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Hepatoprotection by dandelion (*Taraxacum officinale*) and mechanisms

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ABSTRACT

The protection of the liver as an essential organ in the body against oxidative stress and deleterious compounds has been the subject of recent investigations. Among different compounds, medicinal plants play an important role due to their hepatoprotective effects. *Taraxacum officinale* or "common dandelion" is a popular plant that has been traditionally used for its hepatoprotective effects. Currently, there are limited clinical studies on its hepatoprotective effects. The aim of this review article is to evaluate the hepatoprotective effects of dandelion and its mechanism of action. We reviewed literature up to July 2019 on "*Taraxacum officinale*" or "dandelion" and hepatoprotection. Currently available pharmacological studies indicate that dandelion extracts have hepatoprotective effects against chemical agents due to its antioxidant and anti-inflammatory activities. The anti-inflammatory effects of dandelion, the prebiotic effects of its oligofructans, inhibitory effects against the release of lipopolysaccharides and fasting induced adipose factor, digestive enzymes, and enhancing effects of lipogenesis, reduce lipid accumulation and liver inflammation, which directly or indirectly improve the liver functions. Given emerging evidence on hepatoprotective effects of dandelion, designing large human clinical studies is essential.

KEYWORDS: Dandelion; Hepatoprotective effects; Antioxidant; Anti-inflammatory

1. Introduction

Liver is a vital organ with numerous functions in the body, which transforms and cleans the body from chemical substances. Although, the main function of liver is the body detoxification from common toxins, chemicals and heavy metals, but liver is affected by radical oxygen species (ROS) and oxidative stress plays a critical role in initiation and progression of liver injuries. Furthermore, liver is the metabolic organ for metabolism of carbohydrates, lipids, proteins to produce the energy. Exogenous (alcohol, drugs, environmental toxins, virus, and UV light), and endogenous (obesity, insulin resistance, steatosis, hepatocellular carcinoma, chronic hepatitis, fibrosis/cirrhosis) agents are the main reasons for oxidative stress in the liver. Liver injuries by oxidative stress cause irretrievable alteration in DNA, lipids and proteins. Different types of liver diseases like zonal necrosis, hepatitis, cholestasis, steatosis, granuloma, vascular lesions, and neoplasm are involved in liver disorders[1]. Furthermore, drugs, air pollution, inflammation, triglyceride accumulation, obesity, insulin resistance and microorganisms play essential roles in liver functions and related disorders. Medicinal plants are traditionally used for their hepatoprotective effects[2] and *Taraxacum officinale*, also known as "common dandelion", is one important medicinal plant as a hepatoprotective agent, which is used for treatment of hepatobiliary problems[3]. Dandelion is a popular hepatoprotective medicinal plant in different traditional medicines. The high content of minerals, fibers, vitamins, and essential fatty acids make it as a favorite food source[4]. Dandelion is a French word from "dent de lion" with meaning of lion's tooth. The scientific name of dandelion comes from taraxis and akeomai, with meaning of "benefit for inflammation"[5]. Dandelion roots are used in different cuisines of at least 54 countries. Dandelion is used in folk medicine of China, India and Russia as liver tonic[3]. Different traditional systems including Ayurveda[6], Siddha and Unani recommended using the dandelion for management of liver disorders such as jaundice, liver and gallbladder's disorders[7−9]. Dandelion roots in combination with other plants are used in the powder form as a sedative agent and for regulating the urine discharge and urine burning sensation in India[10], and this combination is applied as blood purifier and for treatment of hepatitis, jaundice, and

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fever[4]. Dandelion leaves or roots are used for liver complaints in Himalaya region[11]. Oral administration of dandelion roots increases the bile flow and is known as cholagogue[12]. Dandelion is one ingredient of "Taemyeongcheong" and "kimchi" that is used for liver complaints[13], and also eaten as food and salad by Germans, French and Italian for its hepatoprotective effects[14]. Dandelion leaves infusions are used in Mexico[15], Pakistan[16], Bolivia[17], and Canada[18] for hepatic, biliary, kidney and spleen ailments. Moreover, dandelion roots eliminate the toxins from liver and kidneys, dissolve the gallstones, increase the appetite and stimulate the bile flow[19].

Although there are some review articles[20–22] on phytochemistry of dandelion and its health benefit, due to traditional believes on its hepatoprotective effects and its use in many hepatoprotective products and limited review article on its effectiveness, this review article is designed to focus on its hepatoprotective effects and its related mechanism of actions.

At first, we conducted an investigation on chemical composition of dandelion and its importance as a hepatoprotective agent.

2. Chemical composition of dandelion

The chemical composition of dandelion plays an important role in its biological activities. Therefore, before evaluating the potency of dandelion as a hepatoprotective agent, we consider the chemical composition from different parts of dandelion.

The chemical composition of dandelion has been the subject of different investigations. Dandelion plant is rich in vitamins, inulin, phytosterols, amino acids, and minerals, particularly in potassium[23,24], sesquiterpenes, triterpenes, phytosterols, and phenolic compounds[5].

Oligofructans[25], chicoric acid and the related monocaffeyltartaric acid, hydroxycinnamic acids, chlorogenic acid[23], triterpenoids[26], lupane-, bauerane-, and euphane-type triterpenoids, 18β,19β-epoxy-21β-hydroxylupan-3β-yl acetate, 21-oxolup-18-en-3β-yl acetate, betulin, officinatrione, 11-methoxyolean-12-en-3-one, eupha-7,24-dien-3-one, and 24-oxoeupha-7,24-dien-3β-yl acetate[27], taraxinic acid derivatives[4], caffeic acids, *p*-hydroxyphenyl acetic acid[28], rutin[29], apigenin, hesperidin, myricetin, sesquiterpene lactones, hydroxyphenylacetic acid[30], synergic acid, vanillic acid[31] were isolated from dandelion roots.

Flavonoid glycosides (luteolin 7-glucoside, luteolin 7-diglucosides), coumarins, cichoriin, aesculin[23], sesquiterpenoid phytoalexin (Lettucenin A)[32], 4-hydroxyphenylacetate inositol esters[21], aesculin[4], caffeic acid, chlorogenic acids, apigenin, isovitexin[30], chicoric acid[31] were identified in dandelion leaves. In addition, dandelion flowers contained flavonoid glycosides, free luteolin and chrysoeriol[23].

Polyphenols (hydroxycinnamic acid derivatives and flavonoid glycosides) are abundant in dandelion aerial parts[33]. In one study, the phenolic content of young leaf dandelion extract was higher than that of its root[33]. The extraction by 50% and 80% hydro-alcohol with or without formic acid at 60 ℃ for 3 h exhibited that the phenolic and flavonoid content of hydro-alcohol 80% with formic acid was higher than hydro-alcohol 80% without formic acid. Extraction time and temperature had no effects on total flavonoid and phenolic content of dandelion leaf extract. Total phenolic content of leaf was higher than its stem, followed by flower and roots. Total flavonoid content of leaf was higher than flower, followed by stem and roots. Chicoric acid was identified as a major phenolic

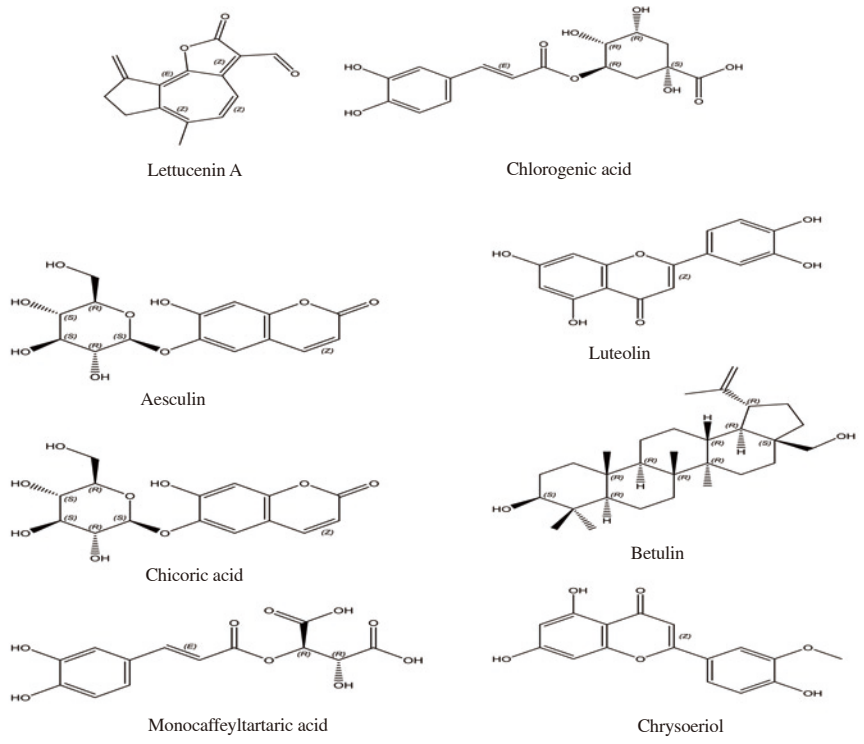

Figure 1. The chemical components of dandelion.

compound in dandelion ethanol extract[31] (Figure 1).

The results of these investigations exhibited that the chemical composition of each part of dandelion is changed by different parts, extraction method, solvent, and temperature. Therefore, a direct correlation can be found between the biological activity of dandelion and its chemical compositions.

3. Hepatoprotective effects of dandelion against toxic agents

Although dandelion is known as a hepatoprotective plant in different traditional systems, the recent studies have been limited to its protective effects against chemical toxic agent in animal studies.

There are different investigations that evaluated the efficacy of dandelion against chemical agents. Carbon tetrachloride (CCL_4) as hepatotoxic haloalkane is capable to produce hepatocellular fatty degeneration and centrilobular necrosis. CCL_4 increased the activities of liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP)]. The liver weight and liver hydroxy proline content were increased in the presence of CCL_4 and the activity of hepatic copper zinc superoxide dismutase (Cu/Zn SOD) was reduced[34]. Intra-peritoneal administration of dandelion root hydro-alcoholic extract for 4 weeks normalized the activity of ALP, Cu/Zn SOD enzymes and reduced the hepatic hydroxyl proline level in CCL_4-induced hepatic fibrosis in mice. Dandelion root extract significantly reduced the enlargement of liver, hepatic fibrinous deposits, and restored histological architecture. Glial fibrillary acidic protein (GFAP) and α-smooth muscle actin (α-SMA) expressions were reduced after treatment with dandelion root extract, while metallothionein (MT) Ⅰ/Ⅱ expression was increased in dandelion ethanol extract[29]. α-SMA and GFAP expressions are responsible for fibrosis in chronic liver injury[34]. Up-regulation of MT Ⅰ/Ⅱ expression had protective effects against liver injury[35]. Dandelion extract showed hepatoprotective effects against CCL_4 induced hepatic fibrosis by reducing the α-SMA and GFAP and inducing the MT Ⅰ/Ⅱ expression. Liver fibrosis is associated with excessive accumulation of extracellular matrix protein in the liver. Dandelion root extract reduced the collagen deposits in necrotic area and reversed the hepatic fibrosis, which was associated with reduction in GFAP and α-SMA and increase in the Cu/Zn SOD activity, suggesting its hepatoprotective effect[29].

Ethanol increases ROS production and reduces the cell viability of liver. Hot aqueous extract of dandelion root had protective effects against alcohol-induced liver damage in ICR mice and HepG2/2E1 cell lines without any cytotoxic effects. Dandelion extract (1 g/kg bw/day) significantly reduced the serum AST, ALT, ALP, lactate dehydrogenase and malondialdehyde (MDA) levels. Dandelion also significantly increased the hepatic antioxidant enzymes [catalase, glutathione peroxidase (GPx), glutathione-S-transferase (GST), glutathione reductase (GR) and glutathione (GSH)]. Reduction in lipid peroxidation and increase in antioxidant enzymes were caused by dandelion hot water extract. Ethanol induced the oxidative stress that was associated with reduction in cell viability, whereas dandelion aqueous extract increased the cell viability in the presence of ethanol[36]. The result of the previous study exhibited that the hepatoprotective effects of dandelion root extract are related to its antioxidant activities. Dandelion root extract increased the antioxidant enzymes and ameliorated the liver enzymes, therefore protecting the liver against oxidative stress induced by ethanol.

The hepatoprotective effects of dandelion leaf extract were confirmed against sodium dichromate induced liver injury in rats. Oral daily administration of dandelion leaf hot water extract (500 mg/kg) for 30 d decreased the total cholesterol, triglycerides, AST, ALT, lactate dehydrogenase, MDA and chromium concentration in rat's blood and liver. Thyroid-stimulating hormone level reached to normal level in sodium dichromate treated animal after pretreatment with dandelion leaf extract, which was associated with increase in antioxidant enzymes activities (SOD, catalase, GPx levels) and reduction in DNA fragmentation[37]. As the results of this study confirmed, up-regulation of hepatic antioxidant enzymes may be responsible for its hepatoprotective effects[38]. Other than the antioxidant activities of dandelion, the anti-fibrotic effects of dandelion aqueous extract have been confirmed. Dandelion inactivates the hepatic stellate cells and enhances the hepatic regenerative capabilities[39].

Dandelion is used in combination with other herbal extract as hepato-protective agents and commonly is used in combination with *Silybum marianum* (*S. marianum*). The protective effect of oral dandelion extract (100 mg/kg/day) and its combination with *S. marianum* extract (100 mg/kg/day) was evaluated in CCL_4 treated female Wistar albino rats. Combination of dandelion and *S. marianum* extracts in CCl_4 treated animals decreased the serum ALP and GGT enzyme activities and MDA level in the kidney tissue, and increased the GSH level and GST enzyme activities. The hepatoprotective effects of dandelion were a little weaker than *S. marianum* extract[40]. The results of animal studies confirmed the hepatoprotective effects of hot aqueous extracts of dandelion roots and leave against chemical compounds and the extract improved the liver, and antioxidant enzymes. Although the hepatoprotective effects of dandelion were confirmed in animal studies, there is no clinical study on its efficacy, it will be worthwhile, if the chemical compounds responsible for its hepatoprotective effects will be known and these compounds are chosen as standard for clinical trials.

4. Identified chemical compounds responsible for hepatoprotective effects of dandelion

Among different parts of dandelion extracts, aqueous extracts of dandelion roots and leaves have been used as hepatoprotective agents. Different components may be responsible for its hepatoprotective effects. Total phenolics, flavonoids, tannins, polysaccharides and ascorbic acids are the main components of hot aqueous extract of dandelion leaf with the ability to scavenge the free radicals[37]. Dandelion extracts had effective reducing power and free

radical scavenging effects[41]. It has been confirmed that dandelion leaf extract (EC_{50}: 1.9 μg/mL) had much higher antioxidant activity than its root extracts (EC_{50}: 12.6 μg/mL) and crude powdered roots (EC_{50}: 65 μg/mL). Taraxol, taraerol, laevulin, inulin are found in dandelion extracts responsible for its hepatoprotective effects. Some compounds isolated from dandelion leaf aqueous extracts, especially its luteolin and polyphenol contents, had hepatoprotective effects against CCL_4-induced liver injury[42,43].

In addition, the dandelion's polysaccharides reduced the oxidative stress and liver inflammation. Oral administration of 304 and 92 mg/kg polysaccharides (Top1 and Top2) for 7 d reduced the serum AST, and ALT and thus was effective against CCL_4-induced hepatitis in Sprague-Dawley rats[43].

Polyphenols, flavonoids, and polysaccharides are responsible compounds for hepatoprotective effects of dandelion. Therefore, the dandelion extracts can be standardized on the basis of one of these compounds.

5. Effects of dandelion on human condition related to its hepatoprotective effects

Although there is no clinical study on hepatoprotective effects of dandelion extracts, there is some evidence in human studies which confirm its potency in protection of liver.

5.1. The role of oligofructans in dandelion and its effects on liver functions

The prevalence of nonalcoholic fatty liver disease (NAFLD) is associated with worldwide epidemic of obesity. There is a positive correlation between intestinal microorganisms and development of obesity and NAFLD. Portal venous system connects the liver and gut, therefore the liver gets hurt by bacteria, bacteria endotoxin and cytokines[44].

Altered gut bacteria induce the release of LPS, fasting induced adipose factor (FIAF), and endogenous ethanol that stimulate the hepatic fat deposition and produce the inflammation in the liver and damage the liver function (Fibrosis/Cirrhosis, steatohepatitis, steatosis and NAFLD). The use of probiotics and prebiotics as diets is for regulating the intestinal microbial ecosystems[45]. Prebiotics act as the source of carbon and energy for stimulating the beneficial intestinal bacteria. Dandelion roots are rich in oligofructans, which are known as prebiotics[25]. High prebiotic fiber content of dandelion acts as the source of carbon and energy for stimulating the Bifidobacteria or other probiotics[25]. The bifidogenic effect of dandelion root was confirmed against fourteen Bifidobacteria strains[25]. Prebiotics are resistant to gastric acidity and mammalian enzymes and they are fermented by gut bacteria. Prebiotics or non-digestible fibers induce the growth or activity of intestinal beneficial bacteria and influence on lipid metabolisms[46]. Reduction in growth of gut dysbiosis is associated with reduction in release of LPS, FIAF, and alcohol. In addition, prebiotic compounds induce the intestinal beneficial bacteria that reduce the lipid accumulation[47] and oxidative stress[48]. The results of preclinical studies confirmed that the prebiotic effects of dandelion extracts reduced the inflammation and oxidative stress in the body. Reduction in oxidative stress and ethanol production in the liver is the main cause of reduction of liver inflammation.

5.2. Anti-obesity effects of dandelion

Obesity is the most common background condition for development of liver diseases with metabolic origin[49]. There are some documents on anti-obesity effects of dandelion. Plants with inhibitory effects against pancreatic lipase have potential to be used as an anti-obese agent. The removal of fatty acids chains from triglycerides at the positions of α and α' is performed by pancreatic lipase, which produces the lipolytic compounds. Inhibition of pancreatic lipase is an attractive target for control the obesity[50]. Dandelion ethanol extract inhibited the pancreatic lipase activity (IC_{50}: 78.2 μg/mL) compared with orlistat (IC_{50}: 0.22 μg/mL), in *in vitro* condition[51,52]. The result of this study was in accordance to the other study, in which young fresh dandelion leave ethanol extract exhibited 90.2% pancreatic lipase inhibition activity (IC_{50} = 78.2 μg/mL)[51]. However, the result of this study[51] was in contrast to the other research that showed dandelion extract as a weak pancreatic lipase inhibitory agent[53]. α-Glucosidase inhibitors are used to develop the compounds for management of obesity and related disorders. The inhibition of α-glucosidase suppresses the cleavage of glucose from disaccharides and oligosaccharides[54]. Dandelion root and herb ethanol extract (100 μg/mL) exhibited weak inhibitory effects against α-glucosidase activity (lower than 20%). Inhibition of angiotensin converting enzymes is important for management of hypertension related to obesity[55]. Dandelion extract showed weak xanthine oxidase, and ACE inhibitory effects[53]. The results of above studies confirmed the acceptable inhibitory effects of dandelion against pancreatic lipase activity.

Hypertrophy and hyperplasia of adipocytes are the other reasons for obesity and identified by expanded adipose tissue, which is associated with disruption in normal functions of adipose and amplifying the secretome in the body. The systemic effects in the liver lead to insulin resistance and hepatic lipid accumulation[56].

The positive role of dandelion roots and leaf on lipid metabolism, adipogenesis and restoring the liver function is demonstrated. Dandelion leaf and roots inhibited the lipogenesis and adipocyte differentiation in 3T3-L1 pre-adipocytes[30]. Dandelion root extract (400, 500, 600 μg/mL) reduced the size and the number of adipocytes and increased the lipolysis activity. Leaf extract and crude powdered roots of dandelion reduced the triglyceride accumulation in mature adipocytes and the effect of leaf extract was higher than the root extracts[41]. Dandelion root hydro-alcoholic extract (30 μg/mL) for 10 and 20 d showed anti-adipogenic effects on human primary visceral pre-adipocytes (P10, P20 and A7 cells). Dandelion extract induced apoptosis (76.91%-81.00%) and inhibited the adipogenesis in P10 and P20 cell lines, which increased the release of free glycerol and decreased the triglyceride accumulation

and lipogenesis[28]. Therefore, dandelion had anti-obesity effects by different mechanisms, which is associated with reduction in liver inflammation.

5.3. Beneficial effects of dandelion on type 2 diabetes

Insulin resistance is the primary cause of hyperglycemia and the main pathogenesis of type 2 diabetes. There is an association between high insulin resistance and hepatogenesis[57]. The anti-diabetic effects of dandelion were the focus in some studies. The result of a systemic review showed that among 20 animal and human studies, only one diabetic rat study exhibited the hypoglycemic effects of dandelion[58]. In other study, the anti-diabetic effect of 5 g dandelion leaf or root powder for 9 d was compared with placebo on sixty type 2 diabetic patients. After taking the dandelion powder, fasting blood glucose was monitored before and during the treatment periods. The results showed that dandelion leaf and root powder significantly reduced the fasting blood glucose levels of type 2 diabetic patients compared with placebo group[59].

Glucose homeostasis is affected by oxidative stress, as the result of auto-oxidation and protein glycation[60]. High lipid peroxides and reduction of oxidative defense are associated with β-cell dysfunction and impair the insulin secretion[61]. Dandelion extracts stimulated the release of insulin in pancreatic β-cells, and exhibited the hypoglycemia effects. Treatment of rat insulinoma cells (INS-1E cells) with 40 μg/mL dandelion or glibenclamide in the presence of glucose (6.0 mM) increased the insulin secretion in INS-1E cells compared to normal glucose (3.0 mM)[62]. Dandelion as one ingredient of SR2004, clinically decreased the HbA1c, fasting blood glucose, lipid profile, and total cholesterol in patients with type 2 diabetes mellitus[63]. Oral administration of dandelion can improve the insulin sensitivity in type 2 diabetic patients. Diabetic diseases are associated with liver dysfunctions and improvement in diabetic conditions is associated with correct liver functions.

5.4. Hypoglycemic effects of dandelion and improvement in the oxidant condition in the body

Although there is a close relation between type 2 diabetes and hyperglycemia, due to frequency of studies, this subject was evaluated in a distinct part. There are studies which exhibited that dandelion had hypoglycemic effects by improvement in the liver and antioxidant enzymes. Feeding the hybrid grouper with basal diet containing dandelion extract (0, 0.1%, 0.2%, 0.4% and 0.8%) for 8 weeks had no significant impact on growth performance and feed utilization. Dandelion extract reduced the whole body's crude lipid percent and increased the crude protein percent in muscle. Dandelion extract increased the mRNA level of antioxidant enzymes (catalase, GPx and GR) and improved the liver enzyme activities. Reduction in whole body's crude lipid was associated with reduction in inflammatory condition in fish spleen and kidney. Furthermore, dandelion extract increased the survival rate and total blood cell count in CCL_4 treated hybrids[64]. The results of this research in fish exhibited that dandelion extract regulates lipid metabolism related genes expression in fish, which is related to reduction in crude lipid content in the whole body. The immunity status was improved in dandelion treated fish by enhancing the antioxidant enzymes and decreasing the inflammation in the kidney and spleen. Furthermore, the plasma triglyceride levels were reduced in ICR mice after consumption of dandelion ethanol extract which was attributed to the pancreatic lipase inhibitory effects of flavonoids in dandelion[51,52].

Dandelion root and leaf (1%) had hypolipidemic and antioxidant effects in rabbit fed high cholesterol diet. Dandelion root extract reduced the AST, ALT, triglyceride and LDL-cholesterol and increased the creatine kinase, and HDL-cholesterol. Dandelion leaf and root extract significantly increased the GSH, GPX, SOD and decreased the lipid peroxidation (TBARS), GST and formation of atherosclerotic lesions. Dandelion root extract improved the atherogenic index, and prevented the oxidative damage[65]. GSH as the most abundant cellular thiol antioxidant enzyme protects the liver from injuries[66]. Damage in body tissue or organs increases the ALT and AST and lipid peroxidation in the body[67]. Dandelion leaf extract had protective effect against liver injury in high fat diet induced hepatic steatosis[68]. Steatosis is caused by triglyceride accumulation in the liver[1]. C57BL/6 mice group fed a high fat diet supplemented with dandelion leaf extract reduced lipid accumulation, which was associated with reduction in liver and body weights, triglyceride, total cholesterol, serum fasting glucose level and insulin[68].

Fatty acids are metabolized by two pathways of mitochondrial β-oxidation to produce ATP, or by esterification to produce triglycerides and very low-density lipoproteins[69]. Reduction in triglycerides and total cholesterol after dandelion leaf extract supplementation exhibited the role of dandelion leaf extract in controlling the fatty acid metabolism[68].

Plasma HDL acts as cholesterol translocator from peripheral tissue to liver for catabolism. Therefore, dandelion extract improves the liver enzymes and liver functions by inhibiting the pancreatic lipase, decreasing the lipogenesis and reducing the inflammation in the liver.

One important property of dandelion is its anti-inflammatory and antioxidant effects. Dandelion methanol or aqueous extract exhibited the antioxidant and anti-inflammatory activities in LPS-stimulated RAW 264.7 cells. Nitric oxide (NO) production was suppressed by dandelion methanol or aqueous extracts with IC_{50} of 79.9 and 157.5 μg/mL, respectively. Dandelion methanol extract and aqueous extracts inhibited the MDA concentration. The GSH content and anti-oxidant enzymes (catalase, SOD, GPx) were increased after treatment by dandelion methanol or aqueous extracts in a dose dependent manner. Catalase and SOD activities were increased by methanol dandelion extract, which were higher than its aqueous extract[70]. Among different kinds of dandelion extracts (hot aqueous, aqueous, ethanol and methanol), hot aqueous and methanol extracts of dandelion roots had higher antioxidant and anti-inflammatory effects against LPS-induced macrophages, which was associated with reduction in NO and MDA production. Luteolin and

chicoric acid are responsible for antioxidant and anti-inflammatory effects[42]. Betulin, 18β,19β-epoxy-21β-hydroxylupan-3β-yl acetate, and 24-oxoeupha-7,24-dien-3β-yl acetate showed inhibitory effects against NO in LPS activated mouse peritoneal macrophages without any cytotoxic effects as same as *L*-NMMA, suggesting its anti-inflammatory effects[27].

Dandelion methanol extract (100 μg/mL) had anti-inflammatory effect in LPS stimulated human umbilical vein endothelial cells. Dandelion methanol extract at 50, 100 and 200 μg/mL had no effect on viability of human umbilical vein endothelial cells. In addition, its methanol extract reduced the adherence of LPS induced THP-1 cells to baseline and LPS induced monocyte adhesion to endothelial cells [71].

The antioxidant activity of dandelion leaf extract (hydro-ethanol 50% with formic acid) was higher than root extracts. Dandelion extract suppressed ROS in HT-29 cells and LPS induced inflammatory signaling NF-κB p65 and COX-2 activity. Dandelion extract also inhibited LRR, PYD, caspase-1, NLRP3 inflammasome mediated IL-1β, and IL-8. The inflammasome activation was suppressed through scavenging ROS and inhibiting inflammation[31].

Dandelion leaf aqueous extract (100 and 200 μg/mL) exhibited the anti-inflammatory effects in rat mammary micro-vascular endothelial cells. Endothelia ICAM-1 was increased during the inflammation, which regulates the adhesion of effector cells to endothelium. Dandelion aqueous extract significantly inhibited TNF-α and ICAM-1. In addition, dandelion aqueous extract reduced the expression of TNF-α and ICAM-1 in *Staphylococcus aureus* induced mastitis in mammary gland tissues[72]. Dandelion phenolic extracts showed better antioxidant activity than that of flavonoids extracts[73]. The extracts with high content of hydroxycinnamic acid showed the highest radical scavenging effects in DPPH system and higher anti-coagulant effects[21]. Dandelion ethanol extracts also demonstrated protective effects against glutamate-induced oxidative damage by inducing the Nrf2/heme oxygenase 1 (HO-1) pathways in HT22 cells. Moreover, dandelion ethanol extract (50-400 μg/mL) had no significant effects on cell viability of HT22 cell lines. Its ethanol extract increased the expression of HO-1 in a dose dependent manner. Besides, dandelion ethanol extract increased the expression of Nrf2 and inhibited the glutamate induced cytotoxicity and ROS generation by inducing the HO-1 expression[74].

Taraxasterol inhibited the production of LPS induced TNF-α, IL-1β and NF-κB activation in BV2 microglia cells. The formation of lipid rafts was disrupted, which was associated with inhibition of TLR4 translocation in lipid rafts. LXRα-ABCA1 signaling pathway and cholesterol efflux were activated by taraxasterol (a pentacyclic triterpene compound)[75]. Taraxasterol inhibited the iNOS and COX-2 expression in LPS-stimulated RAW264.7 cells[76], as well as IL-1β-induced NO and PGE2 production in human osteoarthritic chondrocytes[77]. The anti-inflammatory and anti-oxidant effects of dandelion play an important role in its hepatoprotective effects.

5.5. Effect of dandelion on blood properties

The main action of liver is purifying the blood. Dandelion is known as blood purifier and its fresh leaves are rich in irons, so it is used in salad or sometimes with egg and for anemia in Slovenia[78]. Injection of dandelion ethanol extract (50, 100 and 200 mg/kg) to adult female (Balb/C) mice for 20 d significantly increased the number of RBC, WBC, lymphocytes and hemoglobin level rate[79]. Therefore, dandelion can be used as blood purifier by increasing the number of RBC.

6. Molecular mechanism of hepatoprotective effects of dandelion

The molecular mechanism of hepatoprotective effects of dandelion is explained in Figure 2. AMPK as energy sensor and one important metabolic pathway decreases fatty acid synthase and acetyl CoA carboxylase (ACC) by suppressing SREBP-1c. AMPK is activated upon depletion of ATP and adipocyte derivative hormones such as adiponectin, resistin and leptin. Lipid accumulation was suppressed by treatment with dandelion leaf ethanol extract, which was associated with reduction in insulin resistance and lipid *via* AMPK pathway. A significant increase in activation of liver adenosine monophosphate activated protein kinase (AMPK) and muscle protein was observed after treatment with dandelion leaf extract, which inhibited the liver's lipid accumulation and decreased the insulin resistance. Glucose uptake and phosphorylation of AMPK (pAMPK)/ACC increased in C2C12 myotubes after treatment with dandelion extract[68].

Dandelion ethanol extract reduced the serum insulin, fasting glucose level and homeostatic model assessment for insulin resistance in high fat diet induced mice, which was associated with improvement in insulin sensitivity.

Dandelion (Tops polysaccharides) reduced the CCL_4 induced hepatic lesions in mice, which was associated with reduction in NF-κB, iNOS, COX-2, TNF-α, and IL-1β (regulatory inflammatory mediators) and up-regulation of antioxidant enzymes and GSH level. The free radical scavenging effects of Tops were exhibited by reduction in TBARS concentration[43]. It has been found that NO production and iNOS expression were inhibited by Top2 in a dose dependent manner[80]. Although COX-2 expression was inhibited by Top2[43], the results of other study exhibited[80], COX-2 was not suppressed by Top treatment. Top, especially Top2, inhibited the production of TNF-α in LPS induced RAW 264.7 cells. NF-κB regulates the expression of iNOS, COX-2, and TNF-α. Nrf2 and NF-κB are regulated by MAPK and PI3K/Akt. Top suppressed the phosphorylation levels of $I_κBα$, p65, and Akt, while had no effect on ERK, JNK and p38, which was associated with inhibition of inflammatory cytokines. Tops initiated partly the cell recovery following the cell mortality by *tert*-butyl hydroperoxide, which showed other relevant mechanisms rather than PI3K/Akt and HO-1 were responsible for Tops initiated cell recovery[80]. HO-1 expression was induced in RAW 264.7 cells in the presence of Top1 and Top2. Nrf2 nuclear accumulation was

also induced in the presence of Tops in a dose dependent manner. Tops regulated Nrf2 mediated HO-1 expression in RAW 264.7 cells by PI3K/Akt signaling cascade. PI3K/Akt is the upstream signaling molecules in modulation of NF-κB and Nrf2. Treatment of Akt and JNK using LY294002 and SP600125 abrogated Top induced HO-1 protein expression[80]. The anti-oxidative effects of Tops were caused through Nrf2 transcription factor and PI3K/Akt signaling pathway, and led to production of HO-1 in RAW 264.7 cells. HO-1 exhibited protective effects against oxidative and inflammatory stimuli. Therefore, Tops inactivated the NF-κB pathway and reduced the LPS induced inflammatory mediators. In addition, up-regulation of Nrf2-mediated HO-1 increased the cyto-protective effects in murine macrophages. Top mediated anti-inflammatory effect in RAW 264.7 cells was associated with reduction in iNOS and TNF-α expression and up-regulation of HO-1 protein.

Dandelion methanol and water extracts inhibited *iNOS* gene expression and NF-κB in a dose dependent manner. Nitric oxide synthase controls the production of NO and the iNOS expression and is regulated by TNF-κB[70]. Mononuclear cell adhesion is caused by endothelial VCAM-1. Dandelion methanol extract reduced the VCAM-1, pro-inflammatory cytokines and monocyte chemo-attractant protein 1. LPS induced nuclear translocation of NF-κB was suppressed by dandelion without any effect on MAPK activation. Dandelion extract also reduced the VCAM-1 and MCP-1 mRNA, TNF-α, IL-1β, and IL-6 expression, and also inhibited the phosphorylation of IκBα, which was associated with inhibition of NF-κB nuclear translocation and suppression of NF-κB pathway[71].

7. Daily dose of dandelion in traditional medicine

Dandelion is used in "materia medica for the relief of famines" as dietary and edible vegetable. It is used single or in combination with other plants as granule, hard shelf capsule, tablet or injection for heat relief, inflammation and detoxification of the body. In Chinese Pharmacopeia, the typical daily dose of dandelion is 10-15 g[20]. The daily dose of dandelion as a whole herb and its roots is 4-10 g raw material equivalent[81]. Moreover, dandelion leaf of 3-5 g is used as a diuretic and choleretic agent in British Herbal Pharmacopeia, while its roots are used for hepatic function. The daily dose for leaf tincture is 5-10 mL, which is used twice daily. For cholelithiasis or gall stone disease, 4-10 g dried leaf or 2-8 g dried root is used three times a day. Dandelion tea is prepared with 4-10 g dried leaf or 2-8 g dried root in 150 mL boiling water for 10-150 min and one cup is used three times a day. Five to ten mL tincture (1:5) used three times a day are recommended[82]. In other text, 4-10 g/day crude dried leaves or 50 g fresh dandelion are recommended. In USA, 3-5 mL dandelion tincture is used three times a day. The LD_{50} of dandelion is greater than 20 g/kg body weight[18]. So, dandelion is generally recognized for its safety and is well tolerated without any negative effects in human[83].

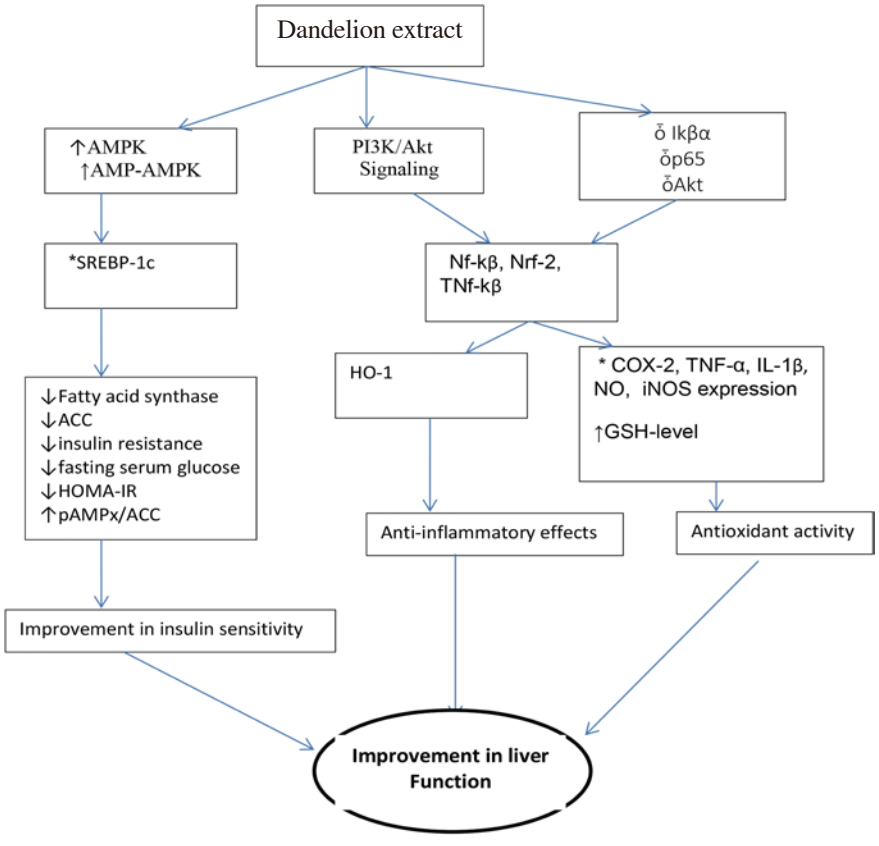

Figure 2. Molecular mechanism of hepatoprotective effects of dandelion.

8. Conclusion

Dandelion is a popular hepatoprotective plant in different medicinal systems. It is named piss-a-bed in old European texts and known as a laxative agent. Dandelion is diuretic, and is used for kidney and liver disorders[36,84]. Their actions are bitter tonic, and choleretic. The diuretic effects of dandelion leaf are stronger than dandelion roots[54]. Dandelion is also used in wine with good taste[85]. Whole herb of dandelion is recommended for appetite loss and dyspepsia. Its roots had benefical effect on bile flow disturbance and urine obstruction apart from appetite loss and dyspepsia[81]. Current animal studies exhibited the efficacy of dandelion against the cytotoxic effects of CCL_4, ethanol and sodium dichromate by improvement of liver and antioxidant enzymes. Improvement in liver function is associated with restoring histopathology of the liver cells. Polysacharides (Top1, Top2), flavonoids, phenolic, tannins, ascorbic acids, taraxol, taraerol, laevulin, inulin and luteolin are chemical compounds that are responsible for hepatoprotective effects of dandelion. Different mechanisms may be responsible for hepatoprotective effects of dandelion. Oligofructans as prebiotic compounds of dandelion induce the growth of intestinal probiotics and inhibit the release of LPS and FIAF and lipid accumulation in the body. Dandelion has anti-obesity effects *via* inhibition of digestive enzymes, lipid metabolism and adipogenesis. The lipogenesis effects of dandelion are associated with reduction of inflammation in the body and liver and improvement of insulin resistance and anti-oxidant condition. Although different documents confirmed the hepatoprotective effects of dandelion, preparing standard extracts of dandelion with high contents of effective compounds and designing large clinical studies with standard extracts are required for further evaluating the hepatoprotective effects of dandelion.

Conflict of interest statement

There is no conflict of interest.

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Authors' contributions

Mohaddese Mahboubi has written, revised and approved the final manuscript and Mona Mahboubi helped to gather the information from reliable sources.

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