Open Access Mini-Review

Journal of Renal Endocrinology

J Renal Endocrinol 2015;1(1):e09.

http://www.jrenendo.com

Nickan Research Institute

Silymarin and its properties; a nephrology viewpoint

Hamid Nasri*

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

Citation: Nasri H. Silymarin and its properties; a nephrology viewpoint. J Renal Endocrinol. 2015;1(1):e09.

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

Received: 9 April 2015, Accepted: 17 June 2015, ePublished: 4 July 2015

Nickan Research Institute, Isfahan, Iran

***Corresponding Author:** Prof. Hamid Nasri, Email: hamidnasri@med.mui.ac.ir

Implication for health policy/practice/research/ medical education
Silymarin can improve human health via antioxidant, immunostimulatory, anti-inflammatory, anticancer, hepatoprotective, and also renal protective activities.

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 diethylnitrosamine 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 peroxidase 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 as a result of silymarin (4). Likewise, Sobolova et al (24) observed that silymarin lowered cholesterol absorption in rats fed high cholesterol diet; consequently, it decreased

liver VLDL, cholesterol, and triglyceride content.
Flavonoids administration resulted to inhibition of cholesterol synthesis, cellular cholesterol esterification, triglyceride synthesis, and also HMG-CoA reductase activity (56). Similarly, silybin lowered cholesterol synthesis via suppressing HMG-CoA reductase activity which is the limiting enzyme of cholesterol synthesis (57).

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 CCl4 (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.

Funding/Support

None.

References

1. Rafieian-Kopaei M, Baradaran A, Merrikhi A, Nematbakhsh M, Madihi Y, Nasri H. Efficacy of co-administration of garlic extract and metformin for prevention of gentamicin-renal toxicity in Wistar rats: a biochemical study. Int J Prev Med. 2013;4:258-64.
2. Baradaran A, Nasri H, Rafieian-Kopaei M. Oxidative stress and hypertension: possibility of hypertension therapy with antioxidants. J Res Med Sci. 2014;19:358-67.
3. Nasri H, Rafieian-Kopaei M. Oxidative stress and aging prevention. Int J Prev Med. 2013;4:1101-2.
4. Shaker E, Mahmoud H, Mnaa S. Silymarin, the antioxidant component and Silybum marianum extracts prevent liver damage. Food Chem Toxicol. 2010;48:803-6.
5. Nasri H. Antioxidants for prevention of gentamicin-induced nephrotoxicity. Iran J Kidney Dis. 2014;8:1-2.
6. Nasri H, Rafieian-Kopaei M. Protective effects of herbal antioxidants on diabetic kidney disease. J Res Med Sci. 2014;19:82-3.
7. Pepping J. Milk thistle: *Silybum marianum*. Am J Health Syst Pharm. 1999;56:1195-97.
8. Boulos L. Flora of Egypt. 1st ed. Cairo, Egypt: Al Hadara Publishing Inc; 2000.
9. Morazzoni P, Bombardelli E. *Silybum marianum*. Fitaoterapia. 1995;66:3-42.
10. Wilasrusmeebcef C, Kitturac S, Shahb G, Siddiquib J, Bruchbe D, Kittur DS. Immunostimulatory effect of Silybum Marianum (milk thistle) extract. Med Sci Monit. 2002;8:BR439-443.
11. Fraschini F, Demartini G, Esposti D. Pharmacology of silymarin. Clin Drug Invest. 2002;22:51-65.
12. Crocenzi FA, Roma MG. Silymarin as a new hepatoprotective agent in experimental cholestasis: new possibilities for an ancient medication. Curr Med Chem. 2006;13:1055-74.
13. Saller R, Meier R, Brignoli R. The use of silymarin in the treatment of liver diseases. Drugs. 2001;61:2035-63.
14. Rafieian-Kopaei M. Medicinal plants and the human needs. J Herbmed Pharmacol. 2012;1:1-2.
15. Bosisio E, Benelli C, Pirola O. Effect of the flavanolignans of *Silybum marianum* L. on lipid peroxidation in rat liver microsomes and freshly isolated hepatocytes. Pharmacol Res. 1992;25:147-54.
16. Baer-Dubowska W, Szaefer H, Drajka-Kuzniak V. Inhibition of murine hepatic cytochrome P450 activities by natural and synthetic phenolic compounds. Xenobiotica. 1998;28:735-43.
17. Agrawal R, Agrawal Ch, Ichikawa H, Singh RP, Aggarwal BB. Anticancer potential of silymarin:from bench to bed side. Anticancer Research 2006;26:4457-98.
18. Ramasamy K, Agrawal R. Multitargeted therapy of cancer by silymarin. Cancer Lett. 2008;269:352-362.
19. De La Puerta R, Martinez E, Bravo L. Effect of silymarin on different acute inflammation models and on leukocyte migration. J Pharm Pharmacol. 1996;48:968-70.
20. Dehmlow C, Erhard J, de Groot H. Inhibition of Kupffer cell functions as an explanation for the hepatoprotective properties of silibinin. Hepatology. 1996;23:749-54.
21. Kolarovic J, Popovic M, Zlinská J, Trivic S, Vojnovic M. Antioxidant activities of celery and parsley juices in rats treated with doxorubicin. Molecules. 2010;15:6193-204.
22. Das SK, Vasudevan DM. Protective effects of silymarin, a milk thistle (*Silybium marianum*) derivative on ethanol-

induced oxidative stress in liver. Indian J Biochem Biophys. 2006;43:306-311.
23. Metwally MAA, El-Gellal AM, EL-Sawaisi SM. Effects of silymarin on lipid metabolism in rats. World Appl Sci J. 2009;6:1634-7.
24. Sobolova L, Skottova N, Vecera R, Urbanek K. Effect of silymarin and its polyphenolic fraction on cholesterol absorption in rats. Pharm Res. 2006;53:104-12.
25. Wolf P. Biochemical diagnosis of liver diseases. Indian J Clin Biochem. 1999;14:59-90.
26. Loguercio C, Federico A. Oxidative stress in viral and alcoholic hepatitis. Free Radic Biol Med. 2003;34:1-10.
27. Rainone F. Milk thistle. Am Fam Physician. 2005;72:1285-1288.
28. Govind P, Sahni YP. A review on hepatoprotective activity of silymarin. International Journal of Research in Ayurveda and Pharmacy. 2011;2:75-79.
29. Halim AB, El-Ahmady O, Hassab-Allah S. Biochemical effect of antioxidants on lipids and liver function in experimentally-induced liver damage. Ann Clin Biochem. 1997;34:656-63.
30. Campos R, Garido A, Guerra R. Silybin dihemisuccinate protects against glutathione depletion and lipid peroxidation induced by acetaminophen on rat liver. Planta Medicine. 1989;55:417-9.
31. Munter K, Mayer D, Faulstich H. Characterization of a transporting system in rat hepatocytes:studies with competitive and non-competitive inhibitors of phalloidin transport. Biochemistry, Biophysics Acta. 1986;860:91-98.
32. Faulstich H, Jahn W, Wieland T. Silybin inhibition of amatoxin uptake in the perfused rat liver. Arzneimittelforschung. 1980;30:452-454.
33. Sonnenbichler J, Zetl I. Biochemical effects of the flavanolignane silibinin on RNA, protein and DNA synthesis in rat livers. In: Cody V, Middleton E, Harbourne JB, eds. Plant Flavonoids in Biology and Medicine: Biochemical, Pharmacological, and Structure-Activity Relationships. New York, NY: Alan R. Liss, Inc; 1986:319-331.
34. Polyak SJ, Morishima C, Lohmann V, Pal S, Lee DY, Liu Y. Identification of hepatoprotective flavonolignans from silymarin. Proc Natl Acad Sci U S A. 2010; 107:5995-9.
35. Zuber R, Modriansky M, Dvořák Z, Rohovský P, Ulrichová J, Šimánek V, et al. Effect of silybin and its congeners on human liver microsomal cytochrome P450 activities. Phytother Res. 2002;16;632-8.
36. Kosina P, Maurel P, Ulrichová J, Dvořák Z. Effect of silybin and its glycosides on the expression of cytochromes P450 1A2 and 3A4 in primary cultures of human hepatocytes. J Biochem Mol Toxicol. 2005;19:149-53.
37. Bansal AK, Trivedi R, Soni GL, Bhatnagar D. Hepatic and renal oxidative stress in acute toxicity of N-nitrosodiethylamine in rats. Indian J Exp Biol. 2000;38:916-20.
38. Feher I, Deak G, Muzes G. Liver protective action of silymarin therapy in chronic alcoholic liver diseases. Orv Hetil. 1989;130:2723-7.
39. Jatwa R, Kar A. Protective effect of l-ornithine-l-aspartate and silymarin on chemically induced kidney toxicity and thyroid dysfunction in mice. EXCLI J. 2008;7:139-50.
40. Hawke RL, Schrieber SJ, Soule TA. Silymarin ascending multiple oral dosing phase I study in noncirrhotic patients with chronic hepatitis C. J Clin Pharmacl. 2010;50:434-49.
41. Pradeep K, Raj Mohan CV, Gobianand K, Karthikeyan S. Silymarin modulates the oxidant–antioxidant imbalance during diethylnitrosamine induced oxidative stress in rats. Eur J Pharmacol. 2007;560:110-16.
42. Vailati A, Aristia L, Sozze E, Milani F, Inglese V, Galenda P. Randomized open study of the dose-effect relationship of a short course of IdB 1016 in patients with viral or alcoholic hepatitis. Fitoterapia. 1993;64:219-31.
43. Kosina P, Kren V, Gebhardt R, Grambal F, Ulrichova J, Walterova D. Antioxidant properties of silybin glycosides. Phytother Res. 2002;16:S33-S39.
44. Valenzuela A, Aspillaga M, Vial S. Selectivity of silymarin on the increase of the glutathione content in different tissues of the rat. Planta Medicine. 1989;55:420-422.
45. Baradaran A, Nasri H, Nematbakhsh M, Rafieian-Kopaei M. Antioxidant activity and preventive effect of aqueous leaf extract of Aloe Vera on gentamicin-induced nephrotoxicity in male Wistar rats. Clin Ter. 2014;165:7-11.
46. Nasri H, Nematbakhsh M, Ghobadi S, Ansari R, Shahinfard N, Rafieian-Kopaei M. Preventive and curative effects of ginger extract against histopathologic changes of gentamicin-induced tubular toxicity in rats. Int J Prev Med. 2013;4:316-21.
47. Nasri H, Shirzad H, Baradaran A, Rafieian-kopaei M. Antioxidant plants and diabetes mellitus. J Res Med Sci 2015;20:491-502.
48. Tamadon MR, Baradaran A, Rafieian-Kopaei M. Antioxidant and kidney protection;differential impacts of single and whole natural antioxidants. J Renal Inj Prev. 2013;3:41-2.
49. Rafieian-Kopaei M, Baradaran A, Rafieian M. Plants antioxidants:From laboratory to clinic. J Nephropathol. 2013;2:152-3.
50. Muriel P, Mourelle M. Prevention by silymarin of membrane alterations in acute CCl4 liver damage. J Appl Toxicol. 1990;10:275-9.
51. Lucena MI, Andrade RJ, De la Cruz JP, Rodriguez-Mendizabal M, Blanco E, et al. Effects of silymarin MZ-80 on oxidative stress in patients with alcoholic cirrhosis. Results of a randomized, double-blind, placebo-controlled clinical study. Int J Clin Pharmacol Ther. 2002;40:2-8.
52. Varga Z, Czompa A, Kakuk G, Antus S. Inhibition of the superoxide anion release and hydrogen peroxide formation in PMNLs by flavonolignans. Phytother Res. 2001;15:608-12.
53. Minor T, Isselhard W. Orthotopic Liver Transplantation in the Rat: Comparison of Models with and without Rearterialization of the Graft. Eur Surg Res. 1993;25:287-93.
54. Mari M, Wu D, Nieto N, Cederbaum AI. CYP2E1-dependent toxicity and upregulation of antioxidant genes. J Biomed Sci. 2001;8:52-5.
55. Skottova N, Krecman V. Dietary silymarin improves removal of low density lipoproteins by the perfused rat liver. Acta Univ Palacki Olomuc Fac Med. 1998;141:39-40.
56. Anderson JW, Johnstone BM, Cook-Newll ME. Meta analysis of the effects of soy protein intake on serum lipids. N Engl J Med. 1995;333:276-82.
57. Nassuato G, Iemmolo RM, Strazzabosco M, Lisrussi F, Fragasso A, Orlando R, et al. Effect of silibinin on bilary lipid composition:experimental and clinical study. J Hepatol. 1991;12:290-5.
58. Johnson VJ, He Q, Osuchowski MF, Sharma RP. Physiological responses of a natural antioxidant flavonoid mixture, silymarin, in BALB/c mice:III. Silymarin inhibits T-lymphocyte function at low doses but stimulates inflammatory processes at high doses. Planta Med. 2003;69:44-9.
59. Dorai T, Aggarwal BB. Role of chemopreventive agants in cancer therapy. Cancer Lett. 2004;215:129-40.
60. Singh RP, Tyangi AK, Zhao J, Agarwal R. Silymarin inhibits growth and causes regression of established skin tumors in SENCAR mice via modulation of mitogen-activated protein kinases and induction of apoptosis. Carcinogenesis. 2002;23:499-510.
61. Bhatia N, Agarwal R. Detrimental effect of cancer preventive phytochemicals silymarin, genistenin and epigallocatechin

3-galate on epigenetic events in human prostate carcinoma DU145 cells. Prostate. 2001;46:98-107.
62. Šimánek V, Škottová N, Bartek J, Psotova J, Kosina P, Balejova L, et al. Extract from Silybum marianum as a nutraceutical:A double-blind placebo-controlled study in healthy young men. Czech J Food Sci. 2001;19:106-10.
63. Abraham P, Wilfred G, Catharine SP. Oxidative damage to the lipids and proteins of the lungs, testis and kidney of rats during carbon tetrachloride intoxication. Clinica Chimica Acta. 1999;289:177-9.
64. Tirkey N, Pilkhwai S, Kuhad A, Hesperidin CK. A citrus bioflavanoid, decreases the oxidative stress produced by carbon tetrachloride in rat liver and kidney. BMC Pharmacol. 2005;5:1-21.
65. Sonnenbichler J, Scalera F, Sonnenbichler I, Weyhenmeyer R. Stimulatory effects of silibinin and silicristin from the milk thistle Silybummarianum on kidney cells. J Pharmacol Exp Ther. 1999;290:1375-83.
66. Rastogi R, Srivastava AK, Rastogi AK. Long term effect of aflatoxin B1 on lipid peroxidation in rat liver and kidney:Effect of picroliv and silymarin. Photother Res. 2001;15:307-10.
67. Dietzmann J, Thiel U, Ansorge S, Neumann KH, Tager M. Thiol-inducing and immunoregulatory effects of flavonoids in peripheral blood mononuclear cells from patients with end-stage diabetic nephropathy. Free Radic Biol Med. 2002;33:1347-54.
68. Cecen E, Dost T, Culhaci N, Karul A, Ergur B, Birinioglu M. Protective effects of silymarin against doxorubicin-induced toxicity. Asian Pac J Cancer Prev. 2001;12:2697-704.