

BIOLOGICAL APPROACHES TO SILYMARIN AND ITS ASSOCIATION WITH METALLIC COMPOUNDS AND ZN(II)

ABORDAGENS BIOLÓGICAS DA SILIMARINA E SUA ASSOCIAÇÃO COM COMPOSTOS METÁLICOS E ZN (II)

ENFOQUES BIOLÓGICOS DE LA SILIMARINA Y SU ASOCIACIÓN CON COMPUESTOS METÁLICOS Y ZN(II)



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ABSTRACT

This study presents a qualitative literature review on silymarin, a complex of flavonolignans extracted from milk thistle, with emphasis on its biological studies and its association with metallic compounds, highlighting the zinc (II) ion. Silymarin exhibits antioxidant, anti-inflammatory, and hepatoprotective properties; however, its clinical application is limited by factors such as low aqueous solubility, rapid elimination, and reduced cellular permeability. Research involving silymarin in inorganic compounds is relatively recent, particularly studies associated with the zinc (II) ion. This association emerges as a promising strategy to improve bioavailability, chemical stability, and pharmacological activity of the compound. The literature review was conducted across different databases, covering publications from 2021 to 2025. Original articles, case reports, and experimental studies addressing mechanisms of association, chelation, bioavailability, biological activity, or therapeutic applications of silymarin, either alone or combined with metallic ions, were included. After screening titles and abstracts, 14 articles were selected for full analysis. The results indicate that the association of silymarin with metallic ions, especially zinc (II), may positively influence its biological and pharmacological properties, reinforcing its therapeutic potential.

Keywords: Silymarin. Metallic Compounds. Biological Potential.

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RESUMO

Este trabalho apresenta uma revisão bibliográfica qualitativa sobre a silimarina, um complexo de flavonolignanas extraído do cardo-mariano, com ênfase em seus estudos biológicos e em sua associação com compostos metálicos, destacando o íon zinco (II). A silimarina apresenta propriedades antioxidantes, anti-inflamatórias e hepatoprotetoras, entretanto, sua aplicação clínica é limitada por fatores como baixa solubilidade em meio aquoso, rápida eliminação e reduzida permeação celular. As pesquisas envolvendo a silimarina em compostos inorgânicos são relativamente recentes, destacando-se aquelas associadas ao íon zinco (II). Essa associação surge como uma estratégia promissora para melhorar a biodisponibilidade, a estabilidade química e a atividade farmacológica do composto. O levantamento bibliográfico foi realizado em diferentes bases de dados, abrangendo publicações no período de 2021 a 2025. Foram incluídos artigos originais, relatos de caso e estudos experimentais que abordassem mecanismos de associação, quelação, biodisponibilidade, atividade biológica ou aplicações terapêuticas da silimarina, tanto isolada quanto associada a íons metálicos. Após a triagem dos títulos e resumos, 14 artigos foram selecionados para análise completa. Os resultados indicam que a associação da silimarina com íons metálicos, especialmente o zinco (II), pode influenciar positivamente suas propriedades biológicas e farmacológicas, reforçando seu potencial terapêutico.

Palavras-chave: Silimarina. Compostos Metálicos. Potencial Biológico.

RESUMEN

Este trabajo presenta una revisión bibliográfica cualitativa sobre la silimarina, un complejo de flavonolignanos extraído del cardo mariano, con énfasis en sus estudios biológicos y en su asociación con compuestos metálicos, destacando el ion zinc (II). La silimarina presenta propiedades antioxidantes, antiinflamatorias y hepatoprotectoras; sin embargo, su aplicación clínica está limitada por factores como baja solubilidad en medio acuoso, rápida eliminación y reducida permeabilidad celular. Las investigaciones que involucran la silimarina en compuestos inorgánicos son relativamente recientes, destacándose aquellas asociadas al ion zinc (II). Esta asociación surge como una estrategia prometedoras para mejorar la biodisponibilidad, la estabilidad química y la actividad farmacológica del compuesto. La revisión bibliográfica se realizó en diferentes bases de datos, abarcando publicaciones del período 2021 a 2025. Se incluyeron artículos originales, reportes de caso y estudios experimentales que abordaran mecanismos de asociación, quelación, biodisponibilidad, actividad biológica o aplicaciones terapéuticas de la silimarina, tanto aislada como asociada a iones metálicos. Tras la revisión de títulos y resúmenes, se seleccionaron 14 artículos para análisis completo. Los resultados indican que la asociación de la silimarina con iones metálicos, especialmente el zinc (II), puede influir positivamente en sus propiedades biológicas y farmacológicas, reforzando su potencial terapéutico.

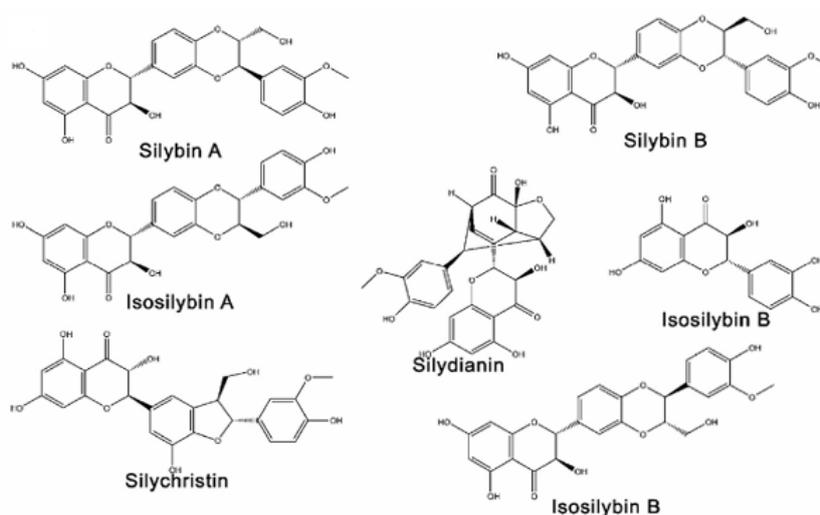
Palabras clave: Silimarina. Compuestos Metálicos. Potencial Biológico.

1 INTRODUCTION

Silymarin is a compound consisting of seven flavolignans (silybin A, silybin B, isosilybin A, isosilybin B, silychristin, isosilychristine and silidianine), Figure 01, extracted from *Silybum marianum* (milk thistle), has stood out as one of the main agents studied in hepatoprotective and neuroprotective therapies, due to its antioxidant and anti-inflammatory properties (Sayyad et al., 2025). In addition, it is widely used in traditional medicine in several European countries, which reinforces its historical and therapeutic value.

Figure 1

Structure and nomenclature of the main compounds found in silymarin



Source: Sayyad et al., 2025.

In recent years, it has aroused growing scientific interest due to its protective effect on several organs, such as the stomach, lungs, kidneys, pancreas, colon, skin, prostate, bladder, and central nervous system (CNS), and these effects reflect its broad therapeutic potential, encompassing anticancer, hepatoprotective, cardioprotective, hypocholesterolemic, neuroprotective activities, among others (Almutary et al., 2025; Macit et al., 2023).

Despite these advantages, the therapeutic application of silymarin is limited by factors such as low solubility in aqueous media, rapid elimination, and reduced permeation by intestinal cells, which compromises its bioavailability and clinical efficacy (Aboshanab et al., 2020). In view of these limitations, alternative strategies have been explored to improve their pharmacokinetic properties, especially the development of nanostructured systems and the association with metal ions.

Among the metal ions of biological interest, zinc(II) (Zn^{2+}) stands out for its broad participation in physiological processes, acting as a structural and functional element of

numerous enzymes, regulatory proteins, and transcription factors (Thompson et al., 2022). A key characteristic of Zn^{2+} is its tendency to form highly soluble positively charged ions in biological fluids, which favors its interaction with natural ligands and its bioavailability in living systems (Oliveira et al., 2022).

In this context, the association of silymarin with zinc(II) (Zn^{2+}) emerges as a promising strategy to overcome its pharmacokinetic limitations. The formation of silymarin- Zn^{2+} complexes/associates can result in greater chemical stability, increased solubility, better biological permeation, and potentiation of the compound's pharmacological activity (Halevas et al., 2021). In general, the interaction between natural ligands and metal ions can confer greater stability, solubility, lipophilicity, and biological activity, in addition to enabling new mechanisms of pharmacological action (Silva et al., 2021).

Metal ions play a key role in biological systems, being widely recognized for their participation in processes such as enzymatic catalysis, signal transduction, electron transfer, and synaptic transmission (Walencik et al., 2024). In addition to acting as biological cofactors, these ions are considered strategic components in the construction of advanced supramolecular systems, both of natural and synthetic origin.

This is due to the fact that the properties of metal compounds can be rationally modulated through the choice of ligands/molecules, the functionalization of the associated groups, and the oxidation state of the metal, factors that directly influence the dosage, bioavailability, and therapeutic efficacy of the compounds (Unavane et al., 2025). In this way, the metallic association is consolidated as an effective strategy to improve the pharmacokinetic performance of natural compounds with inherent limitations, such as silymarin.

In this sense, this work aims to carry out a literature review on silymarin, with emphasis on its interactions with metallic compounds, especially zinc(II), highlighting the role of these complexes in the modulation of its biological and pharmacological properties.

2 DEVELOPMENT

This is a literature review, with a qualitative approach, aimed at gathering, analyzing and synthesizing recent scientific evidence about silymarin, as well as its interactions with the zinc(II) ion and its association with metallic compounds.

The bibliographic survey was carried out in the following electronic databases: World Wide Science, Scientific Electronic Library Online (SciELO), Integrated Library System (SiBi), ScienceDirect, Google Scholar and PubMed. These databases were selected for their

comprehensiveness and relevance in the indexing of national and international scientific journals in the areas of health sciences, pharmacology, chemistry and biotechnology.

The following terms were used as descriptors in Portuguese and English: "silymarin", "silymarin and metallic compounds", "silymarin and zinc", as well as their English counterparts ("silymarin", "silymarin and metallic compounds" and "silymarin and zinc"). The descriptors were combined using Boolean operators ("AND" and "OR"), in order to increase the sensitivity of the search and ensure the retrieval of relevant studies.

As inclusion criteria, original articles, case reports, and experimental studies published between 2021 and 2025, available in full, that addressed silymarin alone or in association with metals, with an emphasis on association mechanisms, chelation, bioavailability, biological activity, or therapeutic applications, were considered.

Duplicate studies, publications outside the delimited period, studies that did not address the area of human health, reviews, and articles without access to the full text were excluded.

After the search stage, the selected studies were submitted to the reading of the titles and abstracts for initial screening. Then, 14 articles were chosen and read in full, and information was extracted as shown in Table 01. Data analysis was performed in a descriptive and interpretative manner, allowing the organization of the findings into thematic axes, according to the descriptors, subdividing them into three: Silymarin, Silymarin and Metallic Compounds and Silymarin with Zinc (II).

Table 1

Articles analyzed in the integrative review on the subject

Silymarin (Silymarin)						
Title	Authors	Year	Objective	Magazine/periodical	Database	DOI
Antioxidant actions of thymoquinone, silymarin and curcumin in an experimental model of aortic ischemia-reperfusion in albino Wistar rats.	Mustafa Yardımcı, Mustafa Göz, Mehmet Salih Aydın, Nazım Kankılıç and Ebru Temiz.	2023	To determine the antioxidant effects of thymoquinone, silymarin and curcumin against ischemia-reperfusion injury associated	Brazilian Journal of Cardiovascular Surgery	Scielo	10.21470/1678-9741-2021-0462

			with the abdominal aorta.			
Effects of Silymarin Plus Glutathione on the Prevention of Hepatic Ischemia-Reperfusion Injury.	Dilara Aliyeva, Ramazan Amanvermez, Kağan Karabulut and Seda Gün.	2022	To examine the therapeutic effects of silymarin (SM) plus glutathione (GSH) on IR liver injury using a rat model of hepatic IR.	Brazilian Journal of Pharmaceutical Sciences	Scielo	10.1590/s2175-97902022e20561
Increasing the bioavailability of silymarin using natural bioenhancers: an in vivo pharmacokinetic study.	Shamama Javed, Kanchan Kohli and Waquar Ahsan.	2022	Explore the use of three natural bioenhancers, namely lysergol, piperine and fulvic acid, which are used in a variety of fixed-dose combinations with silymarin for the preparation of oral formulations.	Brazilian Journal of Pharmaceutical Sciences	Scielo	10.1590/s2175-97902022e20160
Efficacy of Silymarin in the Treatment of COPD via P47phox Signaling Pathway.	Lin XU, Qingying Song, Zhanghong Ouyang, Mengning Zheng, Xiangyan Zhang and Cheng Zhang.	2022	To confirm the important role and prospect of application of silymarin in the treatment of COPD in clinical practice.	Food Science and Technology	Scielo	10.1590/fst.52821
Investigating the anticancer and antimetastatic effect of silymarin	Srithika Srinivasan, Aruchamy Mohanprasanth, Ahmed	2024	To investigate the impact of silymarin on A549	Toxicology Reports	Science Direct	10.1016/j.toxrep.2024.101746

against lung cancer.	Nadeem and Muthupandian Saravanan		lung cancer cell proliferation, particularly by examining its impact on MMP-2 and MMP-9 expression and activity.			
Evaluation of the efficacy of oral nano-silymarin formulation in hospitalized COVID-19 patients.	Hossein Aryan, Ramin Hamidi Farahani, Mohsen Chamanara, Sepideh Elyasi, Mahmoud Reza Jaafari, Mahboubeh Haddad, Ashraf Tavanaee Sani, Mohamed Afshar Ardalan and Reza Mosaed	2022	To investigate the efficacy of oral nano-silymarin in hospitalized COVID-19 patients.	Phytotherapy Research	Pubmed	10.1002/PTR.7537
Silymarin supplementation in active rheumatoid arthritis.	Georgeta Stefanovici Zugravu, Carmen Pintilescu, Carmen-Marinela Cumpat, Sorin Dan Miron and Anca Miron	2024	To evaluate the impact of silymarin on rheumatoid arthritis.	Medicine	Pubmed	10.3390/medicine60060999
Silymarin and metallic compounds.						
Title	Author(s)	Year	Objective	Magazine/periodical	Database	DOI
Therapeutic potential of silymarin as a natural iron	Nahid Reisi, Nafiseh Esmaeil, Marjan	2022	To demonstrate the iron-chelating	Clinical Case Reports	World Wide Science	10.1002/ccr3.5293

chelating agent in β -thalassemia intermedia.	Gharagozlo and Behjat Moayedi		effects of silymarin monotherapy on β -thalassemia, suggesting that silymarin can be used safely and effectively in the treatment of iron overload conditions.			
Synthesis, characterization, and toxicity evaluations of silymarin-laden Ni-Fe metal-organic structures: Evidence from <i>in vitro</i> and <i>in vivo</i> evaluations.	Fatemeh Rahimi, Sheida Shahraki, Mohammad Reza Hajinezhad, Sonia Fathi-Karkan, Shekoufeh Mirinejad, Saman Sargazi, Mahmood Barani and Ramin Saravani	2024	To seek to synthesize, describe and analyze <i>in vivo</i> and <i>in vitro</i> the biological consequences of Silymarin-loaded Ni-Fe MOFs.	Journal of Drug Delivery Science and Technology	Google Scholar	10.1016/j.jddst.2024.105372
Silymarin-encapsulated liposomal formulation: an effective treatment modality against liver dysfunction associated with copper toxicity and neurobehavioral abnormalities in Wistar rats.	Tuba Maryam, Nosheen Fatima Rana, Sultan M. Alshahrani, Tahreem Tanweer, Salma Saleh Alrdahe, Yasmene F. Alanazi, Farhat Batool, Misha Fatima, Ifat Alsharif, AmerSohail	2023	To assess the beneficial properties of silymarin against copper toxicity, the phenotypic pathological condition of WD, and whether it can be used as supportive therapy for these patients.	Molecules	Google Scholar	10.3390/molecules28031514

	Kashif and Farid Menaa					
Silymarin with Zinc(II)						
Title	Author(s)	Year	Objective	Magazine/periodical	Database	DOI
Enhanced burn healing by multifunctional alginate-chitosan hydrogel involving silymarin and zinc oxide nanoparticles.	Moein Valadi Maryam Doostan, Kamyar Khoshnevisan, Mahtab Doostan and Hassan Maleki	2024	Manufacture a biocompatible hydrogel composed of alginate and chitosan loaded with silymarin NPs and green ZnO.	Burns	Science Direct	10.1016/j.burns.2024.07.021
Silymarin Dehydroflavonolignans Chelate Zinc and Partially Inhibits Alcohol Dehydrogenase.	Václav Tvrđý, Marcel Hrubša Katerina Valentová, Eduard Jirkovský, David Biedermann, Vladimír Kren and Premysl Mladenka	2021	To test whether (a) silymarin flavonolignans can chelate zinc ions and (b) whether such chelating capacity can be biologically relevant.	Nutrients	Google Scholar	10.3390/nu13124238
The protective effect of different combination doses of zinc sulfate and silymarin against toxicity induced by antituberculosis drugs.	Wardah Siddique, Nazia Rashid, Muhammad Asif Faheem, Iram Kamal, Fouzia Kanwal and Gulpash Saghir	2025	To induce hepatotoxicity with Rifampicin and INH in albino rats, to estimate the histoprotective effect of the combination of ZnSO ₄ and Silymarin.	Journal of Islamabad Medical & Dental College	Google Scholar	10.35787/jimdc.v14i1.1296
Beneficial effects of silymarin in combination with zinc against radiation.	Roghayeh Javan, Ayoob Rostamzadeh, Mohammad	2021	To evaluate the radioprotective effects of silymarin (SIL) and zinc, alone	International Journal Morphology	Google Scholar	10.4067/S0717-95022025000301070

	-Shafi Mojadadi, Kosar Hosseinpur, Davood Nasiry and Amir Raoofi		and in combination, against radiation-induced testicular toxicity (IR) in mice.			
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Source: Prepared by the authors.

The analyzed studies convergently demonstrate that silymarin exerts relevant antioxidant and anti-inflammatory effects, which manifest themselves in a manner dependent on the pathophysiological context and the experimental model adopted, as well as interactions with metal ions, such as zinc(II) that can modulate its biological properties, either through direct complexation, interference in zinc-dependent enzymatic systems or functional synergy in delivery systems and formulations advanced.

In experimental ischemia-reperfusion models, silymarin significantly reduced systemic oxidative stress, as well as modulating inflammatory pathways associated with tissue injury, with superior or comparable performance to other antioxidant phytochemicals, such as thymoquinone and curcumin (Yardimci et al., 2023). In association with glutathione, a synergistic effect on liver protection was observed, with a reduction in inflammatory cytokines, lipid peroxidation, and histopathological damage, reinforcing the role of silymarin as a cytoprotective agent in conditions of acute oxidative stress (Aliyeva et al., 2022). In the randomized controlled trial conducted by Aryan et al. (2022), the administration of nano-silymarin in hospitalized patients with COVID-19 did not result in a significant improvement in overall clinical outcomes, only in ALT levels, which reinforces its hepatoprotective effect.

On the other hand, in oncological models, silymarin showed a selective cytotoxic effect, through the inhibition of the metalloproteinases MMP-2 and MMP-9, zinc-dependent enzymes, promoting apoptosis, cell cycle blockade, and inhibition of tumor migration and metastasis, which evidences its ability to act antagonistically according to cell status (Srinivasan et al., 2024). This mechanistic versatility is clinically supported by the randomized trial conducted in patients with active rheumatoid arthritis, in which silymarin supplementation as an adjuvant therapy resulted in a significant reduction in disease activity and functional and psychosocial improvement, even in the absence of significant changes in classic inflammatory markers, suggesting that clinical benefits may precede detectable biochemical changes (Zugravu et al., 2024).

Additionally, pharmacokinetic studies point to the low oral bioavailability of silymarin as a cross-sectional limitation, although the effects observed in humans indicate that

prolonged exposures or pharmaceutical optimization strategies may be sufficient to promote relevant therapeutic benefits, such as nanoformulations or complexation/association with other metals, especially zinc (II) (Javed et al., 2022). In the study by Reisi et al. (2022), patients treated with silymarin significantly reduced serum ferritin levels after six months of supplementation of patients with β -thalassemia intermedia.

In addition, studies evaluating silymarin combined with zinc(II) show a mechanism where derivatives of silymarin, specifically dehydroflavonoligans, have the ability to chelate Zn^{2+} ions, forming stable complexes under physiological conditions, with significant affinity for zinc(II), resulting in partial inhibition of the enzyme alcohol dehydrogenase (Tvrđý et al., 2021). In consonance, in the study by Siddiqui et al., (2025), in a model of hepatotoxicity by isoniazid and rifampicin, robust results show better results from the association of silymarin-zinc, with a more pronounced reduction in ALT, AST, FA and bilirubins, better histological preservation of the liver, compared to administration alone. Reinforcing this metallic interaction, in the study with liposomal encapsulation of silymarin (SLNPs) associated with zinc in copper toxicity (Maryam et al., 2023), demonstrating that zinc (II) acts synergistically, enhancing the antioxidant and cellular stabilizing action of silymarin, evidenced by greater efficacy in reducing liver enzymes (ALT and AST), histopathological improvement of the liver, and attenuation of neurobehavioral changes.

In the studies by Javan et al. (2025) demonstrated that silymarin and zinc ion, especially in combined administration, can improve sperm parameters and radiation-related infertility problems. The improvement of sperm parameters and testicular cell structure in zinc ion receptor groups can be attributed to the protective properties and increased levels of antioxidants in the cells, the authors report that zinc ion protects normal cells through mechanisms, increased sperm DNA integrity, decreased ROS content, and also improves reproductive function during the prepubertal period with cisplatin administration.

3 CONCLUSION

The present literature review shows that silymarin has a complex and multifactorial pharmacological profile, whose biological activity cannot be attributed exclusively to its classical antioxidant properties. The analyzed data consistently demonstrate that silymarin interacts functionally with metal ions, highlighting the zinc (II) ion as the central element, configuring itself as a phytocomplex with the ability to form metal complexes and associates, which play a relevant role in the modulation of its biological and pharmacological properties.

In addition, the association of silymarin with zinc(II) demonstrated a synergistic effect, resulting in greater therapeutic efficacy when compared to the isolated use of each agent, especially in models of liver toxicity and inflammatory processes.

Finally, silymarin is a pleiotropic, safe and promising phytochemical with antioxidant, anti-inflammatory and cellular stress modulating actions, whose efficacy depends on the pathological context, route of administration and duration of exposure, presenting high translational potential.

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