Zahedan J Res Med Sci. 2026 July; 28(3): e170006 https://doi.org/10.5812/zjrms-170006

Published Online: 2026 May 26 **Case Report**

Hepatoprotective Effects of a Combination of Three Medicinal Plants on Carbamazepine-Induced Liver Injury: A Case Report

Alireza Ebadollahi-Natanzi [1, *], Gholamreza Arab-Rahmatipour [2]

[1] Department of Medicinal Plants, Imam Khomeini Higher Education Center, Agricultural Research, Education and Extension Organization (AREEO), Karaj, Iran
[2] Department of Biochemistry, Farabi Hospital Laboratory, Tehran University of Medical Sciences, Tehran, Iran

[*] ***Corresponding Author:*** Department of Medicinal Plants, Imam Khomeini Higher Education Center, Agricultural Research, Education and Extension Organization (AREEO), Karaj, Iran. Email: a.ebadollahi@areeo.ac.ir

Received: 2 February, 2026; **Revised:** 6 May, 2026; **Accepted:** 13 May, 2026

Abstract

Introduction: The global incidence of liver disease has increased, and some drugs can cause adverse effects, underscoring the need for alternative medicine approaches. This report evaluated the hepatoprotective effects of a combination of three medicinal plants, *Silybum marianum*, *Cichorium intybus*, and *Ziziphus vulgaris*, in a patient with elevated levels of liver injury marker enzymes.

Case Presentation: The patient was a 27-year-old man with tonic-clonic seizures who had been receiving chronic carbamazepine treatment and had elevated liver injury marker enzyme levels. The results showed that the combination of *Silybum marianum*, *Cichorium intybus*, and *Ziziphus vulgaris* significantly reduced the elevated serum levels of aspartate transaminase, alanine aminotransferase, and alkaline phosphatase in the patient ($P < 0.05$), decreasing to 34.0 ± 3.16, 40.5 ± 3.83, and 370.5 ± 4.76 U/L, respectively. These findings suggest that total flavonoid and phenol doses of 200.84 and 149.00 mg/day, respectively, could alleviate carbamazepine-associated side effects.

Conclusions: Based on this case report, the combination of *Cichorium intybus*, *Silybum marianum*, and *Ziziphus vulgaris* may exert hepatoprotective effects, as reflected by improved liver enzyme levels following herbal therapy.

Keywords: Carbamazepine, Epilepsy, Liver Enzymes, Medicinal Plants

1. Introduction

The liver is one of the most important organs in the human body and serves several functions, including metabolism and the removal of xenobiotics from vital body systems. The liver encounters toxic substances and metabolites; therefore, it can be continuously exposed to numerous chemicals and microbial and viral agents (1). In many cases, metabolic activation occurs during hepatic detoxification pathways mediated by liver microsomal enzymes, including cytochrome P-450, and this process can ultimately generate toxic substances and reactive species that can cause severe damage to various tissues, including the liver (2). Adverse drug reactions (ADRs) represent one of the most complex issues in clinical medicine (3). Changes in biochemical parameters in the human body may be related to differences in the expression of metabolizing enzymes, the presence of different metabolic pathways, and the effects of immunological reactions (4).

Epilepsy is a neurological disorder characterized by loss of consciousness and conditions associated with convulsions. Currently, various drugs are used to treat epilepsy, such as phenytoin, carbamazepine, phenobarbital, and valproic acid (5).

In some cases, antiepileptic drugs can cause severe adverse effects, such as blood disorders, hirsutism, gingival hyperplasia, idiosyncratic liver toxicity, and weight gain (6). Among these drugs, carbamazepine (CBZ) is one of the best-known and oldest antiepileptic drugs and helps control seizures by blocking sodium-dependent channels (7). According to the literature, carbamazepine use in patients with epilepsy can be accompanied by serious adverse effects, such as aplastic

How to Cite: Ebadollahi-Natanzi A, Arab-Rahmatipour G. Hepatoprotective Effects of a Combination of Three Medicinal Plants on Carbamazepine-Induced Liver Injury: A Case Report. Zahedan J Res Med Sci. 2026;28(3):e170006. doi: https://doi.org/10.5812/zjrms-170006

anemia, jaundice, Stevens-Johnson syndrome, lupus erythematosus, and toxic epidermal necrolysis (8).

Recently, the use of plant-based drugs has increased in developed and developing countries because of their notable efficacy, acceptable safety, availability, and lower cost (9). Some crude plant extracts used in traditional medicine are considered rich sources of preventive and protective agents for humans and animals, particularly for the liver. These properties are attributed to plant-based antioxidant compounds, including vitamin C, carotenoids, lycopene, and flavonoids, which can inhibit free radicals and related damage (10, 11). In this regard, other plant extracts, such as those obtained from *Silybum marianum* and *Cichorium intybus*, have demonstrated antioxidant effects (12).

In Iran, liver diseases resulting from adverse drug effects and viral hepatitis are somewhat prevalent (13). Regarding the use of traditional medicine for the treatment of liver disorders, three plants, *Silybum marianum* (SM), *Cichorium intybus* (CI), and *Ziziphus vulgaris* (ZV), were selected to evaluate their therapeutic effects in a patient with liver disorders due to drug side effects. Another aim of this study was to attenuate CBZ-dependent side effects and the resulting liver damage in a patient with epilepsy.

2. Case Presentation

The patient was a 27-year-old man weighing 75 kg who had been under care for tonic-clonic seizures for approximately the previous 2 years. During this period, he had been receiving carbamazepine (CBZ) at 800 mg/day and phenobarbital (PHB) at 100 mg/day. The patient's serum liver enzyme levels were elevated, including aspartate transaminase (AST) at 58.3 ± 6.37 U/L, alanine aminotransferase (ALT) at 91.8 ± 12.3 U/L, and alkaline phosphatase (ALP) at 546.3 ± 20.1 U/L. Other values obtained from biochemical and hematological tests were within the normal range (Table 1). The patient did not experience any epileptic seizures during these experiments or before the treatment protocol began. The patient complied with the medicinal plant prescription for his disease in this study, and written consent was obtained to continue the study.

2.1. Treatment Protocols

Silybum marianum seeds were obtained from the Kelardasht district in Mazandaran province, northern Iran. The other two medicinal plants, ZV and CI, were collected from Kashan city in Isfahan province, Iran.

All stages of the selection and preparation procedures for the three medicinal plants were based on separate human and animal studies and standard methods adopted from previous studies (14-16). Because no human clinical study has been designed using the combination of these three medicinal plants to simultaneously control CBZ side effects in patients and prevent and/or attenuate CBZ-associated liver injury, the treatment protocol was based on extrapolated evidence from related human and animal studies.

The treatment protocol was performed in accordance with ethical principles under the framework of the Declaration of Helsinki for human experiments and animal studies conducted using the three medicinal plants mentioned above (17). The experiment was fully explained to the patient, and his compliance and fully informed consent were obtained through a written agreement signed by the patient. Written informed consent was also obtained from the patient for publication and presentation of this case.

Treatment was based on the combined use of CI extract at 88 mg/kg body weight/day, SM pulverized seeds at 6.6 mg/kg body weight/day, and ZV at 133 mg/kg body weight/day, and continued for 4 weeks.

Treatment evaluation was based on changes in the patient's liver enzyme levels, with reversal of liver enzymes to normal levels considered a positive treatment response. Treatment comparisons were performed using SPSS software, version 20. A paired t-test was used to analyze the data. $P < 0.05$ was considered statistically significant.

3. Discussion

As shown in Table 1, the patient's liver enzyme levels decreased and reached near-normal limits 1 month after the initial treatment. The measured AST, ALT, and ALP levels in this patient were 37.5 ± 4.97, 43.0 ± 3.00, and 370.0 ± 5.00 U/L, respectively. After 2 months of treatment, the AST and ALT levels were within normal limits, corresponding to 34.0 ± 3.16 and 40.5 ± 3.83 U/L, respectively. The ALP level approached the normal range and was measured at 370.5 ± 4.76 U/L.

The measured total phenol and flavonoid levels in the patient are shown in Table 2.

AST, ALT, and ALP are among the most important liver enzymes routinely evaluated to detect liver diseases. Increased levels of these enzymes indicate hepatocellular damage because they are located in the cytoplasm and are released into the blood when cellular damage occurs (1, 18).

Studies of antiepileptic drugs, such as carbamazepine and valproate, have shown that these drugs can initiate oxygen-dependent tissue damage

Table 1. Blood Parameter Levels of the Patient Before and After Treatment with the Combination of Three Medicinal Plants [a, b]

Chemical Parameters	Before Treatment	One-Month Treatment	Two-Month Treatment	Normal Range for Men
Fasting blood sugar (mg/dL)	80.33 ± 5.51	78.33 ± 1.53	87 ± 3.60	70 - 110
Urea (mg/dL)	21.66 ± 1.53	25.32 ± 2.08	27 ± 1.73	19 - 44
Creatinine (mg/dL)	1.00 ± 0.10	0.93 ± 0.06	0.97 ± 0.05	0.7 - 1.4
Uric acid (mg/dL)	5.83 ± 0.15	5.73 ± 0.25	5.6 ± 0.17	3.6 - 8.20
Cholesterol (mg/dL)	157.0 ± 6.08	150.6 ± 4.04	158.0 ± 1.53	> 200
HDL-cholesterol (mg/dL)	39.33 ± 1.53	42.00 ± 1.73	40.00 ± 1.00	< 35
LDL-cholesterol (mg/dL)	80.66 ± 2.51	71.00 ± 1.00	77.00 ± 1.52	> 130
Triglycerides (mg/dL)	85.00 ± 3.00	81.67 ± 3.21	88.33 ± 1.53	> 200
Calcium (mg/dL)	9.53 ± 0.29	9.4 ± 0.17	9.40 ± 0.10	8.3 - 10.3
Phosphorus (mg/dL)	3.9 ± 0.26	3.83 ± 0.06	3.73 ± 0.23	2.5 - 4.5
Na (mEq/L)	138.0 ± 2.00	138.7 ± 1.52	138.00 ± 1.00	135 - 145
K (mEq/L)	4.63 ± 0.15	4.73 ± 0.05	4.57 ± 0.06	3.5 - 5
AST (U/L)	58.3 ± 6.37	37.5 ± 4.97	34.0 ± 3.16	< 37
ALT (U/L)	91.8 ± 12.30	43.0 ± 3.00	40.5 ± 3.83	< 41
ALP (U/L)	546.3 ± 20.10	370.0 ± 5.00	370.5 ± 4.76	64 - 306
Total bilirubin (mg/dL)	1.00 ± 0.10	ND	0.9 ± 0.1	0.2 - 1.4
Direct bilirubin (mg/dL)	0.20 ± 0.10	ND	0.2 ± 0.00	≤ 0.3
Creatine phosphokinase (U/L)	34.0 ± 1.00	ND	42 ± 2.00	24 - 195
Lactate dehydrogenase (U/L)	243 ± 2.00	ND	253 ± 2.00	< 480
White blood cell ($\times 10^3/\mu L$)	7.7 ± 0.91	7.4 ± 0.2	8.03 ± 0.06	4 - 10
Red blood cell ($\times 10^6/\mu L$)	4.94 ± 0.06	4.83 ± 0.4	4.85 ± 0.05	3.9 - 5.8
Hemoglobin (g/dL)	14.6 ± 0.20	14.4 ± 0.17	14.2 ± 0.10	14 - 18
Hematocrit (%)	44.2 ± 0.26	43.9 ± 0.10	43.3 ± 0.17	40 - 54
Platelet ($\times 10^3/\mu L$)	304 ± 9.53	297 ± 1.00	284 ± 3.60	150 - 450
Prothrombin time (s)	12.8 ± 0.28	13 ± 0.00	13 ± 0.00	12 - 13.5
Partial thromboplastin time (s)	32 ± 2.00	34 ± 2.00	36 ± 1.00	24 - 36
International normalized ratio	1	1	1	> 1

[a] Values are mean ± SD of different replicates (N = 3) from five measurements. Abbreviation: ND, not determined.

[b] Paired *t*-test was used to compare the means.

Table 2. Flavonoid and Phenol Amounts Received by the Patient Per Day During the Study [a]

Plants	Amount of Total Flavonoids [b] (mg/day)	Amount of Total Phenols [c] (mg/day)
SM	69.50	62.30
ZV	5.56	4.81
CI	125.78	81.89
Total	200.84	149

[a] Silymarin was administered at a dose of 20.46 mg/day. Abbreviations: CI, cichorium intybus; SM, silybum marianum; ZV, *Ziziphus vulgaris*.

[b] Quercetin equivalent.

[c] Gallic acid equivalent.

through several mechanisms and thereby affect antioxidant systems (19). Higher doses of carbamazepine may result in enzymatic activity with reduced antioxidant properties due to oxidative stress. Furthermore, chronic use of this drug can cause an imbalance between antioxidant and oxidant pools in the human body; accordingly, the production of reactive oxygen species (ROS) may exceed the antioxidant defense capacity (20).

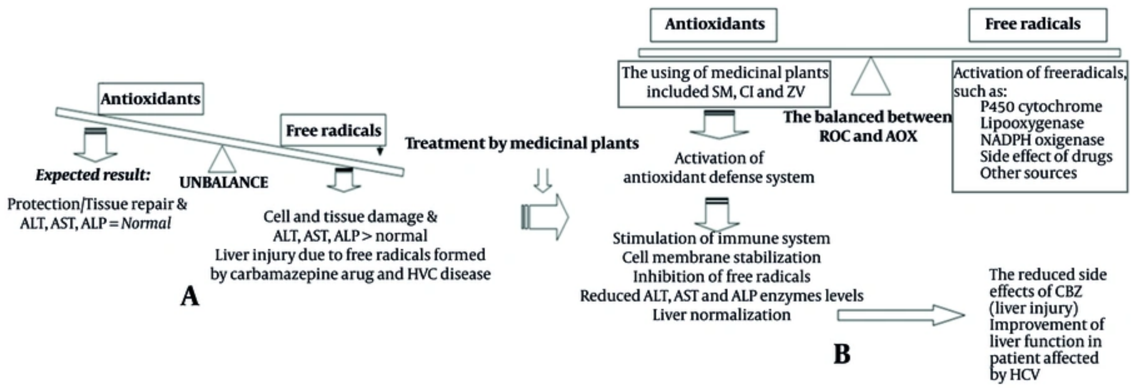

Figure 1. Presumed mechanisms by which SM, CI, and ZV medicinal plants activate the antioxidant defense system through enzymatic or nonenzymatic pathways and inhibit free radicals due to specific constituents, including flavonoids, phenolic compounds, and carotenoids, thereby balancing free radicals and antioxidant systems. Abbreviations: CI, Cichorium intybus; SM, Silybum marianum; ZV, Ziziphus vulgaris.

The presence of important flavonoids, such as silybin (SBN), silydianin (SDN), and silychristin (SCN), in SM seeds was one of the main reasons for including SM seeds in this study. Silymarin is believed to exert hepatoprotective effects through different mechanisms, including cell membrane stabilization and free radical inhibition. By increasing cellular glutathione, silymarin can induce DNA polymerase gene expression, which consequently increases rRNA levels and supports liver cell regeneration (21).

Some pharmaceutical properties observed in ZV are related to the antioxidant properties of flavonoid compounds present in this plant. Studies on this plant have shown that, due to the presence of active compounds, it can inhibit histamine release and interfere with the activation of cholinesterase and cyclooxygenase (COX) I and II enzymes (22).

The medicinal plants used in this study contain notable antioxidant and flavonoid compounds (Table 2). In this respect, a previous study showed that flavonoids can increase the antioxidant capacities of glutathione, reduced glutathione (GSH), glutathione peroxidase (GPx), and catalase (CAT), thereby producing hepatoprotective effects by reducing tissue damage, particularly liver damage (23). The presumed mechanisms underlying the protective activities of these three medicinal plants briefly include activation of the defense system through both enzymatic and nonenzymatic pathways, followed by increases in GSH and other defense systems, such as CAT and GPx. Through the nonenzymatic pathway, major components present in the three medicinal plants, including ascorbic acid, carotenoids, flavonoids, anthraglycosides, and phenolic compounds, may act together with the enzymatic pathway to stimulate the immune system, inhibit free radicals, and stabilize cell membranes. As a result, liver function may normalize, and AST, ALT, and ALP levels may return to normal values (Figure 1).

Considering the data of this study, because the proposed mechanism of carbamazepine-induced liver toxicity is free radical production, concurrent use of the three medicinal plants *Silybum marianum*, *Cichorium intybus*, and *Ziziphus vulgaris* could inhibit free radical production.

Acknowledgements

The authors appreciate the Pathobiology Laboratory of Farabi Hospital and the patient's cooperation. The authors also appreciate the Research Vice-Chancellor of IHEC for providing research facilities and laboratory support.

Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

Authors' Contribution: Gholmreza Arab-Rahmatipour performed haematology and biochemistry tests and wrote the initial draft of the article. Alireza Ebadollahi-Natanzi designed the study and participated in the process of determining the treatment protocol and experimental methods, writing and analysis, and as the study supervisor, submitted the final version.

Conflict of Interests Statement: The authors declare that there is no conflict of interest.

Data Availability: The data presented in this study are uploaded during submission as a supplementary file and are openly available for readers upon request.

Funding/Support: No funding/support was received during this study.

Informed Consent: A written informed consent was obtained from the patient for the publication of this case report.

References

1. Barouki R, Samson M, Blanc EB, Colombo M, Zucman-Rossi J, Lazaridis KN, et al. The exposome and liver disease - how environmental factors affect liver health. *Journal of Hepatology*. 2023;**79**(2):492-505. [PubMed ID: 36889360]. [PubMed Central ID: PMC10448911]. https://doi.org/10.1016/j.jhep.2023.02.034.
2. Rendic S, Guengerich FP. Survey of human oxidoreductases and cytochrome P450 enzymes involved in the metabolism of xenobiotic and natural chemicals. Chem. Res. *Toxicol*. 2015;**28**(1):38-42. [PubMed ID: 25485457]. [PubMed Central ID: PMC4303333]. https://doi.org/10.1021/tx500444e.
3. Ebadollahi-Natanz A, Arab-Rahmatipour G. An overview on toxicity, adverse effects and therapeutic properties of some medicinal plants. Razi J. Med. *Sci*. 2023;**30**(7):1-20. https://doi.org/10.47176/rjms.30.156.
4. Armani S, Geier A, Forst T, Merle U, Alpers DH, Lunnon MW. Effect of changes in metabolic enzymes and transporters on drug metabolism in the context of liver disease: Impact on pharmacokinetics and drug-drug interactions. Br. J. Clin. *Pharmacol*. 2024;**90**(4):942-958. [PubMed ID: 38148609]. https://doi.org/10.1111/bcp.15990.
5. Kaplan YC, Demir O. Use of phenytoin, phenobarbital carbamazepine, levetiracetam lamotrigine and valproate in pregnancy and breastfeeding: risk of major malformations, dose-dependency, monotherapy vs polytherapy, pharmacokinetics and clinical implications. Curr. *Neuropharmacol*. 2021;**19**(11):1805-1824. [PubMed ID: 33573557]. [PubMed Central ID: PMC9185784]. https://doi.org/10.2174/1570159x19666210211150856.
6. French JA, Gazzola DM. New generation antiepileptic drugs: what do they offer in terms of improved tolerability and safety? Ther. Adv. Drug. *Saf*. 2011;**2**(4):141-158. [PubMed ID: 25083209]. [PubMed Central ID: PMC4110862]. https://doi.org/10.1177/2042098611411127.
7. Üstün Özek S, Gurses C. Carbamazepine: There are still unknowns. Turk. J. *Neurol*. 2024;**30**(4):272-275. https://doi.org/10.4274/tnd.2023.04484.
8. Koliqi R, Polidori C, Islami H. Prevalence of side effects treatment with carbamazepine and other antiepileptics in patients with epilepsy. Mater. *Sociomed*. 2015;**27**(3):167-171. [PubMed ID: 26236162]. [PubMed Central ID: PMC4499297]. https://doi.org/10.5455/msm.2015.27.167-171.
9. Wang B, Liu Q, Zhao W, Zhang T, Zhang D, Sutcharitchan C, et al. Revolutionizing drug discovery from natural products: The roles of artificial intelligence and multi-omics in accelerating innovation. *Acta Pharmaceutica Sinica B*. 2025. https://doi.org/10.1016/j.apsb.2025.12.030.
10. Ghanbari AU, Jalili CU, Shahveisi KU, Raissi FU, Mazini FU, Akhshi NU. Antioxidant, anti-apoptotic and anti-inflammatory effects of acacetin against deltamethrin-induced hepatotoxicity in mice: a biochemical and histopathological study. *koomesh*. 2023;**25**(4). e152847. https://doi.org/10.5812/jjnpp-152847.
11. Hadadian S, Moradzadegan A. Investigating the Toxicity caused by photodynamic therapy with a Low-power Diode Laser with a wavelength of 810 nm compared to a combination of Curcumin in breast cancer cells. *Gene Cell Tissue*. 2023;**11**(1). e138519. https://doi.org/10.5812/gct-138519.
12. Arshad A, Pervaiz S, Errum A, Mahmood A, Asghar H, Maqsood S, et al. Evaluation of antidiabetic effect of Silybum marianum and Cichorium intybus extracts. *Pakistan Journal of Medical & Health Sciences*. 2022;**16**(1):820-823. https://doi.org/10.53350/pjmhs22161820.
13. Anushiravani A, Ghajarieh Sepanlou S. Burden of liver diseases: A review from Iran. *Middle East journal of digestive diseases*. 2019;**11**(4):189-1891. [PubMed ID: 31824620]. [PubMed Central ID: PMC6895850]. https://doi.org/10.15171/mejdd.2019.147.
14. Madani H, Talebolhosseini M, Asgary S, Naderi GH. Hepatoprotective activity of Silybum marianum and Cichorium intybus against thioacetamide in rat. Pakistan. J. *Nut*. 2008;**7**(1):172-176. https://doi.org/10.3923/pjn.2008.172.176.
15. Mohammadi SM, kianbakht S, Rezazadeh S, Ziaee M, Fallah Huseini H. Clinical efficacy of Silybum marianum seed extract in treatment of type 2 diabetes mellitus and non-alcoholic fatty liver disease: a narrative review. J. Med. *Plants*. 2020;**19**(73):12-26. https://doi.org/10.29252/jmp.1.73.12.
16. Maddahi SZ, Jokar A, Kamalinejad M, Behnampur N. The efficacy of Jujube syrup on the prevention of drug-induced hepatotoxicity in pulmonary tuberculosis patients: A pilot randomized double-blind placebo-controlled clinical trial. *Pharmacol Res Perspect*. 2022;**10**(1). e00902. [PubMed ID: 34939363]. [PubMed Central ID: PMC8929366]. https://doi.org/10.1002/prp2.902.
17. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bull. World. Health. *Organ*. 2001;**79**(4):373-374.
18. Balouchzad A, Rahimi HR, Ebadollahi AR, Minaei-Zan B, Sabzevari O. Aqueous extract of Iranian green tea prevents lipid peroxidation and chronic ethanol liver toxicity in rats. J. Pharmacol. *Toxicol*. 2011;**6**(8):691-700. https://doi.org/10.3923/jpt.2011.691.700.
19. Nazıroğlu M, Yürekli VA. Effects of antiepileptic drugs on antioxidant and oxidant molecular pathways: focus on trace elements. Cell. Mol. *Neurobiol*. 2013;**33**(5):589-599. [PubMed ID: 23584684]. [PubMed Central ID: PMC11497999]. https://doi.org/10.1007/s10571-013-9936-5.
20. Santhrani T, Maheswari E, Saraswathy G. Carbamazepine provoked hepatotoxicity: Attenuation by vitamin C. *Oxidants and Antioxidants in Medical Science*. 2013;**2**(1):1. https://doi.org/10.5455/oams.270113.or.026.
21. Wu JW, Lin LC, Hung SC, Chi CW, Tsai TH. Analysis of silibinin in rat plasma and bile for hepatobiliary excretion and oral bioavailability application. J. Pharm. Biomed. *Anal*. 2007;**45**(4):635-641. [PubMed ID: 17692492]. https://doi.org/10.1016/j.jpba.2007.06.026.
22. Zhuang H, Jing N, Wang L, Jiang G, Liu Z. Jujube powder enhances cyclophosphamide efficiency against murine colon cancer by enriching CD8(+) T cells while inhibiting eosinophilia. *Nutrients*. 2021;**13**(8):2700. [PubMed ID: 34444860]. [PubMed Central ID: PMC8401958]. https://doi.org/10.3390/nu13082700.
23. Li L, Qin Y, Xin X, Wang S, Liu Z, Feng X. The great potential of flavonoids as candidate drugs for NAFLD. Biomed. *Pharmacother*.

2023;**164**. 114991. [PubMed ID: 37302319]. https://doi.org/10.1016/j.biopha.2023.114991.