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Therapeutic and Preventive Potential of Ursolic Acid with Special Emphasis on Hepatoprotective and Cardioprotective Effects

Ghose D, Bhardwaj M and Mazumder PM*

Department of Pharmaceutical Sciences and Technology, BIT Mesra, India

***Corresponding author:** Papiya Mitra Mazumder, Professor (Pharmacology), Department of Pharmaceutical Sciences and Technology, BIT Mesra, Ranchi-835215 India, Email: pmitramazumder@bitmesra.ac.in

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Abstract

Ursolic acid, it is a pentacyclic triterpene abundantly present in various medicinal plants, has garnered extensive attention for its multifaceted bioactive properties. It is widely distributed in fruits, leaves, herbs, and flowers. It has demonstrated significant therapeutic potential against diverse ailments, including cancers, inflammation, aging, obesity, diabetes, dyslipidemia, and liver injuries. This review focuses on ursolic acid's structural attributes, natural sources, biosynthesis, and pharmacological effects, particularly emphasizing its hepatoprotective and cardio protective mechanisms. Most studies have explored ursolic acid's impacts on peroxisome proliferator activated receptors, liver X receptor, farnesoid X receptor, and pregnane X receptor, revealing potent anti-inflammatory, anti-hyperlipidemic, anti-cancer, cardio protective and hepato protective attributes. In vitro and in vivo investigations highlight ursolic acid's efficacy in reducing accumulation of lipids in hepatic cells, mitigation of non-alcoholic steatohepatitis, and preventing the progression of liver fibrosis. This comprehensive review provides valuable insights into ursolic acid's diverse therapeutic applications, underscoring its potential as a promising natural compound for combating a spectrum of health challenges.

Keywords: Ursolic Acid; Cardioprotective; Hepatoprotective; Therapeutic Approach

Abbreviations: UA: Ursolic Acid; PPAR-α: Peroxisome Proliferator Activated Receptor α; eNOS: Endothelial Nitric Oxide Synthase; PCTs: Pentacyclic Triterpenoids; BCS: Biopharmaceutical Classification System; OSCs: Oxygen-squalene Cyclases; BCS: Biopharmaceutical Classification System; HSCs: Rat Liver Stellate Cells; ARE: Antioxidant Response Element; GST: Glutathione s-transferase; MPT: Mitochondrial Permeability Transition; ATPase: Adenosine Triphosphatase; VSMC: Vascular Smooth Muscle Cells; HUVECs: Human Umbilical Vein Endothelial Cells; cGMP: Cyclic Guanosine Monophosphate; OSCs: Oxygen-squalene cyclases; NADES: Natural Deep Eutectic Solvents; FFAs: Free Fatty Acids; NASH: Nonalcoholic Steatohepatitis.

Introduction

Ursolic acid (UA) has many different pharmacological properties. But in this review cardioprotective and hepatoprotective nature has been discussed here. UA itself has antioxidant and anti-inflammatory property [1]. It shows the effect on liver and heart mostly with these effects. It acts as Peroxisome proliferator activated receptor α (PPAR- α) agonist to alleviate the liver disorders and inhibits nuclear factor kappa-light-chain-enhancer of activated B cells (Nfκb/Akt) mediated pathway [2]. It shows the effect on heart by its antioxidant effects [3]. Due to oxidative stress myocardial infarction occurs, but UA prevents the DNA damage in heart.

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It protects heart by another mechanisms, it has vasorelaxant property as well. It has endogenous nitric oxide (NO) relaxant property via stimulation of endothelial nitric oxide synthase (eNOS) which is important for hypertension and atherosclerosis [4].

Ursolic Acid

This is 3β-hydroxy-12-urs-12-ene-28-oic acid (Figure 1) a naturally occurring pentacyclic triterpenoid carboxylic acid; is the main ingredient in many traditional medicinal herbs [5]. It is well known to have various of biological properties, which includes protection against inflammation, tumor, and having antioxidant properties that can counteract both endogenous and exogenous biological stimuli [6].

The pentacyclic triterpenoids (PCTs) are a class of C30 isoprenoid compounds that are widely distributed in plants. They are produced biosynthetically by the help of folding and cyclization of squalene ring, by which it results in the dammarenyl ring system. This ring structure and stereochemistry differ slightly from that of major sterols. UA is found in a wide range of plants as an aglycone of triterpene saponins or as a free acid [7]. Triterpenoids are generated by the action of mevalonic acid and consist of six isoprene molecules [8].

They are frequently connected to polysaccharide gums and can be found in plant resin, cork, and waxy coatings. Triterpenoids, also referred to as saponins, are substances that either exist naturally unchanged or are modified by glycosylation. Non-glycosylated triterpenoids produce a lipophilic membrane that acts as a barrier to keep out water from leaves, stems, and fruits [9]. PCTs are the most prevalent and extensively dispersed type of triterpenoids. Four fundamental ring skeletons are used to classify PCTs: ursane, oleanane, friedelane, and lupine. In lupine , there are four six-member rings and one five-member rings, in olenane there are five six- members rings with two methyl groups each, in ursane there are five six-member rings with one methyl group each. UA, asiatic acid (AA, ursane group), oleanolic acid (OA), β-amyrin (oleanane group), and betulin (lupine group) are the terpenoids that have been studied the most [9,10].

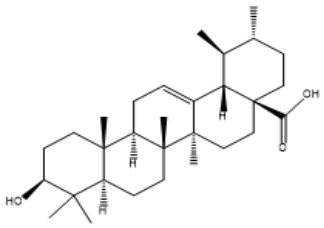

Figure 1: Ursolic Acid Structure.

Structural Property

UA (3β-3-hydroxy-urs-12-ene-28-oic acid) is a PCT, having the chemical formula $C_3OH_{48}O_3$ and a molecular mass of 456.71 g/mol. UA completely dissolves in alcoholic sodium hydroxide and glacial acetic acid [7], but it doesn't dissolve in water. It is typically produced by folding and cyclizing squalene, which lengthens the UA'sfifth ring and adds another ring. This process starts with the dammarenyl cation. The three oxygen atoms in the molecule activate double or triple neutral ligands and donate electron pairs to the transition metal atom [12,13].

Natural sources of URSOLIC Acid

Triterpenes can be extracted from a variety of therapeutic plants; the *Lamiaceae* family is one of the most well-known sources, as leaves of *Rosmarinus officinalis*, a classic commercial source [14]. Additionally, UA has been found in a number of sources, namely in and in certain commercially dried fruits, leaves, and flowers. It has recently been discovered that wild edible mushrooms contain the triterpenic acids ursolic and oleanolic for the first time [15]. Triterpenoids found in cuticular waxes provide a protective effect against biotic stressors including infections and herbivores on the mechanical qualities of the fruit surface. These compounds are also partially responsible for the allelopathic potential of fruits. The main triterpene found in argan fruit and leaves is ursolic acid, which is produced as a byproduct of the argan oil industry [16]. It can be found in waste products like those used to make juice, apple peels, the leftovers from processing apples or persimmons, especially peels, unripe and overripe fruits that are harvested, like elderberries, and raffinates, like leftover rosemary that is used to extract carnosic acid. Another source might be forestry wastes, such as Eucalyptus sp. bark.

Numerous berries have been shown to contain UA and related PCTs, including *Vaccinium macrocarpon* (cranberries) and other Vaccinium species [17]. The fruit peel of the apple (*Malus domestica*) [18] the leaves of the thyme (*Thymus vulgaris*) [19], the bark and leaves of Eucalyptus, the leaves and barks of *Sambucus nigra*, the leaves of *Origanum vulgare*, the leaves of rosemary (*Rosmarinus officinalis*) [20], the leaves and flowers of hawthorn (Crataegus sp.) [21], the leaves and flowers of marjoram (*Origanum majorana*), the leaves and flowers of lavender (*Lavandula angustifolia*) [22], the leaves of coffee (*Coffea arabica*), the leaves of sage (*Salvia officinalis*), and the wax layer of a variety of edible fruits are also known to contain UA in relatively high concentration [23,24].

Different Natural Sources with their Parts

As previously indicated, UA may be obtained from a variety of natural sources by employing various extraction methods and shown in Table 1.

Natural Sources	Part of the Plant	Scientific Name	Method of Extraction and Solvents	References
Apple	Peels	*Malus domestica*	Ultrasonic cleaner with hydrophobic deep eutectic solvents (Menthol: Thymol) (1: 1)	Li, et al. [25]
Eucalyptus	Bark	*Teriticornis globulus*	Soxhlet extraction with dichloromethane. Solid liquid extraction with natural deep eutectic solvents (NADES) (Menthol: Thymol) (1:2)	Silva, et al. [26]
Argan	Fruits	*Argania spinosa*	Maceration with absolute ethanol.	Khallouki, et al. [16]
Thyme	Leaves	*Thymus vulgaris*	A series of chromatographic and extraction procedures using ethanol, n-hexane, ethyl acetate, n-butanol, and distilled water.	Shimada, et al. [27]
Rosemary	Leaves	*Rosemary officinalis*	Ultrasonic extraction with 90% ethanol at material/solvent ratio 1:15.	Bernatoniene, et al. [28]
Tulsi	Leaves	*Ocimum sanctum*	Methanol, acetonitrile, acetone, and ethyl acetate are used in a batch extraction process. (1:120, solid to solvent ratio).	Vetal, et al. [29]

Table 1: The Natural Sources of UA and its Method of Extraction from them.

Biosynthesis of UA

Huge concentrations of UA and similar triterpene compounds, such as α and β-amyrin, betulinic acid, uvaol, and oleanolic acid, are found in plants. Because the enzymes that are responsible for their formation are present and active in different species, their amount and composition vary [24]. Fruit peels from apples (*Malus domestica*), marjoram (*Origanum majorana*), oregano (*Origanum vulgare*), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*), thyme (*Thymus vulgaris*), lavender (*Lavandula angustifolia*) leaves and flowers, eucalyptus (*Eucalyptus teriticornis*) leaves and bark, black elder (*Sambucus nigra*) leaves and flowers, hawthorn (Crataegus sp.) leaves and flowers, coffee (*Coffea arabica*) leaves, and the wax layer of many edible fruits are examples of plant matrices with a high content of ursolic acid [30,31]. The formation of UA along with associated compounds in plant tissues occurs in three stages. The first step involves making isopentenyl diphosphate (IPP), a building block with five carbons that is needed to make all terpenic compounds (Figure 2) [24]. It's been long believed that this molecule can only be obtained by the mevalonate pathway (MVA). Through a six-step process, this cytosol-carried metabolic route changes two molecules of Acetyl-CoA (produced in the citric acid cycle) into one molecule of IPP [32]. A different procedure known as the deoxyxylulose/methylerythritiol phosphate (DXP) pathway (Figure 2), has been identified by recent studies. By the help of pyruvate and glyceraldehyde-3-phosphate, IPP is produced in this plastid located mechanism [32]. The absence of the required enzymes prevents the plastid from synthesizing triterpenes none the less, the potential for overlap between the two options that are offered is taken into account [33].

The process of synthesising 2, 3-oxidosqualene and cyclizing it to create α-amyrin is the second step in the creation of UA (Figure 2). Squalene is produced from IPP molecules and their isomer dimethylallyl diphosphate (DMAPP) by way of the intermediates farnesyl and geranyl pyrophosphate. Next, this molecule is oxidized to 2, 3-oxidosqualene by squalene epoxidase. Oxygen-squalene cyclases (OSCs) are a class of enzymes that catalyze the cyclization and reorganization of the terpenoid chain, resulting in the creation of several scaffolds, among them α-amyrin. α/β- amyrin 28-monooxygenases, a class of cytochrome P450 enzymes, modify α-amyrin in the final stage. The UA biosynthesis process ends when the methyl group-containing C-28 is changed into a carboxyl [34].

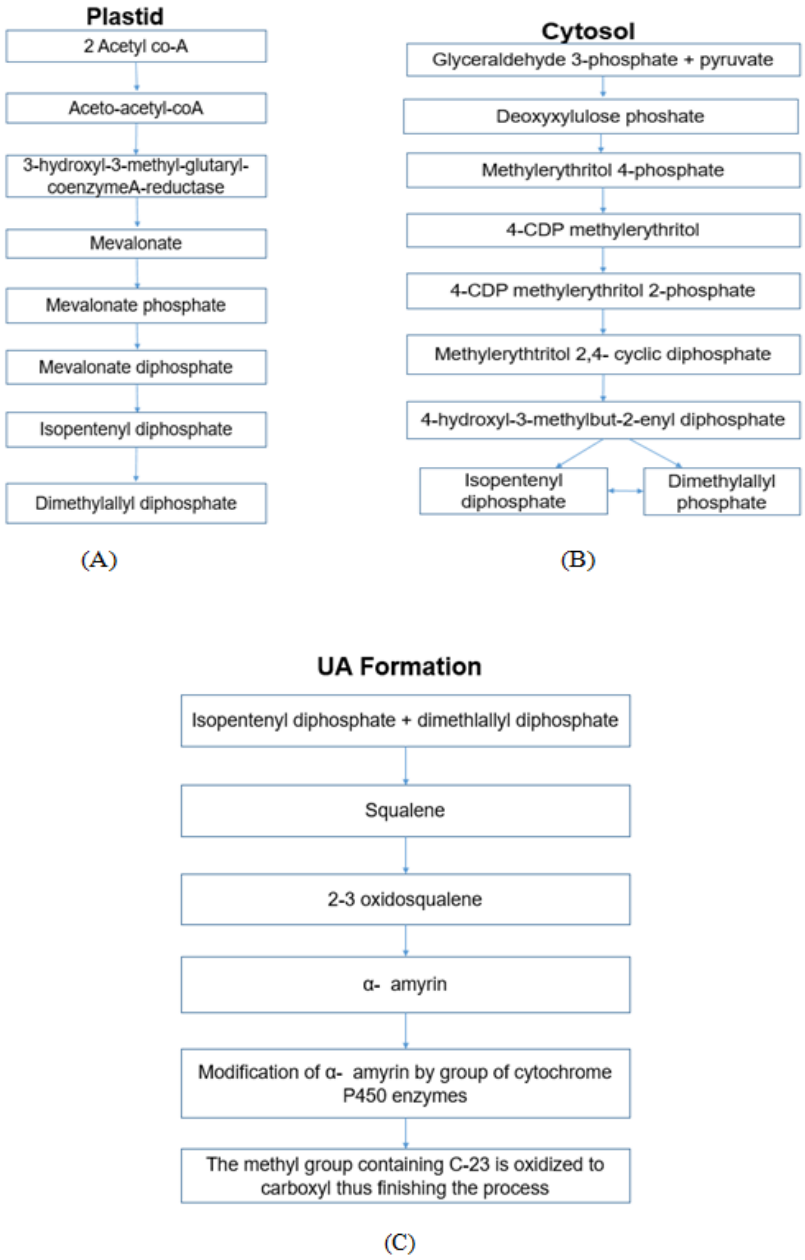

Figure 2: Different steps of biosynthesis of UA: (A) Formation of IPP & DMAPP in plastid, (B) Formation of IPP & DMAPP in cytosol (DXP pathway), (C) Ultimate stage of UA formation.

Limitations of using Natural UA

UA has a low bioavailability and is practically insoluble in water. Because of its limited pharmacological effects resulting from its low water solubility and difficulty penetrating biological membranes [35].

According to the biopharmaceutical classification system (BCS), UA is a class IV pharmaceutical product [36]. The oral bioavailability of these medications was low due to their delayed disintegration and limited penetration through the gastrointestinal mucosa [37]. Owing to these variables, novel approaches namely, drug delivery technologies have been created in an effort to enhance this UA molecule's biopharmaceutical properties. Many UA delivery methods have been effectively employed to date, including liposomes [38], niossomal gels [39], nano-emulsions [40], mesoporous

silica nanoparticles, solid lipid nanoparticles [41], and solid dispersions [42]. These preparations will modify UA's pharmacokinetic characteristics.

Pharmacological Properties of UA

Natural terpene compound UA has a variety of medicinal uses. It has protective effect on liver, lung, kidney, brain, anti-inflammatory, antitumor, antidiabetic, antimicrobial, antifungal, antiviral properties [5,43]. Some of them are shown in Table 2.

Effects	Animal Model	Mechanism of Action	Dosage and Routes of Administration	References
Hepatoprotective	Wistar rats, 4-6weeks, 180–230 g Hepatotoxicity induced by carbon tetra chloride	Inhibition of microsomal membranes' liquid peroxidation, as indicated by the creation of malondialdehyde. Increase in mitochondrial glutathione and corresponding reduction in the amount of oxidized glutathione. Glutamate oxalate transaminase is reduced.	Used for five days as a pretreatment (1, 2.5, and 5 mmol/kg in olive oil). Administered intragastrically.	Martin-Aragón, et al. [44]
Cardioprotective	Adult male albino rats (120-140 gm) A subcutaneous injection of isoproterenol hydrochloride (ISO, 85 mg kg−1 b.w.) dissolved in physiological saline for two days in a row to cause myocardial ischemia.	It prolongs the life of the cardiac cell membrane against necrotic damages by acting as a membrane stabilizer. By inactivating the enzyme cyclooxygenase and seemingly directly scavenging superoxides and hydroxyl radicals, it lowers the amount of cardiac lipid peroxides. Reduces the activity of myeloperoxidase and inhibits the infiltration of neutrophils into the damaged myocardium.	Used for seven days at doses of 20, 40, and 60 mg kg−1 b.w. Administered subcutaneously.	Senthil, et al. [45]
Nephroprotective	Wistar albino rats of either sex, 150– 200 g, Gentamicin sulfate (dissolved in isotonic saline) administered intraperitoneally at a dose of 80 mg/kg/day caused renal damage.	Prevents lipid peroxidation and guards against damage brought on by free radicals. Suppresses the excessive production of nitric oxide (NO) and uses its strong antioxidant properties to keep intracellular glutathione levels stable.	Used as a medication (2, 5 10 mg kg 1) and given for three days both before and after gentamicin sulphate treatment. Administered orally.	Pai, et al. [46]

Neuroprotective	10-week-old male Kunming strain mice, 30gms. D-galactose (D-gal) (50 mg/kg) was used to produce neurotoxicity for eight weeks. The prefrontal cortex has significantly higher amounts of advanced glycation end products (AGEs), protein carbonyl, and reactive oxygen species (ROS) when D-gal is injected. This causes neurodegeneration and aging of the brain.	In mice treated with D-gal, it improves behavioral impairment in the prefrontal cortex and reduces AGEs, reactive oxygen species, or and protein carbonyl levels. The mice administered with D-gal, the prefrontal cortex of them, it lowers the expression of CD11b, glial fibrillar acidic protein (GFAP), and receptor for advanced glycation end products (RAGE) and decreases the amount of cells which are activated in microglia (CD11b stained cell), active glial (GFAP-stained cell), along with AGEs coupling to its receptor (RAGE-positive cells).	Utilized as a treatment (10 mg kg-1) by oral gavage in distilled water containing 0.1 percent Tween-80 (dH2O/0.1% Tween-80) for eight weeks.	Lu, et al. [47]
Anti-inflammatory	Male Sprague-Dawley rats weighing 200–250 grams, 6–8 weeks old. Cecal ligature and puncture (CLP) caused inflammation similar to sepsis and its associated significant consequence (acute lung damage).	Decreased ratio of lung wet to dry weight, leukocyte and protein infiltration, myeloperoxidase activity, and malondialdehyde content are all effects of ursolic acid. Moreover, UA significantly decreased the serum concentrations of tumor necrosis factor-a, interleukin-1b, and interleukin-6. Additionally, it inhibited the lung's expression of inducible nitric oxide synthase and cyclooxygenase-2, that take part in the process of creating prostaglandin E2 and NO.	Used as treatment (10 mg kg-1) intraperitoneally 24 hours after Cecal ligature and puncture (CLP).	Hu, et al. [48]

Table 2: Some pharmacolological activities of UA in different animal models and their mechanism of action.

UA as Hepatoprotective

One of the body's most vital organs is the liver. Numerous metabolic processes are carried out by it, including as the breakdown of red blood cells, synthesis of hormone and enzymes for digestion, storage of fat-soluble and glycoside vitamins, and detoxification of xenobiotics [49]. Because of the liver's strategic location and diverse range of tasks, it can be affected by a number of illnesses, including cirrhosis, cholelithiasis, drug-induced liver damage, and hepatitis. Thankfully, the liver is the only internal body part that can

regenerate; it can regain its entire size from as little as 25% of its initial mass [24]. Good protective activity of UA was shown against a variety of drugs that pose a hazard to the liver. UA extracted from Eucalyptus tereticornis extracts was tested against toxicity of alcohol in hepatocytes of rats that are isolated [50]. They found out that this triterpene could reduce hepatocyte viability loss by up to 76%. Also, for the comparative study an *in-vivo* study was done with rats that had been given alcohol [51]. They found that UA reduced the levels of lipid peroxidation indicators and total bilirubin while raising serum protein and circulatory antioxidants. Biochemical measurements and histopathological observations correlated. Medications that cause liver intoxication were examined including paracetamol and tetrachloride respectively [44,52]. In the UA-treated samples, both of these articles showed improved serum indicators and an increase in hepatocyte viability. It had been examined that how UA affected metabolic disorders in mice and rats fed a high-fat diet [53,54]. The first group focused on hepatic lipid build up and found that the thiazolidinedione family antidiabetic drug rosiglitazone, when combined with UA therapy significantly decreased hepatic marker enzyme activity as well as hepatic lipid accumulation.

In addition, the combined medication raised the fatty acid oxidative genes and decreased the expression of lipogenic genes. The latter team found that by enhancing important enzymes involved in lipid metabolism, UA successfully reduced hepatic steatosis caused by high-fat diets through a pathway involving PPAR-α. Hepatic PPAR-α was considerably reduced in the non-alcoholic fatty liver disease (NAFLD) state. Steatosis development has been demonstrated to be prevented by activating PPAR-α. In line with the in vitro work, which suggested UA may be a possible PPAR-α agonist, our investigation clearly showed that UA restored the down-regulation of PPAR-α caused by HFD at both the mRNA and protein levels.

- During fasting and postprandial periods, the liver controls the body's glucose and lipid balance as well as energy metabolism. The liver is the metabolic centre responsible for controlling blood glucose levels. It releases glucose from glycogenolysis as well as gluconeogenesis during fasting and primarily focuses on glucose in relation to postprandial glycolysis and glycogen synthesis [55-57]. Furthermore, by converting extra-fatty acids into ketone bodies and storing fats and cholesterol from the meal to power extra hepatic cells including the brain and muscular tissue in the skeleton during fasting, the liver maintains the control of lipid metabolism [56]. Several master regulators that track the movement of lipids and glucose throughout the body tightly control each of these metabolic processes [58,59]. This process involves a highly regulated transition among the production and breakdown of fatty acids. Several transcriptional regulators and the nuclear receptors control this process in the liver. PPAR-α functions as a nutritional sensor by controlling the rate of catabolization and biosynthesis of free fatty acids (FFAs), and it is the primary transcriptional regulator of genes involved in lipid metabolism.
- In the liver, PPARα raises the concentration of high-density lipoprotein (HDL). The liver's increased cellular uptake is caused by an accumulation of free fatty acids in the body. Hepatocyte transport protein binds to free fatty acids. Next, inflammation happens when the PPARα gene interacts to transport proteins within the nucleus. (Figure 3)
- Since there are currently no FDA-approved medications for treating nonalcoholic steatohepatitis (NASH), lifestyle modifications particularly weight loss are the mainstay of treatment [60]. Triggering inflammatory responses and regulating lipids are two important functions of transcription factors PPARs, which make them excellent candidates for NAFLD treatment. However, there hasn't been much success focusing solely on PPAR-α thus far. Fibrate and gemfibrozil are examples of fibrates that function as PPARα agonists and ameliorate some of the symptoms of NASH, such as the functioning of the liver, lipid profile, and sensitivity to insulin, but they have a number of negative side effects and have no effect on histopathology. (e.g., decreased renal function, a rise in creatinine levels and homocysteine [61-65].
- Serum alanine aminotransferase, or ALT, levels in dyslipidaemia-affected NASH patients [66] and NASH histological characteristics in mice [67] are altered by pemafibrate, a new selective PPAR-αmodulator. According to a recently completed phase II trial (NCT03350165), which was double-blind, placebo-controlled, randomised and multicentre, pemafibrate dramatically lowers liver stiffness while having no effect on liver fat content [68].
- Saroglitazar which is a dual-PPARα/γ agonist, was studied in a randomized, double-blind, placebo-controlled trial (EVIDENCES IV, NCT03061721), dramatically improved insulin resistance, atherogenic dyslipidemia, serum ALT, and liver function [69]. Two clinical trials are now being conducted to estimate the safety, acceptability, and efficacy of saroglitazar in NAFLD patients who have received a liver transplant (NCT03639623) and in female patients suffering from polycystic ovarian syndrome (NCT03617263). According to a Phase IV trial (NCT02285205). Another dual-PPARα/γ agonist is lobeglitazone that can improve lipid profiles, glycaemic control, and liver enzymes in those who have NAFLD and type 2 diabetes (T2DM) [70].
- To sum up, treating NASH is a difficult undertaking. Thus, it appears that agonists that can activate PPARα in conjunction with additional PPAR members are a viable class of medications for the treatment of NASH.

The goal of some researchers was to determine whether administering UA could benefit individuals with hepatic fibrosis. They conducted experiments on rat liver stellate cells (HSCs) and discovered that UA causes these cells to undergo apoptosis, which somewhat improves fibrosis [71].

A regulatory sequence known as the antioxidant response element (ARE) is involved in the coordinated transcriptional activation of genes that code for several antioxidant enzymes and phase II detoxifying enzymes. These enzymes play a major role in protecting cells from oxidative stress, redox cycling, and neoplasia. The oxidative stress-induced nuclear translocation of Nuclear factor E2-related factor 2 (Nrf2), which is typically thought to be sequestered in the cytoplasm by the cytoskeleton-binding Kelch-like ECH-associated protein 1 (Keap1) protein, is a crucial regulatory step leading to ARE activation. However, Nrf2 separates from Keap 1 and moves into the nucleus in response to inducer activation, (Figure 3) where it dimerizes with a few cofactors and binds to ARE [72].

- Mice with hepatic injury exhibit decreased expression levels of quinone oxidoreductase-1 (NQO1), glutathione S-transferase (GST), and heme oxygenase-1 (HO-1). In the sick condition, Nrf2 expression levels in cytoplasma fractions are noticeably higher. The translocation of Nrf2 from the cytoplasm to the nucleus fraction was significantly enhanced by UA pretreatment. It's interesting to note that UA treatment only markedly raised the liver's nuclear Nrf2, HO-1, NQO1, and GST expression levels [72].

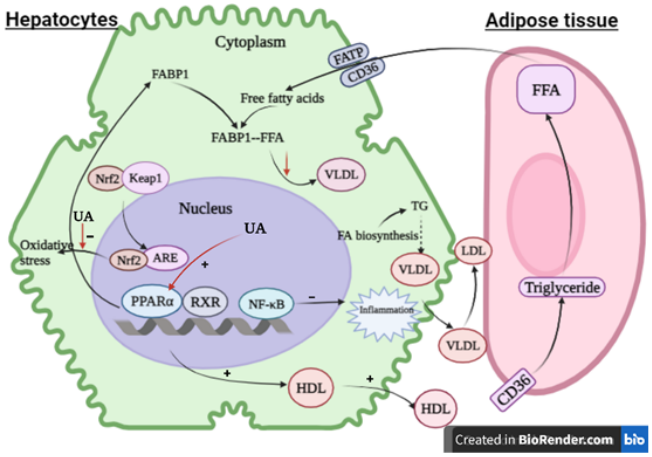

Figure 3: Schematic representation of UA as hepatoprotective (UA as selective PPARα agonist, as inhibitor in oxidative stress through Nrf2-ARE pathway) (FFA:Free fatty acid, TG: triglyceride, HDL: high density lipoprotein, VLDL: very low density lipoprotein, CD36: fatty acid transporter, FABP1: fatty acid binding protein 1, Nrf2: Nuclear factor E2-related factor 2, Keap1: Kelch-like ECH-associated protein 1, ARE: antioxidant response element, PPARα:Peroxisome proliferator activated receptor alpha, RXR: Retinoid X receptor, NFκb: Nuclear factor kappa-light-chain-enhancer of activated B cells).

- In summary, both in vitro and in vivo, UA selectively promotes apoptosis in activated HSCs. Further research is necessary to fully understand the molecular processes causing this cell-specific apoptosis induction, but it's most likely that UA prevents the cell-survival signalling pathways mediated by Akt and NFκb (Figure 4), which in turn activates downstream caspases and causes mitochondrial permeability transition (MPT), which in turn causes apoptosis in activated HSCs. Prospective methodologies for clinical implementation appear to hold promise in establishing a novel therapeutic intervention for hepatic fibrosis across a range of persistent liver ailments [71].
- MPT and downstream caspase activation generated by UA suggest that, like gliotoxin, UA primarily induces conventional apoptotic cell death via mitochondria [73]. Furthermore, the anti-apoptotic impact of UA is probably largely dependent on the suppression of NFκB activation (Figure 4). It is hypothesised that one of the primary mechanisms serving as a cell-survival signal in activated HSCs is constitutive activation of NFκB [74]. It has been demonstrated that the majority of substances that cause HSCs to undergo apoptosis also prevent NFκB activation [73-76]. Additionally, it has been demonstrated that stimulation of the Akt-PI3K pathway in a variety of cell types is a crucial signal for cell survival. UA causes Akt phosphorylation levels in HSCs to drop, suggesting that inhibiting the PI3K-Akt

pathway might be a different strategy to cause HSCs to undergo apoptosis. It is postulated that in activated HSCs, concurrent suppression of NFκB and PI3K-Akt signals jointly triggers the apoptotic signal cascades and results in cell death. It appears that pharmacological blockage of the PI3K-Akt pathway with LY294002 is insufficient to induce apoptosis in HSCs because it did not trigger apoptosis in activated HSCs. They found that following a partial hepatectomy in mice, ursolic acid could improve liver regeneration [77]. There has been a notable rise in the ratio of liver to body weight when compared to the control group. Additionally, the generation of cyclins and C/EBP proteins has been stimulated [77].

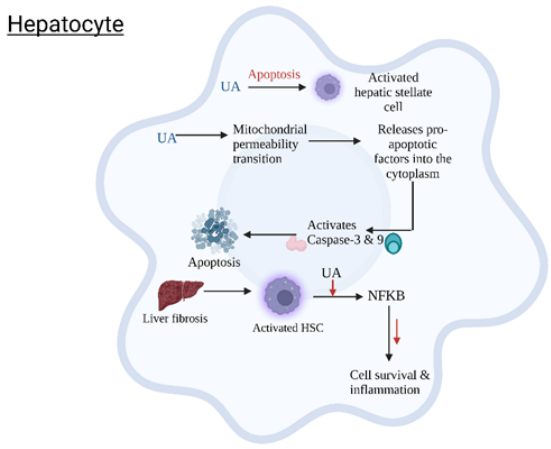

Figure 4: Representaion of UA as hepatoprotective through NFκB pathway.

UA as Cardioprotective

- In developed nations, cardiovascular illnesses account for the majority of deaths and morbidities. They are to blame for roughly 30% of all fatalities globally. The most prevalent conditions affecting the cardiovascular system include varicose veins, atherosclerosis, hypertension, myocardial infarction, or heart attacks [78]. While not all cardiovascular disorders are fatal, they all cause severe reductions in life expectancy and involve high social and economic expenses [79]. At first the effects of UA on the heart and circulatory system were documented by some researchers [80]. It was found that UA therapy could cause a 32% reduction in the heart rates of genetically hypertensive rats. Numerous directions have been explored through more research. Aguirre-Crespo, et al. [4] conducted research on ursolic acid's vasorelaxant [4].
- Vasorelaxant effects of UA are demonstrated. It has to do with changing the nitric oxide-cyclic guanosine mono phosphate (NO-cGMP) signaling pathway. By stimulating endothelial nitric oxide synthase (eNOS), UA has the ability to release NO, which is beneficial for treating hypertension and other cardiovascular conditions (Figure 5) [81].

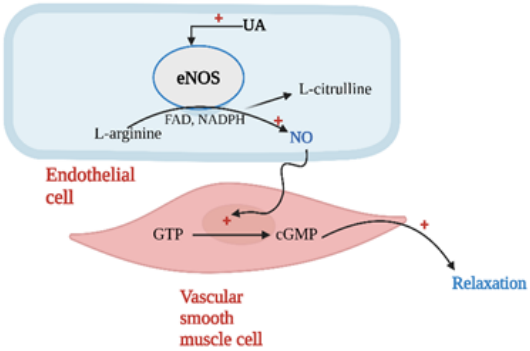

Figure 5: UA as cardioprotective through generation of eNOS and stimulates vasorelaxation (eNOS: Endothelial nitric oxide synthase, FAD: flavin adenine dinucleotide, NADPH: nicotinamide adenine dinucleotide phosphate hydrogen, NO: nitric oxide, GTP: guanosine triphosphate, cGMP: cyclic guanosine monophosphate).

NO generation and release in an isolated thoracic aorta and in vivo on Wistar rats, respectively, were linked to the activity of UA [4,82]. Angiotensin I-converting enzyme (ACE), which is essential for controlling blood pressure, was the subject of Shimada and Inagaki's study Shimada and Inagaki (2014).

Additionally, ursolic acid has been employed as a chemical with a strong preventive effect in myocardial infarctions that are experimentally generated (by administering isoproterenol). The concentration of membrane-bound proteins, lipid profiles, lipid peroxidation products, and heart indicators in the serum of Wistar rats treated with isoproterenol was examined [45].

- The absence of adenosine triphosphatase (ATPase) activity during ischemia may produce irreversible necrotic changes in the impacted cardiac cell in addition to functional loss.
- Pretreatment with UA has the ability to increase the activity of membrane-bound ATPase, which isoprenaline has reduced. This may be because ursolic acid has antioxidant activity, antihyperlipedemic, and membrane-stabilizing actions.

They discovered that UA exhibited cardioprotective properties by being able to stop changes and return enzyme activity to normal levels. Two investigations by Radhiga et al. expanded and corroborated these results [83,84]. According to reports, UA was able to stabilize the levels of many blood components

and indicators. Furthermore, research has demonstrated the anti-apoptotic action on cardiac muscle cells.

Saravanan, et al. [85] work also revealed heart-protective characteristics of UA [85]. They looked into the oxidative stress that rats given ethanol experienced. Similar to the aforementioned studies, ursolic acid raised antioxidant levels and the activity of enzymes that scavenge free radicals while decreasing the amounts of products from lipid peroxidation in cardiac tissue. The administration of ursolic acid also guards against blood vessel damage.

According to Pozo, et al [86] at a dose of 6 mg/kg body weight per day, UA can stop the development of neointima in the carotid artery of rats [86].

- Ursolic acid has been shown to compete with TGF-β1 receptor (Growth factor of tranformation) binding recently [87]. This TGF-β1 pathway Inhibits this signaling pathway has been demonstrated to prevent neointima development and the start of various fibrotic diseases [88]. The TGF-β1 pathway is essential for constrictive remodeling associated with angioplasty. Therefore, it is reasonable to propose that ursolic acid's "in vivo" effects may be somewhat accounted for by its ability to decrease TGF-β1 system activity.
- Pentacyclic triterpenes, including ursolic acid, show potential for treatment against vascular diseases by suppressing NF-κB and matrix metalloproteinase (MMPs). Particularly, UA decreases MMP-9, which is linked to cellular migration and proliferation following vascular damage [89,90] in addition, oleanolic, betulinic, and ursolic acids block NF-κB [89] while other research indicates that stopping neointimal development only by blocking vascular smooth muscle cells (VSMC) migration with MMP inhibitors is insufficient [91]. This is a crucial action because proinflammatory cytokines in cultured VSMCs activate [92] NF-κB in a rat carotid injury model [93].

The protective function of UA against C-reactive protein-induced damage to human umbilical vein endothelial cells (HUVECs) is explained by the authors in their study [94]. According to their findings, UA reduced the negative effect in a way that was dose-dependent. Scientists disagree about the effect of ursolic acid on atherosclerosis since some research suggest positive effects while others suggest harmful effects. For instance, Ullevig et al discovered that giving diabetic mice UA prevented monocyte dysfunction and reduced the development of accelerated atherosclerosis [95], while Messner, et al. [96] showed that UA administration stimulated the formation of atherosclerotic plaque in mice [96]. Kim, et al. [98] have demonstrated the possible detrimental effect of UA ingestion [97]. They found that this triterpene can increase platelet aggregation susceptibility; therefore individuals who are prone to cardiovascular events should utilize it with caution [98].

Conclusion

Nowadays, cardiac disorders and liver diseases are very common in people due to their irregular lifestyles, but the synthetic drugs that are used have multiple adverse effects. Ursolic acid a which is plant derived natural compound is found in fruits, vegetables, easily available in natural sources like different fruits and vegetables and could be a the new therapeutic entity for these complications. This review specifically discusses the mechanistic pathway of ursolic acid as cardioprotective and hepatoprotective have been discussed here. This would allow the researchers to pave the way for more effective therapeutic interventions in diverse health conditions.

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