MINIREVIEWS

Novel insights into the mechanisms whereby isoflavones protect against fatty liver disease

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Abstract

Fatty liver disease (FLD) is a growing public health problem worldwide. There is an urgent requirement for alternative and natural medicine to treat this disease. As phytochemicals, isoflavones have attracted considerable attention for the prevention of FLD. Numerous studies have revealed that isoflavones protect against FLD through various pathways which modulate fatty acid β-oxidation, lipid synthesis, and oxidative stress. Recently, the aldose reductase (AR)/polyol pathway has been reported to be involved in the development of FLD by modulating hepatic fructose production, peroxisome proliferator-activated receptor (PPAR)α activity, cytochrome P450 (CYP)2E1 expression, and gut bacterial endotoxin-induced cytokine release. It has been reported that some isoflavones are potent AR inhibitors. Here, we review the anti-FLD actions of isoflavones and the proposed mechanism whereby isoflavones protect against FLD, with regard to the AR/polyol pathway. We propose that isoflavones block the AR/polyol pathway and in turn reduce fructose production and subsequent fat accumulation in the liver in diabetic or high-glucose-diet mice. In addition, in rodents with alcoholic liver disease or nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, inhibition of AR by isoflavones may improve PPARα-mediated fatty acid oxidation, reduce hepatic steatosis, and attenuate CYP2E1-mediated oxidative stress or AR/gut bacterial endotoxin-mediated cytokine overproduction, to alleviate progression of FLD.

Key words: Isoflavones; Fatty liver disease; Aldose reductase; Fructose; Peroxisome proliferator-activated receptor α; Cytochrome P450 2E1; Endotoxin

Core tip: The aldose reductase (AR)/polyol pathway has recently been reported to be involved in the development of fatty liver disease (FLD) *via* various pathways. Some isoflavones have been reported to be potent AR inhibitors. Here, we review the anti-FLD actions of isoflavones and the proposed mechanism whereby isoflavones protect against FLD, with regard to the AR/polyol pathway. We propose that isoflavones block the AR/polyol pathway to suppress fructose production in the liver, improve peroxisome-proliferator-activated-receptor-α-mediated fatty acid oxidation, ameliorate cytochrome-P450-2E1-mediated oxidative stress, and attenuate AR/gut bacterial endotoxin-mediated cytokine overproduction, which in turn alle-

viates the progression of FLD.

INTRODUCTION

Fatty liver disease (FLD) is a condition where neutral fat accumulates in liver cells, and may be accompanied by progressive inflammation of the liver. In light of the contribution of alcohol, fatty liver may be termed alcoholic liver disease (ALD) or non-alcoholic fatty liver disease (NAFLD), and the more severe forms of NAFLD as non-alcoholic steatohepatitis (NASH). It is difficult to distinguish ALD from NAFLD histologically. The histological spectrum of ALD includes steatosis, hepatitis and fibrosis, and NAFLD can mimic the entire spectrum of hepatic changes in ALD.

FLD is a growing public health problem worldwide. The prevalence of NAFLD is approximately 30% in developed countries and nearly 10% in developing nations[1]. FLD is increasingly recognized as an important cause of end-stage liver disease[2]. Current treatments for FLD focus on the factors that may cause the disease. In general, these treatments include weight loss, cholesterol management, blood glucose control, or treatment of alcoholism. Although several pharmacological agents for the prevention of FLD have been investigated, they have been found to be effective, but have side effects[3]. Thus, there is an urgent requirement for alternative and natural medicine to treat this disease. Isoflavones are phytochemicals and have been reported to prevent FLD in numerous studies through the regulation of peroxisome proliferator-activated receptors (PPARs), carbohydrate responsive element binding protein and Wnt signaling, to regulate fatty acid β-oxidation, lipid synthesis and oxidative stress[4]. Recently, the aldose reductase (AR)/polyol pathway has been reported to be involved in the development of FLD[5-7]. Of note, isoflavones such as genistein, daidzein and puerarin have been recognized as AR inhibitors[8,9]. However, only a few studies have investigated the effect of isoflavones on FLD by inhibition of AR. Thus, this article reviews the biological effects of isoflavones on FLD, and the mechanisms whereby isoflavones protect against ALD and NAFLD/NASH, with regard to the AR/polyol pathway.

CAUSES OF ALD AND NAFLD

The causes of FLD are alcoholism, toxins, inherited metabolic disorders, and certain drugs. Almost all heavy drinkers develop fatty liver. NAFLD has been consistently associated with insulin resistance and the metabolic syndrome (obesity, diabetes mellitus, hypertension, and dyslipidemia)[10]. Although many investigations have been carried out to elucidate the mechanisms of ALD development, the pathogenesis of ALD is still not fully understood. It is generally accepted that increased release of proinflammatory cytokines, induced oxidative stress, and elevated gut bacterial endotoxins play important roles in the development of ALD[11,12]. In contrast, the underlying cause of NAFLD/NASH is still not clear. However, there are several factors, which may be involved including insulin resistance[13,14], toxic inflammatory cytokines[15], oxidative stress inside liver cells[14,16], gut microbiota[17], endoplasmic reticulum stress[18], and genetics[19]. Day *et al*[20] proposed the hypothesis of "two hits" to clarify the mechanisms underlying the progression from steatosis to steatohepatitis. The first hit is insulin resistance, which causes hepatic steatosis and excess fatty acids. The second hit is oxidative stress and associated lipid peroxidation and cytokines within the liver, which may initiate progression from steatosis to steatohepatitis and ultimately to cirrhosis. Recently, Basaranoglu *et al*[21] suggested that possible candidates for the second hit included increased oxidative stress, lipid peroxidation and release of toxic products, decreased antioxidants, adipocytokines, transforming growth factor-β, Fas ligand, mitochondrial dysfunction, fatty acid oxidation by cytochrome P450s, peroxisomes, excess iron, small intestinal bacterial overgrowth, and the generation of gut-derived toxins such as lipopolysaccharide and ethanol. In addition to the two-hit hypothesis, a "multiple parallel hits" hypothesis was recently proposed by Tilg *et al*[18] to clarify the mechanisms underlying the development of liver inflammation. Many parallel hits derived from the gut and/or the adipose tissue may promote liver inflammation, such as endoplasmic reticulum stress, adipocytokines, and innate immunity.

ISOFLAVONES FOR PREVENTION OF FLD

Isoflavones are phytochemicals found in various legumes including soybean, kudzu, red clover, fava beans, alfalfa, chickpeas and peanuts. Numerous reports indicate that the consumption of isoflavones has many health benefits, including protection against menopausal symptoms, osteoporosis, cardiovascular disease, atherosclerosis, hyperlipidemia, and cancer[22,23].

Recent studies have demonstrated that isoflavones can protect against ALD or NAFLD (Table 1). The most studied isoflavones are soy isoflavones, including genistein and daidzein. Among the soy isoflavones, genistein is the most beneficial and protects against both ALD and NAFLD/NASH in rodents[24-33]. In addition to soy isoflavones, kudzu isoflavones and their main bioactive component,

Table 1 Effects of soy, kudzu and red clover isoflavones on fatty liver disease in rodents

Experimental model	Treatment	Effects	Ref.
Mice fed high-fat diet	Genistein	Alleviates NAFLD by stimulating hepatic fatty acid β-oxidation and increasing antioxidative enzyme	Lee *et al*[24]
Rats fed high-fat diet	Genistein	Prevents emergence of NASH by attenuating oxidative stress	Yalniz *et al*[25]
Rats fed MCD diet	Soy isoflavone	Prevents liver damage by decreasing lipid peroxidation in NASH model	Ustundag *et al*[26]
Rats fed high-fructose diet	Genistein	Reduces NAFLD *via* activation of antioxidant profiles and decreases IL-6 and TNF-α	Mohamed Salih *et al*[27]
Mice fed high-fat diet	Genistein	Reduces NAFLD by regulating adipocyte fatty acid β-oxidation and adipogenesis	Kim *et al*[28]
Rats fed high-fat diet	Genistein	Slows down NASH progression by inhibiting IκB-α phosphorylation, nuclear translocation of NF-κB p65 subunit, and activation of JNK	Ji *et al*[29]
Rats provided with ethanol	Genistein	Ameliorates alcoholic liver injury and liver fibrosis by reducing lipid peroxidation, recruiting the anti-oxidative defense system, inhibiting CYP2El activity, and promoting extracellular matrix degradation	Huang *et al*[30]
ApoE^{-/-} mice fed high-fat diet	Genistein	Alleviates metabolic abnormalities including hypercholesterolemia and NASH in *ApoE*^{-/-} mice	Kwon *et al*[31]
Mice fed high-fat diet	Daidzein	Prevents NAFLD through the direct regulation of hepatic de novo lipogenesis and insulin signaling, and the indirect control of adiposity and adipocytokines	Kim *et al*[32]
Rats fed high-fat diet	Daidzein	Reduces weight gain and fat content in liver by affecting PPARα/γ and stearoyl coenzyme A desaturase 1	Crespillo *et al*[33]
Rats fed high-fat diet	Puerarin	Reduces NAFLD *via* hepatic leptin signaling activation (leptin receptor/ JAK2/STAT3)	Zheng *et al*[34]
Rats provided with ethanol	Puerarin	Prevents acute alcoholic liver injury by inhibiting oxidative stress	Zhao *et al*[35]
Mice provided with ethanol	Tectoridin	Protects against ethanol-induced liver steatosis by modulating disturbance of PPARα pathway and ameliorating mitochondrial function	Xiong *et al*[36]
Hepatocytes treated with ethanol	Puerarin	Restores viability of cells and reduces lipid accumulation in ethanol-treated hepatocytes by activating autophagy *via* AMPK/mTOR-mediated signaling	Noh *et al*[37]
Mice fed high-fat diet	*Puerariae* flower extract (isoflavone-rich)	Exerts anti-fatty liver effects by suppressing lipogenesis in the liver	Kamiya *et al*[38]
Rats provided with the Liber-DeCarli liquid diet	Puerarin	Alleviates chronic alcoholic liver injury by inhibiting endotoxin gut leakage, Kupffer cell activation, and endotoxin receptors expression	Peng *et al*[39]
db/db diabetic mice	Red clover extract (isoflavone-rich)	Reduces liver TG and cholesterol levels by activating hepatic PPARα and inhibiting hepatic fatty acid synthase	Qiu *et al*[40]
Mice fed cholesterol-enriched diet	2-heptyl-formononetin, formononetin	Induces hepatic steatosis, but decreases markers of inflammation and liver injury	Andersen *et al*[42]
Mice fed MCD diet	Red clover extract (isoflavone-rich)	Improves hepatic steatosis, but does not alleviate liver inflammation	Qiu *et al*[41]

AMPK: Adenosine 5′-monophosphate-activated protein kinase; IκB: Inhibitor of NF-κB; JAK2: Janus kinase 2; mTOR: Mammalian target of rapamycin; STAT3: Signal transducer and activator of transcription 3; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; TNF: Tumor necrosis factor; IL: Interleukin; MCD: Methionine-choline-deficient; PPAR: Peroxisome proliferator-activated receptor.

puerarin, have received considerable attention due to their beneficial effect on ALD and NAFLD/NASH[34-39]. Red clover isoflavones have also attracted attention. We reported that red clover isoflavones can improve hepatic steatosis in db/db obese diabetic mice[40] and methionine-choline-deficient (MCD) diet-induced NASH mice[41]. However, we did not find that red clover isoflavones alleviated liver inflammation in MCD-diet-induced NASH mice. Surprisingly, for-mononetin, one of the major isoflavones in red clover, is reported to induce hepatic steatosis and decrease markers of inflammation and liver injury in mice fed a cholesterol-enriched diet[42]. There are few data on the effect of biochanin A, the other major isoflavone in red clover, on FLD. It is known that biochanin A can protect against CCl₄-induced liver fibrosis[43]. Therefore, the effect of biochanan A and formononetin on FLD cannot be concluded from the present studies and requires further investigation.

AR/POLYOL PATHWAY IN FLD

The polyol pathway is a glucose metabolic shunt that is defined by two enzymatic reactions catalyzed respectively by AR (EC1.1.1.21) and sorbitol dehydrogenase (SDH, EC1.1.1.14). AR catalyzes the rate-limiting reduction of glucose to sorbitol with the aid of co-factor NADPH and then SDH converts sorbitol to fructose using NAD^{+}[44].

It is well documented that the AR/polyol pathway is involved in the development of diabetes complications[45,46]. Elevated AR can lead to serious diseases affecting the heart and blood vessels, eyes, kidneys and nerves. AR is induced in diseased liver, other than in the above mentioned tissues that are vulnerable to complications of diabetes. AR was detected in the livers of two human subjects with ALD, but was undetected in healthy humans[47]. Moreover, AR is induced in human livers obtained

from patients undergoing liver transplantation for fulminant (acute) liver failure or end-stage liver disease from cirrhosis due to various chronic liver diseases, including ALD, chronic hepatitis B and C, primary biliary cirrhosis, autoimmune hepatitis, and hepatocellular carcinoma[48]. These studies indicate that AR may play an important role in the development of liver injuries. Recently, investigations were conducted to elucidate the role of AR in the development of FLD. Lanaspa *et al*[5] demonstrated that genetic ablation of the AR gene resolved high-glucose-diet-induced hepatic steatosis in mice. We previously demonstrated that inhibition of AR ameliorated hepatic steatosis in db/db diabetic mice[6], and lentivirus-mediated knockdown of the AR gene alleviated MCD-diet-induced NASH in db/db mice[7]. These studies confirm the involvement of AR in the development of FLD.

ISOFLAVONES PREVENT HIGH-GLUCOSE-INDUCED FATTY LIVER BY BLOCKING THE AR/POLYOL PATHWAY

Numerous reports show that isoflavones have significant AR inhibitory activity. Park *et al*[9] reported that genistein, daidzein and puerarin inhibited AR in rat lens with IC_{50} values of 4.5, 7.9 and 44.7 μmol/L, respectively, whereas formononetin exhibited weak AR inhibitor activity (IC_{50} > 100 μmol/L). Hsieh *et al*[49] reported that genistein inhibited AR in rat lens with an IC_{50} of 16.9 μmol/L, while Choi *et al*[50] reported that genistein inhibited AR in pig lens with an IC_{50} of 20 μmol/L. Moreover, tectoridin has also exhibited potent activity, with an IC_{50} value of 1.08 μmol/L[51]. Furthermore, biochanin A shows better binding interactions with AR than epalrestat, a synthetic AR-specific inhibitor, which indicates that biochanin A possesses significant AR inhibitory activity[52].

Recently, Lanaspa *et al*[5] found that mice deficient in AR were protected against fatty liver after exposure to 10% glucose for 14 wk. They demonstrated that the metabolic conversion of glucose to endogenous fructose by the AR/polyol pathway in the liver is a key step in the development of glucose-induced fatty liver in mice. In addition, we demonstrated that inhibition of AR ameliorates hepatic steatosis in db/db diabetic mice[6]. Therefore, we postulate that isoflavones can block the AR/polyol pathway and subsequently reduce fructose production in the liver and alleviate fatty liver in humans and animals with high glucose diet or in diabetic conditions. Indeed, genistein, daidzein and red clover isoflavones improve hepatic steatosis and dyslipidemia in diabetic mice, although their mechanisms of action are reported to be through different pathways[40,53].

ISOFLAVONES PREVENT FLD BY SUPPRESSING AR AND SUBSEQUENTLY IMPROVING PPARα-MEDIATED FATTY ACID OXIDATION

It is well established that PPARα, a nuclear receptor, is a central regulator for hepatic lipid catabolism[54]. It regulates the enzymes involved in fatty acid oxidation, for example, acyl-CoA oxidase (ACO), carnitine palmitoyl transferase (CPT)-1, and liver fatty acid binding protein. The ablation of PPARα gene causes the development of FLD[55,56]. Administration of PPARα agonists improves MCD-diet-induced NASH[57,58] and ethanol-induced liver injury[59]. Genistein, daidzein, biochanin A and formononetin are well known PPARα agonists[60,61]. Genistein and daidzein alleviate NAFLD in animals fed a high-fat diet by stimulating the hepatocyte and adipocyte PPARα pathway and fatty acid β-oxidation[24,28,33]. Red clover isoflavones also reduce liver triglycerides and cholesterol levels in db/db mice by activating hepatic PPARα[40]. These studies indicate that some isoflavones may act as PPARα agonists to prevent FLD.

Overexpression of AR in hepatocytes stimulates extracellular signal-regulated kinase (ERK)1/2 activation, sequentially phosphorylates hepatic PPARα at the OH group of serine 12 and 21, and reduces mRNA expression of ACO and CPT-1, two target genes transcriptionally regulated by PPARα[62]. This study indicates that AR overexpression in hepatocytes inhibits lipid degradation by suppressing PPARα activity. In diabetic db/db mice with hepatic steatosis, elevated hepatic AR also stimulates ERK1/2 activation and phosphorylates PPARα and suppresses its activity. The AR inhibitor, zopolrestat, attenuates the phosphorylation of PPARα and the suppression of PPARα activity, which improves hepatic steatosis in db/db mice[6]. These studies indicate that AR inhibitors may improve hepatic steatosis by modulating the phosphorylation of PPARα and its transcriptional activity. Indeed, genistein can reduce the level of phosphorylated PPARα and increase the mRNA expression of ACO in high-glucose-treated HepG2 cells (unreported data). Mezei *et al*[63] demonstrated that soy isoflavones modulate lipid metabolism in part *via* a PPARα-dependent mechanism in mice fed a high-fat diet. CPT-1 mRNA is consistently found to be induced by soy isoflavones in obese Zucker rats[64] and ACO mRNA is induced by soy isoflavones in Agouti (A(vy)/a) mice fed an AIN-93G diet to alleviate hepatic steatosis[65]. These studies suggest that isoflavones may improve FLD, at least in part, *via* the regulation of AR/PPARα mediated fatty acid oxidation.

ISOFLAVONES PREVENT FLD BY SUPPRESSING AR/CYP2E1-MEDIATED OXIDATIVE STRESS

Oxidative stress within the liver may act as the second hit and initiate the progression from steatosis alone to steatohepatitis and ultimately to cirrhosis[16,20]. Isoflavones as antioxidants have been well documented[66,67]. Genistein is reported to activate antioxidative enzymes and attenuate oxidative stress in animals fed a high-fat diet, thus alleviating NAFLD and preventing the emergence of NASH[24,25]. Puerarin is also reported to prevent acute alcoholic liver injury by inhibiting oxidative stress[35].

There is accumulating evidence that cytochrome P450 (CYP)2E1 plays an important role in the pathogenesis of liver tissue injury[68]. Upregulation of CYP2E1 may initiate lipid peroxidation by the production of reactive oxygen species (ROS) and promote liver inflammation[69]. Previous studies have shown that CYP2E1 activity correlates with ethanol-induced liver injury, and alcohol-induced hepatotoxicity is reduced when CYP2E1 is inhibited by inhibitors or by ablation of the CYP2E1 gene[70-73]. In addition to ALD, elevated CYP2E1 protein expression and activity are also found in both humans and animals with NAFLD/NASH and promote the progression of NAFLD/NASH[74-76].

We found that overexpression of AR in hepatocytes results in induction of CYP2E1 mRNA and protein, and simultaneously, ROS production is also induced by AR overexpression. Lentivirus-mediated knockdown of the AR gene attenuates MCD-diet-induced CYP2E1 expression, reduces the levels of lipid peroxidation, suppresses expression of proinflammatory cytokines, and alleviates NASH in db/db and C57BL/6 mice[7]. Our observation indicates that CYP2E1 expression is induced by elevated AR in fatty liver and generates ROS production, resulting in oxidative stress. AR inhibitors may alleviate steatohepatitis by attenuating CYP2E1 induction.

Several studies have revealed that isoflavones can reduce expression of CYP2E1 in healthy or diseased animals with liver injury. Soybean extract (rich in isoflavones) significantly decreases hepatic CYP2E1 expression in healthy rats[77] or in rats with high-fat-diet-induced NASH[78]. In addition, genistein significantly inhibits CYP2E1 activity and protects against alcohol-induced chronic liver injury in rats[30]. Moreover, in mice, pretreatment with puerarin prior to the administration of CCl4 significantly suppresses the expression of CYP2E1 protein, and prevents hepatic malondialdehyde formation[79]. These studies suggest that the protective effects of isoflavones against hepatotoxicity possibly involve mechanisms related to its ability to block CYP2E1 activity. We propose that isoflavones inhibit AR activity and, at least in part, cause the subsequent suppression of CYP2E1 activity to alleviate oxidative stress and improve liver inflammation in humans and animals with ALD or NASH, although there is no direct evidence that isoflavones suppress CYP2E1 activity by blocking the AR/polyol pathway.

ISOFLAVONES PREVENT FLD BY SUPPRESSING AR/GUT BACTERIAL ENDOTOXIN-MEDIATED CYTOKINE PRODUCTION

In addition to oxidative stress, the gut bacterial endotoxin, toxic lipopolysaccharide (LPS), plays an important role in the development of alcoholic liver injury[12] or NAFLD/NASH[80]. Bacterial endotoxin reaches the liver through the portal circulation to activate hepatic Kupffer cells (special macrophages located in the liver) and stimulate their production of NO and cytokines, which subsequently cause damage to hepatocytes. Inhibition of the AR prevents nuclear factor (NF)-κB-dependent activation of tumor necrosis factor (TNF)-α, interleukin (IL)-12, IL-6, and macrophage chemoattractant protein-1 in livers of mice injected with LPS[81]. Moreover, pharmacological inhibition or siRNA ablation of AR prevents the biosynthesis of inflammatory cytokines and chemokines in LPS-activated RAW264.7 murine macrophages[81,82]. These studies indicate that inhibition of AR can prevent LPS-induced production of cytokines and chemokines in mice.

Pretreatment of RAW264.7 macrophages with genistein, luteolin, luteolin-7-glucoside and quercetin inhibits LPS-stimulated TNF-α and IL-6 release, whereas eriodictyol and hesperetin only inhibit TNF-α release[83]. Of these, luteolin and quercetin are the most potent inhibitors of cytokine production, with an IC50 < 1 and 5 μmol/L for TNF-α release, respectively. The cytokine-production-inhibiting potential of these flavonids is in accordance with their AR inhibitory activity (IC50: luteolin 0.5-0.6 μmol/L, quercetin 3.3-7.73 μmol/L, and genistein 4.5-16.9 μmol/L against rat lens AR), suggesting that these compounds inhibit LPS-stimulated cytokine production, at least in part, through inhibition of AR activity.

Genistein is reported to have a beneficial effect on LPS-induced injury in rodent liver, RAW264.7 murine macrophages, and murine Kupffer cells. Zhao *et al*[84] reported that genistein suppresses hepatic production of LPS-induced TNF-α, IL-1β and IL-6 in rats. *In vitro* preincubation of liver slices from naïve rats with genistein suppresses LPS-induced TNF-α production in a dose-dependent manner. Both *in vivo* and *in vitro* administration of genistein suppresses LPS-induced liver proinflammatory cytokine overproduction. Lin *et al*[85] reported that genistein treatment significantly protects against
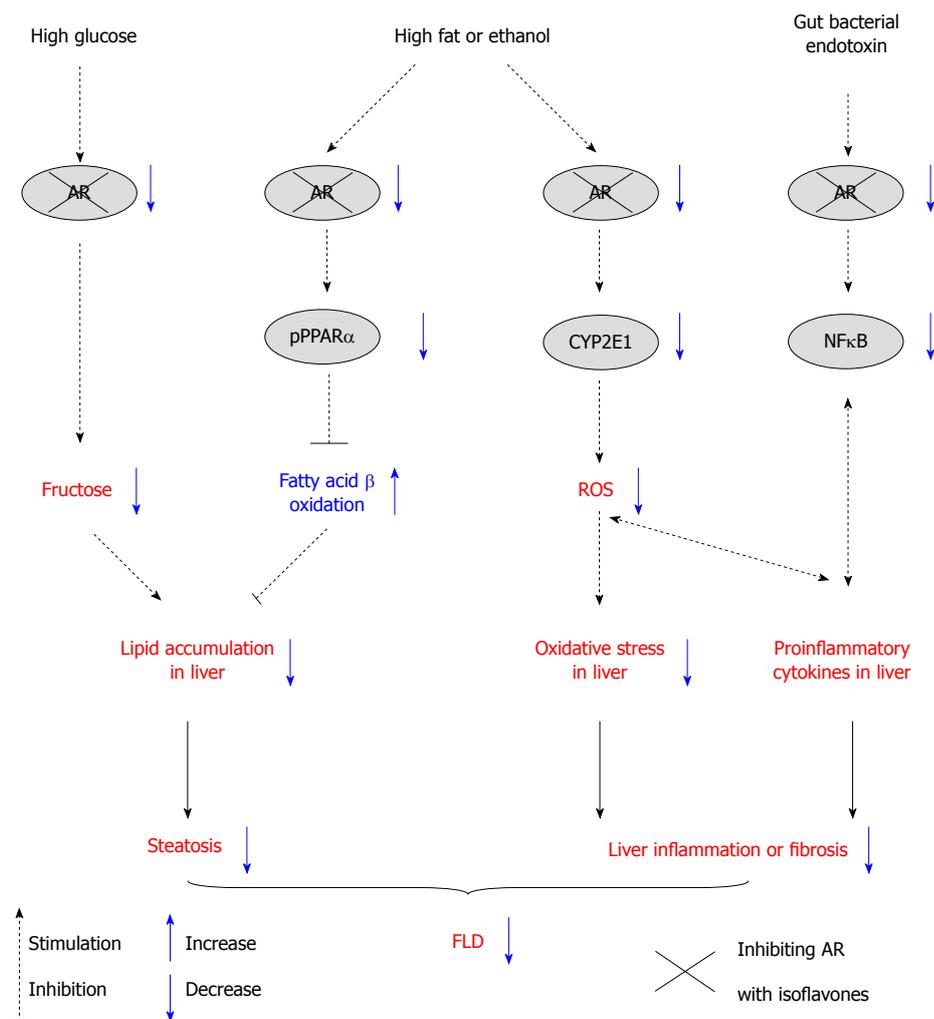
Figure 1 Proposed mechanism whereby isoflavones protect against fatty liver disease. Isoflavones inhibit the AR/polyol pathway to suppress fructose production in the liver, improve phosphorylated PPAR-α-mediated fatty acid oxidation, ameliorate CYP2E1-mediated oxidative stress, and attenuate AR/gut bacterial endotoxin-mediated cytokine overproduction, which in turn alleviates the progression of FLD. FLD: Fatty liver disease; AR: Aldose reductase; PPAR: Peroxisome proliferator-activated receptor; ROS: Reactive oxygen species.

LPS/D-galactosamine-induced liver injury in mice, and alleviates proinflammatory cytokines, including TNF-α and NO/inducible NO synthase, by inhibiting NF-κB activity.

The preventive effect of genistein on LPS-stimulated cytokine production has been found to be through inhibition of tyrosine kinase activity[86]. Genistein is a well-known inhibitor of tyrosine kinase, whereas daidzein does not inhibit tyrosine kinase activity. Genistein attenuates the liver injury caused by LPS in rats, whereas daidzein does not, which indicates the involvement of tyrosine kinase in LPS-induced liver injury. However, the AR inhibitory potential of daidzein is also weaker than that of genistein. Inhibiting AR activity is not an exclusive mechanism by which isoflavones protect against endotoxin-induced liver injury.

CONCLUSION

Collectively, isoflavones have been found to alleviate ALD and NAFLD/NASH in rodents, and these effects are partially achieved by the following mechanisms: (1) blocking the AR/polyol pathway to reduce fructose production in the liver under high-glucose conditions; (2) suppressing hepatic AR activity, which in turn improves PPARα-mediated fatty acid oxidation; (3) inhibiting AR activity and subsequently ameliorating CYP2E1-mediated oxidative stress; and (4) attenuating AR/gut bacterial endotoxin-mediated cytokine overproduction. The proposed mechanisms of action of isoflavones regarding the AR/polyol pathway are depicted in Figure 1.

Therefore, isoflavones may be useful in preventing ALD and NAFLD/NASH. Clarifying the mechanisms of action of isoflavones regarding the AR/polyol pathway will help to develop efficient anti-FLD medications. However, the literature reviewed in this paper was limited to animal models. Human data on the anti-FLD effect of isoflavones are scarce. Further clinical trials are necessary to affirm the beneficial effect of isoflavones on FLD in humans.

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