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Review

Silymarin impacts on immune system as an immunomodulator: One key for many locks

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ABSTRACT

Silymarin is a flavonoid complex extracted from the *Silybum marianum* plant. It acts as a strong antioxidant and free radical scavenger by different mechanisms. But in addition to antioxidant effects, silymarin/silybin reveals immunomodulatory affects with both immunostimulatory and immunosuppression activities. Different studies have shown that silymarin has the anti-inflammatory effect through the suppression of NF-κB signaling pathway and TNF-α activation. It also has different immunomodulatory activities in a dose and time-dependent manner. As an immunomodulator agent, silymarin inhibits T-lymphocyte function at low doses while stimulates inflammatory processes at high doses. Studies have shown that silymarin has attenuated autoimmune, allergic, preeclampsia, cancer, and immune-mediated liver diseases and also has suppressed oxidative and nitrosative immunotoxicity. Silymarin also has indicated dual effects on proliferation and apoptosis of different cells. In conclusion, based on the current review, silymarin has a broad spectrum of immunomodulatory functions under different conditions. Recognizing the exact mechanisms of silymarin on cellular and molecular pathways would be very valuable for treatment of immune-mediated diseases. Also further studies are needed to assess the utility of silymarin in protection against autoimmune, cancer, allergic and other diseases in human subjects.

1. Introduction

Flavonoids are a group of naturally occurring polyphenolic compounds that are commonly found in the plant kingdom. These compounds have a benzo-γ-pyrone structure with at least one hydroxyl group and exhibit spectrum of biochemical activities affecting basic cell functions such as proliferation, differentiation, and apoptosis. Besides, flavonoids have been found to possess antioxidant activities dependent on their functional hydroxyl groups by scavenging free radicals and/or by chelating metal ions [1,2].

The *Silybum marianum* (milk thistle plant) is a member of the daisy family (Asteraceae) which originates from mountains of the Mediterranean region. The milk thistle plant grows mainly in North Africa, the Mediterranean region and the Middle East (now also grown in the U.S.) [3]. It is used as a source of the drug, for > 2000 years to treat liver and gallbladder disorders such as hepatitis and cirrhosis. It also protects the liver against poisoning from various chemical and environmental toxins such as snake bites, insect stings, toxic mushroom, alcohol, and acetaminophen [4–7]. Silymarin is a unique flavonoid complex extracted from fruits and seeds of *Silybum marianum*. It consists of a family of flavolignans; silybin A, silybin B, isosilybin A, isosilybin B, silychristin, isosilychristin, silydianin and the flavonoid taxifoline. In addition to flavolignana, silymarin extract contains small amounts of flavonoids, and approximately 20% to 35% of fatty acids and polyphenolic compounds. But Silybin (synonymous with silibinin) is the major biologically active component of (70–80%) of the silymarin complex and it is a mixture of silybin A and silybin B (Fig. 1) [8–10]. That is why compounds containing milk thistle constituents showing silybin content in various studies, are used to explain the biological activity of silymarin.

Silymarin displays strong antioxidant and free radical scavenging abilities by inducing superoxide dismutase, increasing cellular glutathione content and inhibiting lipid peroxidation. Another antioxidant mechanism of silymarin results from metal ions (iron, cooper, etc.) chelation ability of this compound [11–14]. Apart from hepatoprotective and antioxidant effects, silymarin/silybin has been described to exhibit anticarcinogenic, immunomodulatory and anti-inflammatory activities [15–21].

On the other hand, several studies have suggested that silymarin/silybin reveals immunomodulatory affects with both

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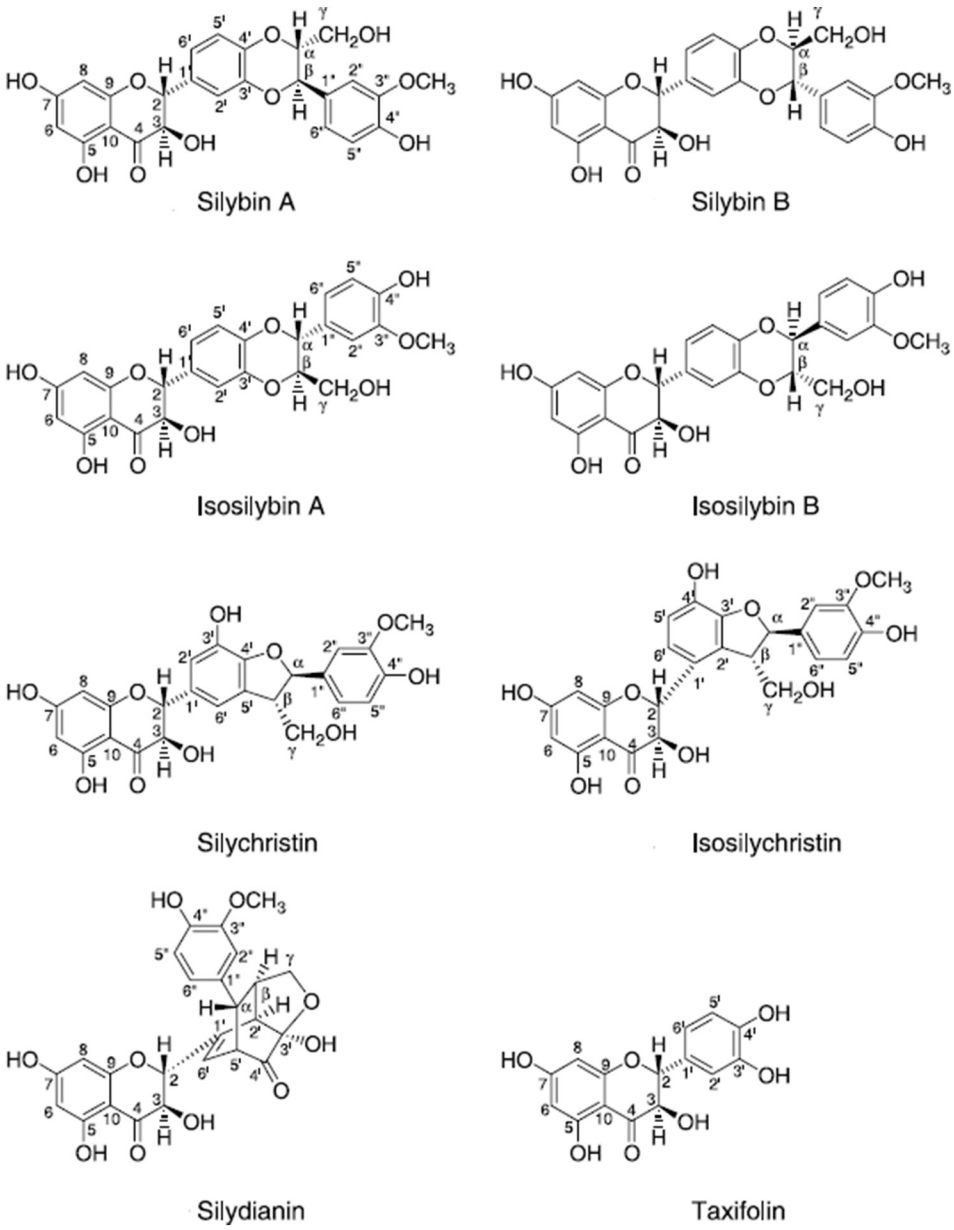

Fig. 1. Chemical components of *Silybum marianum*. These compounds have been distinguished in three milk thistle extracts available commercially as silymarin [10].
Silybin (synonymous with silibinin) is the major active component (50–70%) of the silymarin complex and it is a 1:1 mixture of silybin A and silybin B.

immunostimulatory and immunosuppression activities in a dose and time-dependent manner. The present review focuses on the immunomodulatory effects of silymarin, which have been assessed in different studies.

2. The inhibitory effects of silymarin on transcription factors (NF-κB, Stat3 and MEK/ERK)

2.1. Anti-inflammatory effects

Several studies have indicated the role of nuclear factor-kappaB (NF-κB) inflammatory activations in the development of different diseases [22,23]. Silymarin has a potent anti-inflammatory action throughout the suppression of NF-κB regulated gene products, including cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), and inflammatory cytokines [15,24,25].

NF-κB is responsible for transcription of genes involved in immune responses, inflammation, and carcinogenesis [26]. In the cytoplasm of the unstimulated cells NF-κB dimer (p50/p65), which is present in inactive form bounds to inhibitory kappa B (IκB) protein. NF-κB is activated by a variety of stimuli, including microbial components, pro-inflammatory cytokines, phorbol esters, oxidants, phosphatase inhibitors and ultraviolet radiation via triggering of various sensors such as Toll-like receptors (TLRs) what results in degradation of IκB (Fig. 2). Following the degradation of IκB, NF-κB subunits translocate into the nucleus and bind to DNA sequences to induce target genes expression [27].

The important role of NF-κB in the pathogenesis of inflammation suggests that inhibitors of the NF-κB pathway could be effective targets for treatment of chronic inflammatory diseases. Silibinin has been demonstrated to inhibit NF-κB activation through suppression of inhibitory kappa B (IκB) degradation, thereby precludes both translocation of NF-κB into the nucleus and initiation of gene transcription related to the inflammatory response [28]. Kang et al. have shown that silymarin (6.25, 12.5, 25, 50 μg/ml) suppresses LPS (200 ng/ml) induced interleukin-1b (IL-1b), prostaglandin E2 (PGE2) production and COX-2 expression in isolated mouse peritoneal macrophages via suppression of NF-κB [29]. Also, silymarin blocks NF-κB activation induced by phorbol ester, LPS, okadaic acid, and ceramide. The effects of silymarin on NF-κB inhibition are specific, as it has not affected AP-1