

Silymarin: An interesting modality in dermatological therapeutics

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Introduction

Silymarin is a plant-derived flavonoid which is extracted from the fruits and seeds of milk thistle (*Silybum marianum* L. Gaertn.), which belongs to the family Asteraceae.¹ The extract of milk thistle has been used as a general medicinal herb used to treat the disorders of the spleen, liver, and gallbladder since as early as the 4th century BC, and was first reported by Theophrastus.² In modern times, it has been primarily used in liver disorders including hepatitis, alcoholic liver diseases, and cirrhosis.³⁻⁵ Extensive chemoprevention studies have been performed in several *in-vitro* and *in-vivo* animal models to test the efficacy of silymarin and establish its mechanism of action against skin carcinogenesis.^{6,7} Silymarin is available in both topical and oral formulations and has been used in multiple conditions in dermatology, such as melanoma and nonmelanoma skin cancers,⁸ melasma, rosacea, psoriasis, atopic dermatitis, acne, wound healing, cosmeceuticals, as well as in anti-aging therapy. The photoprotective mechanisms of silymarin and silybin on the skin are mainly due to their ability to reduce and suppress the harmful effects of solar UV radiation, such as UV-induced oxidative stress, inflammation, immune responses, and DNA damage, as well as the induction of apoptosis.⁹ Pharmacological studies have revealed that silymarin is nontoxic even at higher than physiological doses, which suggests its safe use for the treatment of various diseases.³ No significant interaction of silymarin has been reported. The safety and efficacy of this herbal drug in liver disease has been analyzed in a review by Saller *et al.*⁵

The main source of our information was PubMed, Google Scholar, and Scopus including original articles and review articles. The keywords “Silymarin,” “Silymarin in dermatology,” and “silibinin” were used for the search.

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Structure

Silymarin is a complex mixture of four flavonolignan isomers, namely, silybin, isosilybin, silydianin, and silychristin with an empirical formula C₂₅H₂₂O₁₀ [Figure 1].¹⁰ Among the isomers, silybin is the major and most active component and represents approximately 60–70%, followed by silychristin (20%), silydianin (10%), and isosilybin (5%). Silymarin also contains taxifolin, which has significant free radical scavenging properties.

Pharmacokinetics

Silymarin is insoluble in water and is typically administered as a sugar-coated tablet¹¹ or as an encapsulated standardized extract.¹² The absorption by oral route is low. The peak plasma levels after an oral dose are achieved after 4–6 h in experimental animals and human beings^{11,12} and elimination half-life is approximately 6 h.¹³ About 20–40% of the administered dose of silymarin is excreted in bile as sulphates and glucuronide conjugates in human beings.⁵

Mechanism of Action of Silymarin

Silymarin: Photocarcinogenesis and DNA repair

Table 1 shows the various mechanisms through which silymarin exerts its effects in various dermatological conditions. Ultraviolet radiation, especially ultraviolet B (UVB), is strongly absorbed by cellular DNA, resulting in DNA damage by the formation of cyclobutane pyrimidine dimers and 6–4 photoproducts. The oxidative stress involving generation of free radicals and reactive oxygen species (ROS) and depletion of antioxidant machinery are important factors with respect to the photocarcinogenesis of skin.^{30,31} Therefore, an agent having antioxidant properties such as silymarin that protects from UVB-induced DNA damage may be useful against photocarcinogenesis.⁶

There is also significant reduction in the occurrence of post-UVB exposure sunburn and cutaneous edema by treatment with silymarin.⁶ Therefore, free radical scavenging system is a key pathway through which silymarin inhibits the process of carcinogenesis, which otherwise causes DNA damage. Other possible mechanisms observed in few animal studies have shown that silybin treatment

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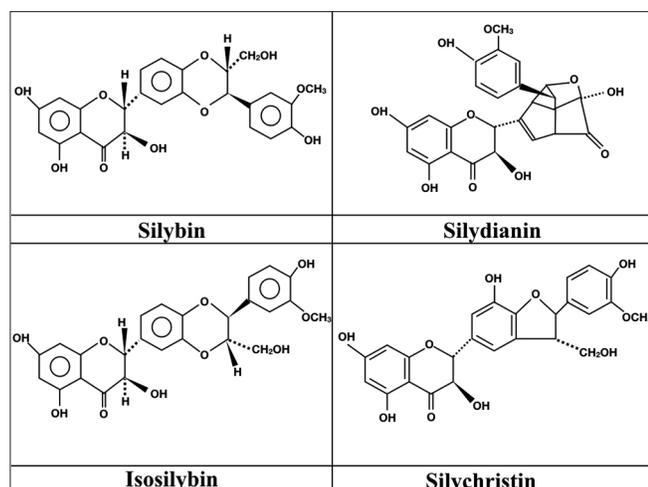


Figure 1: Structure of flavonolignan isomers of silymarin

activates p53, which is a key molecule in regulating DNA repair machinery along with cell cycle and apoptosis, and reduces the number of UVB-induced thymidine dimer positive cells in mouse skin epidermis.^{24,25}

Immunomodulatory effects of silymarin

UVB-induced immunosuppression occurs due to the release of cytokines that permit the development of various skin tumors.³² It is now evident that many tumors, including melanoma and nonmelanoma skin cancers, appear to produce IL-10, and the immunosuppressive effects of IL-10 may be one of the mechanisms by which these tumors escape immunologic control.³³⁻³⁵ The reversal of UVB-induced immunosuppression by silymarin treatment was associated with decreased production of IL-10 in UV irradiated skin and draining lymph nodes.¹⁴ The downregulation of contact hypersensitivity (CHS) responses caused by IL-10 may be mediated by the inhibition of antigen presentation. It was also shown that UV-induced infiltrating cells, particularly MHC+ CD11b+ cells (MHC type II), have a role in the UV-induced suppression of contact hypersensitivity.²³ Therefore, reduction of MHC+ CD11b+ cell type in UVB-irradiated skin by silymarin prevents UV-induced suppression of contact hypersensitivity. This is also confirmed by the fact that silymarin treatment inhibited myeloperoxidase activity, in UVB-irradiated skin in an animal study.¹⁴

Gharagozloo *et al.* investigated the effect of silymarin on cell cycle and PI3K/Akt/mTOR signalling pathway of activated T lymphocytes *in vitro*.²⁶ Peripheral blood mononuclear cells (PBMC) were isolated from healthy volunteers and cultured in complete RPMI (Roswell Park Memorial Institute) medium with 10, 50, and 100 μ M silymarin or dimethyl sulphoxide (DMSO) and incubated for 24–96 h. A significant G1 arrest in the cell cycle of activated T lymphocytes was found after 96-h incubation with 100 μ M silymarin without causing cell death. Silymarin also significantly inhibited the level of phospho-S6 ribosomal protein and mTOR activity in cell lysates of activated T cells after 72-h incubation in comparison with DMSO. The same author also observed that silymarin can inhibit T cell activation and proliferation, notably acting on the pathways of NF-kappa B activation/translocation and IL-2 production.¹⁸ These immunomodulatory effects of silymarin may have a significant impact in the fields of transplantation and autoimmunity.

Table 1: Mechanism of action of silymarin

*Silymarin and its antioxidant potential*¹⁴⁻¹⁷

- Inhibition of UVB-induced intracellular production of H₂O₂
- Inhibition of nitric oxide production by protection against UVB-induced expression of inducible nitric oxide synthase
- Inhibits UVB-induced expression levels of ERK1/2 and p38 proteins of MAPK family
- Inhibits chemical (TPA, BPO)-induced lipid peroxidation
- Membrane stabilization

Anti-inflammatory effect of silymarin^{6,14,17-22}

- Inhibits the expression of IL-1 α as well as TNF- α
- Inhibits myeloperoxidase activity
- Inhibits lipoxygenase and cyclooxygenase activity resulting in the inhibition of prostaglandin metabolite formation
- Inhibits the expression of inducible nitric oxide synthase as well as the production of nitric oxide in UV-treated skin

Immunomodulatory effects of silymarin^{14,23}

- Decreases the production of IL-10 in UV-irradiated skin and draining lymph nodes
- Inhibition of antigen presentation
- Reduction in infiltration of MHC + CD11b + cell type into UVB-irradiated skin
- Inhibition of myeloperoxidase activity

Photoprotection and DNA repair effects of silymarin^{6,24,25}

- Anti-oxidant
- Protects from UVB-induced DNA damage (photocarcinogenesis)
- Activates p53 (key molecule in regulating DNA repair machinery along with cell cycle) and apoptosis
- Reduces the number of UVB-induced thymine dimers

Effect of silymarin on EGFR-mediated mitogen signalling^{6,27}

- Inhibits activation of receptor tyrosine kinase EGFR and its intrinsic kinase activity and subsequently inhibits the activation of an immediate downstream target

Inhibition of melanin synthesis^{28,29}

- Inhibits l-DOPA oxidation activity of tyrosinase
- Decreases the expression of tyrosinase protein

UVB: Ultraviolet B, MAPK: Mitogen activated protein kinase, TPA: 12-O-tetradecanoylphorbol 13-acetate, BPO: Benzoyl peroxide, UV: Ultraviolet, DNA: Deoxyribonucleic acid, MHC: Major histocompatibility complex, DOPA: Dihydroxyphenylalanine, IL-1 α : Interleukin 1 alpha, TNF- α : Tumor necrosis factor-alpha, EGFR: Epidermal growth factor receptor

Silymarin and skin chemical carcinogenesis

Silymarin has also shown promising results as a chemopreventive and/or therapeutic agent in various skin chemical carcinogenesis models in both animal and human studies.^{15,16,19} Overexpression of receptor and/or protein tyrosine kinases and the epidermal growth factor receptor (EGFR) signalling are important pathways in various cutaneous tumors, and oxidative stress has been identified as one of the inducers of these pathways.^{17,20} Studies have shown that silymarin inhibits both ligand-induced activation of receptor tyrosine kinase EGFR and its intrinsic kinase activity, and its inhibitory effect on the activation of the EGFRShc-ERK1/2 pathway indicates its skin cancer chemopreventive efficacy.²¹

Silymarin and its antioxidant potential

Skin is constantly exposed to free radical-generating agents such as solar UV radiation, ozone, and other environmental pollutants.³² Topical treatment with silymarin resulted in the inhibition of UVB-induced intracellular production of H₂O₂, inhibition of nitric

oxide production by protection against UVB-induced expression of inducible nitric oxide synthase, inhibition of infiltrating CD11b+ cell types, inhibition of UVB-induced expression levels of ERK1/2 and p38 proteins of mitogen activated protein kinase (MAPK) family, and subsequently inhibited the activation of NF- κ B/p65 by inhibiting the degradation of I κ B α and activation of IKK α .^{14,22,36} Together, these antioxidant activities demonstrate that silymarin has the ability to protect the skin from the adverse biological effects of UVB radiation via modulation of the MAPK and NF- κ B signalling pathways and provide a molecular basis for the anti-carcinogenic effect.

Similarly, silymarin strongly inhibits TPA (12-O-tetradecanoylphorbol 13-acetate) and benzoyl peroxide (BPO)-induced lipid peroxidation in mouse skin epidermis supporting its strong *in-vivo* antioxidant activity.³⁷

Anti-inflammatory effects of silymarin

The anti-inflammatory properties of silymarin have been studied by various authors.^{6,14,27}

The mechanism of anti-inflammatory effect of silymarin observed in different studies are silymarin inhibits the expression of IL-1 α as well as TNF- α , UVB, TPA, and benzoyl peroxide induced increase in myeloperoxidase activity, TPA and UVB induced lipoxygenase and cyclooxygenase activity resulting in inhibition of prostaglandin metabolite formation and expression of inducible nitric oxide synthase (iNOS).^{6,14-16,37}

Inhibition of melanin synthesis

Silymarin inhibited L-dihydroxyphenylalanine (L-DOPA) oxidation activity of tyrosinase, the rate-limiting melanogenic enzyme, in cell based-systems, however it did not directly affect cell-free tyrosinase activity. Furthermore, western blot analysis indicated that silymarin decreased the expression of tyrosinase protein, thus explaining its effect in melasma.^{28,29} The various mechanisms of action of silymarin have been summarized in Table 1.

Application of Silymarin in Dermatology

The various possible clinical indications of silymarin have been listed in Table 2.

Skin cancers

Vaid *et al.* showed that silymarin not only prevents skin cancers but also prevents melanoma cell migration via the β -catenin signalling pathway.⁸ Chatterjee *et al.* observed the inhibition of development of nonmelanoma skin cancers in mice by applying silymarin-containing sunscreens via blocking the production of pyrimidine dimmers formed as a result of ultraviolet radiation exposure.³⁸

Silymarin and ultraviolet protection

The UV protective effect of silymarin was reviewed by Mehraban and Feily.⁵⁸ Silymarin decreased apoptosis and DNA damage caused by UV radiation via the nucleotide excision repair mechanism on epidermal cells, which makes silymarin a viable option for prophylaxis of skin cancers.⁵⁹ The inhibitory effects of silymarin on photocarcinogenesis by downregulation of the immunosuppressive cytokine and interleukin-10 and upregulation of the immunostimulator cytokine, interleukin-12, were also studied by Meeran *et al.*⁶⁰

Silymarin and melasma

Altaei reported a study involving 96 adults clinically diagnosed as melasma.²⁹ Patients were randomized in a double-blinded manner; Group I was prescribed silymarin (7 mg/ml) cream, Group II silymarin (14 mg/ml) cream, and Group III was administered placebo. Silymarin was applied topically to the affected areas twice daily for 4 weeks. The response was evaluated by lesion size, melasma area and severity index score, and physician global assessment. Clinically, all patients showed excellent pigment improvement and lesion size reduction with silymarin compared to that of the first week. In group I, complete clearing of the lesion was seen after the fourth week, in group II after 3 weeks of treatment, whereas no significant change was observed in group III. No side effects were observed.²⁹ Silymarin was also beneficial in treating UVA-induced skin damage in a dose-dependent manner in *in-vitro* studies.^{40,41}

Silymarin and rosacea

Berardesca *et al.* demonstrated that the combination therapy of silymarin and methylsulfonylmethane can be useful in the treatment of rosacea, especially in the rosacea subtype-1, erythematotelangiectatic phase.⁴² It was effective in reducing skin erythema, pruritus, papules and skin color.⁴²

Silymarin as radioprotector and prevention of radiodermatitis

Adhikari *et al.* found silymarin to be a promising radioprotector.⁴³ They used a fraction (INM-7035) with the composition of silybin A and B (39.9% and 57.4%, respectively). Free radical scavenging activities of INM-7035 against superoxide radicals (>68%), hydroxyl radicals (>33.75%), 2,2-diphenyl-1-picrylhydrazyl (DPPH) (67.2%), and 2,2-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) (32.4%) were also evaluated. INM-7035 completely inhibited lipid peroxidative stress in case of membranes against supra-lethal radiation stress in the liposomal system. The ability of INM-7035 to modulate

Table 2: Applications of silymarin in dermatology*

Skin cancers ^{8,38}
Sunscreens ^{14,39}
Melasma (Ib) ^{29,40,41}
Rosacea (III) ⁴²
Radioprotector ⁴³
Psoriasis ^{44,45}
Acne (Ib) ⁴⁶
Actinic keratosis prevention ⁴⁷
Cosmeceuticals ⁴⁸
Atopic dermatitis ^{49,50}
Wound healing ⁵¹⁻⁵³
Anti-aging ⁵⁴
Irritant contact dermatitis ⁵⁵
Prevention of radiodermatitis (III) ⁵⁶
Antibacterial ⁵⁷
Autoimmune disorders ¹⁸

*Categories of evidence - Ia: Evidence for meta-analysis of randomized controlled trials, Ib: Evidence from at least one randomized controlled trial, IIa: Evidence from at least one controlled study without randomization, IIb: Evidence from at least one other type of quasi-experimental study, III: Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies and case-control studies, IV: Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

the levels of NF-kappa B, indicated its inherent potential as a radioprotective bioactive constituent.⁴³

A study was conducted in 101 breast cancer patients undergoing postsurgical radiotherapy by Becker-Schiebe *et al.*⁵⁶ Of these, 51 patients were treated with silymarin-based cream. Only 9.8% of patients using silymarin-based cream showed grade 2 toxicity in week 5 of radiotherapy in comparison to 52% with the nonsilymarin-based group. At the end of radiotherapy, 23.5% of patients in the silymarin-based study group developed no skin reactions versus 2% in nonsilymarin-based group. They concluded that silymarin cream may be a promising and effective treatment for the prevention of acute skin lesions caused by radiotherapy of breast cancer patients.⁵⁶

Silymarin and psoriasis

There are anecdotal reports of efficacy of silymarin in the treatment of psoriasis.^{44,45} Khan *et al.* found that silymarin gel has promising antipsoriatic activity.⁶¹

Silymarin and acne

A randomized, prospective clinical trial on 56 patients in the age range of 14–35 years showed the beneficial effects of silymarin, N-acetylcysteine, and selenium in patients with acne vulgaris, as indicated by the clinical improvement and biochemical findings.⁴⁶

Actinic keratosis prevention

There are various agents that can be used in the prevention of AK, with silymarin being one of them. Berman and Amini have reviewed the pharmacotherapy of actinic keratosis (AK).⁴⁷

Atopic dermatitis

The effect of topical silymarin in atopic dermatitis induced by dust mite extract in NC/Nga mice was studied by Kang *et al.* who found that it reduced atopic dermatitis-like lesions and suppressed mast cell infiltration in mice skin.⁴⁹ In addition, silymarin also reduced plasma levels of IL-4 and IgE in these mice. Hence, silymarin might be beneficial for the treatment of AD.⁴⁹ Recently, Mady *et al.* showed that silymarin pluronic-lecithin organogel (PLO) formulation significantly relieved inflammatory symptoms of AD such as redness, swelling, and inflammation.⁵⁰

Silymarin and contact dermatitis

Topical silymarin has shown benefit when applied to mice skin damaged by chemical induced irritant contact dermatitis.⁵⁵

Wound healing

Sharifi *et al.* carried out a study to evaluate the effect of topical application of silymarin on excision wounds in rats.⁵¹ Rats were divided into three groups viz. control, vehicle, and treatment. Vehicle and treatment groups received polyethylene glycol and silymarin, respectively. They found that silymarin significantly stimulates epithelialization and reduces inflammation in full-thickness wounds in rats. Oryan *et al.* also found that topical application of silymarin improved the morphological, biochemical, and biomechanical properties of experimentally-induced wound defects in rats.⁵² In another study, Tabandeh *et al.* found that silibinin acts by increasing stromelysin-1 gene expression and extracellular matrix constituents including glycosaminoglycans and collagen contents and promotes a faster wound healing process.⁵³ Therefore, silymarin has the potential of being one of the therapeutic options for wound healing.

Silymarin as anti-ageing agent, sunscreen, and cosmeceutical

Pientaweeratch *et al.* studied the anti-aging property of amla, silymarin, and sapota and found these agents to have antioxidant, anti-collagenase, and anti-elastase activities in *in-vitro* studies.⁵⁴ They found that the extracts might be added as a mixture to gain overall anti-aging effects. Topical and oral anti-oxidants such as silymarin, slow ageing processes and act as sunscreens.³⁹ Oxidative stress is one of the major mechanisms for skin aging, and silibinin with its proven antioxidant activity could be useful for treating many dermatologic conditions as well as skin aging. Thus, this supports the scientific rationale for the effective use of silibinin in cosmeceutical preparations.⁴⁸

Antibacterial and antiadherence activities of silymarin

Evren *et al.* studied the antibacterial and antiadherent properties of silymarin and its effects on bacterial biofilm viability. A minimum inhibitory concentration between 60 and 120 µg/mL inhibited gram positive bacteria. The biofilm viabilities decreased to 13% and 46% at 1 and 0.5 mmol/L concentrations, respectively. There was also a marked reduction in biofilm/adherence formation in the silymarin-treated group in comparison to silymarin-untreated group. This study showed that silymarin is endowed with antibacterial and anti-adherence/biofilm properties.⁵⁷

Drug interaction

The major concern for the use of silymarin is liver toxicity which it may cause via the inhibition or induction of cytochrome-P450 and drug–drug interaction. However, no significant interaction has been reported till now.⁶² Silymarin has been found to be hepatoprotective in children receiving methotrexate-based chemotherapy protocols.⁶³

Adverse effects

Silymarin is reported to have a very good safety profile. Both animal and human studies have shown that silymarin is nontoxic even when given in higher doses (>1500 mg/day). However, a laxative effect is noted at these doses. Most common adverse effect observed is that of the gastrointestinal tract [Table 3] such as bloating, dyspepsia, nausea, irregular stools, and diarrhoea. These were observed in 2–10% of patients in clinical trials, which were similar to placebo.⁶⁴ Others adverse effects include pruritus, headache, exanthema, malaise, asthenia, and vertigo.⁵ Some serious adverse events were reported in three patients by Jacobs *et al.* A 57-year-old lady developed serious symptoms of gastroenteritis associated with collapse whereas the other two reported cases were allergic in nature after ingestion of herbal tea containing silymarin.⁶⁴ Silymarin increases lactation most probably by elevating the circulating prolactin level and was traditionally used by nursing mothers for stimulating milk production. However, no studies are available regarding its safety in pregnant women and newborns while on breast milk.^{65,66}

Conclusion

Silymarin is widely used as a hepatoprotective agent for various disorders of the liver because of its good safety profile and effectiveness. Recently, its use has been investigated in many dermatological conditions due to its anti-oxidant, anti-inflammatory, immunomodulatory, and membrane-stabilizing properties. Although silymarin has shown promising results in various dermatologic conditions in humans, most of the publications available are on animal studies. At present, silymarin is being used for various skin disorders such as melasma, anti-aging, sunscreen, acne, rosacea,

Table 3: Adverse effects of silymarin*Common adverse effects*

Bloating
Dyspepsia
Nausea
Irregular stools and diarrhoea

Serious adverse effects

Collapse
Allergic reaction

Less common adverse effects

Pruritus
Headache
Exanthema
Malaise
Asthenia
Vertigo

psoriasis, skin cancer, photoprotection, cosmeceuticals, and so on. However, the evidence base in humans is still not very strong, and more clinical trials are needed to evaluate the clinical efficacy of standardized silymarin preparations against various dermatologic conditions.

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Conflicts of interest

There are no conflicts of interest.

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