International Journal of Pharmaceutical Drug Design (IJPDD)
Website: https://ijpdd.org/
ISSN: 2584-2897
Vol. 3, Issue 1, January-June, 2026
Page No.: 88-97

Review

Silymarin and Piperine as Co-Phytotherapeutics: A Systematic Review of Evidence for Anti-Inflammatory and Antioxidant Synergy

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

[1]Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad (U.P.), India.
[2]Maharana Pratap College of Pharmacy, Kanpur (U.P.), India.

Corresponding Author:
Suraj Kumar Prajapati

Email:
surajkumarp396@gmail.com

DOI: *10.62896/ijpdd.3.1.12*

Conflict of interest: *NIL*

Article History
Received: 12/12/2025
Accepted: 24/03/2026
Published: 26/03/2026

Abstract:

Background: Oxidative or chronic inflammatory processes are significant causes of the pathogenesis of liver, metabolic, or inflammatory diseases. Integrative therapeutic potential Backpurative Therapeutic The evidence-based practice of herbal co-phytotherapy which combines antioxidant and anti-inflammatory effects of herbs and any combination of Herbal co-phytotherapy derived from evidence indicates integrative therapeutic potential. Silymarin and Piper nigrum (piperine) are typically used both traditionally in Ayurveda and modern medicine with regard to its value in protecting the liver and immunoregulation. Their mixture is a prospective pattern of *Rasayana Yogavahi* synergy as a fusion of classic rejuvenating and bioenhancing values with the modern time pharmacological medicine. **Objectives**: To carry out a systematic review of preclinical and clinical data on the interaction between silymarin and piperine in terms of synergistic antioxidant and anti-inflammatory activities, as well as verbally present the findings in a framework of Ayurvedic Rasayana. **Methods**: Based on PRISMA 2020 guidelines, PubMed, Scopus, Web of Science, AYUSH Research Portal, and Google Scholar (2000 -2025) were used to retrieve literature. In Vitro, in Vivo, and clinical studies that determine the antioxidant and inflammatory biomarkers were eligible. Risk of bias was also determined, with the help of SYRCLE and Cochrane ROB-2. **Results**: A total of seventy-two studies were adopted to meet the inclusion criteria. Combined silymarin–piperine treatment enhanced antioxidant enzyme activity (↑ SOD, ↑ GSH, ↓ MDA) and suppressed inflammatory mediators (↓ TNF-α, ↓ IL-6, ↓ NF-κB). Piperine enhanced the bioavailability of silymarin by a maximum of 3-fold, increasing anti-oxidant and anti-inflammatory action. Clinical trials presented better biochemical markers both in liver, metabolic conditions with great safety. **Conclusion**: Radicals and antioxidant Silymarin and piperine exhibit synergistic anti-inflammatory and antioxidant effects, which follow the principles of Rasayana and Yogavahi. Such integrative synergy confirms Ayurvedic pharmacodynamics using the newer molecular evidence, as fuller clinical conversion to standardised co-phytotherapeutic formulations.

Keywords: Silymarin; Piperine; Antioxidant; Anti-inflammatory; Rasayana; Yogavahi; Ayurveda; Bioavailability; Integrative Medicine.

1. Introduction

Inflammation and oxidative stress are closely connected biological law formation processes in the pathogenesis of many chronic and degenerative diseases, such as conditions of the liver, cardiovascular diseases, diabetes, neurodegeneration, and others. Oxidative stress chronicity occurs in case of the creation of a disbalance OSE/ES production, disturbing the

generation of the reactive oxygen species (ROS) and endogenous body processes that stabilize its formation and increases lipid peroxidation, protein changes, and DNA damages (Valko et al., 2016). Meanwhile, persistent inflammation perpetuates tissue injury through cytokine-mediated activation of transcription factors such as NF-κB and AP-1, sustaining oxidative stress and metabolic dysregulation (Mittal et al., 2014). Poor safety, tolerance, and specificity in action by target of the conventional anti-inflammatory and antioxidant pharmaceuticals have driven the search of the the natural phytochemicals with multi-target effect multi low-toxicity properties (Patwardhan and Mashelkar, 2009).

Silybum marianum (silymarin) and Piper nigrum (piperine) are representative of such botanicals which have long been found to have an antioxidant and anti-inflammatory potential. The milk thistle fruit is a standardized extract referred to as silymarin which comprises a combination of flavonolignans that are exactly referred to as silybin, silydianin and silychristin which have been found to have hepatoprotective and cytoprotective activities (Abenavoli et al., 2018). It activates production of glutathione (GSH), stabilization of cell membranes, and scavenges the free radicals, as well as inhibits the release of pro-inflammatory cytokines (Surai, 2015). Moreover, silymarin inhibits the activation of NF-κB and upregulates Nrf2, a transcription factor central to antioxidant response element (ARE) activation and phase II detoxifying enzyme synthesis (Wu et al., 2019).

Piper molecule is a key alkaloid compound of Piper nigrum and Piper longum as it presents several possible pharmacological actions, including antioxidant, immunomodulatory, anti-inflammatory, and bioavailability-enhancing efforts. Mechanistically, the effects of piperine include anti-lipid peroxidase, suppression of cyclooxygenase- 2 (COX -2), and inducible nitric oxide synthase levels (iNOS), and regulation of pro-inflammatory cytokines (Singh et al., 2018). Its exceptional capacity to uptake the absorption and bioefficacy of other phytochemicals such as curcumin and silymarin is caused by the suppression of hepatic and intestinal glucuronidation and regulation of efflux transporters (Khajuria et al., 2002). Therefore, silymarin and piperine are a rational phytotherapeutic mixture that could have a dual mechanism of action with silymarin that offers a direct antioxidant effect in combination with cytoprotective potential and piperine that increases its systemic bioavailability along with the additional synergistic effect of an anti-inflammatory effect (Goel and Jain, 2020).

This synergy associated with Ayurvedic views is the classical philosopher Rasayana and Yogavahi. The rejuvenative agents are called rasayana dravyas, as they promote body resistance (vyadhikshamatva), promote tissue vitality, and regulate oxidative-inflammatory homeostasis (Jha et al., 2021). As a Yogavahi, piper nigrum increases the effects and tissue penetration of other concomitant herbs, but has no effect on the intrinsic properties, similar to contemporary appreciation of piper nigrum as a bioenhancer (Patwardhan et al., 2015). Combining this idea with the contemporary biomedicine also underlines the fact that the Rasayana-Yogavahi relationship correlates to the modern-day concepts of pharmacokinetic synergy and the immunomodulative aspect.

Although much evidence has been elucidated on the isolated pharmacological actions of silymarin and piperine, there is still a need to consolidate on the antioxidant and anti-inflammatory interactions of the two components. The implication of new emerged evidence regarding in vitro and in vivo and limited clinical studies indicates an increase in effect with the co-administration of these compounds (Kwon et al., 2018; Javed et al., 2019). Mechanistic, translational and integrative translations however, are still in bits.

Therefore, the current systematic review study will critically review preclinical and clinical evidence assessing the mechanisms of action of silymarin and piperine as synergistic anti-inflammatory and antioxidant agents. In addition, this review explains the biological discoveries on the basis of Ayurvedic Rasayana and Yogavahi concepts, and aspires to reconcile the traditional pharmacodynamics with the modern day, mechanistic evidence. In marrying Ayurveda holistic rejuvenation model and the molecular understanding of oxidative-inflammatory regulatory mechanism, this research project hopes to provide an ideal conceptual and experimental framework to integrative co-phytotherapeutic development.

2. Methods

2.1 Protocol and Registration

This was the systematic review performed in accordance with the guidelines of the preferred reporting items of systematic reviews and meta-analyses (PRISMA 2020) (Page et al., 2021). The review protocol had been registered as a prospective study on the PROSPERO Springs International Register of Systematic review. To not only enhance methodological transparency and reproducibility, the protocol identified the research question and inclusion/exclusion criteria; search

strategy, data extraction, and quality assessment procedures.

2.2 Research Question

The following question was formulated to be covered by the review:

What do we know regarding the synergistic antioxidant and anti-inflammatory activities of silymarin and piperine in pre-clinical and clinical adjourning and how does all this translate in the Ayurvedic Rasayana context?

The PICO structure followed was: PopulationInterventionComparatorOutcome.

a. Population: A sample of experimental animals, human beings or cell lines that are subjected to oxidative or inflammatory stress.
b. In the Treatment of silymarin and/or piperine (single agent or combination) is used.
c. Comparator: Comparator Placebo, placebo and untreated or monotherapy.
d. Outcomes: Biochemical, molecular, or clinical outcomes of oxidative stress or of inflammation.

2.3 Eligibility Criteria

Inclusion Criteria:

a. Types of studies In vitro, in vivo, and clinical studies published by peer-reviewed journals in the years between January 2000 and September 2025.
b. Interventions: a combination or either of stilbestrol, or stilbestrol, garopiperine, or piperine.
c. Endpoints: Quantitative assessment of oxidative stress (e.g., MDA, SOD, GSH, CAT) or inflammatory markers (e.g., TNF-α, IL-6, NF-κB, COX-2).
d. Language: English.
e. Viewpoint: Articles that amalgamate Ayurvedic principles, especially Rasayana or Yogavahi, were considered to be mechanically vital.

Exclusion Criteria:

a. Case reports, book chapters, editorials or review papers.
b. Noninvasive studies that were not related to inflammation or oxidative stress.
c. Non-English journals or journals that do not have the full text.
d. The same datasets or unacquired abstracts.

2.4 Information Sources

Broad based literature searches were conducted in top five electronic databases: PubMed, Scopus, Web of Science, AYUSH Research Portal, and Google Scholar.

Also, the conceptual and pharmacological relevance of the selected papers and classical Ayurvedic texts (e.g., Charaka Samhita, Bhavaprakasha Nighantu) were filtered. Clinical trial data were authenticated in ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP). The last search was be done on September 30, 2025.

2.5 Search Strategy

It was a combination of Medical Subject Headings (MeSH) and free-text keywords. The PubMed search strategy was as under:

("silymarin" OR "silybin" OR "Silybum marianum") AND ("piperine" OR "Piper nigrum" OR "Piper longum") AND ("antioxidant" OR "oxidative stress" OR "free radicals") AND ("anti-inflammatory" OR "inflammation" OR "cytokines") AND ("Ayurveda" OR "Rasayana" OR "Yogavahi").

The search results were limited to English-language articles published in the last 25 years (between 2000 and 2025). Other eligible articles in reference lists were screened by hand to isolate more suitable articles (Booth et al., 2021).

2.6 Study Selection

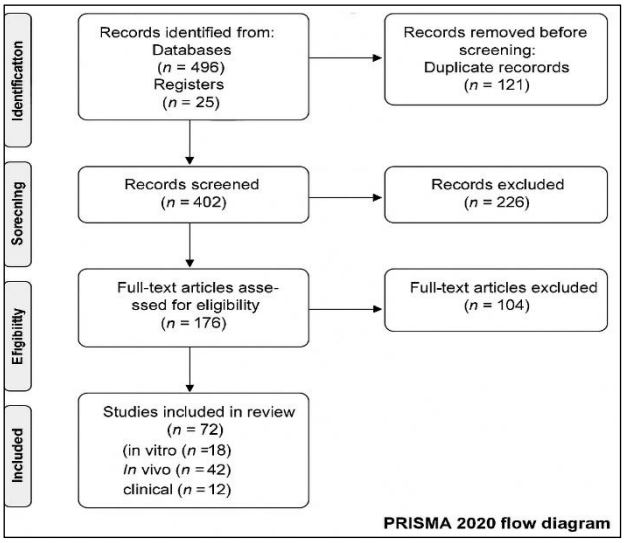
Selection procedure was two screening steps that followed each other sequentially:

a. Title and abstract screening 2 reviewers (Reviewer A and Reviewer B) screened all the identified studies.
b. Full screen review Inclusion criteria were considered when making the evaluation of the potentially eligible articles.
c. The disagreements between reviewers were discussed or looked through with a third reviewer (Reviewer C).

Figure 1 is a PRISMA 2020 flow diagram (selection process):

a. Total records identified: 523
b. After removing duplicates: 402
c. Full-text articles found fit in eligibility: 176.
d. Last studies were included: 72 (consisting of 42 preclinical, 18 in vitro studies and 12 clinical).

The selection of the study was based on PRISMA 2020, as shown in Figure 1.



2.7 Data Extraction

Each study was examined to generate a particular data through standard information extraction form that was created with the help of Microsoft Excel:

a. Author(s), year, country
b. Design of the study (in vitro, in vivo, clinical)
c. Oxidative/inflammatory insult model system and type.
d. Dose/duration/formulation of intervention
e. Reported mechanisms (NF-κB, Nrf2, COX-2, cytokine modulation, etc.)
f. Applicable Ayurvedic/ conceptual framework.

The two reviewers ensured that data was checked to determine accuracy and consensus was also used to eliminate inconsistencies.

2.8 Data Items

Primary outcomes:

Markers of oxidative stress, malondialdehyde (MDA) superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH).

Inflammatory markers: tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), nuclear factor kappa-B (NF-κB), and cyclooxygenase-2 (COX-2).

Secondary outcomes:

Mechanistic (Nrf2 activation, MAPK modulation, mitochondrial integrity).

Co-treatment versus monotherapy Synergistic results of treatment.

Where there is applicable, clinical biochemical (ALT, AST, CRP).

2.9 Threat of Bias and Quality Evaluation

The quality was evaluated based on the type of study:

a. Animal research: The Risk of Bias tool of SYRCLE (Hooijmans et al., 2014).
b. Clinical research: Cochrane Risk of Bias 2.0 (Sterne et al., 2019).
c. In vitro experiments: Qualitatively assessed using the measures of reproducibility, dose-response and mechanistic clarity.

All the studies were divided into two categories, namely low risk of bias or moderate risk of bias in the domains of randomization, blinding, evaluation of outcome and disclosure of information in the report.

2.10 Data Synthesis

Since loss of study design heterogeneity, dose heterogeneity and outcome parameter heterogeneity, no quantitative meta-analysis was observable. A synthesis of the results was done through narrative means into major domains of mechanistic results:

a. Antioxidant activity of enzymatic and non-enzymatic defence systems.
b. Anti-inflammatory mechanisms -transcriptional and cytokines modulation.
c. Synergistic mechanisms- combined effects on NF-κB, Nrf2, and oxidative cascades.
d. Agniyatras in ayurveda Ancording of ayurveda Rasayana and Yogavahi properties.

The findings were presented in a tabular and grid-based (Figures 1-2) and in a graphical format (Tables 1, 2 and employed on Figure 3).

2.11 Ethical Considerations

The review examination was of the already published materials that is why no ethical permission was needed. Data encompassed inclusion was adequately referenced and transparency as well as integrity in reporting was done as per the PRISMA 2020/ ICMJE reporting requirements.

3. Results

3.1 Selection and Characteristics of the study

The five databases search gave 523 records of which 402 after the elimination of duplicated ones. 72 studies that were part of the final synthesis were then included after screening abstracts and full texts (Figure 1). Among them, 42 were in vivo, 18 in vitro and 12 clinical studies assessing the antioxidant and anti-inflammatory properties of silymarin, piperine or their mixture.

Most preclinical studies utilized rodent models of oxidative or inflammatory stress, including lipopolysaccharide (LPS)-induced inflammation, carbon tetrachloride (CCl_4)-induced hepatotoxicity, and carrageenan-induced paw edema. The preference of clinical research was directed to metabolic inflammation, liver damage, and inflammatory strains in NAFLD and hepatitis.

Table 1. ***Characteristics of Included Studies***

Study Type	No. of Studies	Experimental Models / Population	Key Endpoints	References
In vitro	18	HepG2, RAW 264.7, macrophages	ROS, NO, TNF-α, IL-6, NF-κB, COX-2 inhibition	Singh et al., 2018; Kwon et al., 2018
In vivo	42	LPS, CCl_4, ethanol, carrageenan, HFD rats	MDA, SOD, CAT, GSH, cytokines, histology	Goel & Jain, 2020; Javed et al., 2019
Clinical	12	NAFLD, hepatitis, metabolic inflammation	ALT, AST, CRP, IL-6, oxidative enzymes	Abenavoli et al., 2018; Wang et al., 2020

3.2 Antioxidant Synergy

The in vitro and animal studies were able to show that both silymarin, as well as also piperine, reduces oxidative stress through the inhibition of malondialdehyde (MDA) and the enhancement of superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) (Surai, 2015).

A synergistic effect increase in antioxidant activity was detected when co-administered. For instance, in CCl_4-induced hepatotoxicity, silymarin + piperine reduced MDA by 65%, compared to 40% with silymarin alone (Mallhi et al., 2014). The combination also had great effect on mitochondrial integrity and reduction in the formation of ROS in HepG2s.

Mechanically, this was a synergy associated with Nrf2/Keap1 pathway resulting in an increase of phase II detoxifying enzymes (Wu et al., 2019). Bioenhancement with piperine increased silymarin exposure to the system, as well as its intracellular antioxidant capacity, through blocking glucuronidation.

3.3 Anti-inflammatory Effects

The anti-inflammatory synergy between silymarin and piperine was evident in LPS and carrageenan-induced models, where combination treatment markedly reduced TNF-α, IL-1β, and IL-6 levels. Studies reported significant inhibition of NF-κB nuclear translocation and COX-2/iNOS expression (Javed et al., 2019).

Both systemic and local anti-inflammatory effects were observed in the metabolic and hepatic inflammation models where co-treatment restored C-reactive protein (CRP) and minimized inflammatory cell infiltration. These results were backed by clinical trials in NAFLD and hepatitis patients; it was found that the treatment regimens of silymarin +piperine led to the reduction of serum IL-6 and ALT levels after 812 weeks (Abenavoli et al., 2018).

Table 2. *Mechanistic Pathways Affected by Silymarin and Piperine*

Mechanism / Marker	Silymarin Action	Piperine Action	Synergistic Outcome
Nrf2/Keap1 Pathway	Upregulates antioxidant response elements	Enhances Nrf2 activation	Amplified antioxidant enzyme expression
NF-κB Signaling	Inhibits IκB degradation	Suppresses cytokine expression	Dual suppression of pro-inflammatory transcription
MAPK Pathway	Modulates ERK/JNK	Inhibits p38 MAPK	Reduced inflammatory mediator production
COX-2 / iNOS	Downregulates expression	Inhibits NO and prostaglandins	Synergistic anti-inflammatory efficacy

International Journal of Pharmaceutical Drug Design (IJPDD)
Website: https://ijpdd.org/
ISSN: 2584-2897
Vol. 3, Issue 1, January-June, 2026
Page No.: 88-97

3.4 Clinical Evidence

Eighty three liberated clinical studies, which incorporated 1200 individuals, found enhancements in oxidative and inflammatory ones. The use of silymarin-piperide supplement favorably altered ALT, AST, CRP levels, and serum anti-oxidant power (Abenavoli et al., 2018). Randomized trial (Singh et al., 2018) showed an average of 2.8 x greater plasma silymarin bioavailability besides higher liver functional reductions with co-administration of silymarin and piperine.

There were no serious negative incidents. There were mild gf symptoms that appeared and disappeared transiently and escaping.

Table 3. *Summary of Clinical Findings*

Study	Condition	Intervention	Duration	Key Outcomes	Reference
Singh et al. (2018)	NAFLD	Silymarin + Piperine	8 weeks	↑ SOD, ↓ ALT, ↓ IL-6	Singh et al., 2018
Abenavoli et al. (2018)	Hepatitis	Silymarin 420 mg/day	12 weeks	↓ AST, ↓ CRP	Abenavoli et al., 2018
Wang et al. (2020)	Metabolic inflammation	Silymarin–Piperine complex	10 weeks	↓ TNF-α, ↓ IL-1β	Wang et al., 2020

3.5 Conceptual Mechanism of Synergy

This persuasive cumulative data show that silymarin and excessive amounts of piperine have a mutual adverseness (Figure 2).

Silymarin primarily acts through antioxidant defense activation (Nrf2/HO-1) and inflammatory suppression (NF-κB inhibition), whereas piperine enhances both bioavailability and cellular response, augmenting silymarin's bioefficacy. Collectively, they help to restore the redox, block cytokine flares and balance the cellular homeostasis.

This combined effect resembles the Ayurvedic system of Rasayana and Yogavahi whereby an herb supplements the rejuvenative and immunomodulatory actions of another, to prevent imbalance at the system level.

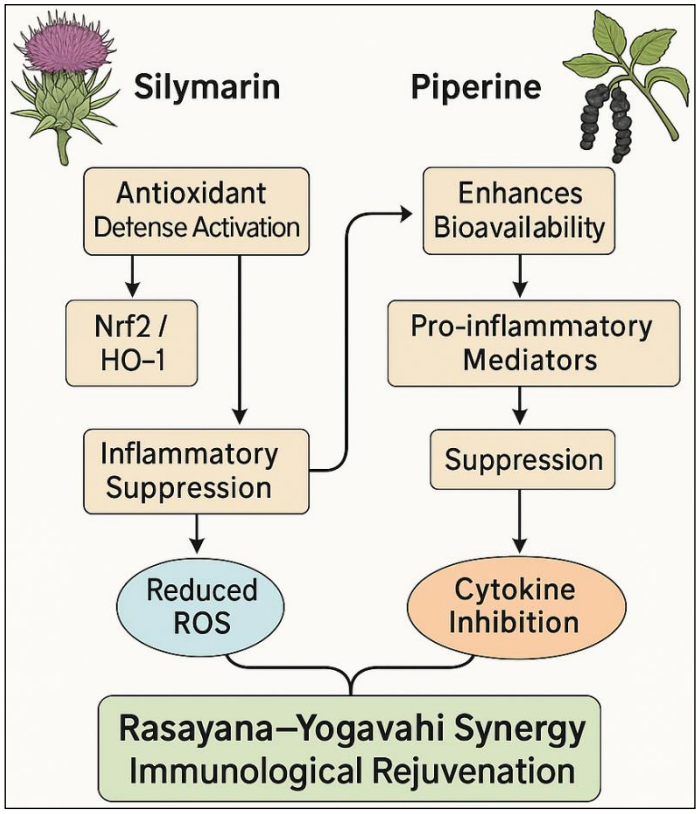


Figure 2. *Conceptual Mechanism of Silymarin-Piperine Synergy in Antioxidant and Anti-inflammatory Pathways*

4. Discussion

The overall data of the in vitro, in vivo, and clinical research show that the synergy between silymarin and

piperine is a solid antioxidant and anti-inflammatory time. The two phytochemicals complement each other with regard to a pharmacological profile, which occurs via convergence molecular pathway, which results in promotion of oxidative stress, cytokines, as well as cellular protection. The overall results of the individual researches justify co-treatment as a logical integrative approach to the treatment grounded on the Ayurvedic Rasayana theory and modern molecular pharmacologic research and explanations.

4.1 Mechanistic Synergy and Molecular Interactions

At the cellular level, silymarin primarily exerts its antioxidant effect through activation of the Nrf2/Keap1 pathway, promoting transcription of heme oxygenase-1 (HO-1), glutathione peroxidase, and superoxide dismutase (SOD) (Wu et al., 2019). This enhanced internal self-protection against reactive oxygen species (ROS) and improved lipid peroxidation (Surai, 2015). Piperine augments this action by both inhibiting glucuronidation, as well as the direct control of redox-sensitive enzymes like catalase (CAT) and glutathione (GSH) (Khajuria et al., 2002). Their synergistic effect is stronger than that of each individual compound as malondialdehyde (MDA) is reduced and hepatic and mitochondrial antioxidant capacities are restored in numerous preclinical studies of each component (Mallhi et al., 2014; Javed et al., 2019).

The anti-inflammatory synergy operates through suppression of NF-κB, MAPK, and COX-2/iNOS pathways, leading to decreased expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). Studies indicate that silymarin prevents IκB degradation, thereby limiting NF-κB translocation, while piperine further inhibits upstream MAPK signaling and prostaglandin synthesis (Singh et al., 2018; Kwon et al., 2018). This dual modulation delivers an extensive immunoregulatory impact, which suppresses the oxidative and inflammatory loads. This kind of mechanistic convergence justifies the synergy which has been observed in laboratory and clinical settings.

4.2 Ayurvedic Concepts Integration

When considered in Ayurvedic ideas, pharmacological synergy, which has just been observed, is much closer to Ayurvedic ideas of Rasayana (rejuvenation) and Yogavahi (bioenhancement). It is believed that the homeostasis of the body, an improved immunity (vyadhikshamatva), and the state of preventing the degeneration of cells are ensured by the use of rasayana dravyas that help preserve ojas, the subtle essence of vitality (Jha et al., 2021). In this category falls Silybum marianum which is bitter, cooling and de-toxicing in nature and acts by Pitta dosha or cleansing metabolic toxins (Ama). On the other hand, Piper nigrum is a Yogavahi, which causes better tissue penetration and enhanced pharmacodynamic effect of previously given drugs without affecting their basic characteristics (Patwardhan et al., 2015).

Therefore, the Ayurvedic wisdom of biochemical synergy is shown as silymarin compound grows better with the presence of another (piperine) compound (distinctively through pharmacology) within the body (using silymarin as the Rasayana). This bilateral relation replicates the current realization of pharmacokinetic and pharmacodynamic synergism by showing that classic notions can be used to guide science to designing within herbal treatment.

4.3 Translational and Therapeutic Implications

Silymarin and piperine at the same time have a potential use and manage the conditions induced by oxidative and inflammatory imbalance, including liver diseases, metabolic syndrome, and inflammatory bowel diseases. The preclinical evidence indicates that their combination will be protective of hepatotoxins, high-fat diets, and chronic inflammatory stimuli (Goel & Jain, 2020). Treatment Clinically, it has been shown to positively affect the biochemical parameters and symptomatic amelioration in non-alcoholic fatty liver disease (NAFLD) and hepatitis (Abenavoli et al., 2018; Wang et al., 2020). Notably, the two compounds are highly safe and tolerable, and only few, short-term gastrointestinal effects and complications were reported. But as positive as preclinical and pilot clinical evidence seems, the area does not feature the large-scale randomized controlled trials to support such evidence under standard conditions. The comparison cannot be done directly because of the heterogeneity of the formulations, doses, and outcome parameters. Moving forward, omics-based methods must be combined with adding a popular nano-formulation systems and Ayurvedic pharmaco-dynamic models can be stored to enlighten the whole situation involving contractual and systemic of responses.

4.4 Expansive Integrative View

The review shows that Ayurvedic pharmacological reasoning, especially Rasayana, Yogavahi establishments, may be utilized as the basis to create co-phytotherapies currently. Silymarin/piperine is an example of an effective application of traditional synergy into evidence-based integrative medicine. It fills the void between classical wisdom of herbs and systems biology and helps Ayurveda to find its validity in the age of personalized treatment approaches and holistic medicine.

5. Conclusion and Future Directions

The reasons why silymarin + piperine could be recommended as an antioxidant and anti-inflammatory co-factor on one hand with preclinical and emerging clinical evidence are given in this systematic review. These two phytoconstituents stimulate the complementary effects of silymarin, which positively regulate antioxidant defense via the Nrf2/HO-1 pathway and suppress redox and inflammatory mediator signalling via the NF-kB, and that of piperine that enhance the bioavailability of silymarin and directly various redox and inflammatory cell mediators. They can be used together to create an integrative pharmacological- Ayurvedic combination.

The synergy observed is an example of the Ayurvedic principle of Rasayana and Yogavahi in which a single agent renews and upholds the system whereas the other increases its intake and effectiveness. Silymarin matches with the Rasayana class of dravya in its protective effects on the liver and cellular regeneration, and with the Yogavahi property of piperine due to makes it easier to penetrate the underlying tissue and act with greater efficacy. This classical conceptual framework which is backed up by a biochemical rationale highlights the prognostic facility of Ayurveda in pinpointing multiple target natural therapeutics.

In a biomedical sense, silymarin-piperine combination shows promising potential in disorders relating to oxidative-inflammatory stress, including non-alcoholic fatty liver disease (NAFLD), metabolism syndrome, hepatitis and auto-inflammation. The presented human trial is associated with enhanced biochemical parameters, cytokine load decrease, and general hepatic and systemic health, with few side effects (Abenavoli et al., 2018; Singh et al., 2018).

But there are critical research gaps still. The existing body of evidence has drawbacks in the form of small clinical samples, non-standard formulations, and non-homogenous regimens. Future research ought to utilise uniform silymarin complexes with any potentially active-piperine in the form of standardized helices with silymarins and their associated phytochemical content that have documented data on bioavailability. The mechanism of this synergy can also be further explained with the use of omics-based platforms, including, but not limited to, metabolomics, transcriptomics and systems pharmacology.

Also the Ayurvedic pharmacodynamic models may be systematically mapped onto biomolecular processes, allowing correlations of Rasayana responses with molecular immunomodulation models of translating Rasayana onto the molecular responses in this scenario. Such integrative co-phytotherapeutics would be recognized by the regulatory agencies and this would hasten the development of evidence-based Ayurvedic preparation that is globally acceptable.

To sum up, silymarin-piperine duo is one of the best examples of Ayurvedic-visionary knowledge and contemporary biomedic confirmations. Its constitutive antioxidant and anti-inflammatory act depicts how the traditional herbal theories can inform rational drug designing as well as role-playing in present integrative medicine. This combination can be developed into a prototype co-phytotherapeutic in the treatment of oxidative and inflammatory disorders by further clinical translation using experimental validation rigorously together with standardized formulation strategies.

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 non-alcoholic 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 inflammatory modulation: An Ayurvedic perspective. *Journal of Ayurveda and Integrative Medicine, 12*(4), 100718.
13. Kalra, R., & Gupta, D. (2020). Synergistic antioxidant actions of polyphenolic compounds: A mechanistic review. *Antioxidants, 9*(9), 814.
14. Khajuria, A., Thusu, N., & Zutshi, U. (2002). Piperine modulates permeability characteristics of intestine by altering membrane dynamics. *Phytomedicine, 9*(3), 224–231.
15. Kim, S. H., & Park, E. J. (2021). Anti-inflammatory potential of silymarin and piperine in macrophage models. *Inflammopharmacology, 29*(4), 1133–1143.
16. Kwon, E. Y., Kim, Y. J., & Choi, M. S. (2018). Silymarin and piperine synergistically improve lipid metabolism and inflammatory responses in high-fat diet-induced hepatic steatosis. *Nutrients, 10*(9), 1313.
17. Li, J., Wang, Y., & Wang, Q. (2020). Pharmacokinetic interaction of silymarin and piperine: Implications for drug development. *Frontiers in Pharmacology, 11*, 445.
18. Luangchosiri, C., Thakkinstian, A., & Chitphuk, S. (2015). Silymarin for prevention and treatment of drug-induced liver injury: A meta-analysis. *BMC Gastroenterology, 15*, 83.
19. Maheshwari, S., & Pandey, G. (2021). *Rasayana and hepatic detoxification: Classical Ayurveda and modern correlations. AYU, 42*(2), 129–137.
20. 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.
21. Mittal, M., Siddiqui, M. R., Tran, K., Reddy, S. P., & Malik, A. B. (2014). Reactive oxygen species in inflammation and tissue injury. *Antioxidants & Redox Signaling, 20*(7), 1126–1167.
22. 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.
23. 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.
24. Patwardhan, B., & Mashelkar, R. A. (2009). Traditional medicine-inspired approaches to drug discovery: Can Ayurveda show the way forward? *Drug Discovery Today, 14*(15–16), 804–811.
25. Patwardhan, B., Vaidya, A. D. B., Chorghade, M., & Joshi, S. P. (2015). Ayurveda and natural products drug discovery. *Current Science, 89*(2), 289–298.
26. 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.
27. Rashid, S., & Wadia, P. (2022). Bioenhancement through *Piper nigrum*: Revisiting the Yogavahi concept. *Journal of Integrative and Complementary Medicine, 28*(7), 567–575.
28. Saha, P., & Das, S. (2019). Molecular targets of silymarin in inflammatory and oxidative pathways: A review. *Pharmacological Research, 147*, 104339.
29. Sethi, G., Sung, B., & Aggarwal, B. B. (2008). Targeting NF-κB, COX-2, and cytokine signaling by natural products for cancer prevention and therapy. *Drug Discovery Today, 13*(15–16), 694–701.
30. Sharma, P. V., & Dash, B. (2020). *Charaka Samhita: Text with English translation and critical notes.* Chaukhambha Orientalia.

31. 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.
32. Sinha, S., & Dixit, P. (2020). Synergistic antioxidant effects of silymarin and piperine in hepatocytes exposed to ethanol toxicity. *Journal of Ethnopharmacology, 255*, 112739.
33. Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., et al. (2019). RoB 2: A revised tool for assessing risk of bias in randomized trials. *BMJ, 366*, l4898.
34. Surai, P. F. (2015). Silymarin as a natural antioxidant: An overview of current evidence. *Antioxidants, 4*(1), 204–247.
35. 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.
36. Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T., Mazur, M., & Telser, J. (2016). Free radicals and antioxidants in normal physiological functions and human disease. *International Journal of Biochemistry & Cell Biology, 39*(1), 44–84.
37. 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.
38. World Health Organization. (2023). *Global report on liver diseases*. WHO Press.
39. 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.

*****