Silymarin and its properties; a nephrology viewpoint

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Abstract
In this mini-review, the biological actions silymarin are reviewed. Milk thistle (Silybum marianum) is widely used in a traditional medicine. Silymarin, the active components of milk thistle, contains three isomers including silybin, silydianin and silychristine. Silybin is the most proportion and biologically the most active ingredient of silymarin. It possesses various properties including hepatoprotective, anti-cancer, anti-inflammatory, antioxidant, as well as hypocholesteromic activities.

Keywords: Silymarin, Hepatic injury, Silybum marianum, Reactive oxygen species, Antioxidant Flavonoids, Kupffer cells

Introduction
Since liver is the main metabolic organ of metabolism and excretion, liver damage is the most common problem affecting human health. In turn, it results to cirrhosis, liver cancer, fatty liver, chronic hepatitis C, and other liver disorders in human (1,2). These damages result mainly from many environmental contaminants that many people are continually subjected to them (3,4). Therefore, it needs to administrate hepatoprotective agents to protect human health.

Nowadays, bioactive components existed in medicinal plants has been remarkably attracted to improve health due to the various beneficial properties (5,6). One of the most attracting medicinal plants is milk thistle (7). Milk thistle (Silybum marianum), the member of Asteraceae family, is native of Mediterranean and North Africa area (8) widely used in a traditional medicine (9). Silymarin is active principal of milk thistle (10) containing three isomers such as silybin, silychristin, and silydianin (11,12). Silybin is the main active component amongst silymarin isomers (13). The difference between silymarin and other flavonoids is that its isomers are replaced by a coniferyl alcohol group. Silymarin is not water soluble; thereby, it is administrated in encapsulated form (10). It is excreted via either the bile or the kidneys (14). Silymarin has different activities such as hepatoprotective (15,16), anti-cancer (17,18), anti-inflammatory (19,20), antioxidant (21,22), and hypocholesteromic (23,24) effects. Shaker et al (4) found a decline in the serum enzyme activities of liver as a consequence of ethanolic extract of S. marianum. It was reported that S. marianum extract decreased the DPPH concentration in vitro even after 30 minutes.

Since there are many researches regarding the hepatoprotective effect of silymarin, it seems to determine the modes of action of silymarin on biological activities are crucial.

Materials and Methods
PubMed, EBSCO, directory of open access journals (DOAJ), Google Scholar, and Web of Science were searched with key words as; silymarin, hepatoprotective activity, hepatic injury, Silybum marianum, reactive oxygen species, antioxidant activity, flavonoids and Kupffer cells.

The hepatoprotective activity of silymarin
The hepatic injury is usually the result of xenobiotics related to distortion of these metabolic functions (25). When toxins are absorbed in the intestinal tract, they transfer to liver, in turn, injuring the liver. On the other hand, reactive oxygen and nitrogen species involve hepatocyte, Kupffer, stellate and endothelial cells leading to liver disease (26). Free radicals are generated by either hepatocyte mitochondria and citochrome P450 enzymes, or endotoxin-activated macrophages (Kupffer cells) and neutrophils (4). Milk thistle has been found to aid in the elimination of toxins and to protect liver (27).

The proposed mechanisms for hepatoprotection efficacy of silymarin are (28);
1- Activity against lipid peroxidation resulting from scavenging free radicals and the ability to raise the cellular content of glutathione (16,29,30).
2- The ability to regulate membrane permeability and stability in the presence of xenobiotic agents (31).
3- The ability to regulate nuclear expression through steroid-like activity (32,33).
4- Inhibition of transformation of stellate hepatocytes...
into myofibroblasts; consequently, it prevents to deposit collagen fibers resulting in cirrhosis (34). Moreover, silymarin has been found to stimulate hepatocyte protein synthesis, promoting hepatic tissue regeneration (33). Silymarin plays regulatory action on cellular and mitochondrial membrane permeability; increasing membrane stability against xenobiotic injury (31). As a result, it prevents the toxin absorption into the hepatocytes via occupying the binding site and also inhibiting many transport protein at the membrane (32). Silymarin inhibits the hepatic cytochrome P450 detoxification system. Baer-Dubowska et al (16) found that silybin inhibited numerous hepatic cytochrome P450 enzyme activities in mice. The inhibition of toxin bio-activation might be responsible for the limitation of toxic effects as a result of protection against free radicals produced by enzymes of the cytochrome system. Silybin has been shown to display inhibition of catalytic activities of cytochrome P450 isoenzymes (35). However, silybin does not involve in the expression of cytochrome P1A2 and cytochrome P3A4 (36).

Bansal et al (37) studied the effect of silymarin in rats, challenged with diethylthiouracil that induced oxidative stress. They reported that silymarin administration decreased the activities of serum ALT, and AST. In addition, in a study with 36 patients in relation with chronic alcoholic liver disease, silymarin at 420 mg/d could normalize the serum transaminases (AST, ALT, γ-GT) after 6 months of treatment (38). It was reported that administration of silymarin decreased the serum enzyme activities including alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase in mice exposed to carbon tetrachloride (39). Hawke et al (40) observed that intake of the high oral dosage of silymarin (700 mg/d) lowered chronic hepatitis C viral loads and alanine aminotransferase in infected patients. This might be due to prevention of liver damage via maintaining the integrity of plasma membrane, suppressing the leakage of enzymes through membranes (37,41).

The anti-inflammatory activity of silymarin
Several mechanisms have been proposed for anti-inflammatory activity of silymarin such as inhibition of leukotriene and prostaglandin synthesis, stabilization of mast cell, inhibition of neutrophil migration, suppression of inflammatory cytokines such as IL-2, IL-4, IL-10, and TNF, and also Kupffer cell inhibition (19,20). Silymarin interferes with leukotriene formation in Kupffer cell, in turn, inhibiting hepatic stellate cell activation to fibrogenesis (20).

The effect of silymarin on gene expression
The similarity of silymarin structure to steroid hormones is responsible for its protein synthesis (42,43). In fact, silymarin enters inside of the nucleus and affects RNA polymerase enzymes leading to hasten protein and DNA synthesis (33). Silymarin causes regenerative of the liver via increasing DNA polymerase; consequently, it increases liver cell regeneration (44).

The antioxidant activity of silymarin
Free radicals including the superoxide radical, hydroxyl radical, hydrogen peroxide, and lipid peroxide radicals induced liver damages (2,3). These reactive oxygen species (ROS) induced lipid peroxidation of poly unsaturated fatty acid in the cell membrane bilayer. Therefore, they damage the cell and cell contents (6,45). Lipid peroxidation results from interaction between free radicals and unsaturated fatty acids in lipids (46). Thereby, researchers have followed to administer natural antioxidants to inhibit lipid peroxidation resulting from ROS (47-49). The cytoprotective effects of silymarin are mainly associated with antioxidant activity and scavenging free radical property of this remedy (50). Lucena et al (51) found an increase in glutathione and a decline in lipid peroxidation in peripheral blood cells as a consequence of silymarin intake.

Silymarin has been shown to possess antioxidant activity via increasing superoxide dismutase activity in erythrocyte and lymphocyte (38,52). Silymarin protects cell membranes and increases their resistance to harmful compounds through alterations in their physiochemical characteristics. On the other hands, silymarin interacts with reactive oxygen species; consequently, it converts them to less toxic compounds (21). Das et al (22) found that administration of silybin decreased serum thiobarbituric acid reactive substance level, glutathione-s-transferase activities and superoxide dismutase, and increased serum glutathione content, catalase and glutathione peroxide activities in rats exposed to ethanol. Hepatic glutathione content manifests its important relation with lipid peroxidation due to its ability to bind with free radicals which cause lipid peroxidation (53). On the other hand, the level of glutathione plays detoxification and protective roles especially those toxic substances interfering with oxidative stress (54).

The hypocholesterolemic activity of silymarin
Silymarin intake improved LDL-C levels in rats fed a high-cholesterol diet (55). Metwally et al (23) exhibited that injection of 100 mg/kg silymarin for 7 days decreased serum total lipids, triglycerides, cholesterol, LDL-C, and VLDL in rats. Shaker et al (4) reported that silymarin extract decreased serum cholesterol and LDL-C concentration. However, the level of HDL-C was elevated (700 mg/d) lowered chronic hepatitis C viral loads and serum alanine aminotransferase in infected patients. This might be due to the normalization of serum aminotransferase with antioxidant activity and scavenging free radical property of this remedy (38,52). Silymarin protects cell membranes and increases their resistance to harmful compounds through alterations in their physiochemical characteristics. On the other hands, silymarin interacts with reactive oxygen species; consequently, it converts them to less toxic compounds (21). Das et al (22) found that administration of silybin decreased serum thiobarbituric acid reactive substance level, glutathione-s-transferase activities and superoxide dismutase, and increased serum glutathione content, catalase and glutathione peroxide activities in rats exposed to ethanol. Hepatic glutathione content manifests its important relation with lipid peroxidation due to its ability to bind with free radicals which cause lipid peroxidation (53). On the other hand, the level of glutathione plays detoxification and protective roles especially those toxic substances interfering with oxidative stress (54).
Silymarin and its properties

The immunomodulatory activity of silymarin
Silymarin manifested immunomodulatory effects. Johnson et al (58) showed that silymarin at low dosage inhibited T-lymphocyte in mice. The expressions of TNF, IL-1β and IL-6 mRNA were enhanced in a dose-dependent manner.

Anticancer activity of silymarin
Silymarin exhibited anticancer effect. Silymarin suppressed the proliferation of several tumor cells (17). It interfered with the expressions of cell cycle regulators and proteins induced apoptosis. Thereby, silymarin modulates imbalance between cell survive and cell apoptosis (18). Silymarin binds to both estrogen and androgen receptors (17). Silybin acts on the receptor level; as a result, it affects different processes involved in carcinogenesis or in the cancer proliferation and modulations of mitogenic, signaling and cell cycle regulators (59,60) resulting in growth inhibition and death (61).

The cardioprotective activity of silymarin
Since heart is very susceptible to reactive oxygen species due to its highly oxidative metabolism, silymarin has the cardioprotective effect as a result of enhancing antioxidant capacity of tissue (62).

The renal protective activity of silymarin
The excess free radicals’ generation has been found to induce oxidative stress leading to many pathological disorders in many tissues including liver, heart and also kidney (63,64). In vitro studies showed that silymarin protects kidney against oxidative stress resulting from paracetamol, cisplatin and CCI4 (63,65) and aflatoxin B1 (66). This effect might be because of decreasing the risk of oxidative stress damage and increasing the thiol status in the kidney (67). Cecen et al (68) showed that silymarin protects doxorubicin-induced oxidative stress and toxicities to the rat kidney.

Conclusion
Silymarin can improve human health via antioxidant, immunostimulatory, anti-inflammatory, anti-cancer, hepatoprotective and also renal protective activities.

Author's contribution
HN was the single author of the manuscript.

Conflicts of interest
The author declared no competing interests.

Ethical considerations
The author of this manuscript declares that he has followed the ethical requirements for this communication. Also, Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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