Egyptian Herbal Monograph

Volume 1

Wild Medicinal Plants

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Silybum marianum L. Gaertn. شوك الجمل

1. Names & Synonyms (1)

***Silybum marianum* L. Gaertn.** (2).

Family: Compositae (Asteraceae) (2).

Syns.: Carduus marianus L. (2).

Arabic: Shawk Sennari شوك سناري, Shok El-Gamal شوك الجمل (3).

English: Milk thistle and St. Mary's thistle (3).

2. Geographical distribution

Nile region, Oases of the Western Desert as well as the Mediterranean coastal strip and Sinai (3).

3. Parts used for medicinal purposes

Dried ripe fruits, freed from the pappus (1).

4. Major chemical constituents (2-6)

- Flavonolignans: Silymarin mixture mainly (silybin A, silybin B, isosilybin A, isosilybin B, silychristin, isosilychristin, silydianin).
- Flavonoids: Taxifolin, apigenin, kaempferol and their derivatives.
- Fixed oil: Linoleic, oleic, palmitic and stearic acids.
- Sterols: Tocopherol (vitamin E) and phospholipids.
- Others: Mucilage, sugars, amines and saponins.

5. Traditional medicinal uses (7, 8)

A. Symptomatic relief of digestive disorders, sensation of fullness and indigestion.

B. Support the liver function, after serious conditions have been excluded by physician.

***S. marianum* is a traditional medicinal plant for use in the specified indications exclusively based upon long-standing use.**

6. Herbal preparations correlated to medicinal use (7)

1. Comminuted herbal substance as herbal tea for oral use.
2. Powder herbal substance.
3. Dry extracts (using acetone/ ethyl acetate / ethanol/ water or mixture of ethanol: water in different concentration).
4. Silymarin.

Herbal preparations (2-4) are in a pharmaceutical dosage form. The pharmaceutical form should be described by the pharmacopoeia full standard term.

7. Posology and method of administration correlated to medicinal use

General Dosages

140 - 600 mg of silymarin (calculated as silibinin/silybin) per day; Not to exceed 200 mg per single dose (7).

Adults and elderly (8):

Preparation 1

Single dose: 3-5 g in 100 ml of boiling water, daily dose: 2 or 3 times daily, before meals.

Preparation 2

Single dose: 300–600 mg, daily dose: 2-3 times daily, up to 1800 mg daily, before meals.

Preparation 3

- Extraction solvent acetone:

Single dose: 82-239 mg dry extract, daily dose: 2-3 times daily, up to 478 mg, before meals.

-Extraction solvent ethyl acetate:

Single dose: 123-250 mg dry extract, daily dose: 3-4 times daily.

- Extraction solvent ethanol 96% (V/V) or hydroalcoholic:

Single dose: 200 mg dry extract, daily dose: 200 mg dry extract.

Preparation 4

140-600 mg (calculated as silibinin/silybin) per day; Not to exceed 200 mg per single dose (7).

Duration of use: *S. marianum* should be used at least 3 weeks to see beneficial effects (7).

Method of administration: Oral use (7,8).

8. Contraindications

- Hypersensitivity to active substances and to other plants of the same family.
- Hormone-sensitive conditions such as breast, uterine and ovarian cancers, endometriosis or uterine fibroids (9, 10).

9. Special warnings and precautions for use

- If the symptoms worsen during the use of the medicinal product, a doctor or a pharmacist should be consulted.
- The use in children and adolescents under 18 years of age is not recommended (7, 8,11).
- If icterus or a change in colour of urine or stool appears, a doctor should be consulted immediately (8).

10. Interactions with other medicinal products and other forms of interaction

None reported (8).

11. Fertility, pregnancy and lactation

- Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended (8-10).
- No fertility data available (8).

12. Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed (8).

13. Undesirable effects

- If adverse reactions occur, a doctor or a pharmacist should be consulted.
- Adverse effects are mainly transient, non-serious, gastrointestinal complaints. It is stated that silymarin may occasionally produce a mild laxative effect (2).

14. Overdose

No case of overdose has been reported (8).

15. Relevant biological activities

-The Clinical outcome, biochemical profile and the antiperoxidative effects of silymarin MZ-80 during 6 months treatment were investigated in sixty consecutive patients with alcoholic liver cirrhosis. The patients were randomized to receive either silymarin MZ-80 (S) (150 mg *t.i.d.* per day) or placebo (P) for periods of 6 months. Silymarin is well-tolerated and produces a small increase in glutathione and a decrease in lipid peroxidation in peripheral blood cells in patients with alcoholic liver cirrhosis. Despite these effects no changes in routine liver tests were observed during therapy (12).

-A comparative study was performed in patients (pts) with chronic hepatitis C and alcoholic liver disease. In addition, the effects of a flavonolignan drug silymarin were assessed. 10 pts with chronic hepatitis C, 5 pts with alcoholic hepatitis and 13 pts with alcoholic cirrhosis have been investigated. Biochemical liver tests were determined. Silymarin treatment of one month duration resulted in normalization of serum bilirubin in 55% of treated pts, AST became normal in 45%, and RBC hemolyzate MDA level normalized in similar rate. A significant increase in both GSH and retinoids was found. Alterations in oxidative stress and antioxidant defense system were shown in chronic hepatitis C, not only in alcoholic liver disease (13).

-The hepatoprotective activity of the nanoemulsion formulation of silymarin against carbon tetrachloride (CCl4))-induced hepatotoxicity on Wistar rats was assessed by determining biochemical parameters and histopathological properties. The nanoemulsion-treated group showed significant decreases in glutamate oxaloacetate transaminase, pyruvate transaminase, alkaline phosphotase, total bilirubin and tissue lipid peroxides and increased total protein, albumin, globulin and tissue glutathione as compared to toxicant. The results indicate an excellent potential of the nanoemulsion formulation for the reversal of CCl4-induced liver toxicity in rats as compared to standard silymarin (14).

-The alterations in sulfur containing amino acid metabolism induced by silymarin in association with its effects on the antioxidant capacity of liver were determined on male mice which treated with silymarin (100 or 200 mg/kg, p. o.) every 12 h for a total of 3 doses and sacrificed 6 h after the final dosing. The results demonstrate that silymarin enhances hepatic glutathione generation by elevating cysteine availability via an increment in cysteine synthesis and an inhibition of its catabolism to taurine, which may subsequently contribute to the antioxidant defense of liver (15).

-The in vitro antioxidative and oxidative DNA, protein and lipid damage protective effects of milk thistle (Silybum marianum) seed ethanol extract was investigated. The extract was found to have protective effect against DNA, protein and lipid oxidation induced by hydroxyl radical and it can protect DNA from damage. The inhibitory activity of seed extract against hydroxyl radical-induced DNA, protein and lipid damage may be mainly responsible for the cancer chemoprevention and hepatoprotection effects (16).

- Silymarin is a natural antioxidant, and this action is believed to contribute to the hepatoprotective effects of milk thistle (MT) preparations. Natural antioxidants have been shown to have beneficial effects in the preclinical models of NAFLD as well as in the pilot clinical trials. It has been reported that silymarin markedly increases the expression of superoxide dismutase in the patients with nonalcoholic steatohepatitis and decreases the oxidative stress in the *β*-thalassemia patients. Silymarin has no direct effect on ethanol metabolism and has no role in reducing ethanol levels or on the rate at which ethanol is removed from the body but the results suggest that antitoxic effects of MT are likely due to its antioxidant and free radical scavenging properties (17).

-Silymarin is a suitable candidate to treat drug-induced and toxic liver injury. It exerts a regulatory action on cellular and mitochondrial membrane permeability in association with an increase in membrane stability against the xenobiotic injury. Also, silymarin can prevent the absorption of toxins into the hepatocytes by occupying the binding sites as well as by inhibiting many transport proteins at the cell membrane (17).

-Silymarin exerts anti-inflammatory actions and attenuates autoimmune and immune-mediated liver diseases, possibly via suppression of oxidative and nitrosative immunotoxicity and T-lymphocyte function (18, 19).

- Anti-inflammatory activities of silymarin or MT extracts have been observed in a number of rat/mouse models of liver diseases, including cholestatic liver injury, restraint stress-induced acute liver, the stelic animal model of steatohepatitis, zidovudine/isoniazid-induced liver toxicity and, finally, a model of steatohepatitis induced by a methionine and choline deficient diet (20).

-A number of studies have shown that silymarin exerts anti-inflammatory action via suppression of the release of cytokines such as tumor necrosis factor-*α* (TNF-*α*), adhesion molecules, such as E-selectin, as well as via suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-*κ*B) signaling, nitric oxide and 5-lipoxygenase pathways (20).

- Specifically, silymarin inhibits/suppresses: (a) the TNF-*α*-induced activation of mitogen-activated protein kinase and c-Jun N-terminal kinase and as well as the TNF-*α*-induced cytotoxicity and caspase activation, (b) both the kappa B motif of NF-*κ*B DNA binding activity and its dependent gene expression in hepatoma cells as well as the translocation of NF-*κ*B p65 protein through phosphorylation to the nucleus without affecting its ability to bind the DNA, and (c) lipopolysaccharides (LPS)-induced production of NO in isolated mouse peritoneal macrophages. A recent relevant study has shown that the NAD+/SIRT2 pathway is an important mediator through which silybin prevents the NLRP3 inflammasome activation in mice with liver steatosis (20).

-Milk thistle (MT) extracts, silymarin, and active components such as silybin have been shown to stimulate hepatic regeneration in partially hepatectomized rat livers. In several preclinical studies, silybin stimulated ribonucleic acid (RNA) polymerase-I and ribosomal RNA, leading to a more rapid formation of ribosomes, which, in turn, accelerate protein synthesis. The stimulating effect of silybin on ribosome formation can have therapeutic implications in the repair of damaged hepatocytes and the restoration of normal liver functions (17).

-The Hepatoprotective effects of silymarin in non-human primates (twelve baboons) with alcoholic liver disease was assessed. The baboons were fed alcohol with or without silymarin for 3 years with a nutritionally adequate diet. The results were showed that silymarin opposed the alcohol-induced oxidative stress and retards the development of alcohol induced hepatic fibrosis in baboons (20).

- The properties of an optimized dose of encapsulated crude Silymarin (SMR) extracted by the milk thistle seeds (SMR) on antidiabetic activity and liver fibrosis induced by paracetamol in male albino rat have been assessed. Hepatic fibrosis was assessed by measuring liver enzymes. According to the optimized study, the long-term induction of SMR (300 mg/kg) significantly amplified survival time of rats with paracetamol induced hepatic injuries. the results suggest that SMR acts as a hepatoprotective agent by inhibiting the fibrogenesis and apoptosis in liver, as well as insulin resistance (21).

-Non-alcoholic steatohepatitis (NASH) is a progressive form of non-alcoholic fatty liver disease (NAFLD characterized by hepatocellular injury and initial fibrosis severity has been suggested as an important prognostic factor of NASH. Silymarin was investigated whether it could suppress the activation of hepatic stellate cell (HSCs) in NASH induced by methionine- and choline-deficient (MCD) diet fed to insulin-resistant rats. The study demonstrates the possible protective effect of silymarin against diet induced NASH by disturbing the role of the inflammatory cytokine, TNF-α, and suppressing the activation of HSCs (22).

-The mechanisms regulating the anti-fibrogenic and anti-inflammatory activity of Silybin were assessed. Experiments were performed on hepatic stellate cells (HSC) isolated from human liver and activated by culture on plastic. The results of the study provide molecular insights into the potential therapeutic action of Silybin in chronic liver disease. This action seems to be mostly related to a marked inhibition of the production of pro-inflammatory cytokines, a clear antioxidant effect and a reduction of the direct and indirect pro-fibrogenic potential of HSC (23).

- Animal studies have shown that in the early stages of the fibrotic process, silymarin is able to inhibit the fibrogenetic mechanisms and the progression of the initial liver fibrosis. In these studies, a reduction of collagen and pro-collagen III content after biliary obstruction in the rat by 30% with 50 mg/kg/day of silymarin have been observed. Experiments aiming at investigating the mode of action have shown that

silymarin (a) suppresses the expression of pro-fibrogenic pro-collagen-α1 and TIMP-1, most likely via down-regulation of TGF-β1 mRNA, inhibits NF-κB; (b) retards the activation of HCS; and (c) alters the expression of genes involved in cytoskeleton organization and mitochondrion electron-transfer chain. Silymarin is also able to ameliorate liver fibrosis induced by carbon tetrachloride in rats in combination with sitagliptin, a dipeptidyl peptidase-4 inhibitor clinically used as an oral antidiabetic agent. Interestingly, silymarin prevents liver fibrosis in a juvenile model of nonalcoholic steatohepatitis, which can have clinical relevance in the light of the increasing incidence of NAFLD in adolescents. The antifibrotic action of silymarin could be improved with new formulations of silymarin as nanoparticles. Indeed, a special formulation silymarin-loaded Eudragit® RS100 nanoparticles has been shown to resolve cholestasis-induced liver fibrosis by restoring hepatic regenerative capabilities (17).

-A study retrospectively tracked and analyzed the data of 602 patients, out of which 230 were alcohol induced; 131 with alcohol-induced liver damage (ALD), 13 with liver cirrhosis, and 86 with fatty liver; to assess the effects of water soluble Silymarin (Liverubin™) (a patented, water-soluble liver formulation, with 140 mg of silymarin per tablet) on important hepatic biochemical parameters. Liverubin™ treatment is found to bring about effective lowering of abnormally elevated hepatic biochemical parameters and is observed to be a promising safe and effective drug in cases of alcoholic liver disease (24).

16. Additional information:

- The bioavailability of silymarin could be increased by Phospholipids (25-27).
- Silymarin is poorly soluble in water, teas have been analyzed with about 10% original levels of silymarin from the fruits. Thus, for hepatic benefits, the concentrated extract is recommended (28).

17. Date of compilation/last revision

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References

1	WHO monographs on selected medicinal plants (2002). Monographs on selected medicinal plants, **2**, 300-316.
2	Barnes, J., Anderson, L. A. and Phillipson, J. D. (2007). Herbal Medicines, 3rd edition. Published by the Pharmaceutical Press. ISBN 978 0 85369 623 0.
3	Hassan, N. M. and Abdallah W. E. (2020). *Silybum marianum* (L.) Gaertn. In: Egyptian Encyclopedia of Wild Medicinal Plants, **10**, 8-33. Academy of Scientific Research and Technology, Cairo, Egypt.
4	Kroll, D. J., Shaw, H. S. and Oberlies, N. H. (2007). Milk Thistle nomenclature: Why it matters in cancer research and pharmacokinetic studies. *Integrative Cancer Therapies,* **6**(2), 110–119.
5	Graf, T. N., Cech, N. B., Polyak, S. J. and Oberlies, N. H. (2016). A validated UHPLC-tandem mass spectrometry method for quantitative analysis of flavonolignans in milk thistle (*Silybum marianum*) extracts. *J. Pharm. Biomed. Anal.*, **126**, 26-33.
6	Chambers, C. S., Holečková, V., Petrásková, L., Biedermann, D., Valentová, K., Buchta, M. and Křen, V. (2017). The silymarin composition… and why does it matter? *Food Res. Int.,* **100**(3), 339-353.
7	http://webprod.hc-sc.gc.ca/nhpid-bdipsn/monoReq.do?id=138&lang=eng
8	European Union Herbal Monograph on *Silybum marianum* (L.) Gaertn., fructus (2018). EMA/HMPC/294187/2013. Committee on Herbal Medicinal Products (HMPC).
9	https://www.rxlist.com/consumer_milk_thistle_carduus_marianum/drugs-condition.htm
10	https://www.webmd.com/vitamins/ai/ingredientmono-138/milk-thistle
11	Mosby's Handbook of Herbs and Natural Supplements, 4th ed., ISBN: 978-0-323-05741-7.
12	Lucena, M. I., Andrade, R.J ., de la Cruz, J. P., Rodriguez-Mendizabal, M., Blanco, E. and Sánchez de la Cuesta, F. (2022). 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*., **40**(1), 2-8. doi: 10.5414/cpp40002.
13	Pár, A., Róth, E., Rumi, G. Jr., Kovács, Z., Nemes, J. and Mózsik, G. (2000). Oxidatív stressz és antioxidáns védelem alkoholos májbetegségben és krónikus C hepatitisben [Oxidative stress and antioxidant defense in alcoholic liver disease and chronic hepatitis C]. *Orv Hetil*., **141**(30), 1655-1659.
14	Parveen, R., Baboota, S., Ali, J., Ahuja, A., Vasudev, S. S. and Ahmad, S. (2011). Effects of silymarin nanoemulsion against carbon tetrachloride-induced hepatic damage. *Arch. Pharm. Res*., **34**(5), 767-74. doi: 10.1007/s12272-011-0510-8.
15	Kwon, D. Y., Jung, Y. S., Kim, S. J., Kim, Y. S., Choi, D. W. and Kim, Y. C. (2013). Alterations in sulfur amino acid metabolism in mice treated with silymarin: a novel mechanism of its action involved in enhancement of the antioxidant defense in liver. *Planta Med*., **79**(12), 997-1002. doi: 10.1055/s-0032-1328704.
16	Serçe, A., Toptancı, B. Ç., Tanrıkut, S. E., Altaş, S., Kızıl, G., Kızıl, S. and, Kızıl, M. (2016). Assessment of the antioxidant activity of *Silybum marianum* seed extract and its protective effect against DNA oxidation, protein damage and lipid peroxidation. *Food Technol. Biotechnol*., **54**(4), 455-461. doi: 10.17113/ftb.54.04.16.4323.

17	Abenavoli, L., Izzo, A. A., Milić, N., Cicala, C., Santini, A. and Capasso, R. (2018). Milk thistle (*Silybum marianum*): A concise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases. *Phytother. Res*., **32**(11), 2202-2213. doi: 10.1002/ptr.6171.
18	Esmaeil, N., Anaraki, S. B., Gharagozloo, M. and Moayedi, B. (2017). Silymarin impacts on immune system as an immunomodulator: One key for many locks. *International Immunopharmacology*, **50**, 194–201.
19	Milic, N., Milosevic, N., Suvajdzic, L., Zarkov, M. and Abenavoli, L. (2013). New therapeutic potentials of milk thistle (*Silybum marianum*). *Natural Product Communications*, **8**, 1801–1810.
20	Lieber, C. S., Leo, M. A., Cao, Q., Ren, C. and Leonore M., DeCarli, L. M. (2003). Silymarin retards the progression of alcohol-induced hepatic fibrosis in Baboons. *J. Clin. Gastroenterol*., **37**(4), 336–339.
21	Mukhtar, S., Xiaoxiong, Z., Qamer, S., Saad, M., Mubarik, M. S., Mahmoud, A. H. and Mohammed, O. B. (2021). Hepatoprotective activity of silymarin encapsulation against hepatic damage in albino rats. *Saudi J. Biol. Sci*., **28**(1), 717-723. doi: 10.1016/j.sjbs.2020.10.063.
22	Kim, M., Yang, S. G., Kim, J. M., Lee, J. W., Kim, Y. S. and Lee, J. I. (2012). Silymarin suppresses hepatic stellate cell activation in a dietary rat model of non-alcoholic steatohepatitis: analysis of isolated hepatic stellate cells. *Int. J. Mol. Med.,* **30**(3), 473-9. doi: 10.3892/ijmm.2012.1029.
23	Trappoliere, M., Caligiuri, A., Schmid, M., Bertolani, C., Failli, P., Vizzutti, F., Novo, E., di Manzano, C., Marra, F., Loguercio, C. and Pinzani, M. (2009). Silybin, a component of sylimarin, exerts anti-inflammatory and anti-fibrogenic effects on human hepatic stellate cells. *J. Hepatol*., **50**(6), 1102-11. doi: 10.1016/j.jhep.2009.02.023.
24	Nanda, V., Gupta, V., Sharma, S. N., Pasricha, A., Karmakar, A. K., Patel, A., Bhatt, V. M., Kantroo, B. L., Kumar, B., Paul, N. K. and Attam, R. (2014). Effect of Liverubin™ on hepatic biochemical profile in patients of alcoholic liver disease: a retrospective study. *Minerva Med*., **105**(6 Suppl 2), 1-8.
25	Méndez-Sánchez, N., Dibildox-Martinez, M., Sosa-Noguera, J., Sánchez-Medal, R. and Flores-Murrieta, F. J. (2019). Superior silybin bioavailability of silybin-phosphatidylcholine complex in oily-medium soft-gel capsules versus conventional silymarin tablets in healthy volunteers. *BMC Pharmacol Toxicol*., **20**(1), 5. doi: 10.1186/s40360-018-0280-8. Erratum in: *BMC Pharmacol Toxicol.*, **20**(1), 14. Erratum in: *BMC Pharmacol Toxicol*., (2021), **22**(1), 37.
26	Morazzoni, P., Magistretti, M. J., Giachetti, C. and Zanolo, G. (1992). Comparative bioavailability of Silipide, a new flavanolignan complex, in rats. *Eur. J. Drug Metab. Pharmacokinet*., **17**(1), 39-44. doi: 10.1007/BF03189986. Erratum in: *Eur. J. Drug Metab. Pharmacokinet.,* **17**(2), 165.
27	Filburn, C. R., Kettenacker, R. and Griffin, D. W. (2007). Bioavailability of a silybin-phosphatidylcholine complex in dogs. *J. Vet. Pharmacol. Ther*., **30**(2), 132-138. doi: 10.1111/j.1365-2885.2007.00834.x.
28	Blumenthal, M., Goldberg, A., and Brinckmann, J., editors (2000). Milk Thistle Fruit. In: Herbal Medicine: Expanded Commission E Monographs. Newton, MA: Integrative Medicine Communications, 257–263.