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Original Article

Explaining Uncertain Hepatoprotective Effects: When Silibinin Co-Administered with Other Drugs

Silibinin Diğer İlaçlarla Birlikte Uygulandığında Belirsiz Hepatoprotektif Etkilerin Açıklanması

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ABSTRACT

Objective: This study investigated the herb-drug interaction between silibinin and carbamazepine (CBZ) and the potential risk of adverse drug reactions (ADR) when silibinin is co-administered with other drugs.

Methods: Primary fresh hepatocytes were cultured, and an methylthiazolyldiphenyl-tetrazolium bromide assay was performed after administration of different concentrations of CBZ, and silibinin. Meanwhile, a retrospective study on hepatic adverse reactions involving the combination of silibinin with other drugs was performed using the Food and Drug Administration Adverse Event Reporting System (FAERS).

Results: The protective effects of silibinin on CBZ do not appear on hepatocytes in a dose-dependent manner. When silibinin (25μM) was co-administered with CBZ (2mM), the cell viability increased from 47.8% to 75.9% ($p<0.05$), while increasing the silibinin concentration to 50μM with CBZ (2mM), the hepatocyte viability significantly declined from 47.8% to 38.7% ($p<0.05$). In the FAERS database, the risk of adverse reactions significantly increases when combined with silibinin. The silibinin co-administration was significantly associated with hepatotoxicity reports.

Conclusions: The results of the cell experiment showed that silibinin's liver protective effects were uncertain when it was combined with CBZ. FAERS database analysis revealed elevated risks of ADRs with silibinin co-administration, collectively highlighting the necessity for vigilance against unanticipated herb-drug interactions.

Keywords: Silibinin, carbamazepine, hepatotoxicity, adverse drug reactions, herb-drug interaction, Food and Drug Administration adverse event reporting system

ÖZ

Amaç: Bu çalışmada silibinin ve karbamazepin (CBZ) arasındaki bitki-ilaç etkileşimi ve silibinin diğer ilaçlarla birlikte uygulandığında potansiyel advers ilaç reaksiyonu (ADR) riski araştırılmıştır.

Yöntemler: Birincil taze hepatositler kültürlenmiş ve farklı konsantrasyonlarda CBZ ve silibinin uygulamasından sonra metiltetrazolium tetrazolyum testi deneyi yapılmıştır. Bu arada, Gıda ve İlaç Dairesi Advers Olay Raporlama Sistemi (FAERS) kullanılarak silibinin diğer ilaçlarla kombinasyonunu içeren hepatik advers reaksiyonlar hakkında retrospektif bir çalışma yapılmıştır.

Bulgular: Silibininin CBZ üzerindeki koruyucu etkileri hepatositler üzerinde doza bağlı bir şekilde görülmemektedir. Silibinin (25μM) CBZ (2mM) ile birlikte uygulandığında hücre canlılığı %47,8'den %75,9'a yükselmiştir ($p<0,05$); silibinin konsantrasyonu CBZ (2mM) ile birlikte 50μM'a eklendiğinde ise hepatosit canlılığı %47,8'den %38,7'ye düşmüştür ($p<0,05$). FAERS veri tabanında, silibinin ile kombine edildiğinde advers reaksiyon riski önemli ölçüde artmaktadır. Ve silibinin birlikte uygulanması hepatotoksisite raporları ile önemli ölçüde ilişkilendirilmiştir.

Sonuçlar: Hücre deneyinin sonuçları, silibininin CBZ ile kombine edildiğinde karaciğer koruyucu etkilerinin belirsiz olduğunu göstermiştir. FAERS veri tabanı analizi, silibinin birlikte uygulanmasıyla ADR riskinin arttığını ortaya koymuş ve beklenmedik Bitki-ilaç etkileşimine (HDI) karşı dikkatli olunması gerektiğini vurgulamıştır.

Anahtar kelimeler: Silibinin, karbamazepin, hepatotoksisite, advers ilaç reaksiyonları, bitki-ilaç etkileşimi, Gıda ve İlaç Dairesi advers olay raporlama sistemi

INTRODUCTION

Silibinin is the major active compound in silymarin, which is a mixture of flavonolignans extracted from *Silybum marianum* seeds. Milk thistle (*Silybum marianum L.*) is a medicinal plant widely used in traditional European medicine. Pharmacological studies indicate that silibinin has a strong capability to protect the liver and cure liver damage caused by various toxicants[1-3]. Silibinin is often used to treat acute and chronic hepatitis, early liver injury, and toxic liver injury.

CBZ is often prescribed as an anti-convulsant, and long-term use of it can cause liver abnormalities.

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Patients on CBZ therapy would often use alternate hepatoprotective therapies concomitantly with CBZ to prevent CBZ associated liver side effects. Silibinin is one of the compounds from hepatoprotective herbs that is commonly used in cases of drug-induced liver injury with mild to moderate hepatocellular damage[4].

The most versatile enzyme systems involved in the metabolism of xenobiotics are cytochromes P450 (CYP450) and Uridine Diphosphate (UDP)-glucuronosyltransferases (UGTs). Silibinin has been reported to have a potential inhibitory effect on CYP450, UGTs, and some efflux transporters such as P-glycoprotein (P-gp)[5-7]. These findings suggest that silibinin may modulate the pharmacokinetics and pharmacodynamics of co-administered drugs through interactions with P-gp, CYP450, UGTs. However, the clinical implications of such herb-drug interactions remain underrecognized in therapeutic settings.

In this experiment, the effect of interactions between CBZ and silibinin on the pharmacokinetics was explored in primary hepatocytes and rats. We also analyzed the data from real-world data in the Food and Drug Administration Adverse Event (AE) Reporting System (FAERS) database to explore the risk of adverse drug reactions caused by silymarin when drugs are combined. For safety reasons, it is important to evaluate the potential pharmacokinetic interaction when silibinin is combined with medication.

METHODS

Reagents

Silibinin (batch no: 130617) was provided by Tasly Pharmaceutiacal Company (Tianjin, China), and CBZ (batch no: 120502) was provided by Sine-Yellow River Pharmaceutiacal Company (Shanghai, China). All reagents were either HPLC-grade or analytical-grade.

Animals and Ethics Statement

Specific pathogen free grade male Sprague-Dawley (SD) rats, weighing 200-220 g, were housed in a controlled environment with a 12-hour light/dark cycle and had free access to food and water. All efforts were made to minimize animal suffering and to use the minimum number of animals necessary to produce reliable scientific data. All animal experiments were approved by the Experimental Animal Welfare Ethics Committee of China Pharmaceutical University (acceptance number: 2020-09-013, date: 10.03.2023).

Primary Hepatocyte Isolation and Culture

Primary hepatocytes were isolated from SD rats using a modified Seglen's two-step *in situ* perfusion method[8], which has been widely validated and applied. A total of 1.5-2 million cells were obtained at a viability greater than 80%, confirmed with the trypan blue dye exclusion test. Cells were then seeded at a density of 1.5×10^5/mL on 96-well plates and a density of 10^6/mL on 6-well plates with Williams' medium E containing 10% FBS and 1% penicillin/streptomycin. The primary hepatocytes were cultured in an incubator with a 95% oxygen/5% CO_2 gas cylinder at 37 °C.

Cell Morphology Observation and methylthiazolyldiphenyl-tetrazolium bromide Assay

The primary hepatocyte was cultured for 12 hours on 6-well plates, then treated with silibinin and CBZ. The primary hepatocytes were then cultured for another 24 hours before cell morphology was observed by a microscope.

The rat primary hepatocytes were seeded in 96-well plates at a concentration of 5000 cells/well. The cell was incubated with Williams' medium E containing different concentrations of silibinin and CBZ for 24 hours. Then, the 20μL 5 g/L methylthiazolyldiphenyl-tetrazolium bromide (MTT) solution was added to each well of the 96- well plate, followed by 4 hours of additional culturing. Every well was treated with 150 μL DMSO after removing the solution, and then shaken for 10 minutes. After this, OD490 was detected.

Statistical Analysis

All experiments were conducted with independent biological replicates. Quantitative data from the MTT assay are presented as mean±standard deviation, derived from at least three independent experiments. Normality of data distribution and homogeneity of variances were assessed using Shapiro-Wilk and Levene's tests, respectively. Dose-response relationships were evaluated by non-linear regression analysis. For multi-group comparisons, when data satisfied both normality and variance homogeneity assumptions, one-way analysis of variance with Tukey's honestly significant difference post-hoc test was employed to control family-wise error rates. For datasets violating these assumptions, non-parametric analyses were performed using the Kruskal-Wallis test followed by Dunn's post-hoc test with Bonferroni adjustment for pairwise comparisons. All statistical analyses were executed in GraphPad Prism 9.0, with $p<0.05$ considered statistically significant.

Pharmacovigilance Study

Data Processing and Exposure Definition

A retrospective, disproportionality pharmacovigilance study was performed from 2015 quarter 1 to 2022 quarter 2 using the FAERS database. Both generic and brand names were used to identify the drug silibinin. AEs in the FAERS were coded in terms of Preferred Terms (PTs) from the Medical Dictionary for Regulatory Activities and all AEs of interest were coded as PTs from the System Organ Class (SOC) of Hepatobiliary disorders. The deduplication step was performed to retain the most recent version of the report[9]. Delete the case report when a null value for either AE or drug is present. After SOC analysis, PT analysis was performed to deliver more comprehensive information.

Disproportionality Analysis

Combination analysis refers to an AE report where two or more drugs are used, and the occurrence of the target AE may be the result of their combination[10]. The reporting odds ratio (ROR) and Bayesian confidence propagation neural networks (BCPNN) of information components (ICs) were used to identify statistical associations between target drugs (combined or not combined with silibinin) and AEs of interest[11]. Target drugs here were defined as drugs that were in combination with silibinin and had developed hepatotoxicity as reported in the FAERS database.

The study takes one report as a unit, which means when silibinin occurs in the report, the report is included in the silibinin therapy group. The analysis could be performed by ROR or IC. The ROR lower limit of the 95% confidence interval ROR_{025} was greater than 1, and at least 3 cases, or the IC lower limit of the 95% confidence interval IC_{025} was greater than 0, were defined as a significant signal, indicating a significant risk of target AEs of the therapy drugs. Only ROR can be used in the comparison of different groups. In PT analysis, the method of IC is used because ROR is prone to signal score inflation when the number of reports is small[12]. Time-to-onset (TTO) (TTO= Time to event-Start of treatment)analysis was performed to evaluate the profile from the start of treatment to event occurrence.

RESULTS

Cell Morphology Observation and methylthiazolyldiphenyl-tetrazolium bromide Assay

The results showed that treating the primary hepatocyte with 25μM silibinin had no obvious effect on cell growth compared with the control group

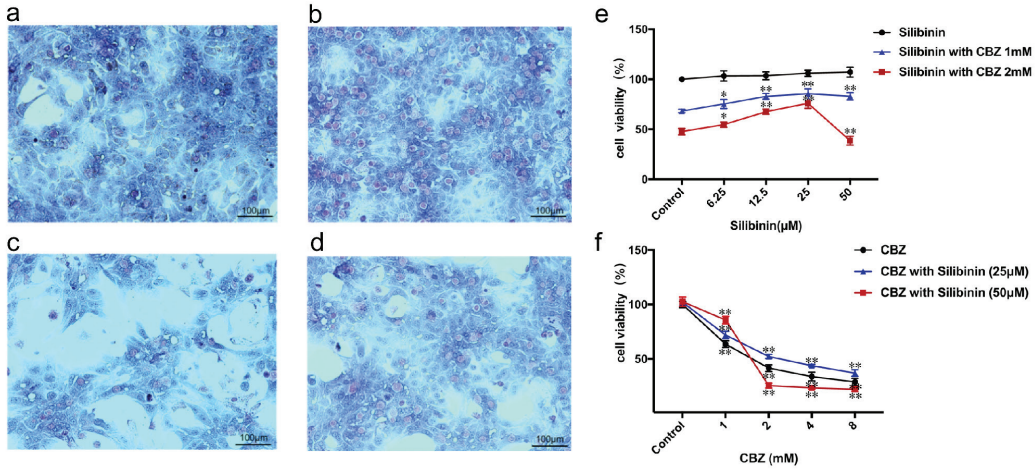


Figure 1. Cell morphology observation (a-d) and MTT assay results (e-f). (a) Treated the primary hepatocyte with neither silibinin nor CBZ (control group); (b) Treated the primary hepatocyte with 25μM Silibinin; (c) Treated the primary hepatocyte with 2mM CBZ; (d) Treated the primary hepatocyte with 2mM CBZ and 25μM silibinin. (e) Treated the primary hepatocyte with different concentration of silibinin; Treated the primary hepatocyte with different concentration of silibinin co-administrated with 1mM and 2mM CBZ. (f) Treated the primary hepatocyte with different concentration of CBZ; Treated the primary hepatocyte with different concentration of CBZ co-administrated with 25μM and 50μM silibinin. *p<0.05, **p<0.01 vs the control group.

MTT: Methylthiazolyldiphenyl-tetrazolium bromide, CBZ: Carbamazepine

(Figure 1a, b). Treating primary hepatocytes with CBZ 2mM caused severe cell damage, which was mitigated when 25μM silibinin was added (Figure 1c, d).

Treating a primary hepatocyte with 6.25μM, 12.5μM, 25μM, or 50μM silibinin had no obvious effect on cell growth. Treating primary hepatocytes with 1mM or 2mM CBZ caused cell damage, which was mitigated when different concentrations of silibinin were added. However, treating the primary hepatocyte with 2mM CBZ caused cell damage that couldn't be mitigated when 50μM silibinin was added. When silibinin (25μM) was co-administrated with CBZ (2mM), the cell viability increased from 47.8% to 75.9% ($p<0.05$); when the concentration of silibinin was increased to 50μM with CBZ (2mM), the hepatocyte viability significantly declined from 47.8% to 38.7% ($p<0.05$) (Figure 1. e).

Primary hepatocytes exhibited a concentration-dependent decrease in viability with increasing CBZ concentrations (0-4 mM). Co-administration of 25 μM silibinin significantly enhanced cell viability across all tested CBZ concentrations. Notably, while 50 μM silibinin partially restored viability in cells treated with 1 mM CBZ, it paradoxically exacerbated cytotoxicity at higher CBZ concentrations (2, 4, 8 mM), resulting in lower viability compared to CBZ treatment alone (Figure 1. f).

Disproportionality Analysis with or without Silibinin Therapy in Food and Drug Administration Adverse Event Reporting System

Reports available in the FAERS database allow the analysis of large amounts of data to detect safety signals. FAERS contains real-world results from a large population. Between the first quarter of 2015 and the second quarter of 2022, a total of 36,603 AEs associated with the combination therapy involving silibinin were documented, including 7814 drugs, of which 50.35% were known to be metabolized by CYP450 and UGTs. Among these events, 42 individual medications were reported with a frequency exceeding 100 instances (Figure 2).

When the target drug was combined with silibinin therapy, hepatotoxicity occurred in 260 reports. In the FAERS database analysis of silibinin, silibinin combined with the target drug had a higher ROR_{025} signal value for hepatotoxicity (4.49 vs 2.57) in SOC analysis in the full database than the target drug without silibinin (Figure 3).

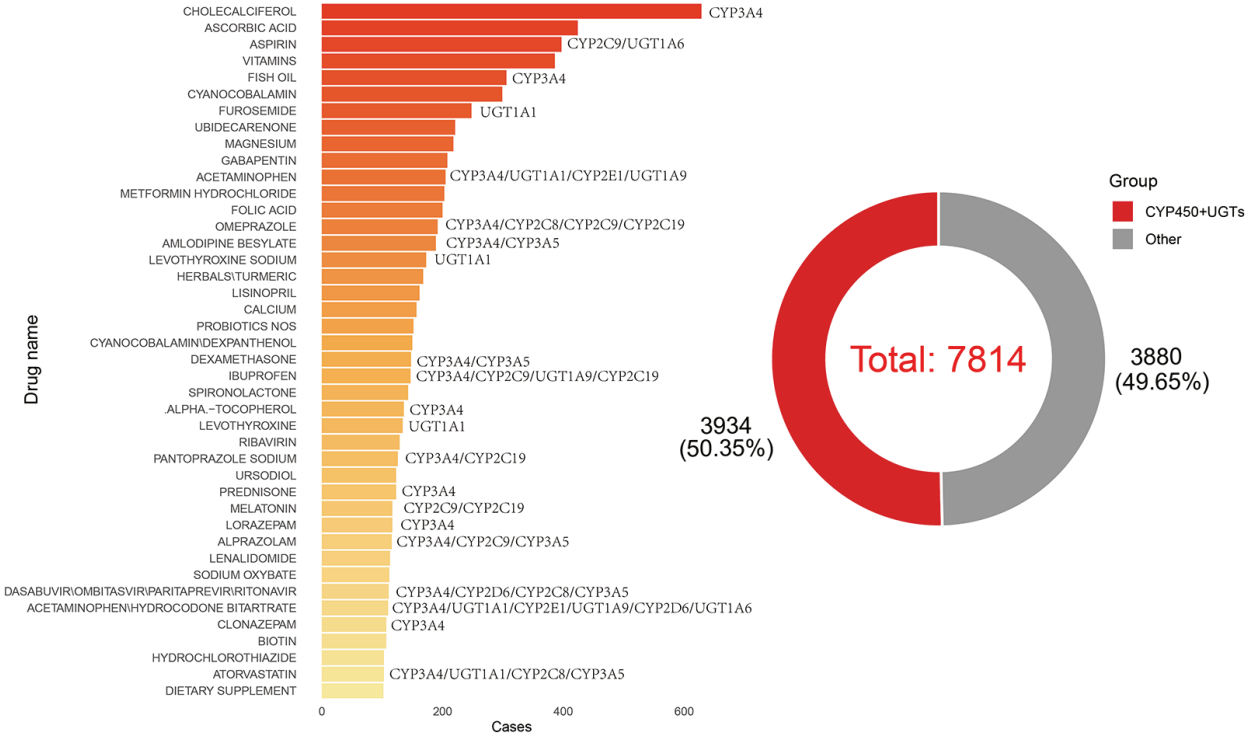
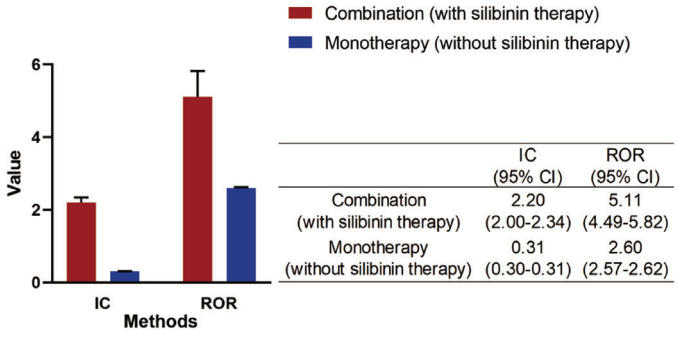


Figure 2. Forty-two drugs from the FAERS database that exhibit an adverse reaction frequency exceeding 100 instances when co-administered with silibinin.

FAERS: Food and frug administration adverse event reporting system



	IC (95% CI)	ROR (95% CI)
Combination (with silibinin therapy)	2.20 (2.00-2.34)	5.11 (4.49-5.82)
Monotherapy (without silibinin therapy)	0.31 (0.30-0.31)	2.60 (2.57-2.62)

Figure 3. Disproportionality analysis of target drugs (with or without silibinin) and hepatotoxicity in full FAERS database. Target drugs here were defined as drugs that were in combination with silibinin and had developed hepatotoxicity in the FAERS database. ROR: reporting odds ratio; IC: information components; CI: Confidence interval. The IC lower limit of the 95% confidence interval was greater than 0 or the ROR lower limit of the 95% confidence interval was exceeded 1, and at least 3 cases were defined as significant.

IC: information component, ROR: Reporting odds ratio, FAERS: Food and Drug Administration Adverse Event Reporting System

Preferred Terms Disproportionality Analysis, Time-to-Onset Analysis and Preferred Term Outcome Analysis with Silibinin Therapy Group

In PT analysis, the IC_{025} value of the silibinin therapy group in the full database is significant for most hepatotoxicity PTs. Ascites (n=22), hepatic cirrhosis (n=20), jaundice (n=20), liver disorder (n=20), and Drug-induced liver injury (n=19) are the top five PT frequencies in the analysis, and the IC_{025} value is 2.03, 2.41, 2.13, 1.45, and 1.62 respectively (Figure 4). The results from Figure 5 found that the median TTO in hepatotoxicity combined with silibinin is about 1 year. The most frequent serious AE in hepatotoxicity associated with silibinin therapy is ascites. The most frequent cause of death is hepatic cirrhosis. The top 5 outcomes of all serious AEs in hepatotoxicity combined with silibinin therapy are ascites, hepatic cirrhosis, liver disorder, hepatocellular carcinoma, and jaundice (Figure 6).

Based on data from the FAERS database, we found that the combination of silibinin with some prescription drugs had a higher ROR_{025} (4.49) for hepatotoxicity than that without silibinin (2.57). In PT analysis, the IC_{025} value in combination with the silibinin therapy group is significant

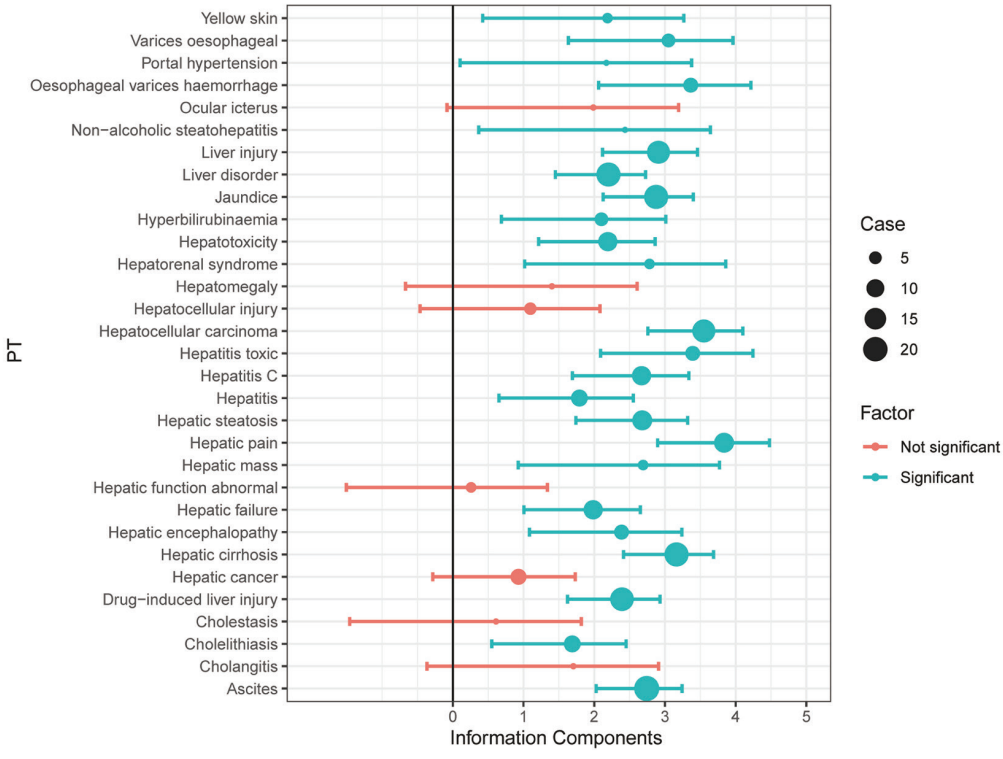


Figure 4. The information components of hepatotoxicity preferred terms associated with silibinin (case number ≥ 3) are presented in the full database. Significance is defined as an IC lower limit greater than 0 for the 95% confidence interval.

IC: Information component, PT: Preferred terms

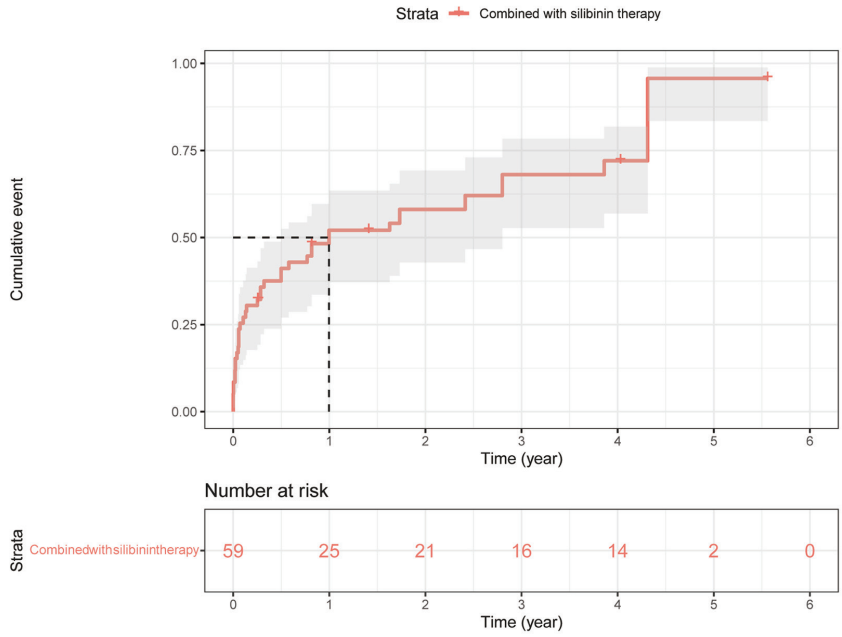


Figure 5. The Time-To-Onset of all hepatotoxicity with silibinin (year).

TTO: Time-To-Onset

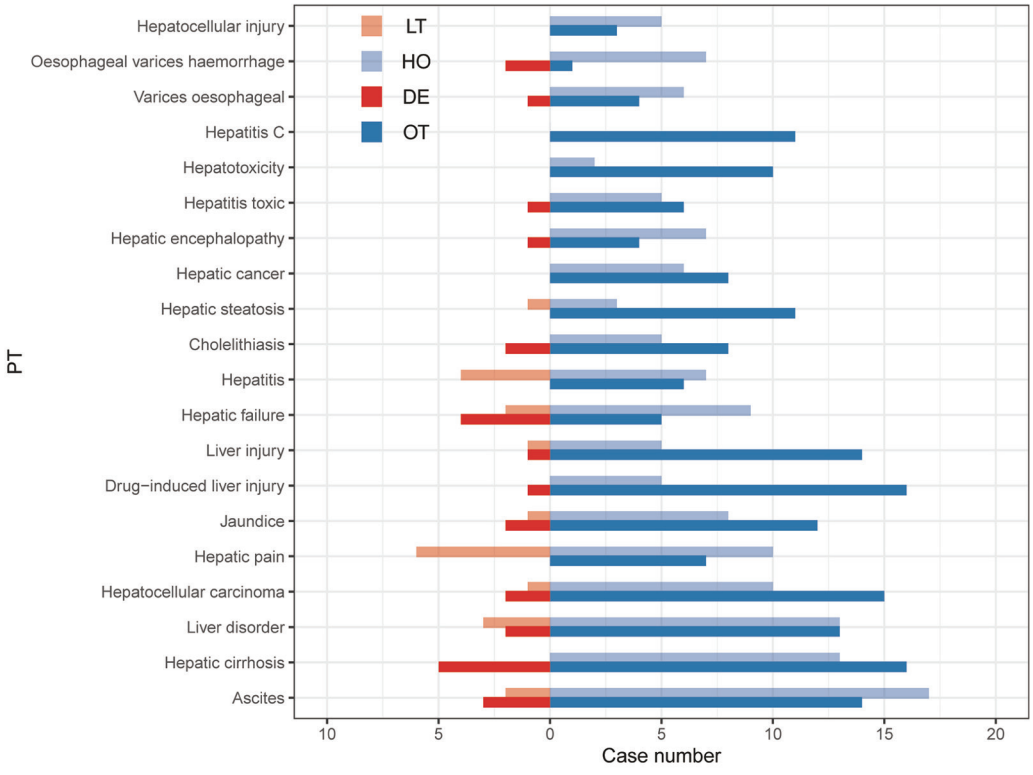


Figure 6. The top 20 preferred terms outcome of hepatotoxicity with silibinin.

LT: Life-Threatening; HO: Hospitalization-Initial or Prolonged; DE: Death; OT: Other Serious (Important Medical Event), PTs: Preferred terms

in most hepatotoxicity PTs. The IC_{025} values for the top five frequently occurring PTs, such as ascites, hepatic cirrhosis, jaundice, liver disorder, drug-induced, and liver injury, are 2.03, 2.41, 2.13, 1.45, and 1.62, respectively.

Analysis of Adverse Reaction Signals for Silibin in Combination with Amlodipine or furosemide in Food and Drug Administration Adverse Event Reporting System

Results from drawing on the FAERS database and employing the ROR method showed that the co-administration of amlodipine and silibinin significantly increases the risk of adverse reactions observed with amlodipine monotherapy. The ROR values for fatigue, nausea, and asthenia were 2.66, 2.04, and 1.91 (Figure 7a). Additionally, the concurrent use of furosemide and silibinin can notably elevate the risk of adverse reactions when compared to amlodipine monotherapy. The ROR values for headache, acute respiratory failure, and encephalopathy are 2.40, 14.79, and 20.02 (Figure 7b).

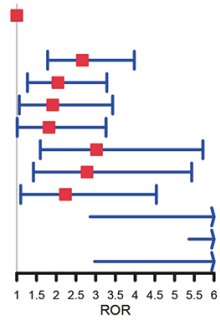
DISCUSSION

This experiment studied both the interaction of silibinin with carbamazepine and pharmacovigilance data on silibinin using the FAERS database. For the primary hepatocyte experiments, the MTT assay showed that the hepatoprotective effect of silibinin was uncertain with a higher concentration of co-administered CBZ. Our previous research in rats, suggested that CBZ increased silibinin clearance, which implies a decreased drug efficacy. This may coincide with the result of uncertain hepatoprotective effects of silibinin in primary fresh hepatocytes.

CYP450 and UGTs are essential for metabolism of many drugs, and they can be inhibited or induced by drugs causing DDIs (drug-drug interactions) that can lead to adverse effects or therapeutic failure. Faisal et al.[6] demonstrated that certain silymarin components/metabolites can inhibit CYP enzymes. 2,3-dehydrosilychristin-19-O-sulfate showed the strongest inhibitory effect on CYP3A4. D'Andrea et

(a)

Group	Cases	ROR value (95% CI)
Amlodipine besylate (Reference)		
Amlodipine besylate combined with silibinin		
Fatigue	28	2.66(1.78–3.98)
Nausea	19	2.04(1.27–3.28)
Asthenia	12	1.91(1.06–3.43)
Fall	12	1.81(1.01–3.26)
Back pain	10	3.02(1.59–5.71)
Insomnia	9	2.78(1.42–5.43)
Anaemia	8	2.23(1.09–4.53)
Neutropenia	7	6.09(2.85–12.98)
Ascites	6	12.14(5.36–27.48)
Stomatitis	6	6.72(2.97–15.19)



(b)

Group	Cases	ROR value (95% CI)
Furosemide (Reference)		
Furosemide combined with silibinin		
Off label use	23	2.75(1.79–4.23)
Confusional state	22	5.59(3.60–8.63)
Headache	17	2.40(1.47–3.93)
Acute respiratory failure	16	14.79(8.88–24.64)
Encephalopathy	16	20.02(12.00–33.39)
Hypertension	16	3.99(2.40–6.63)
Pulmonary oedema	16	7.01(4.21–11.66)
Hypoxia	15	10.19(6.03–17.23)
Brain oedema	14	83.06(47.40–145.56)
Cardiovascular insufficiency	14	183.27(101.99–329.31)

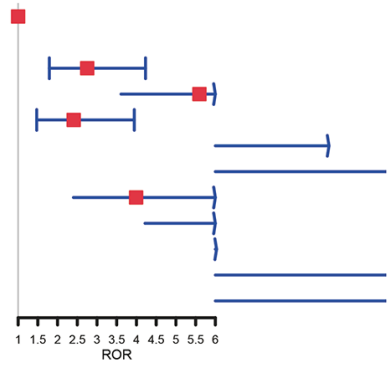


Figure 7. Comparison of adverse reaction signals of amlodipine besylate (a) or furosemide (b) combined with silibinin, based on the proportional imbalance method.

ROR: Reporting odds ratio, IC: Information component

al, showed that silibinin and the metabolite silibinin-glucuronide were also inhibitors of human UGT1A isozymes[7]. Ferreira et al.[13] found that silymarin (silibinin) significantly increased the CBZ concentrations over the 1-2 h post-dosing period compared to the negative control group. Similarly, Wang et al. identified that consecutive administration of water-soluble silymarin significantly increased the K_a of CBZ and the AUC_{0-12} and C_{max} of its metabolite[14].

Moreover, P-gp modulators have been reported as a contributor to DDI. Previous studies have demonstrated that silibinin is a CYP450 and P-gp inhibitor *in vitro*, which leads to increased accumulation of P-gp substrate within cells[15,16]. This has also been confirmed by several recent studies. Lee and Choi[17] found that silibinin significantly inhibited P-gp activity. Compared to the control group, silibinin significantly increased the area under the plasma concentration-time curve and the peak plasma concentration of paclitaxel. Nguyen et al.[18] found that silibinin reduced the efflux of two substrates of P-gp, including digoxin and vinblastine, in Panc-1 cells, indicating the inhibitory effect of silibinin on P-gp. Dobiasová et al.'s[5] research showed that silibinin exhibits the ability to modulate P-gp activity by acting as a competitive inhibitor. It is highly likely that silibinin will change how the combined drugs are processed in the body, possibly leading to ineffective treatment or even increased liver damage.

The analysis of FAERS revealed a significant association between silibinin co-administration and drug-induced hepatotoxic events. Mechanistically, this phenomenon may be attributable to silibinin-mediated inhibition of metabolic enzymes, as evidenced by a focused investigation on amlodipine (primarily metabolized by CYP3A4) and furosemide (UGT1A1-dependent metabolism). The disproportionality analysis using the ROR method demonstrated elevated risks of AEs in silibinin combination therapies. Notably, these herb-drug interactions were frequently associated with severe clinical outcomes, including mortality, hospitalization (initial/prolonged), and life-threatening complications. These findings underscore the necessity for systematic safety evaluation of phytopharmaceuticals in the case of drug combination therapy.

Study Limitations

This study has several limitations. It concentrated exclusively on silibinin's protective role against carbamazepine-induced hepatic injury, without exploring the underlying mechanisms responsible for these effects. Furthermore, the FAERS database operates as a spontaneous reporting system, inherently subject to limitations such as underreporting, duplicate entries, and incomplete case information. The absence of data regarding pre-existing conditions and concomitant medications might also confound the interpretation of the results.

Despite these constraints, the identification of ADR signals within the FAERS database in conjunction with other pharmacological agents offers valuable insights into rational pharmacotherapy. Such findings can inform clinical practice by highlighting potential safety concerns and guiding more judicious prescribing practices.

Future research should aim to address the current study's limitations through mechanistic studies and more comprehensive pharmacovigilance approaches, thereby enhancing our understanding of silibinin's therapeutic profile and its interaction with other drugs.

CONCLUSION

Despite silibinin's established clinical use in hepatic disorders and its role as an adjunct therapy to mitigate drug-induced hepatotoxicity through hepatic function enhancement or toxicity reduction, its widespread availability as an over-the-counter dietary supplement often leads to underestimation of its pharmacological complexity. This study indicates that the combination of silibinin with other prescription drugs, especially those with narrow therapeutic windows or indexes, should be used with caution because of the herb-drug interaction. With the increased popularity of herbal products, prescribers must be aware of potential herb-drug interactions.

Ethics

Ethics Committee Approval: All animal experiments were approved by the Experimental Animal Welfare Ethics Committee of China Pharmaceutical University (acceptance number: 2020-09-013, date: 10.03.2023).

Informed Consent: Since this study was conducted on animals, patient consent was not required.

Footnotes

Author Contributions

Surgical and Medical Practices: D.P., Q.S., Concept: D.P., Q.S., J.L., F.Y., Design: D.P., Q.S., J.L., F.Y., Data Collection and/or Processing: D.P., Q.S., Z.Z., Analysis

and/or Interpretation: D.P., Q.S., Z.Z., Literature Search: D.P., Q.S., S.W., Writing: D.P., Q.S., Z.Z., S.W., J.L., F.Y.

Conflict of Interest: The authors have no conflict of interest to declare.

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