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Possible Uses for Silymarin in Human Health: Systematic Review

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Abstract

Silymarin, from the fruit of *Silybum marianum*, is known for its hepatoprotective action. The aim of this study was to review the mechanisms of action of the silymarin phytocomplex to expand the possibilities for its application in human health. The search for published articles was carried out on the CAPES Journals Portal platform, which covers worldwide scientific databases. Publications from 2010 to 2022 were included. Of the 311 articles retrieved, 21 were included. The articles discuss the diversity of silymarin's applications and the possibility of optimizing its bioavailability using drug delivery systems. Silymarin shows promise in numerous diseases, such as liver, kidney, cardiovascular, respiratory and others. Its antiviral action has been demonstrated in studies and silymarin has the potential to be used as a complementary therapy in the treatment of many diseases, with the expectation that, in the future, it will be used in therapeutic protocols for exclusive use.

Keywords

Silymarin, Flavonoids, Phytotherapeutic Drugs

1. Introduction

The phytocomplex extracted from the fruit of *Silybum marianum* is known as silymarin, which is composed of flavonoids and their isomers, including silybin, silydianin and silicristin, and is recognized for its hepatoprotective action. Records of its medicinal use date back to the 4th century BC, initially related to the administration of extracts from parts of the plant and giving rise to its common name: thistle milk [1] [2].

Parts of the plant can be used to treat diseases related to the digestive system and liver and biliary disorders [3]. The hepatoprotection attributed to silymarin is due to the antioxidant action of silybin, which helps prevent damage to liver

cells by toxins, alcohol and harmful substances [3]; nephroprotective action by reducing insulin resistance and maintaining the glomerular filtration rate [4]; anti-aging and anti-inflammatory effect on the skin [5]; silymarin reduces serum cholesterol levels [6]; it can also reduce the inflammatory process in the airways and contribute to asthma control [4].

Silymarin has been shown to provide protection against hepatic necrosis caused by carbon tetrachloride, as well as against toxic liver damage caused by poisonous mushroom toxins [4]. However, its curative effect is generally weaker than its preventive effect. Furthermore, silymarin stimulates the functions of hepatocytes, including cell proliferation, protein synthesis, oxygen assimilation, energy formation, and repair of damaged cell membranes. This gives liver tissue greater resilience against degenerative and toxic actions [4] [6] [7] and has effect on cirrhosis and hepatocellular carcinoma [8].

Silymarin has been found to have neuroprotective effects through modulation of several antioxidant mechanisms and kinases in cell signaling pathways [9]. It also inhibits the inflammatory response generated during neurodegeneration, has neurotropic effects, regulates neurotransmitters, and inhibits apoptosis. These properties, along with the compound's low cost, availability, and safety profile, provide additional advantages for using silymarin as a potential drug with important clinical benefits. However, the challenge of low bioavailability must be addressed, and robust clinical trials are needed to validate the neuroprotective efficacy of this natural compound. Some authors [10] evaluated the co-administration of silymarin on the changes induced by aspartame in the behaviour and brain of mice, demonstrating a significant attenuation of the effects on the central nervous system. Other effects are protection against cardiotoxicity induced by creatine phosphate and oxidative stress in rats [11]; antitumor and chemo preventive actions [2].

In general, the dry extract is used orally in tablets and capsules, but the bioavailability could be improved with drug delivery systems [12], especially considering its potential to combat other diseases. Thus, it is important to review the molecular mechanisms of silymarin action and interaction with the different types of receptors and cell signals.

The aim of this study was to review the mechanisms of action of the silymarin phytocomplex to expand the possibilities of application in human health.

2. Method

The guiding question for the systematic review was: *Can the use of silymarin as an active ingredient, considering its mechanisms of action and the innovative technologies used for its delivery, be proposed as a potential method for mitigating or controlling systemic autoimmune responses or generalized inflammatory processes?*

The search for relevant articles was conducted on the CAPES Periodicals Portal search engine, to cover the main health databases such as PubMed, LILACS,

and Scielo. Some articles cited in those initially selected were later included to enrich the discussion. The search was carried out using the descriptors indexed in DeCS/MeSH: silymarin; silibum marianum; hepatoprotective; lipoperoxidation; nanotechnology; transdermal absorption; anti-aging effects; antioxidant; pharmaceutical technology.

To select relevant articles, we used the following inclusion criteria: publications from 2010 to 2022, written in any language, and related to the research topic. The extraction, selection, and analysis of the articles were conducted by a main researcher (ABCE), with support from two additional researchers (GMSG and PPB) who also contributed to the discussion.

3. Results

The search retrieved 311 articles and 21 were included for our review (Figure 1). The results were summarized in two tables: pharmacological aspects of silymarin (Table 1) and nanotechnology, chemical studies, and clinical studies (Table 2).

4. Discussion

The beneficial properties of silymarin can be attributed to its unique combination of components, which includes a flavonoid called taxifolin and seven

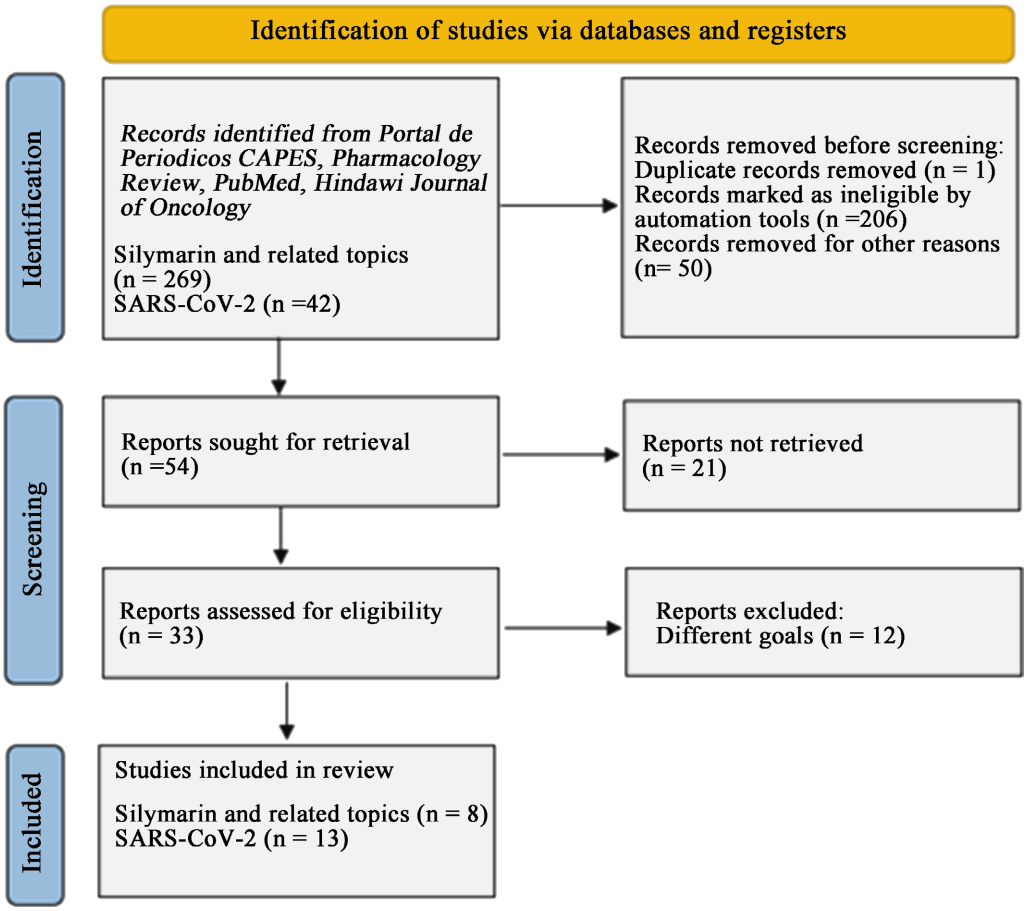

Figure 1. Flowchart of the article selection process.

Table 1. Artic les that discuss the pharmacological aspects of silymarin.

Authors	Theme of the study and the main findings of the authors
Gillessen A, Schmidt HHJ, 2020 [25]	Meta-analysis and review of pharmacological properties. Enumeration of the hepatoprotective properties of silymarin, presenting clinical case studies and clinical follow-up of patients.
Surai PF, 2015 [7]	Illustrate the mechanisms of action and pharmacological properties.
Abenavoli L, *et al.*, 2010 [13]	Historical approach to therapeutic use, with a presentation of the different pharmacological properties of silymarin.
Majnooni MB, *et al.*, 2020 [66]	Silymarin phytochemicals, with different molecular targets and signalling mechanisms, including the reduction of pro-inflammatory and oxidative mediators such as TNF-α, IL-1, IL-6, IL-8, IL-1β, NF-κB, MMPs, iNOS, MAPK, COX-2 and ROS minimize lung damage.
Tvrdý V, *et al.*, 2021 [14]	Pharmacokinetics and interactions of silymarin flavonolignans. The low oral systemic bioavailability of flavonolignans is due to rapid conjugation in intestinal cells or hepatocytes and due to the flux of parental flavonolignans or formed conjugates back into the lumen of the gastrointestinal tract and rapid hepatic excretion.
Di Costanzo A, Angelico R, 2019 [18]	Although clinical trials have proven that silymarin is safe in high doses in humans, there are limiting factors: its low water solubility, low bioavailability and intestinal malabsorption. Thus, nanotechnological strategies can increase bioavailability and provide prolonged release, which seems to be promising to enhance its therapeutic action.
Vargas-Mendoza N, *et al.*, 2020 [3]	Several properties have been attributed to flavolignans (silybin, isosylibin, silicristin, isosylcristine and silidianin): antioxidant and protective activities, probably related to the activation of nuclear factor 2 related to erythroid factor 2 (NFE2) (Nrf2), known as a master regulator of the cytoprotective response. Disruption of Nrf2 signaling has been associated with different pathological conditions. Some silymarin Phyto complexes have been shown to participate in this signaling pathway and suggested as activators that interrupt interactions in the Keap1-Nrf2 system, but also as antioxidants or with additional actions related to Nrf2 regulation.
Karimi G, *et al.*, 2011 [67]	Silymarin has dose-dependent antioxidant, anti-inflammatory, anti-apoptotic action and modifies cell transporters. Therefore, it is promising in complementary medicine.
Khayam MU, *et al.*, 2017 [68]	Discussion on how to develop nanoparticles that allow and facilitate the absorption of oral silymarin solutions; Demonstration that the preparation of silymarin through the APSP and EPN process allows the generation of much more soluble particles than unprocessed silymarin.

Table 2. Articles that discuss the bioactivity of silymarin, nanotechnology, chemical studies, clinical studies and those specific to SARS-COV-2.

Authors	Theme of the study and the main findings of the authors
Sikander M, *et al.*, 2020 [41]	Bibliographic review in the context of the SARS-COV-2 pandemic, with analysis of antivirals, immunomodulators and hepatoprotective nutraceuticals. Identification of damage to hepatocytes caused by the SARS-COV-19 viral infection and by the drugs used for this disease.
Palit P, *et al.*, 2021 [45]	Proposition of new drug targets, Furin and Transmembrane protease serine 2, based on their pathophysiological implication on SARS-COV-2 infection. It is reported that the Spike glycoprotein of CoV-2 harbors a Furin cleavage site which is activated by the host cell enzyme to make the virus more susceptible to its primary receptor, angiotensin-converting enzyme-2. Use of nano-suspension based intra-nasal or oral nebulizer spray, containing a complex of phytocomponents, to treat mild to moderate SARS-COV-2 infection.

Continued

Wang W, *et al*., 2021 [47]	Comparison of Traditional Chinese Medicine and Western Allopathic Medicine. The evaluation of therapeutic approaches in China, during the pandemic, demonstrated the use of antiviral drugs, human immunoglobulins, corticosteroids, and intestinal microbiological regulators aimed at virus infection or immunomodulation.
Wang W, *et al*., 2020 [46]	Comparative study in patients with severe COVID-19 in Wuhan, analyzing 43 male patients aged 57-70 years and the use of traditional Chinese medicine (TCM). TMC granules, combined with usual care, showed no improvement beyond usual care alone. However, the use of TMC granules reduced the 28-day mortality rate and the time to fever alleviation. Nevertheless, CHM granules may be associated with high risk of fibrinolysis.
Palit P, *et al*., 2021 [32]	Evaluation of selected antiviral phytopharmaceuticals capable of binding to specific targets for the management of COVID-19. Inhibition against Chikungunya, Mayaro, and influenza A viruses. The binding affinity of silymarin with an impressive virtual score exhibits significant potential to interfere with SARS-COV-2 replication.
Liu *et al*., 2019 [24]	Development of highly bioavailable silybinin nanoparticles and evaluation of efficiency against HCV infection. Treatment efficiently restricted HCV cell-to-cell transmission, suggesting that they retained silybinin's robust anti-HCV activity. Oral administration of SB-NP in rodents produced no apparent *in vivo* toxicity, in addition its efficiently reduced HCV infection of primary human hepatocytes.
Anand AV, *et al*., 2021 [26]	Verification of the action of herbal compounds, with confirmation of antiviral effects through inhibition of viral replication, lipid metabolism, apoptosis, protein, and cytokine expression; lignins may have potent anti-SARS-COV-2 actions, as they have also shown effects against SARS-COV-2.
Sardanelli AM, *et al*., 2021 [69]	Search for molecules whose biochemical and toxicological profile was known that could be the starting point for the development of antiviral therapies. The results-obtained in silico and *in vitro*-prove that silybin and silymarin are useful as a therapeutic strategy against COVID-19.
Fakhri S, *et al*. 2020 [60]	Survey of several mechanisms of action related to herbal compounds, including silymarin and rutin. Presentation of mechanisms of infection and diffusion of SARS CoV-2.
Majnooni MB, *et al* 2020 [66]	Comprehensive review of SARS-COV-2 mechanisms of action and presentation of herbal medicines with antiviral and anti-inflammatory potential for the airways. Phytochemical compounds showed prominent and significant anti-inflammatory effects in reducing lung damage caused by SARS-COV-2 severe acute respiratory syndrome.
Kumar S, *et al* 2021 [71]	Demonstrate the binding of phytochemicals such as sarsasapogenin, ursonic acid, curcumin, ajmalicin, novobiocin, silymarin and aranotin, piperine, gingerol, rosmarinic acid and alpha terpinyl acetate to the viral protein Nsp15, relevant to the inhibition of SARS-COV-2 replication. Demonstration of the high binding energy of silymarin and rutin and hydrogen bonds. Analysis and design of drugs based on the results and interaction with the Nsp15 protein.
Palit, Mukhopadhyay, Chattopadhyay, 2021. [32]	Discussion of the potential of Silymarin for the management of COVID-19. Silymarin inhibits expression of the host cell surface receptor TMPRSS2. Silymarin's binding affinity with an impressive virtual score exhibits significant potential to interfere with SARS-COV-2 replication.
Speciale A, *et al*., 2021 [70]	Exploring silybinin's in situ ability to interact with key SARS-COV-2 target proteins and *in vitro* effects against cytokine-induced inflammation and dysfunction in human umbilical vein endothelial cells (HUVECs). Silybinin forms a stable complex with the SARS-COV-2 RBD spike protein, has good negative binding affinity with Mpro, and interacts with many residues in the active site of Mpro, thus supporting its potentiality in inhibiting viral entry and replication. Pre-treatment of HUVECs with silybinin reduced TNF-α-induced gene expression of the pro-inflammatory genes IL-6 and MCP-1, as well as of PAI-1, a critical factor in coagulopathy and thrombosis, and of ET-1, a peptide involved in hemostatic vasoconstriction.

flavolignans: silycristin A, silycristin B, silidianin, silybin B, silybin A, isosilybin A, and isosilybin B. Among these, silybin [also known as silybinin] is the most prevalent flavolignan, constituting around 50-70% of the total extracted [3] [15].

Studies conducted *in vitro* and *in vivo* have highlighted comprehensive analysis of the metabolism of silymarin and its flavonolignans. These studies have shown that phase II reactions play a much more dominant role in the metabolism of flavonolignans than phase I reactions, which only have a marginal effect. Phase II metabolism begins in intestinal cells and continues in the liver, with conjugated silymarin metabolites being excreted directly from the intestinal cells into the bile. These conjugates can be cleaved by bacteria in the intestine and reabsorbed, as evidenced by secondary peaks or plateaus observed in some *in vivo* studies [14].

Although there is evidence of metabolic efflux of silymarin in the gut, the extent of conjugation in the gut and the mechanism of efflux of flavonolignans from silymarin are still not fully understood. However, it has been observed that the concentration of silymarin components in the Vein-Portal System is relatively high, and the concentration of total silybin in bile is greater than in the systemic circulation [13] [14] [15] [16] [17].

With regard to pharmacokinetic properties, data compilation and improvement strategies for these properties are presented by Di Costanzo and Angelico [18], that discuss the encapsulation of silymarin, highlighting: 1) nanocrystals, nanosuspensions and solid dispersions: colloidal dispersions of submicron particles of pure drugs, which are stabilized by surfactants or steric polymeric stabilizers [19], to improve bioavailability if administered orally and its dissolution rates, in addition to prolonging the half-life of moderately soluble drugs, such as silymarin; 2) complexes with cyclodextrins and phospholipids: the inclusion complex prepared by the co-precipitation method led to the best results in terms of sustained drug release performance. Kellici *et al.* [20], investigated a lyophilized silymarin-2hydroxypropyl-β-cyclodextrin complex, performing detailed physicochemical analyses on silymarin-cyclodextrin interactions at the molecular level, and verifying the respective bioavailability in MCF-7 cancer cells. Gharbia *et al.* [21] studied the inclusion complexes of silymarin with hydropropylchlorixidine and methyl-b-cyclodextrin, developed in order to improve the antifibrotic activity of silymarin at low therapeutic doses, increasing its solubilization potential and to prevent its metabolic degradation within the gastrointestinal tract after administration oral; 3) lipid-based formulations: designed to effectively encapsulate the silymarin complex in biocompatible and biodegradable polymeric nano systems, such as polymeric micelles, compounds and solid nano dispersions, thus promoting the polymeric erosion of this protection, releasing the phytopharmaceutical in the form of very fine particles to Rapid dissolution and improve oral bioavailability [18] [22]; 4) inorganic nanomaterial compounds: very efficient vectors due to their versatile nanostructure, functional properties and controlled drug release behaviors, which may show excellent biocompa-

tibility, biodegradation, *in vivo* stability, low cytotoxicity and non-immunogenic profiles [23] [24].

Silymarin is consecrated as an herbal medicine for the treatment of liver diseases. Its protective actions are attributed to the antioxidant properties, Gillessen and Schmidt [25] consolidate and reinforce all the principles widely presented many years ago, compiling clinical studies.

Surai [7] propose some antioxidant mechanisms for silymarin: a] direct elimination of free radicals and chelators; b] prevent the formation of free radicals by inhibiting enzymes that produce molecules with free reactive oxygen and molecules with reactive nitrogen, or improve the integrity of mitochondria under stress conditions; c] maintain an ideal redox balance in the cell, activating enzymatic and non-enzymatic antioxidants, mainly through the activation of erythroid factor 2 Nrf2 [nuclear factor-erythroid related factor 2] also proposed by [12]; d] decrease in the inflammatory response by inhibiting nuclear factor kappa B [NF-κB] pathways; e] activation of vitagenes [group of redox-sensitive genes that are involved in sensing stress and preserving cellular adaptive homeostasis] responsible for the synthesis of protective molecules, including the heat shock proteins, thioredoxin and sirtuins, and providing additional protection under conditions of stress that deserve further attention; and f] affect the gut microenvironment, including interactions between silymarin and bacteria, a factor not yet deeply investigated.

The interruption of the inflammatory cascade may be related to the activation of the erythroid factor 2 Nrf2 related to the erythroid nuclear factor [NFE2], known as a master regulator of the cytoprotective response. Nrf-2 is a redox-sensitive nuclear transcription factor capable of inducing associated genes downstream in this cascade. Some silymarin components have been shown to participate in the Nrf-2 signaling pathway as activators that interrupt interactions in the Keap1-Nrf-2 system [an important adaptive mechanism of the antioxidant response to several pathological conditions, such as diabetes] and as antioxidants or with additional related actions regulation of Nrf-2. In the last decade, several efforts have been directed towards the definition, observation and verification of the mechanisms and principles of pharmacotherapeutic action of silymarin [3].

Anand *et al.* [26] performed a comparative study of herbal complexes for antiviral activity. Since silymarin was widely disseminated in eastern culture as a medicine for the treatment of liver diseases, the extrapolation and verification of results in the treatments of hepatitis, including hepatitis C, led to its in-depth investigation. Bioavailability needs to be guaranteed and, in this sense, technological advances have significantly corroborated [27].

Other authors [27] [28] [29] [30] evidence the activity of silymarin against several viruses, including flaviviruses [hepatitis C virus and dengue virus], togaviruses [Chikungunya virus and Mayaro virus], influenza virus, human immunodeficiency virus and hepatitis B virus. Idebroy [31] evaluated therapy with

Legalon® SIL, intended for the treatment of hepatitis C, verifying the decrease in the anti-inflammatory and anti-proliferative gene, associated with a decrease in tumor necrosis factor α [TNF-α] and NF-κB, related to viral transcription mechanisms. Clinical studies presented and compiled by Palit *et al.* [32], also demonstrated the antiviral properties of silymarin and silybinin.

In the context of the Sars-cov-2 pandemic, it has become essential to understand the structure of the virus and its viral capsule, as well as the primary mechanisms of action on the host.

The similarity of the structure and pathology of Sars-cov-2 in relation to other known viruses allows the comparison of the genetic material due to its spherical structure, glycoprotein peaks, hemagglutinin, lipid bilayer, nucleocapsid, and site of infection with Sars-cov-2. This allows the identification of potential active principles for use in combat and in complementary therapies to the therapeutic protocol for Sars-cov-2: *Zika virus* is a positive-sense single-stranded RNA virus with a nucleocapsid, the open reading frames encode a single protein that is processed into the capsid, membrane protein, and envelope structural proteins [33]; *Rabies virus* belongs to the RNA viruses and although it is a negative RNA virus, it has a lipid bilayer membrane covered by transmembrane glycoprotein spikes and a nucleocapsid that covers its genetic material [34]; *Dengue virus* has a positive sense RNA [35]; H1NI [swine flu virus] also affects the respiratory tract with a minimum incubation period of 5 to 7 days and is an enveloped virus with spikes of glycoprotein in the lipid bilayer membrane and also hemagglutinin in the envelope [36]; *Chikungunya virus* is also a spherical virus with an envelope consisting of glycoprotein spikes and a positive-sense single-stranded RNA [37]; *Ebola virus*, although a tube-shaped virus with negative-stranded RNA, has a lipid bilayer membrane and glycoprotein spikes [38].

The Sars-cov2 Mpro and HCV NS3/4A proteases show similarity in the three-dimensional structure and in the arrangement of the active site residues. Furthermore, eight HCV protease inhibitors are also able to bind to the Mpro active site suggesting that HCV protease inhibitors can effectively inhibit Sars-cov-2 protease and Sars-cov-2 replication [39]. The HE spike protein found in Sars-cov-2 and the influenza virus hemagglutinin has a similar function [40].

From the understanding of these principles, Anand *et al.* [26] carried out a review of numerous medicinal plants intended to combat and improve the immune response against viruses with agents similar in structure to Sars-cov-2. Sikander *et al.* [41] describe that the Sars-cov-2 virus uses protein cleavage enzymes to cleave the viral S protein and further facilitate virus-host cell fusion [42] [43]. As shown by Wrapp *et al* [44] in the structure model analysis, Sars-cov-2 binds to Angiotensin I 2 Converting Enzyme [ACE2], a host receptor, with an affinity of more than 10 times higher compared to Sars-cov-2. Hypertensive patients pretreated with an angiotensin-1 receptor blocker showed relative protection against aggravation of the infection and reduced mortality and recovery time [45], assuming that it acts in the containment of the post-infectious cytokine storm and organ damage [as an anti-inflammatory and anti-fibrotic agent].

Some authors [46] [47] discussed the use of various drugs in China, aimed at virus infection or immunomodulation during the pandemic.

Due to the complexity of the disease and factors such as the initial lack of drugs, protocols and vaccines, the scenario of the Sars-cov-2 pandemic has been extremely serious, triggered by an unpredictable pathophysiological response, such as hyperinflammatory disorders, blood clots, pulmonary embolism, thrombosis and organ damage caused by cytokine storm [48] [49] [50]. The immunopathological response of Sars-cov-2 is unprecedented and discordant about host defense with clinical manifestation based on symptoms and immunogenomic variation [51] [52].

Clinical management of patients was often based on trial-and-error with reproposed antiviral drugs such as ritonavir lopinavir [protease inhibitors], remdesivir [adenosine analogue], antiprotozoals such as hydroxychloroquine [endosomal inhibitor], among others [50]. In acute cases, patients sometimes failed to recover due to nonspecific drug binding or adverse drug reaction and comorbid conditions including organ malfunction [53] [54] [55]. This led to the death of these patients [54] [56]. Patients with pre-existing blood coagulopathy may have stroke due to an underlying mechanism that could likely mimic sepsis-like syndrome and disseminated intravascular coagulation [57] [58] [59].

Silymarin may contribute to patient well-being due to effects against various pathophysiological disorders [41], such as in hepatic and neurological tissues [60].

Palit *et al* [32] analyzed the commercially available silymarin and the ingredients recommended by the Food and Drug Administration [FDA], silybin and silybinin, with fundamental contributions to the understanding of the complex pathophysiology involved in the worsening of Sars-cov-2 and clinical trials Recent studies suggest that elevated transaminases, elevated bilirubin, prolonged prothrombin period, hypoproteinemia and other abnormalities in blood tests may predict a greater possibility of worsening of the clinical status of these patients [61]. According to Sikander *et al.* [41] the factors involved in the hepatic aggression associated with Sars-cov-2 are toxicity and injury, promoting cytokine storm, direct viral replication, toxicity induced by antipyretics, hypoxia, induced toxicity by antivirals and pre-existing liver disease.

More than a third of patients with COVID-19 have some abnormalities in liver function tests [62] and the proportion of patients admitted to intensive care units [ICU] with liver injury (61.5%) was greater than patients not admitted to the ICU (25.0%) [63].

Several studies have shown that plant-derived secondary metabolites have a blocking action on the inflammatory cascade of the lower airways, which can be beneficial in reducing the damage caused by viral infections from the Coronaviridae family, including Sars-cov-2. Phytochemicals with various molecular targets and signaling mechanisms have been found to reduce the production of pro-inflammatory and oxidative mediators such as TNF-α, IL-1, IL-6, IL-8, IL-1β, NF-κB, MMPs, iNOS, MAPK, COX-2, and ROS, thus minimizing lung damage.

These protective effects, along with antiviral effects, have drawn attention to the potential use of phytochemicals as strategies to develop new anti-CoV agents for controlling related complications [26] [64]-[71].

5. Conclusion

Silymarin shows promise in hepatoprotection, nephroprotection, anti-aging of the skin, cardiovascular protection, protection against respiratory diseases, prevention and treatment of various types of cancer, anti-diabetes, anti-tuberculosis, neuroprotection, Parkinson's and Alzheimer's, prevention of hemolysis and immunomodulation with blocking of adhesion and adsorption of TCD4+ cells, as well as direct action on the nuclear membrane, hindering the introduction of viral RNA and preventing its replication.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Marjani, M., Baghaei, P., Kazempour Dizaji, M., Gorji Bayani, P., Fahimi, F., Tabarsi, P., *et al.* (2016) Evaluation of Hepatoprotective Effect of Silymarin among under Treatment Tuberculosis Patients: A Randomized Clinical Trial. *Iranian Journal of Pharmaceutical Research*, **15**, 247-252.

[2] Federico, A., Dallio, M. and Loguercio, C. (2017) Silymarin/Silybin and Chronic Liver Disease: A Marriage of Many Years. *Molecules*, **22**, Article 191. https://doi.org/10.3390/molecules22020191

[3] Vargas-Mendoza, N., Madrigal-Santillán, E., Morales-González, A., Esquivel-Soto, J., Esquivel-Chirino, C., García-Luna., *et al.* (2014) Hepatoprotective Effect of Silymarin. *World Journal of Hepatology*, **6**, 144-149. https://doi.org/10.4254/wjh.v6.i3.144

[4] Esposito, T., Sansone, F., Russo, P., Picerno, P., Aquino, R.P., Gasparri, F., *et al.* (2019) A Water-Soluble Microencapsulated Milk Thistle Extract as Active Ingredient for Dermal Formulations. *Molecules*, **24**, Article 1547. https://doi.org/10.3390/molecules24081547

[5] Ganesan, P. and Choi, D.K. (2016) Current Application of Phytocompound-Based Nanocosmeceuticals for Beauty and Skin Therapy. *International Journal of Nanomedicine*, **11**, 1987-2007. https://doi.org/10.2147/IJN.S104701

[6] Ni, X. and Wang, H. (2016) Silymarin Attenuated Hepatic Steatosis through Regulation of Lipid Metabolism and Oxidative Stress in a Mouse Model of Nonalcoholic Fatty Liver Disease (NAFLD). *American Journal of Translational Research*, **8**, 1073-1081.

[7] Surai, P.F. (2015) Silymarin as a Natural Antioxidant: An Overview of the Current Evidence and Perspectives. *Antioxidants*, **4**, 204-247. https://doi.org/10.3390/antiox4010204

[8] Avci, H., Epikmen, E.T., İpek, E., Tunca, R., Birincioglu, S.S., Akşit, H., *et al.* (2017) Protective Effects of Silymarin and Curcumin on Cyclophosphamide-Induced Cardiotoxicity. *Experimental and Toxicologic Pathology*, **69**, 317-327. https://doi.org/10.1016/j.etp.2017.02.002

[9] Devi, K.P., Malar, D.S., Braidy, N., Nabavi, S.M. and Nabavi, S.F. (2017) A Mini Review on the Chemistry and Neuroprotective Effects of Silymarin. *Current Drug Targets*, **18**, 1529-1536. https://doi.org/10.2174/1389450117666161227125121

[10] Onaolapo, A.Y., Abdusalam, S.Z. and Onaolapo, O.J. (2017) Silymarin Attenuates Aspartame-Induced Variation in Mouse Behaviour, Cerebrocortical Morphology and Oxidative Stress Markers. *Pathophysiology*, **24**, 51-62. https://doi.org/10.1016/j.pathophys.2017.01.002

[11] Anestopoulos, I., Sfakianos, A.P., Franco, R., Chlichlia, K., Panayiotidis, M.I., Kroll, D.J., *et al.* (2017) A Novel Role of Silibinin as a Putative Epigenetic Modulator in Human Prostate Carcinoma. *Molecules*, **22**, Article 62. https://doi.org/10.3390/molecules22010062

[12] Gorhe, A., Kulkarni, A., Kandalkar, P. and Jagtap, S. (2020) Silymarin Loaded Novel Drug Delivery for Oral and Topical Administration. *Journal of Drug Delivery & Therapeutics*, **10**, 262-270. https://doi.org/10.22270/jddt.v10i3-s.4125

[13] Abenavoli, L., Capasso, R., Milic, N. and Capasso, F. (2010) Milk Thistle in Liver Diseases: Past, Present, Future. *Phytotherapy Research*, **24**, 1423-1432. https://doi.org/10.1002/ptr.3207

[14] Tvrdý, V., Pourová, J., Jirkovský, E., Křen, V., Valentová, K. and Mladěnka, P. (2021) Systematic Review of Pharmacokinetics and Potential Pharmacokinetic Interactions of Flavonolignans from Silymarin. *Medicinal Research Reviews*, **41**, 2195-2246. https://doi.org/10.1002/med.21791

[15] Wen, Z., Dumas, T.E., Schrieber, S.J., Hawke, R.L., Fried, M.W. and Smith, P.C. (2008) Pharmacokinetics and Metabolic Profile of Free, Conjugated, and Total Silymarin Flavonolignans in Human Plasma after Oral Administration of Milk Thistle Extract. *Drug Metabolism and Disposition*, **36**, 65-72. https://doi.org/10.1124/dmd.107.017566

[16] Hawke, R.L., Schrieber, S.J., Soule, T.A., Wen, Z., Smith, P.C., Reddy, K.R., *et al.* (2010) Silymarin Ascending Multiple Oral Dosing Phase I Study in Noncirrhotic Patients with Chronic Hepatitis C. *The Journal of Clinical Pharmacology*, **50**, 434-449. https://doi.org/10.1177/0091270009347475

[17] Marhol, P., Bednář, P., Kolářová, P., Večeřa, R., Ulrichová, J., Tesařová, E., *et al.* (2015) Pharmacokinetics of Pure Silybin Diastereoisomers and Identification of Their Metabolites in Rat Plasma. *Journal of Functional Foods*, **14**, 570-580. https://doi.org/10.1016/j.jff.2015.02.031

[18] Di Costanzo, A. and Angelico, R. (2019) Formulation Strategies for Enhancing the Bioavailability of Silymarin: The State of the Art. *Molecules*, **24**, Article 2155. https://doi.org/10.3390/molecules24112155

[19] Leone, F. and Cavalli, R. (2015) Drug Nanosuspensions: A ZIP Tool between Traditional and Innovative Pharmaceutical Formulations. *Expert Opinion on Drug Delivery*, **12**, 1607-1625. https://doi.org/10.1517/17425247.2015.1043886

[20] Kellici, T.F., Ntountaniotis, D., Leonis, G., Chatziathanasiadou, M., Chatzikonstantinou, A.V., Becker-Baldus, J., *et al.* (2015) Investigation of the Interactions of Silibinin with 2-Hydroxypropyl-β-Cyclodextrin through Biophysical Techniques and Computational Methods. *Molecular Pharmaceutics*, **12**, 954-965. https://doi.org/10.1021/mp5008053

[21] Gharbia, S., Balta, C., Herman, H., Rosu, M., Váradi, J., Bácskay, I., *et al.* (2018) Enhancement of Silymarin Anti-Fibrotic Effects by Complexation with Hydroxypropyl (HPBCD) and Randomly Methylated (RAMEB) β-Cyclodextrins in a Mouse Model of Liver Fibrosis. *Frontiers in Pharmacology*, **9**, Article 883. https://doi.org/10.3389/fphar.2018.00883

[22] Ma, X. and Williams, R.O. (2018) Polymeric Nanomedicines for Poorly Soluble Drugs in Oral Delivery Systems: An Update. *Journal of Pharmaceutical Investigation*, **48**, 61-75. https://doi.org/10.1007/s40005-017-0372-2

[23] Chen, S., Hao, X., Liang, X., Zhang, Q., Zhang, C., Zhou, G., *et al.* (2016) Inorganic Nanomaterials as Carriers for Drug Delivery. *Journal of Biomedical Nanotechnology*, **12**, 1-27. https://doi.org/10.1166/jbn.2016.2122

[24] Liu, C.H., Lin, C.C., Hsu, W.C., Chung, C.Y., Lin, C.C., Jassey, A., *et al.* (2017) Highly Bioavailable Silibinin Nanoparticles Inhibit HCV Infection. *Gut*, **66**, 1853-1861. https://doi.org/10.1136/gutjnl-2016-312019

[25] Gillessen, A. and Schmidt, H.H. (2020) Silymarin as Supportive Treatment in Liver Diseases: A Narrative Review. *Advances in Therapy*, **37**, 1279-1301. https://doi.org/10.1007/s12325-020-01251-y

[26] Anand, A.V., Balamuralikrishnan, B., Kaviya, M., Bharathi, K., Parithathvi, A., Arun, M., *et al.* (2021) Medicinal Plants, Phytochemicals, and Herbs to Combat Viral Pathogens Including Sars-cov-2. *Molecules*, **26**, Article 1775. https://doi.org/10.3390/molecules26061775

[27] Blaising, J., Lévy, P.L., Gondeau, C., Phelip, C., Varbanov, M., Teissier, E., *et al.* (2013) Silibinin Inhibits Hepatitis C Virus Entry into Hepatocytes by Hindering Clathrin-Dependent Trafficking. *Cellular Microbiology*, **15**, 1866-1882. https://doi.org/10.1111/cmi.12155

[28] Camini, F.C., da Silva, T.F., da Silva Caetano, C.C., Almeida, L.T., Ferraz, A.C., Alves Vitoreti, V.M., *et al.* (2018) Antiviral Activity of Silymarin against Mayaro Virus and Protective Effect in Virus-Induced Oxidative Stress. *Antiviral Research*, **158**, 8-12. https://doi.org/10.1016/j.antiviral.2018.07.023

[29] Lani, R., Hassandarvish, P., Chiam, C.W., Moghaddam, E., Chu, J.J., Rausalu, K., *et al.* (2015) Antiviral Activity of Silymarin against Chikungunya Virus. *Scientific Reports*, **5**, Article No. 11421. https://doi.org/10.1038/srep11421

[30] Dai, J.P., Wu, L.Q., Li, R., Zhao, X.F., Wan, Q.Y., Chen, X.X., *et al.* (2013) Identification of 23-(s)-2-Amino-3-Phenylpropanoyl-Silybin as an Antiviral Agent for Influenza A Virus Infection *in Vitro* and *in Vivo*. *Antimicrobial Agents and Chemotherapy*, **57**, 4433-4443. https://doi.org/10.1128/AAC.00759-13

[31] McClure, J., Margineantu, D.H., Sweet, I.R. and Polyak, S.J. (2014) Inhibition of HIV by Legalon-SIL Is Independent of Its Effect on Cellular Metabolism. *Virology*, **449**, 96-103. https://doi.org/10.1016/j.virol.2013.11.003

[32] Palit, P., Mukhopadhyay, A. and Chattopadhyay, D. (2021) Phyto-Pharmacological Perspective of Silymarin: A Potential Prophylactic or Therapeutic Agent for COVID-19, Based on Its Promising Immunomodulatory, Anti-Coagulant and Anti-Viral Property. *Phytotherapy Research*, **35**, 4246-4257. https://doi.org/10.1002/ptr.7084

[33] Šebera, J., Dubankova, A., Sychrovský, V., *et al.* (2018) The Structural Model of Zika Virus RNA-Dependent RNA Polymerase in Complex with RNA for Rational Design of Novel Nucleotide Inhibitors. *Scientific Reports*, **8**, Article No. 11132. https://doi.org/10.1038/s41598-018-29459-7

[34] Rupprecht, C.E. (1996) Rhabdoviruses: Rabies Virus. In: Baron, S., Ed., *Medical Microbiology* (*4th Edition*), University of Texas Medical Branch at Galveston, Galves-

ton, Chapter 61. https://www.ncbi.nlm.nih.gov/books/NBK8618/

[35] Kuhn, R.J., Zhang, W., Rossmann, M.G., Pletnev, S.V., Corver, J., Lenches, E., *et al.* (2018) Structure of Dengue Virus: Implications for Flavivirus Organization, Maturation, and Fusion. *Cell*, **108**, 717-725. https://doi.org/10.1016/S0092-8674(02)00660-8

[36] Jilani, T.N., Jamil, R.T. and Siddiqui, A.H. (2022) H1N1 Influenza. StatPearls, Treasure Island.

[37] Ganesan, V.K., Duan, B. and Reid, S.P. (2017) Chikungunya Virus: Pathophysiology, Mechanism, and Modeling. *Viruses*, **9**, Article 368. https://doi.org/10.3390/v9120368

[38] Lee, J.E. and Saphire, E.O. (2009) Ebolavirus Glycoprotein Structure and Mechanism of Entry. *Future Virology*, **4**, 621-635. https://doi.org/10.2217/fvl.09.56

[39] Bafna, K., Krug, R.M. and Montelione, G.T. (2020) Structural Similarity of Sars-Cov-2 Mpro and HCV NS3/4A Proteases Suggests New Approaches for Identifying Existing Drugs Useful as COVID-19 Therapeutics. *ChemRxiv* 2020. https://doi.org/10.26434/chemrxiv.12153615

[40] Biswas, A., Bhattacharjee, U., Chakrabarti, A.K., Tewari, D.N., Banu, H. and Dutta, S. (2020) Emergence of Novel Coronavirus and COVID-19: Whether to Stay or Die out? *Critical Reviews in Microbiology*, **46**, 182-193. https://doi.org/10.1080/1040841X.2020.1739001

[41] Sikander, M., Malik, S., Rodriguez, A., Yallapu, M.M., Narula, A.S., Satapathy, S.K., Dhevan, V., Chauhan, S.C. and Jaggi, M. (2020) Role of Nutraceuticals in COVID-19 Mediated Liver Dysfunction. *Molecules*, **25**, Article 5905. https://doi.org/10.3390/molecules25245905

[42] Glowacka, I., Bertram, S., Müller, M.A., Allen, P., Soilleux, E., Pfefferle, S., *et al.* (2011) Evidence That TMPRSS2 Activates the Severe Acute Respiratory Syndrome Coronavirus Spike Protein for Membrane Fusion and Reduces Viral Control by the Humoral Immune Response. *Journal of Virology*, **85**, 4122-4134. https://doi.org/10.1128/JVI.02232-10

[43] Shang, J., Wan, Y., Luo, C., Ye, G., Geng, Q., Auerbach, A. and Li, F. (2020) Cell Entry Mechanisms of Sars-Cov-2. *Proceedings of the National Academy of Sciences of the United States of America*, **117**, 11727-11734. https://doi.org/10.1073/pnas.2003138117

[44] Wrapp, D., Wang, N., Corbett, K.S., Goldsmith, J.A., Hsieh, C.L., Abiona, O., *et al.* (2020) Cryo-EM Structure of the 2019-nCoV Spike in the Prefusion confoRmation. *Science*, **367**, 1260-1263. https://doi.org/10.1126/science.abb2507

[45] Palit, P., Chattopadhyay, D., Thomas, S., Kundu, A., Kim, H.S. and Rezaei, N. (2021) Phytopharmaceuticals Mediated Furin and TMPRSS2 Receptor Blocking: Can It Be a Potential Therapeutic Option for COVID-19? *Phytomedicine*, **85**, Article ID: 153396. https://doi.org/10.1016/j.phymed.2020.153396

[46] Wang, W.Y., Xie, Y., Zhou, H. and Liu, L. (2021) Contribution of Traditional Chinese Medicine to the Treatment of COVID-19. *Phytomedicine*, **85**, Article ID: 153279. https://doi.org/10.1016/j.phymed.2020.153279

[47] Wang, Y., Liu, Y., Lv, Q., Zheng, D., Zhou, L., Ouyang, W., *et al.* (2021) Effect and Safety of Chinese Herbal Medicine Granules in Patients with Severe Coronavirus Disease 2019 in Wuhan, China: A Retrospective, Single-Center Study with Propensity Score Matching. *Phytomedicine*, **85**, Article ID: 153404. https://doi.org/10.1016/j.phymed.2020.153404

[48] Garg, S., Garg, M., Prabhakar, N., Malhotra, P. and Agarwal, R. (2020) Unraveling

the Mystery of Covid-19 Cytokine Storm: From Skin to Organ Systems. *Dermatologic Therapy*, **33**, e13859. https://doi.org/10.1111/dth.13859

[49] Helms, J., Tacquard, C., Severac, F., Leonard-Lorant, I., Ohana, M., Delabranche, X., *et al.* (2020) High Risk of Thrombosis in Patients with Severe Sars-Cov-2 Infection: A Multicenter Prospective Cohort Study. *Intensive Care Medicine*, **46**, 1089-1098. https://doi.org/10.1007/s00134-020-06062-x

[50] Penman, S.L., Kiy, R.T., Jensen, R.L., Beoku-Betts, C., Alfirevic, A., Back, D., Khoo, S.H., Owen, A., Pirmohamed, M., Park, B.K., Meng, X., Goldring, C.E. and Chadwick, A.E. (2020) Safety Perspectives on Presently Considered Drugs for the Treatment of COVID-19. *British Journal of Pharmacology*, **177**, 4353-4374. https://doi.org/10.1111/bph.15204

[51] Toyoshima, Y., Nemoto, K., Matsumoto, S., *et al.* (2020) SARS-CoV-2 Genomic Variations Associated with Mortality Rate of COVID-19. *Journal of Human Genetics*, **65**, 1075-1082. https://doi.org/10.1038/s10038-020-0808-9

[52] Severe Covid-19 GWAS Group, Ellinghaus, D., Degenhardt, F., Bujanda, L., Buti, M., Albillos, A., *et al.* (2020) Genomewide Association Study of Severe Covid-19 with Respiratory Failure. *The New England Journal of Medicine*, **383**, 1522-1534. https://doi.org/10.1056/NEJMoa2020283

[53] Carter, C., Thi Lan Anh, N. and Notter, J. (2020) COVID-19 Disease: Perspectives in Low- and Middle-Income Countries. *Clinics in Integrated Care*, **1**, Article ID: 100005. https://doi.org/10.1016/j.intcar.2020.100005

[54] Renu, K., Prasanna, P.L. and Valsala Gopalakrishnan, A. (2020) Coronaviruses Pathogenesis, Comorbidities and Multi-Organ Damage—A Review. *Life Sciences*, **255**, Article ID: 117839. https://doi.org/10.1016/j.lfs.2020.117839

[55] Zumla, A., Chan, J.F., Azhar, E.I., Hui, D.S. and Yuen, K.Y. (2016) Coronaviruses—Drug Discovery and Therapeutic Options. *Nature Reviews Drug Discovery*, **15**, 327-347. https://doi.org/10.1038/nrd.2015.37

[56] Li, X., Xu, S., Yu, M., Wang, K., Tao, Y., Zhou, Y., *et al.* (2020) Risk Factors for Severity and Mortality in Adult COVID-19 Inpatients in Wuhan. *J Allergy Clin Immunol* 2020, **146**, 110-118. https://doi.org/10.1016/j.jaci.2020.04.006

[57] Al-Samkari, H., Karp Leaf, R.S., Dzik, W.H., Carlson, J.C., Fogerty, A.E., Waheed, A., *et al.* (2020) COVID and Coagulation: Bleeding and Thrombotic Manifestations of Sars-Cov-2 Infection. *Blood*, **136**, 489-500. https://doi.org/10.1182/blood.2020006520

[58] Coppola, A., Lombardi, M., Tassoni, M.I., Carolla, G., Tala, M., Morandini, R., *et al.* (2020) COVID-19, Thromboembolic Risk and Thromboprophylaxis: Learning Lessons from the Bedside, Awaiting Evidence. *Blood Transfusion*, **18**, 226-229.

[59] Lemke, G. and Silverman, G.J. (2020) Blood Clots and TAM Receptor Signalling in COVID-19 Pathogenesis. *Nature Reviews Immunology*, **20**, 395-396. https://doi.org/10.1038/s41577-020-0354-x

[60] Fakhri, S., Piri, S., Majnooni, M.B., Farzaei, M.H. and Echeverría, J. (2021) Targeting Neurological Manifestations of Coronaviruses by Candidate Phytochemicals: A Mechanistic Approach. *Frontiers in Pharmacology*, **20**, Article 621099. https://doi.org/10.3389/fphar.2020.621099

[61] Guan, W.J., Ni, Z.Y., Hu, Y., Liang, W.H., Ou, C.Q., He, J.X., *et al.* (2020) China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England Journal of Medicine*, **382**, 1708-1720. https://doi.org/10.1056/NEJMoa2002032

[62] Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., *et al.* (2020) Epidemiologi-

cal and Clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: A Descriptive Study. *Lancet*, **395**, 507-513. https://doi.org/10.1016/S0140-6736(20)30211-7

[63] Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., *et al.* (2020) Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China. *Lancet*, **395**, 497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

[64] Bellik, Y., Hammoudi, S.M., Abdellah, F., Iguer-Ouada, M. and Boukraâ, L. (2012) Phytochemicals to Prevent Inflammation and Allergy. *Recent Patents on Inflammation & Allergy Drug Discovery*, **6**, 147-158. https://doi.org/10.2174/187221312800166886

[65] Favarin, D.C., de Oliveira, J.R., de Oliveira, C.J. and Rogerio Ade, P. (2013) Potential Effects of Medicinal Plants and Secondary Metabolites on Acute Lung Injury. *BioMed Research International*, **2013**, Article ID: 576479. https://doi.org/10.1155/2013/576479

[66] Majnooni, M.B., Fakhri, S., Shokoohinia, Y., Kiyani, N., Stage, K., Mohammadi, P., *et al.* (2020) Phytochemicals: Potential Therapeutic Interventions against Coronavirus-Associated Lung Injury. *Frontiers in Pharmacology*, **11**, Article 588467. https://doi.org/10.3389/fphar.2020.588467

[67] Karimi, G., Vahabzadeh, M., Lari, P., Rashedinia, M. and Moshiri, M. (2011) "Silymarin", a Promising Pharmacological Agent for Treatment of Diseases. *Iranian Journal of Basic Medical Sciences*, **14**, 308-317.

[68] Sahibzada, M.U.K., Sadiq, A., Khan, S., Faidah, H.S., Naseemullah Khurram, M., *et al.* (2017) Fabrication, Characterization and *in Vitro* Evaluation of Silibinin Nanoparticles: An Attempt to Enhance Its Oral Bioavailability. *Drug Design, Development and Therapy*, **11**, 1453-1464. https://doi.org/10.2147/DDDT.S133806

[69] Sardanelli, A.M., Isgrò, C. and Palese, L.L. (2021) Sars-Cov-2 Main Protease Active Site Ligands in the Human Metabolome. *Molecules*, **26**, Article 1409. https://doi.org/10.3390/molecules26051409

[70] Speciale, A., Muscarà, C., Molonia, M.S., Cimino, F., Saija, A. and Giofrè, S.V. (2021) Silibinin as Potential Tool against Sars-Cov-2: *In Silico* Spike Receptor-Binding Domain and Main Protease Molecular Docking Analysis, and *in Vitro* Endothelial Protective Effects. *Phytotherapy Research*, **35**, 4616-4625. https://doi.org/10.1002/ptr.7107

[71] Kumar, S., Kashyap, P., Chowdhury, S., Kumar, S., Panwar, A. and Kumar, A. (2021) Identification of Phytochemicals as Potential Therapeutic Agents That Binds to Nsp15 Protein Target of Coronavirus (Sars-Cov-2) That Are Capable of Inhibiting Virus Replication. *Phytomedicine*, **85**, Article ID: 153317. https://doi.org/10.1016/j.phymed.2020.153317