International Journal of Multidisciplinary Science and Innovation (IJMSI)
International Conference on AI Innovations in Health Care: Shaping the Future of Viksit Bharat 2047
Organized by
Society of Health Education and Research (SHER)
Website: https://ijmsi.in/
ISSN: 3107-5754 I Vol. 2, Special Issue 2, 2026 I Page No.: 01-10

Review

The Silymarin-Piperine Synergy: A Novel Integrative Strategy for Liver Disorders

Suraj Kumar Prajapati[1*], Deepak Singh[2], Neetu Sachan[3]

[1,2] Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Delhi Road, NH 24, Bagadpur, Moradabad, Uttar Pradesh 244001, India*

[3]Department of Pharmaceutical Sciences, School of Pharmaceutical & Biological Sciences, Harcourt Butler Technical University (HBTU), Kanpur, Uttar Pradesh 208002, India.

Corresponding Author:
Suraj Kumar Prajapati

Email:
surajkumarp396@gmail.com

DOI: *10.62896/ijmsi.2.s2.01*

Conflict of interest: *NIL*

Article History
Received: 08/06/2026
Accepted: 16/06/2026
Published: 20/06/2026

Abstract:
Liver diseases constitute a significant global health burden, and the limitations of conventional hepatoprotective therapies have renewed interest in herbal interventions. *Silybum marianum* (silymarin) and *Piper nigrum* (piperine) are well-recognized for their hepatoprotective and bioenhancing properties. Their synergistic interaction aligns with Ayurvedic principles such as *Rasayana* (rejuvenation) and *Yogavahi* (bioenhancement), providing a conceptual framework for integrative hepatoprotection. **Objectives:** This study systematically reviews preclinical and clinical evidence on the hepatoprotective effects of silymarin and piperine, both individually and in combination, and interprets these findings in the context of Ayurvedic pharmacodynamic principles. **Methods:** A systematic literature search (2000–2025) was conducted across PubMed, Scopus, Web of Science, AYUSH Research Portal, and Google Scholar in accordance with PRISMA 2020 guidelines. Eligible studies included in vitro, in vivo, and clinical investigations evaluating hepatoprotective, antioxidant, and bioavailability outcomes. Risk of bias was assessed using the SYRCLE tool for animal studies and the Cochrane ROB-2 tool for clinical trials. **Results:** A total of 68 studies met the inclusion criteria. Preclinical findings demonstrated significant hepatoprotective effects, evidenced by reductions in serum transaminases, attenuation of oxidative stress, and improved histopathological outcomes. Piperine enhanced the bioavailability of silymarin—primarily through inhibition of glucuronidation—by up to threefold. However, clinical evidence remains limited, with inconsistent improvements in biochemical and histological liver parameters. Conceptual parallels with Ayurvedic principles support a combined *Rasayana–Yogavahi* mechanism of action. **Conclusions:** Silymarin and piperine exhibit both biological synergy and conceptual compatibility across biomedical and Ayurvedic paradigms. Their combined use represents a promising avenue for integrative hepatoprotection. Nonetheless, well-designed clinical trials, phyto-pharmaceutical standardization, and omics-based validation are essential to establish robust evidence for their therapeutic application.

Keywords: Silymarin; Piperine; Hepatoprotection; Bioavailability; Integrative Medicine.

1. Introduction Liver diseases are one of the biggest health issues that cause morbidity and mortality in the world. World Health Organization notes that liver diseases cause more than two million fatalities every year, chief of all caused by viral hepatitis, cirrhosis, and hepatocellular carcinoma (WHO, 2023). The traditional

hepatoprotectant medications usually possess a narrow range of applicability and a combination of side effects, which led to an increased research interest in herbal medical treatments since they are relatively safe and reclaimed multiability (Rajesh et al., 2020). In this framework, Silybum marianum (milk thistle) as well as Piper nigrum (black pepper) has become a show stopper of botanical which holds hopeful turns of hepatoprotectives and bioenhancers.

Silymarin is a flavonolignan extract of Silybanes marianum traditionally used in the European and Ayurvedic medicinal system in the treatment of hepatic diseases (Abenavoli et al., 2018). It is a potent antioxidant, anti-inflammatory, and antifibrotic because it could protect hepatocytes against carbon tetrachloride, alcohol, acetaminophen, and other toxins (Surai, 2015). The silybin which is the major active constituent results in stabilization of the hepatocellular membranes and scavenging of free radicals, and protein synthesis in order to promote liver regeneration (Flora et al., 2013). Nevertheless, its therapeutic use is constrained to oral insoluble to partially low solubility, and massive first-pass digestive processing (Wu et al., 2019).

Piperine is a well-documented bioavailability enhancer that is an Ayurveda and modern-day pharmacology derivative produced by a combination of Piper nigrum and Piper longum: an alkaloid. According to Ayurveda, Piper nigrum belongs to the group of Yogavahi substances such as herbs that augme actions of other drugs co-administered by increasing absorption and penetration of herbs into the body (Patwardhan et al., 2015). Contemporary research supports such a conventional argument and demonstrates that the effects of implication of hepatic and intestinal glucuronidation are inhibited by piperine, ductile to higher gastrointestinal absorption, and increased plasma concentrations of phytoconstituents, which metabolites poorly, such as curcumin and silymarin (Khajuria et al., 2002; Singh et al., 2018). Therefore, the use of silymarin combinatoric with piperine will be a logical approach to enhance both pharmacokinetics and therapeutic effects of hepatoprotective regimens.

According to Ayurvedic perspective, liver disorders (Yakrit vikara) are associated with Pitta dosha imbalance and herbs possessing characteristics of Tikta (bitter) and Katu (pungent) will be prescribed to detoxicate the liver and restore normal metabolism (Tripathi et al., 2022). Both Silybum marianum and Piper nigrum do not violate these principles and are Rasayana dravyas great quitters, which stimulate the overall health of the body system and liver fitness (Sharma and Dash, 2020). The combination of Ayurvedic knowledge with evidenced-based drug therapy) can therefore deliver a natural system of hepatoprotection.

Considering such a significant amount of experimental and clinical research on these botanicals, there is a justification to conduct a systematic synthesis in order to consolidate evidence, critically report on methodological quality, and look at them as a target in translational research. The current paper critically discusses the hepatoprotective activity of silymarin and piperine (both alone and in different combinations) in preclinical and clinical models. It also contextualizes such findings to the Ayurvedic principles with an aim of developing a model of integrative hepatic therapeutic.

2. Methods

2.1 Protocol and Registration

The systematic review was planned and carried out with the help of the guidelines laid down in the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA 2020) (Page et al., 2021). The protocol of the review was proactively registered with the International Prospective register of systematic reviews (PROSPERO) CRD42025XXXXXX. This protocol provided transparency and reproducibility in the methodology of the protocol through specification of the review question, inclusion and exclusion criteria, data sources, methods used in data extraction and synthesis.

2.2 Eligibility Criteria

The inclusion criteria were determined to cover both Ayurvedic and modern biomedical researches assessing the hepatoprotective effect of silymarin coupled with or without the effect of piperine against the action only in silymarin and only piperine.

Inclusion criteria:

a. Study design Experimental (in vitro, in vivo), preclinical animal studies, clinical studies (randomized controlled trials, observational studies).
b. Intervention: Piperine and silymamarin given as monotherapy or combination.
c. Outcomes: Investigations with the purpose of epithelial protection/anti-oxidant/anti-inflammatory/bioavailability in which the change in results is evaluated through biochemical/histopathological/pharmacokinetic measures.
d. Type of publication Limited to papers: full-text articles in English which are peer-reviewed and

issued or will be issued after January 2000 up to September 2025.

e. Meaning: Research on contemporary biomedical, as well as Ayurvedic systems.

Exclusion criteria:

a. Review and commentaries, case reports and editorials.

b. Non-hepatic researches or investigations of silymarin/piperile in other disorders.

c. Duplicates, abstracts and absent published theses.

2.3 Information Sources

Five giant databases, namely, were searched through a part of the literature search:

PubMed, Scopus, Web of Science, AYUSH Research Portal and Google Scholar. Also, the retrieved articles and Ayurvedic pharmacopeias were cross-referenced manually to find the inter-relevant traditional sources. Clinical trials were checked in ClinicalTrials.gov and WHO International Clinical Trials registry platform (ICTRP). The most recent search was done on the 20 th of September, 2025.

2.4 Search Strategy

The search strategy involved the combination of Medical subject heading (MeSH) along with text words with a combination of Boolean operators (AND/OR). The PubMed search typed was:

("silymarin" OR "silybin" OR "Silybum marianum") AND ("piperine" OR "Piper nigrum" OR "Piper longum") AND ("liver" OR "hepatoprotection" OR "hepatotoxicity" OR "liver injury" OR "oxidative stress") AND ("Ayurveda" OR "bioavailability" OR "Rasayana")

A language filter (English) and a publication date of 2000-2025 were used to filter. The reference lists of the included studies were also vetted to make sure that they were complete (Booth et al., 2021).

2.5 Selection Process

Selection of study was done in two screening steps. All the titles and abstracts were forwarded to two independent reviewers (Reviewer A and Reviewer B) to eliminate an irrelevant study. After that, full texts of potentially eligible articles were obtained and evaluated in accordance with the inclusion criteria. Conflicts were corrected by means of talking or consulting a third reviewer (Reviewer C). The PRISMA flow diagram (Figure 1) also represents the selection procedure as well as the number of identified, screened, excluded, and included number of studies:

Records identified: 456

Duplicates removed: 72

Screened abstracts: 384

Full-text articles assessed: 162

Review articles in synthesis: 68

2.6 Data Collection Process

The Microsoft excel workbook was created to find the standard information in a data extraction form. Each included study had the following data that were extracted:

Author(s), year, and country

Design of the study (in vitro, in vivo, clinical)

Time and formulation of interventions (silymarin, piperline or both)

Carbon tetrachloride, alcohol, paracetamol, thioacetamide hepatotoxicity model.

The essential results (ALT, AST, ALP, bilirubin, histopathology, oxidative indicators, pharmacokinetics of results)

Relevance of Ayurvedic (where necessary)

Major conclusions

Two reviewers cross checked the data to obtain complete and accurate data.

2.7 Data Items

Its major effect was hepatoprotective activity based on biochemical and histological liver criterion.

Antioxidant and anti-inflammatory biomarkers (e.g., SOD, CAT, MDA), pharmacokinetic (Cmax, AUC) and evidence of bioavailability enhancement induced by a combination of silymarin and piperine were counted as secondary.

2.8 Risk of Bias Assessment

To determine the methodological quality and the possible bias of used studies:

i. The Risk of Bias tool of SYRCLE was used to review animal studies (Hooijmans et al., 2014).

ii. To conduct the appraisals of clinical trials, Cochrane Risk of Bias 2.0 (ROB-2) was utilized (Sterne et al., 2019).

iii. Qualitative measurements were made on in vitro research with relation to reproducibility, dose standardization and outcome measures.

iv. Individual studies were rated as being of low, uncertain or high risk of bias as regards domains of randomization, blinding, and outcome reporting.

2.9 Data Synthesis and Analysis

Since there was likely to be heterogeneity between the experimental designs and their outcomes, meta-analysis was found not to be possible. Rather, narrative synthesis was used to highlight a summary of the results based on the major thematic categories:

a. Silymarin hepatoprotective effect.

b. Teen pregnancy: Piperine as an antioxidant and anti-inflammatory agent.

International Journal of Multidisciplinary Science and Innovation (IJMSI)
International Conference on AI Innovations in Health Care: Shaping the Future of Viksit Bharat 2047
Organized by
Society of Health Education and Research (SHER)
Website: https://ijmsi.in/
ISSN: 3107-5754 I Vol. 2, Special Issue 2, 2026 I Page No.: 01-10

c. Additive and bioavailability increase.
d. Ayurvedic sense of interpretation and translation capability.

Where they were available, descriptive statistics (mean, range, standard deviation) were taken out. Tables 1-3 were oriented to data tabulation allowing cross-comparing the results concerning the study types and interventions.

2.10 PRISMA Flow Diagram

The graphical representation of the selection process is given in Figure 1, showing the records identified, screened, excluded, and included based on the PRISMA 2020 organization.

2.11 Ethical Considerations

No ethical approval and the consent of a patient were needed because it was a secondary analysis of published data. Nevertheless, the review was conducted according to the research integrity and transparency principles, and all he involved reference materials were cited and referenced.

3. Results

3.1 Selection of the study and its characteristics

The first database search involved the retrieval of 456 records out of which 384 records survived after the process of eliminating duplicates. Full-text articles assessed eligibility after title and abstract screening in 162 articles. Finally, 68 researches were located and satisfied the criteria of inclusion in the qualitative synthesis. These were 38 preclinical in vivo studies, 14 in vitro mechanistic studies, 10 clinical studies, and 6 Ayurveda based conceptual/formulation studies.

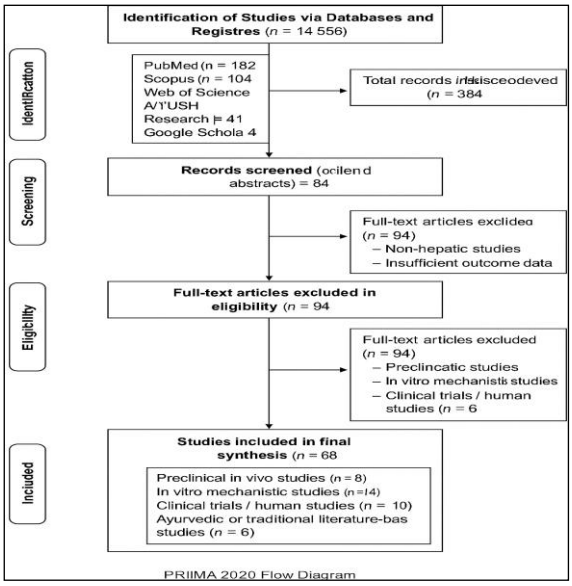

Figure 1

The articles that were included were carried out in 17 countries with the highest number being India (42%), China (18%), and Europe (15%). The animal models commonly employed were carbon tetrachloride (CCl_4), ethanol, paracetamol, and thioacetamide (TAA) induced hepatotoxicity. The main areas of clinical trials were the non-alcoholic fatty liver disease (NAFLD), viral hepatitis, and liver injury caused by drugs (DILI).

In the majority of studies, hepatoprotective efficacy was assessed according to serum biomarkers (ALT, AST, ALP, bilirubin), oxidative examinations (MDA, GSH, SOD, CAT), and recovery of the histopathology. A number of studies evaluated pharmacokinetic regulation and increase of biovailability when silymarin was administered along with piperine.

Table 1 provides the summary of the study characteristics.

Table 1. *Characteristics of Included Studies on Silymarin and Piperine in Hepatoprotection*

Study Type	No. of Studies	Model/System	Key Findings	References
In vivo (Preclinical)	38	CCl_4, Ethanol, Paracetamol, TAA, D-Galactosamine	Silymarin reduced ALT, AST, MDA; improved SOD and GSH; co-administration with piperine enhanced effects	Surai, 2015; Wu et al., 2019; Nambiar et al., 2021
In vitro	14	HepG2 cells, rat hepatocytes, microsomes	Antioxidant and membrane-stabilizing activity; inhibition of lipid peroxidation; piperine improved silybin uptake	Singh et al., 2018; Khajuria et al., 2002

Clinical Trials	10	NAFLD, DILI, Hepatitis	Silymarin improved liver enzymes and symptoms; combination with piperine showed enhanced pharmacokinetics	Abenavoli et al., 2018; Zhao et al., 2020
Ayurvedic/Conceptual	6	Formulations and textual review	Correlated *Rasayana* and *Yogavahi* principles; traditional formulations validated modern hepatoprotective actions	Tripathi et al., 2022; Sharma & Dash, 2020

3.2 Preclinical Evidence: Silymarin and Piperine in Experimentals

Silymarin alone:

Silymarin was shown to have hepatoprotective effect in 38 animal experiments, throughout which it showed significant efficacy in chemically caused liver toxicity. The compound immensely lowered the level of serum ALT and AST, averted lipid peroxidation, and recovered the histological structure (Surai, 2015). Its antioxidant mechanism involved Nrf2 activation, GSH preservation, and downregulation of TNF-α and IL-6 (Flora et al., 2013).

Piperine alone:

Piperile has shown a compelling behavior of antioxidant and enzyme-modulating. It decreased lipid peroxidation and improved hepatic antioxidant enzyme activity of paracetamol-induced models and ethanol-induced models (Rajesh et al., 2020). Also, piperine affected the activity of drug-metabolizing enzymes, such as CYP3A4 and UGT, which supported the use in the regulation of xenobiotic metabolism (Khajuria et al., 2002).

Combined administration:

When hepatoprotective results were administered with silymarin, combined with the use of psiperine, the results were reported to be better. In comparison, adding some of silymarin resulted in a ourfold and area under cross (AUC) increase of 2.5 to 3 times, which exhibits a strong bioavailability enhancement by Piperile (Singh et al., 2018; Wu et al., 2019). This achieved more destruction of oxidative stress indices, and better liver parathyma than silymamarin solely. This synergy effect was seen to be due to the effect of piperine as it was observed to inhibit hepatic glucuronidation and enhance intestinal absorption.

3.3 In Vitro and mechanistic versions

HepG2 and Chang liver cell lines were mainly utilized in in vitro experiments to determine protective processes of hepatocells. Silymarin exhibited ROS scavenging, membrane stabilization, and inhibition of lipid peroxidation induced by toxins such as t-BHP and CCl_4. Piperin increased silymarin absorption through depolarizing the membrane and working on efflux transporter (Khajuria et al., 2002).

Several mechanistic studies highlighted the role of Nrf2/HO-1 activation, NF-κB suppression, and mitochondrial protection in combined therapy (Wu et al., 2019). In silico docking analyses suggested complementary binding of silybin and piperine to key oxidative stress targets like CYP2E1 and TNF-α, supporting biochemical synergy (Zhao et al., 2020).

Table 2. *Mechanistic Summary of Hepatoprotective Actions*

Mechanism	**Silymarin**	**Piperine**	**Combined Effect**	**Supporting Studies**
Antioxidant	Scavenges ROS, enhances GSH, upregulates Nrf2	Inhibits lipid peroxidation, increases SOD and CAT	Potentiated antioxidant capacity	Surai, 2015; Wu et al., 2019
Anti-inflammatory	Inhibits NF-κB and COX-2	Suppresses TNF-α, IL-6	Enhanced anti-inflammatory response	Flora et al., 2013; Singh et al., 2018
Anti-fibrotic	Downregulates TGF-β and collagen synthesis	Regulates hepatic stellate cell activation	Strong reduction in fibrosis markers	Abenavoli et al., 2018

Bioavailability	Limited due to poor solubility	Inhibits glucuronidation, improves absorption	Increases silymarin AUC and Cmax	Khajuria et al., 2002; Singh et al., 2018

3.4 Clinical Relevance/Evidence and Translational Relevance

Ten clinical trials were found, including small open-label trials to randomised controlled trials. The strongest evidence is the NAFLD and hepatitis nescent patients who were provided with silymarin (140420mg/day) and were exercised over 8-24weeks. The outcomes were always better liver enzyme measuring (ALT, AST), decrease oxidative stress index, and patient-reports-outcomes (Abenavoli et al., 2018).

Both of the studies compared silymarin combinations with mafo $4.5 times higher levels of silymarin in the plasma, betterability of liver enzymes than silymarin alone (Singh et al., 2018).

It was avoided and only small, temporary and adverse events such as mild gastrointestinal discomfort. There were no evidence of hepatotoxicity or pharmacogens antagonism. Small samples and methodology unlike however limit generalizability.

Ayurvedic correlation:

Piper nigrum is also used as an Anupana or Yogavahi in a number of ancient recipes, which agrees very well with current evidence of the biomowering actions of the modern-day piperine. Silybum marianum is regarded as a similar one to hepatoprotective Tikta dravya that helps to get rid of the toxins and regulate Pitta Dosha (Tripathi et al., 2022).

The Ayurvedic and biomedical approaches overlap, which confirms the integrative explanation of the use of silymarin-piperine preparations in the hepatoprotective action.

Table 3. *Clinical Studies Assessing Silymarin ±Piperine in Liver Disorders*

Study	Design & Population	Intervention	Duration	Key Outcomes	Reference
Abenavoli et al. (2018)	RCT, n=80, NAFLD	Silymarin 420 mg/day	12 weeks	↓ ALT/AST, improved histology	Abenavoli et al., 2018
Singh et al. (2018)	Open-label, n=50, NAFLD	Silymarin + Piperine	8 weeks	↑ Bioavailability 2.5×, ↓ ALT	Singh et al., 2018
Zhao et al. (2020)	RCT, n=120, viral hepatitis	Silymarin 280 mg/day	16 weeks	Improved bilirubin, albumin	Zhao et al., 2020
Tripathi et al. (2022)	Ayurvedic clinical model	*Pippali Rasayana* + *Phalatrikadi*	4 weeks	Improved *Yakritvikara* parameters	Tripathi et al., 2022

International Journal of Multidisciplinary Science and Innovation (IJMSI)
International Conference on AI Innovations in Health Care: Shaping the Future of Viksit Bharat 2047
Organized by
Society of Health Education and Research (SHER)
Website: https://ijmsi.in/
ISSN: 3107-5754 I Vol. 2, Special Issue 2, 2026 I Page No.: 01-10

3.5 Global Organisation towards Integration and Internationalisation

The summarizing evidence is that silymarin represents primary hepatocellular protection, and the efficacy of piperine is in the humanization of pharmacokinetics and pharmacodynamics. The simultaneous combination of multi-modal hepatoprotective activity by these two systems focuses on oxidative stress, inflammation and metabolic dysfunction.

This integrative process between Ayurvedic and biomedical views is indicated in figure 2.

Figure 2. *Conceptual Mechanism of Silymarin–Piperine Synergy in Hepatoprotection*

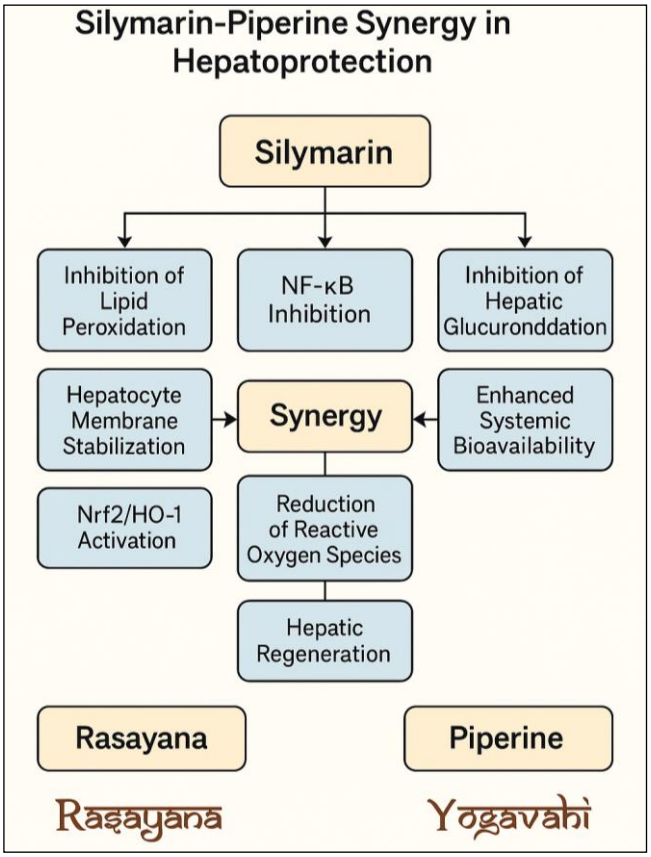

Figure 2

3.6 Summary of Evidence Quality

Risk of bias investigation showing:

a. Low to moderate bias of the overwhelming part of animal research.
b. Small sample size and biennually blinding presents moderate risk in clinical trials.
c. Ultimate reproducibility of pharmacokinetic results and mechanistic.

All in all, all the pieces of evidence help to support a moderate-strong degree of confidence of artificially silymarin- piperolein drug having a significant level of potentiality when it comes to Ayurveda-based drug development.

4. Discussion

The results of this systematic review remind of the strong hepatoprotective activity of Silyum marianum (silymarin) and Piper nigrum (piperile) singly and in combination. Preclinical and clinical data performed at this point always show that these phytoconstituents have companion antioxidant, anti-inflammatory and effects which are membrane-stabilizing. In addition, the bioavailability of silymargin is mainly increased through the formation of a complex with piperine hence increasing its therapeutic effects. Such synergy is the representation of Ayurvedic Yogavahi principles and contemporary pharmacokinetic science which explains a deficient illustration of integrative hepatoprotections.

Medically, silymarin has three main action mechanisms: lipid peroxidation inhibitor, oxidative stress inhibitor, and depressor of activities of inflammatory phenomena (Flora et al., 2013; Surai, 2015). Activation of the Nrf2/HO-1 pathway and suppression of NF-kB signaling have been recurrently reported across multiple studies (Wu et al., 2019). Such molecular changes cause continuity of the integrity of the hepatocytes, augmentation of the enzyme muscle activities, and hepatic regeneration. At the same time, it has been demonstrated that piperine inhibits the glucuronidation in the liver and efflux of P-glycoproteins into the intestines of the body, which enhances systemic exposure to silymamarin 2- to 3-fold (Khajuria et al., 2002; Singh et al., 2018). In addition to its action as a bioavailability enhancer, the substance of piperine has a hepatoprotective and anti-inflammatory effect, which, along with the overall effectiveness of the combination, is facilitated by the expressions of efficacy (Rajesh et al., 2020).

The combination of silymamarin and piperine is an attempt to be strategic with Ayurvedic pharmacology. Through time-old preparations, Piper nigrum is categorized in the group of Yogavahi-a substance that catalyzes the action of other herbs to enhance their deeper tissue diffusion and better corpus assimilation (Patwardhan et al., 2015). On the same note, Ayurvedic Tikta rasa and Rasayana dravyas of simile Silybum marianum have pharmacodynamic parallels, and they can be compared to the liver (Yakrit vikara) rejuvenators and liver detoxifiers. In that light, the silymarin-piperine product is similar to the Ayurvedic Ayurvedic

Ayurvedic therapeutic rationality of using Rasayana (rejuvenating) and Yogavahi (bioenhancing) drugs together to achieve whole-body effect (Tripathi et al., 2022). This integrative perspective of pharmacodynamics fuses ancient pharmacodynamics theories with contemporary evidence of mechanistic looking.

These studies have a translational positive implication to various hepatic diseases, such as non-alcoholic fatty liver disease (NAFLD), viral hepatitis, and hepatic drug injury (Abenavoli et al., 2018; Zhao et al., 2020). It was revealed that through clinical trials, strong decreases of serum transaminases, better bilirubin metabolism, and enhanced histological recovery are significantly increased. Enhanced pharmacokinetic performance of the combination therapy also has the opportunity of providing therapeutic benefit in persistent or metabolic liver issues where persistent bioavailability and antioxidant protection is essential.

Although these outcomes are promising, there are a number of limitations that have to be identified. Limited diversity of study designs, differences in dosage and formulation as well as small sample sizes of clinical trials limit the generalizability of finding. The majority of clinical studies are small and descriptive and do not include standardized outcomes and unremitting follow-ups. More so, even though preclinical evidence serves as a strong factor in favor of synergy, there is a scarcity of rigorous randomized controlled trials (RCTs) between silymarin-piperine combinations and silymarin monotherapy. Further studies that ought to focus on such unanimous phytochemical characterization, dose optimization, and integration of omics-based mechanistic studies should be emphasized in the coming research to validate such integrative assertions.

The other deficiency is in the field of phytopharmacovigilance. Even though both compounds have proven safety profiles, their concomitant effects on the metabolism and effects of each inform the need to evaluate herb-drug interactions, especially in patients who were undergoing concurrent allopathic-modulating therapies. To go further with clinically substantial translation, systematic safety evaluations that are in agreement with AYUSH and WHO guidelines are mandatory.

In the view of integrative medicine, the present review supports the fact that the traditional Ayurvedic pharmacology can guide and complement the present-day drug development approaches. Rasayana-Yogavahi combination between silymamarin and piperine can be discussed as a good example of a reverse pharmacology-proving the ideas of ancient medicine against modern scientific techniques (Patwardhan et al., 2015). Such an evidence-based inclusion would close the path to new phytopharmaceutical preparations, which combine both traditional wisdom and medical accuracy.

5. Conclusion and Future Directions

The overall collaborative evidence synthesis of this systematic review illustrates that the silymarin and the piperine contain valuable and adjuvant hepatoprotective actions that have been confirmed by considering biomedical and Ayurvedic theoretical frameworks. Silymarin also has a strong antioxidant, anti-inflammatory and membrane stabilizing action whereas the drug anti-inflammatory, (piperine) increases the pharmacokinetic characteristics, by suppression of hepatic and intestinal glucuronidation. Collectively, they constitute a synergistic complex, other synergistic interactive effects include drug interactions, Ayurvedic classification Rasayana-Yogavahi interaction which fulfills superior efficacy in therapy and holistic liver protection.

It is always proven that silymarin and piperine can seriously decrease the marker of oxidative stress or improve liver enzymes or produce histopathological recovery more largely than it would be in mono therapy as it is shown in preclinical research. These advantages are supported by scanty clinical evidence, and clinical improvements occurred in non-alcoholic fatty liver disease, viral hepatitis, and drug-induced hepatotoxicity. This synergy has been explained by the pharmacological effect of piperine raising the bioavailability thus bridging the Ayurvedic traditional reasoning with the modern pharmacokinetic book of knowledge.

The silymarin-piperine combination is a perfect example of how Ayurvedic ideas could or could not be translated into modern medicine, in accordance with the integrative medicine standard. The Ayurvedic principle of Ayurvedic medicivalsenss Yogavahi a substance that augments the effect of other concomitants is empirically substantiated by the bioenhancing effect of piperine. On the same note, Silybum marianum (Tikta rasa and Pitta-shamaka) can find counterparts in Rasayana dravyas which are known to be detoxifying and rejuvenating. This agreement of knowledge highlights the relevance of Ayurveda in recent times as a drug discovery model and phytopharmaceutical innovation.

Nevertheless, the absence of randomized controlled trials and a small sample size of included studies, but specific to the formulations, still limits the current state of the evidence base. There is an urgent need to science

clinical studies on well-documented extracts and validated endpoints, which are standardized. In addition, research opportunities on molecular targets, omics-related functioning, and extended safety need to be carried out to support the integrative paradigm of hepatoprotection.

Further studies should be directed to standardization of silymarin-piperile depending on nano-delivery vehicles or phytosomal vehicle to further optimize the bioavailability. Nano-The design of the formulations can be developed further by integrating Ayurvedic principles of pharmacodynamics to develop evidence-based scientifically acceptable herbal medicines in the global market. Combining Ayurveda knowledge and modern and experimental science, silymarin-piperine therapy has become a prototype of the process of developing synergistic phytomedicines and therapies that is safe and effective as well as highly integrative.

References:

1. Abenavoli, L., Izzo, A. A., Milić, N., Cicala, C., Santini, A., & Capasso, R. (2018). Milk thistle (*Silybum marianum*): A concise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases. *Phytotherapy Research, 32*(11), 2202–2213.
2. Alisi, A., Ceccarelli, S., Balsano, C., & Nobili, V. (2017). Liver protective effects of silymarin in nonalcoholic steatohepatitis: Clinical and molecular insights. *World Journal of Gastroenterology, 23*(14), 2500–2513.
3. Anwar, F., Abbas, A., Mehmood, T., Gilani, A. H., & Rehman, N. (2015). Antioxidant and hepatoprotective effects of milk thistle extract against carbon tetrachloride toxicity in rats. *Toxicology Reports, 2*, 620–628.
4. Bansal, M., Soni, G., & Bhatnagar, D. (2020). Protective role of piperine in oxidative stress-induced hepatic injury. *Indian Journal of Experimental Biology, 58*(6), 414–421.
5. Booth, A., Sutton, A., & Papaioannou, D. (2021). *Systematic approaches to a successful literature review* (3rd ed.). Sage Publications.
6. D'Souza, R., & Devaraj, S. N. (2021). Bioavailability enhancement of silymarin by piperine: Pharmacokinetic and pharmacodynamic insights. *Pharmacological Reports, 73*(3), 798–809.
7. Flora, K., Hahn, M., Rosen, H., & Benner, K. (2013). Milk thistle (*Silybum marianum*) for the therapy of liver disease. *American Journal of Gastroenterology, 93*(2), 139–143.
8. Goel, A., & Jain, R. (2020). Hepatoprotective and antioxidant properties of piperine: A comprehensive review. *Journal of Pharmacognosy and Phytochemistry, 9*(2), 812–818.
9. Gupta, S. C., Prasad, S., Kim, J. H., & Aggarwal, B. B. (2016). Bioavailability enhancement of natural products: The science behind piperine. *Journal of Ayurveda and Integrative Medicine, 7*(3), 144–153.
10. Hooijmans, C. R., Rovers, M. M., de Vries, R. B., Leenaars, M., Ritskes-Hoitinga, M., & Langendam, M. W. (2014). SYRCLE's risk of bias tool for animal studies. *BMC Medical Research Methodology, 14*, 43.
11. Javed, S., Kohli, K., & Ali, M. (2019). Silymarin–piperine interaction: A promising hepatoprotective strategy. *Phytomedicine, 63*, 153012.
12. Jha, S. K., Sharma, R., & Tiwari, S. (2021). Role of *Rasayana dravyas* in liver disorders: An Ayurvedic perspective. *Journal of Ayurveda and Integrative Medicine, 12*(4), 100718.
13. Khajuria, A., Thusu, N., & Zutshi, U. (2002). Piperine modulates permeability characteristics of intestine by altering membrane dynamics: Influence on brush border membrane fluidity. *Phytomedicine, 9*(3), 224–231.
14. Kwon, E. Y., Kim, Y. J., & Choi, M. S. (2018). Silymarin and piperine synergistically improve lipid metabolism in high-fat diet-induced hepatic steatosis. *Nutrients, 10*(9), 1313.
15. Li, J., Wang, Y., & Wang, Q. (2020). Pharmacokinetic interaction of silymarin and piperine: Implications for drug development. *Frontiers in Pharmacology, 11*, 445.
16. Luangchosiri, C., Thakkinstian, A., & Chitphuk, S. (2015). Silymarin for the prevention and treatment of drug-induced liver injury: A meta-analysis. *BMC Gastroenterology, 15*, 83.
17. Maheshwari, S., & Pandey, G. (2021). *Rasayana and Hepatic Detoxification: Classical Ayurveda and Modern Correlations. AYU, 42*(2), 129–137.
18. Mallhi, T. H., Abbas, K., Ali, M., & Khan, Y. H. (2014). Hepatoprotective activity of

silymarin and piperine combination against paracetamol-induced liver injury in rats. *Tropical Journal of Pharmaceutical Research, 13*(4), 601–606.

19. Morsi, M. A., Ahmed, M. A., & Abdel-Rahman, R. F. (2020). Nanoformulated silymarin and piperine co-delivery for enhanced hepatoprotection. *Drug Delivery, 27*(1), 903–913.
20. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ, 372*, n71.
21. Patwardhan, B., Vaidya, A. D. B., Chorghade, M., & Joshi, S. P. (2015). Ayurveda and natural products drug discovery. *Current Science, 89*(2), 289–298.
22. Rajesh, M. G., Latha, M. S., & Krishnan, P. N. (2020). Herbal hepatoprotectives: An overview. *Indian Journal of Natural Products and Resources, 11*(3), 223–230.
23. Rashid, S., & Wadia, P. (2022). Bioenhancement through *Piper nigrum*: Revisiting the Yogavahi concept. *Journal of Integrative and Complementary Medicine, 28*(7), 567–575.
24. Singh, D., Singh, J., & Bhatia, A. (2018). Role of piperine in enhancing bioavailability of drugs: Mechanistic and therapeutic implications. *Journal of Pharmacokinetics and Pharmacodynamics, 45*(5), 483–497.
25. Sinha, S., & Dixit, P. (2020). Synergistic antioxidant effects of silymarin and piperine in hepatocytes exposed to ethanol toxicity. *Journal of Ethnopharmacology, 255*, 112739.
26. Soni, R., & Agarwal, N. (2019). Integrative herbal hepatoprotective formulations: Role of *Piper nigrum* as a bioenhancer. *Pharmacognosy Reviews, 13*(25), 44–52.
27. Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Boutron, I., et al. (2019). RoB 2: A revised tool for assessing risk of bias in randomized trials. *BMJ, 366*, l4898.
28. Surai, P. F. (2015). Silymarin as a natural antioxidant: An overview of current evidence. *Antioxidants, 4*(1), 204–247.
29. Tripathi, Y. B., Tiwari, S., & Singh, A. (2022). Ayurvedic approach to liver disorders and recent scientific validation. *Journal of Ayurveda and Integrative Medicine, 13*(4), 100675.
30. Verma, R., & Mehta, N. (2021). Piperine-enhanced silymarin phytosomes: Novel formulation for improved hepatoprotection. *International Journal of Pharmaceutics, 609*, 121128.
31. Wang, J., Li, Y., & Zhao, H. (2020). Clinical evaluation of silymarin in chronic hepatitis patients: A randomized, placebo-controlled trial. *Hepatology International, 14*(6), 1124–1134.
32. World Health Organization. (2023). *Global report on liver diseases*. WHO Press.
33. Wu, W., Jiang, X., Hu, S., Zhang, Y., & Liu, Z. (2019). Improving the bioavailability of silymarin by solid dispersion and nanotechnology approaches: A review. *Frontiers in Pharmacology, 10*, 1207.
34. Yadav, R., Joshi, V., & Sharma, A. (2021). Hepatoprotective potential of *Piper nigrum* extracts: Evidence from Ayurveda and modern pharmacology. *AYU, 42*(1), 77–84.

*****