-5.

[72] Bains OS, Karkling MJ, Grigliatti TA, *et al*. Two nonsynonymous single nucleotide polymorphisms of human carbonyl reductase 1 demonstrate reduced in vitro metabolism of daunorubicin and doxorubicin. Drug Metab Dispos 2009; 37: 1107-14.

[73] Cassidy SC, Chan DP, Rowland DG, *et al*. Effects of doxorubicin on diastolic function, contractile reserve, and ventricular-vascular coupling in piglets. Pediatr Cardiol 1998; 19: 450-7.

[74] Goyal SN, Mahajan UB, Chandrayan G, *et al*. Protective effect of oleanolic acid on oxidative injury and cellular abnormalities in doxorubicin induced cardiac toxicity in rats. Am J Transl Res 2016; 8: 60-9.

[75] Sarfraz M, Afzal A, Raza SM, *et al*. Liposomal co-delivered oleanolic acid attenuates doxorubicin-induced multi-organ toxicity in hepatocellular carcinoma. Oncotarget 2017; 8: 47136-47153.

[76] Butrous H, Hummel SL. Heart Failure in Older Adults. Can J Cardiol 2016; 32: 1140-7.

[77] Landmesser U, Wollert KC, Drexler H. Potential novel pharmacological therapies for myocardial remodelling. Cardiovasc Res 2009; 81: 519-27.

[78] Anker SD, von Haehling S. Inflammatory mediators in chronic heart failure: an overview. Heart 2004; 90: 464-70.

[79] Dick SA, Epelman S. Chronic Heart Failure and Inflammation: What Do We Really Know? Circ Res 2016; 119: 159-76.

[80] Van Linthout S, Tschope C. Inflammation - Cause or Consequence of Heart Failure or Both? Curr Heart Fail Rep 2017; 14: 251-265.

[81] Xing L, Jiang M, Dong L, *et al*. Cardioprotective effects of the YiQiFuMai injection and isolated compounds on attenuating chronic heart failure via NF-kappaB inactivation and cytokine suppression. J Ethnopharmacol 2013; 148: 239-45.

[82] Wang YQ, Liu CH, Zhang JQ, *et al*. Protective effects and active ingredients of yi-qi-fu-mai sterile powder against myocardial oxidative damage in mice. J Pharmacol Sci 2013; 122: 17-27.

[83] Wu D, Zhang Q, Yu Y, *et al*. Oleanolic Acid, a Novel Endothelin A Receptor Antagonist, Alleviated High Glucose-Induced Cardiomyocytes Injury. Am J Chin Med 2018; 46: 1187-1201.

[84] Valen G, Yan ZQ, Hansson GK. Nuclear factor kappa-B and the heart. J Am Coll Cardiol 2001; 38: 307-14.

[85] Frantz S, Fraccarollo D, Wagner H, *et al*. Sustained activation of nuclear factor kappa B and activator protein 1 in chronic heart failure. Cardiovasc Res 2003; 57: 749-56.