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Review Article

Therapeutic effect and molecular associated mechanisms of silymarin on osteoarthritis: A systematic review

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Abstract

Background and aims: Osteoarthritis (OA) is a degenerative joint and common skeletal disease around the world. We aimed to review silymarin and its major active constituent effects and underlying mechanisms for relieving OA.

Methods: The study protocol was designed according to the PRISMA statement. An extensive search was performed in several main databases including PubMed, Web of Science, EMBASE, and Scopus. Considering the inclusion and exclusion criteria of the study, finally, 11 studies were included. The desired data were extracted from the studies and registered into an Excel form and the consequences and mechanisms were surveyed.

Results: Silymarin, inhibits or downregulates IL (interleukin)-1β, IL-6, IL-8, IL-17, tumour necrosis factor alpha (TNF-α), prostaglandin E2 (PGE2), matrix metalloproteinase (MMP)-1, MMP-3, MMP-13, inducible nitric oxide synthase (iONS), cyclooxygenase-2 (COX-2), and high-sensitivity C-reactive protein (hs-CRP). In terms of antioxidant capacity, it decreased reactive oxygen species (ROS), malondialdehyde (MDA), and lipid peroxidation in serum and synovial fluid. In addition, it reduced alkaline phosphatase (ALP), leukocytes (Th17), and HB levels. Silymarin increases superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and glutathione peroxidase (GPx). Moreover, it can up-regulate and increases the anabolism of sirtuin1 (Sirt1), SRY-box transcription factor 9 (SOX9), IL-10, IL-4, tissue inhibitor of metalloproteinase (TIMP-1), Collagen type II and extracellular matrix (ECM) homeostasis.

Conclusion: Because silymarin is a potent anti-inflammatory and antioxidant polyphenolic flavonoid, it can be effectively used as adjunctive therapy in the treatment of OA; however, more clinical trial studies are still needed to determine its side and analgesic effects.

Keywords: Silymarin, Arthritis, Osteoarthritis, Systematic review

Introduction

Osteoarthritis (OA) is a degenerative joint disease and is the most common skeletal disease around the world (1). The incidence of the disease is increasing and it affects especially the elderly (2,3). OA causes a wide range of complications including chronic pain, limitation in the range of motion of the joint, difficulty ambulation, falls, joint stiffness, radiculopathies, and even premature death (4). OA has adverse impacts on the quality of life of patients and especially on the physical subscales and daily living activities (5,6). Moreover, the incidence and disease-adjusted life years of OA increased globally in recent years (7).

Therapies related to OA are based on symptom management and underlying pathophysiology (8). Because the disease is mainly chronic, precautions should be considered in chemical drug administration. Because the long-term use of chemical drugs to relieve the disease symptoms has related complications. Therefore, to manage the disease symptoms that mainly use cyclooxygenase-2 (COX-2) inhibitors and, non-steroidal anti-inflammatory drugs drugs, attention should be paid to their gastrointestinal and cardiovascular side effects (9). In addition, drug interactions and other underlying diseases should be considered in the treatment of OA patients (10,11).

Therefore, finding new and alternative treatment strategies with fewer side effects and easier to use becomes necessary. Herbal remedies become popular all over the world due to fewer complications and lower costs than chemical medicines (12,13). Milk Thistle (*Silybum marianum* L. Gaernt.) is a medicinal plant and its main active ingredient is silymarin. Silymarin is a complex polyphenolic compound containing a mixture of flavonolignans and its major active constituent is called silibinin (14). Several review studies have reported positive effects of silymarin on liver and kidney diseases. Moreover, it improves growth performance and promotes the immune system (15-17). Khazaei et al reported that silymarin inserts cytoprotection effects due to its radical scavenging and antioxidant properties. In addition, they revealed that silymarin has anti-inflammatory effects via the reduction of tumour necrosis factor alpha (TNF-α), and other inflammatory cytokines (17).

Therefore, according to the results of various studies regarding the protective effects of silymarin on different

body tissues and considering that no review study has yet investigated its anti-arthritic properties, in this study, we aimed to determine the protective effects and possible mechanism of silymarin and its major active constituent on OA.

Materials and Methods

Data sources and search strategy

This systematic review protocol was carried out based on the PRISMA guidelines (http://prisma-statement.org/prismastatement/Checklist.aspx). A systematic literature search was undertaken in several meta databases including Web of Science, PubMed, EMBASE, and Scopus on September 15, 2022. The researchers searched using different keywords that were mainly extracted from the MeSH browser. The keywords that were used for the search included: ((“silymarin”) OR (silimarin) OR (“silibinin”) OR (“silybin”) OR (“milk thistle”) AND (osteoarthr*) OR (“arthrosis”)).

The following keywords were used exclusively for searching in PubMed: ((silymarin[MeSH Terms]) OR (carsil[MeSH Terms]) OR (karsil[MeSH Terms]) OR (legalon[MeSH Terms]) OR (silimarin[MeSH Terms]) OR (silibinin[MeSH Terms]) OR (silybin[MeSH Terms]) AND (osteoarthritis[MeSH Terms]) OR (arthritis[MeSH Terms]) OR (arthroses[MeSH Terms]) OR (arthrosis[MeSH Terms]) OR (osteoarthrosis[MeSH Terms]))

After searching for articles in the mentioned databases, a final search was conducted and previous review studies as well as those not found in those databases were included in the study.

Study selection

In the next phase of this systematic review, the founded records were imported into the EndNote X8 (8 November 2016, Thomson Reuters) software. Afterward, duplicates were found and removed. All included articles in terms of titles/abstracts in the electronic databases were independently screened by two authors. With regards to our aim of the review and the inclusion criteria, the studies that addressed the effect of silymarin on OA symptoms were screened. Exclusion criteria included review articles, non-English language, and failure to retrieve the full text of the articles. In the next step and after completing a systematic literature review and screening studies, the full texts of all included studies were retrieved and the abstract/text was reviewed by researchers. It is worth mentioning that no conflict or disagreement exists between the researchers.

The flow diagram of screened articles based on the PRISMA 2020 flowchart is illustrated in Figure 1.

Data extraction

To review the articles, derive the results from the silymarin-associated outcome and categorize the article’s data and provide a report on the data, their information was included in an Excel file designed for this purpose. This form contains titles and variables such as the lead author’s name, publication year, study setting, type of study, clinical approach, time of exposure and dosage, and outcomes. If the extracted information was irrelevant to the aim of the study, it was excluded from the further process.

Results

Search results, study characteristics of selected studies

The PRISMA flowchart illustrated the included and excluded studies that were searched in the main databases (Figure 1). In general, we retrieved about 1126 articles in the initial search. Out of this number, we removed about 372 articles in EndNote due to duplication. Because of not retrieving the full text, some other titles/abstracts were also excluded (n = 2) (18), with the other one investigating the alcoholic extract of *S. marianum* L. on OA (19).

Finally, 11 articles were selected for the final assessment (20-30).

The included studies mainly investigated inflammatory cytokines and in some cases oxidative stress indicators in the form of *in vivo* and *in vitro* studies. Some studies also investigated the factors affecting the restoration and return to the normal condition of the joints (Table 1).

As Table 1 shows, we derived the conclusion that silymarin, revealed powerful anti-inflammatory and antioxidant effects, and some studies had also investigated its effect on hemodynamic and biochemical indicators of blood. However, there were limitations in reporting the toxicity of silymarin and determining its minimum effective dose.

The main effects and mechanism of silymarin on OA

This systematic review aimed to investigate silymarin’s effect and underlying mechanism on OA symptoms. The main possible mechanisms of action of silymarin protective effects are associated with estrogenic and nuclear receptors, blockade and adjustment of cell transporters, and p-glycoprotein (31). Most of the included studies showed that silymarin reduces the complications of OA by inducing its anti-inflammatory and antioxidant properties in the body. The most important possible underlying mechanisms are discussed below.

Anti-inflammatory properties and antioxidant properties

One of the pathological characteristics of OA is inflammation which is known as an innate immune response to disease (32). Cartilage distraction, and synovial and chondrocyte inflammation cause the creation of inflammatory cytokines, chemokines, and local production of inflammatory mediators. The resulting inflammation may act as a contributing factor in the progression of cartilage destruction and impair the ability to repair. Therefore, conditions are provided for the formation of matrix-degrading enzymes such as aggrecanases and metalloproteinases. Therefore, inflammation and permanent cartilage destruction

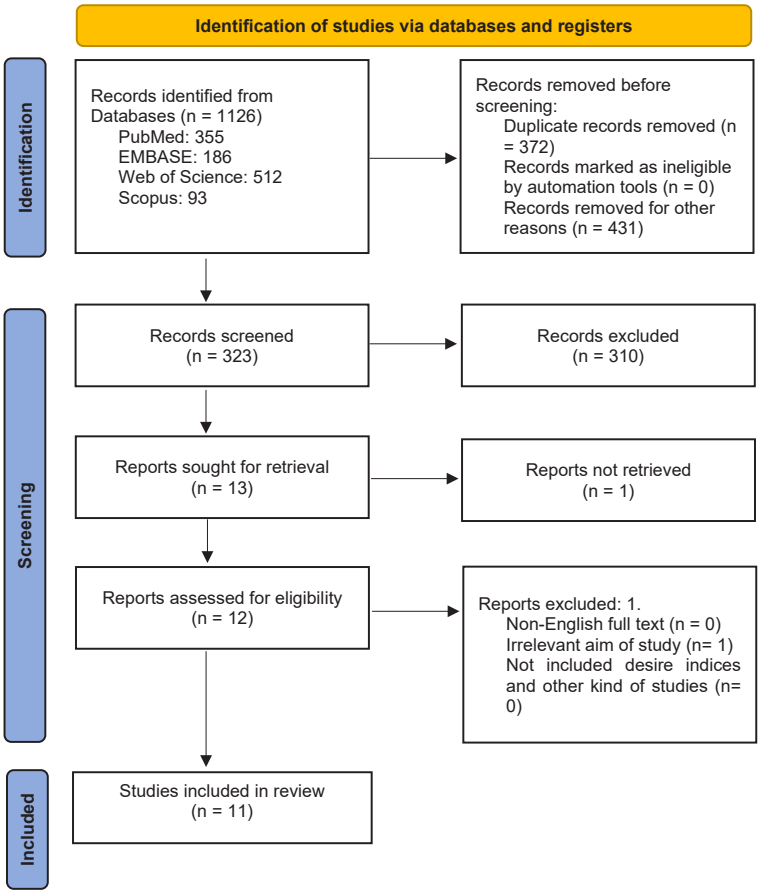

Figure 1. Flow diagram for including studies in the systematic review

are created (33). The evidence shows that the systemic pathways are also involved in this process and the inflammatory reactions that occur in the joint cartilages and synovial fluid may be seen outside the joint in the peripheral blood leukocytes and plasma of patients with OA (34). Studies have shown that silymarin acts as a strong anti-inflammatory substance and by suppressing inflammation, in addition to increasing the joint healing process, it increases its range of motion and reduces pain (21,26). Silymarin and its constitutes downregulated the mRNAs and signaling pathways such as nuclear factor kappa B (NF-κB) and forkhead box O (FOXO) and suppress the LXRα agonism, which can worsen the inflammatory process (34). Through activation of adenosine monophosphate protein kinase (AMPK) and transcription factor 4 (ATF-4) along with the inhibition of the mammalian target of rapamycin (mTOR) signaling, Silymarin can modulate cellular stress and metabolic pathways in inflammation (35).

Moreover, the studies indicate that silymarin inhibits or downregulates IL (interleukin)-1β, IL-6, IL-8, IL-17, TNF-α, prostaglandin E2 (PGE2), inducible nitric oxide synthase (iONS), COX-2, and high-sensitivity C-reactive protein (hs-CRP) (23,26,27,30).

Antioxidant properties

There is a direct association between oxidative stress and the development of OA. Inflammation and biochemical damage and pro-oxidant antioxidant balance in OA cartilage can lead to increased production of reactive oxygen species (ROS) in OA cartilage and cartilage (36). Oxidative stress is directly associated with OA progression and can exacerbate inflammation and activate immune cells. In OA, the levels of IL-1β, ions, TNF-α, and lipid peroxidation elevate in cartilage and serum, and superoxide dismutase (SOD), catalase (CAT), and prolidase decrease. The production of 4-hydroxynonenal also increases due to increased lipid peroxidation and after these changes, the expression of collagen II synthesis and its degradation occurs (37). Therefore, complementary therapy with natural antioxidants slows down the process of cartilage degeneration and prevents lipid peroxidation and further damage (36).

In vitro and *in vivo* studies provided evidence that plant antioxidants can be effectively used in the treatment of OA, so plant-derived antioxidants played an effective role in pain relief and knee function in OA (38,39). Through maintaining optimal redox balance in the cell, silymarin can reduce its antioxidant activity by activating a wide range of non-enzymatic antioxidants and antioxidant enzymes, mostly through the activation of Nrf2. Reducing inflammatory responses by inhibiting NF-κB pathways has protective effects on multiple cells (40).

Table 1. Characteristics of included studies of the effect of silymarin on OA symptoms

Lead author	Publication year	Study setting	Type of study	Study approach, duration and dosage	Main outcomes
Gupta (20)	2000	India	*In vivo* and *in vitro*	25 mg/kg of silymarin was administered for 30 days in induced OA rats.	Silymarin action via inhibition of 5-lipoxygenase for antiarthritic and antiinflammatory activities.
Numan (21)	2007	Iraq	RCT	300 mg/day of silymarin for 8 weeks in knee OA patients	Silymarin had anti-inflammatory and analgesic activities and when co-administered with miloxicam or piroxicam had a synergic effect.
Hussain (22)	2009	Iraq	RCT	300 mg/day of silymarin for 8 weeks in knee OA patients	Silymarin decreases the levels of IL1 alpha and IL-8, C3 and C4 at the end of follow-up.
Ashkavand (23)	2012	Iran	*In vivo* and *in vitro*	Rats received 25and 50 mg/kg, orally silymarin chemically induced OA in rats for 14 days	Reduced synovial and serum levels of IL-1β, malondialdehyde and nitric oxide and safranin O
Ashkavand (24)	2014	Iran	*In vivo* and *in vitro*	Rats received 25and 50 mg/kg, orally silymarin chemically induced OA rats for 14 days	Reduced the ROS, TNF-α, ALP, COX-2 in serum and synovial fluid and decreased reduction in KL grade and normal joint space narrowing
Mortada (25)	2014	Iraq	*In vivo* and *in vitro*	10 mg/kg silibinin zymosan-induced arthritis in rats for 6-48 hours	Reduced in TNF-α, IL-1β, IL-8, and infiltration of leukocytes in synovial fluid
Hussain (26)	2016	Iraq	RCT	120 mg silibinin twice daily in OA patients for 16-week	Reduced the elevated clinical scores, TNF-α, anti-CCP, hs-CRP, IL-8, IL-6, and ESR, and increase IL-10, aL-2 and Hb levels
Zheng (27)	2017	China	*In vivo* and *in vitro*	0, 1, 10, 50μM silibinin applied for 24 and 48 hours on human OA chondrocytes	Inhibited the IL-1β-induced production of NO, PGE2, TNF-α and IL-6, expression of COX-2, iNOS, MMP-1, MMP-3, MMP-13, ADAMTS-4 and ADAMTS-5, degradation of collagen-II and aggrecan in OA chondrocytes
Rezaee-Tazangi (28)	2020	Iran	*In vitro*	2 weeks after the injection of monoiodoacetate, 50 mg/ kg silymarin was applied to rats for 14 days	Matrix staining, SOD, CAT, GSH, and GPx elevated, ROS formation, MDA level, the total Mankin scoring, and knee bend score, were reduced
Saber (29)	2020	Egypt	*In vivo* and *in vitro*	100 mg/kg b.wt/day silymarin applied for 9 and 18 days in induced OA rats	Reduced paw circumference, TNF-α, IL-1β, IL-17, PGE2 and serum RF, and liver lipid peroxidation. They also improvement in serum IL-4 l levels and antioxidant capacity. In addition, decreased synovial hyperplasia and lymphoblastic necrosis, and mitotic figures in the spleen and thymus
Wu (30)	2021	Taiwan	*In vitro*	12.5, 25, 50 and 100 μM of silymarin applied to human primary chondrocytes for 24 hour	50 μM silymarin leads to cell death in IL-1β-stimulated cells, > 25 μM silymarin promotes cell senescence; Moreover, it promotes ECM homeostasis. As well, downregulated the catabolic genes of TNF-α, iONS, IL-1β, MMP-3, MMP-9 and MMP-13, and SOX9; upregulated the anabolic genes of collagen type II alpha 1 and TIMP-1; and restored the expression of chondrogenic phenotype genes SOX9 and SIRT1.

RCT; Randomized clinical trial, OA; Osteoarthritis, IL; Interleukin, ALP; Alkaline phosphatase, ROS; Reactive oxygen species, TNF; Tumour necrosis factor, KL; Kellgren-Lawrence, HB; Haemoglobin, hs-CRP; C-reactive protein, ESR; Erythrocyte sedimentation rate, CCP; Cyclic citrullinated peptide, NO; Nitric oxide, PGE2; Prostaglandin E2, COX-2; Cyclooxygenase-2, iNOS; Inducible nitric oxide synthase, MMP; Matrix metalloproteinase, ADAMTS; A disintegrin and metalloproteinase with thrombospondin motifs, ER; Estrogen receptor, FLS; Fibroblast-like synoviocytes, CIA; Collagen-induced arthritis, NF-κB; Nuclear factor kappa B, SIRT1; Sirtuin1, GPx; Glutathione peroxidase, GSH; Glutathione, SOD; Superoxide dismutase, CAT; Catalase, MDA; Malondialdehyde, , TIMP; Tissue inhibitor of metalloproteinase, ECM; Extracellular matrix, SOX9; SRY-Box Transcription Factor 9

Anti-catabolic/pro-anabolic effects and maintaining cartilage homeostasis

Cartilage homeostasis is maintained by a dynamic balance between cartilage anabolism/catabolism and in the progression of OA, catabolism predominantly affects this dynamic balance more and disrupts the dynamic balance. With these changes, a large amount of cartilage extracellular matrix (ECM) has degenerated (41). Disturbance in cartilage homeostasis can induce by elevated production of MMPs, and ADAMTs, collagen II, and aggrecan are the main reason for the pathogenesis of OA with a possible mechanism mediated partly by SOX-9 (38). Silymarin affects these pathways and reduces levels of MMP1, 3, 13, as well as ADAMTs 4, 5, and collagen II,

thereby reducing the process of cell destruction (28,33).

Anti-apoptotic/proliferous effects

Increased cartilage apoptosis and cartilage destruction occur with progressive thickening and stiffening of the subchondral bone plate, and this causes progressive and chronic OA (42). Excessive apoptosis in cartilage tissue and disruption of its cell proliferation (especially chondrocytes) is mainly associated with the cartilage matrix that is hypocellular and highly fibrillated (43). With the progression of OA, chondrocyte apoptosis also develops and the situation worsens. Although various processes, pathways, genes, and proteins, such as the impact of miRNA, PGE2, IL-1β-induced expression, caspase-3, and SIRT1/P53 plays an important role in regulating apoptosis and can have important effects in therapeutic interventions (38). Silymarin inserts an anti-apoptotic effect chondroprotective effect via activating SIRT1 (SIRT1 activity and thereby inhibited the p53 pathway) to suppress NF-kB activity, and finally inhibit NO production in chondrocytes. Moreover, silymarin plays an important role in regulating the apoptosis of chondrocytes through inhibiting inflammatory cytokines and the NF-κB pathway in rheumatoid arthritis, fibroblast-like synoviocytes, and CIA cells, and inhibiting Th17 cell differentiation (44,45). Therefore, the effect on apoptosis processes and balancing it can be a key point in the treatment of OA.

Taken together, the possible mechanisms of silymarin in reducing OA symptoms and chondroprotective effects are briefly illustrated in Figure 2.

Cytotoxicity

High-dose silymarin in a volume of more than 100 μM can disrupt the mitochondrial activity in unstimulated chondrocytes and finally impair cell viability (30). In addition, the major active constituents of silymarin including silydianin, silybin, and silychristin were not exhibited cytotoxic and genotoxic at 100 μM concentration. Silymarin is safe as adjunctive therapy in humans at commonly prescribed doses. This herbal phytochemical has been well tolerated by patients even with a dose of > 700 mg/3 times a day for 24 weeks. In some people, gastrointestinal disorders such as diarrhea and nausea occurred (46). In another study, silibinin at 1–50 μM concentration did not exhibit a cytotoxic effect on OA chondrocytes (27). In general, the studies included in this review indicate that silymarin does not have significant side effects (at least in normal therapeutic doses), and it can be used as a safe complementary treatment.

Pain is the main symptom and excruciating side effect of OA. The pain caused by the disease can be attributed to a set of complete joint involvement, especially synovial inflammation, cartilage, and joint disruption. In addition, some persistent pain in OA patients may be brought forth by altered sensitivity and pressure on peripheral nerves inside the knee (47). Based on this, one of the limitations observed in the review of the articles was the lack of examination of pain. This issue was due to the limited number of clinical trial studies. However, limited studies have shown that silymarin reduces pain in patients after intervention (21,26).

Other limitations of the included studies were the lack of evaluation of the long-term effects of silymarin on OA and the lack of examination of its different doses. In the current study, the search was not done in all the databases because our access to some databases was limited. This problem was solved by carefully checking and checking the references of the articles included in the study and other review articles.

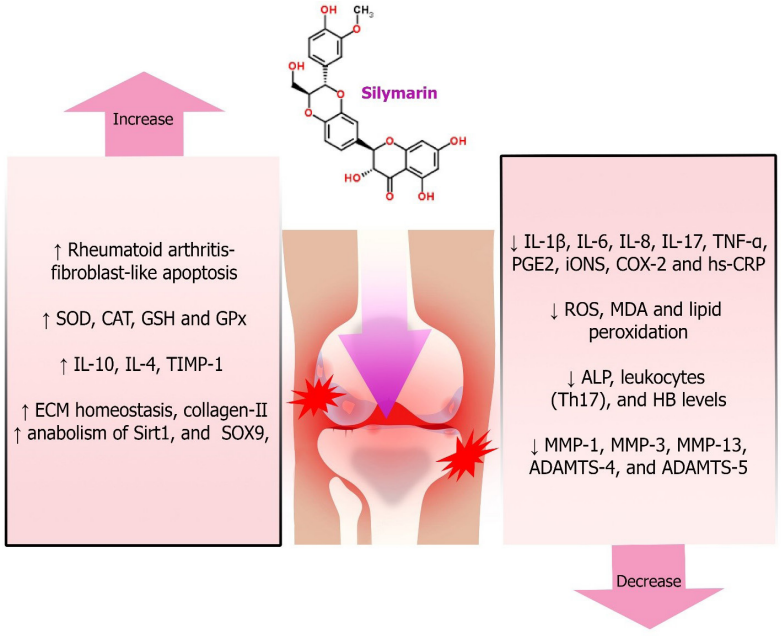

Figure 2. Possible mechanisms of silymarin in relieving OA

Conclusion

The results of the review of the articles included in this study revealed that silymarin has favorable anti-inflammatory and antioxidant activity. This herbal constitute can ameliorate the symptoms of the disease such as pain and movement limitations by affecting the inflammatory and antioxidant pathways or the expression of genes and stopping the process of joint destruction. Moreover, silymarin seems to cause a balance between cellular homeostasis and inhibits the process of matrix degradation and cell death, thereby promoting repair in the joint site. Therefore, silymarin can be used as a safe and cheap adjunctive therapy along with other chemical drugs for the treatment of OA. However, more clinical trial studies are needed to determine its effectiveness on patients' pain and determine its effective dose.

Authors' Contribution

Conceptualization: Shahin Asgari Savadjani, Mohammad Mousavi.
Data curation: Shahin Asgari Savadjani.
Investigation: Mohammad Mousavi.
Methodology: Shahin Asgari Savadjani.
Project administration: Shahin Asgari Savadjani.
Resources: Mohammad Mousavi.
Supervision: Shahin Asgari Savadjani.
Writing–original draft: Shahin Asgari Savadjani, Mohammad Mousavi.
Writing–review & editing: Shahin Asgari Savadjani, Mohammad Mousavi.

Competing Interests

We declare that we have no conflicts of interest.

Ethical Approval

Not applicable.

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