



# HERBS IN PERSPECTIVE OF HEPATOPROTECTIVE ACTIVITY: A REVIEW

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## Abstract

Liver is an important and major vital organ. It showed an accurate function in metabolism and excretion of drugs from the body. Along with that, it also mimics the metabolism and excretion of medicine. The most important purpose of the liver are carbohydrate, protein, fat metabolism and detoxification, secretion of bile and storage of vitamins. Worldwide toxicity of liver, liver cirrhosis and liver illnesses are the major cause. Liver disease (Hepatic disease) is a term that impacts the cells, tissues, systems or factures of the liver. Liver cell harm resulting from various toxic chemical compounds (along with anti-biotic, chemotherapeutic retailers, thioacetamide and paracetamol and so forth.), excessive alcohol intake and microbes are nicely studied. A number of natural tablets show promising hepatoprotective activities in acute and chronic liver damage. In medication the natural products play an essential role because of their protection, efficacy and price effectiveness. Medicinal plants might also function as vital source of doubtlessly useful for the development of effective therapy to fight several liver diseases. In this review we focused and reviewed the various medicinal plants for hepatoprotective effect against hepatotoxicity and other liver diseases.

**Keywords:** Hepatotoxicity, liver, medicinal plant, organs.

## I. Introduction

Liver is the largest organ of our body. It is most vital organ that is responsible for the metabolism of nutrients i.e. carbohydrate, fat & protein. The liver weighs approximately 1500g and accounts for 2.5% of adult body weight. The liver lies mainly in the right upper quadrant of the abdomen where it is hidden and protected by the thoracic cage and diaphragm. The normal liver lies deep to the ribs 7-11 on the right side. The surface of the liver is smooth and dome shaped [23]. The major function of liver is production of bile. The liver secreats 700 to 1200 ml bile per day. The bile consists of bile salts, cholesterol, bilirubin, electrolytes, and water. It helps in the absorption of fats, cholesterol and some vitamins. It helps in the metabolism of bilirubin, fat,

carbohydrates and proteins. Other functions of liver include storage of vitamin and minerals, filtration of blood, production of albumin and angiotensinogen, Inactivation of Toxins and Drugs [6].

The liver disease is the major cause of death every year. Hepatitis, jaundice, fatty liver, acute liver failure, liver cirrhosis are the major liver diseases. Hepatitis is swelling and inflammation of the liver. It can be caused by immune cells of body, viruses, parasites, bacteria etc. Acute liver failure occurs when our liver rapidly loses its ability to function [29].

## II. Hepatotoxicity

Hepatotoxicity is injury or liver damage caused by exposure to drugs or other non-pharmacological agents. Hepatotoxicity can be divided into two types- intrinsic reactions and idiosyncratic reactions. The intrinsic reactions are predictable, less common, dose dependent. These reactions are reproducible in animal models. In this type of hepatotoxicity, the injury is produced through toxic metabolites such as free radicals (generating lipid peroxidation), electrophilic molecules (formation of covalent bonds with hepatic proteins) or active oxygen molecules [5].

### 2.1 Hepatotoxin

The natural or chemical substances which have ability to produce toxicity in liver are termed as hepatotoxins.

### 2.2 Mechanism of Hepatotoxicity

Mechanism of liver injury can be classified as pathophysiological or through chemical induced mechanism.

#### A. Pathophysiologic hepatic damage

- Disruption of the hepatocytes
- Disruption of the transport proteins
- Cytolytic T-cell activation
- Apoptosis of hepatocytes
- Mitochondrial disruption
- Bile duct injury

#### B. Chemical induced hepatic damage

- Direct or intrinsic or predictable drug reactions
- Indirect or unpredictable idiosyncratic drug reactions [9,13].

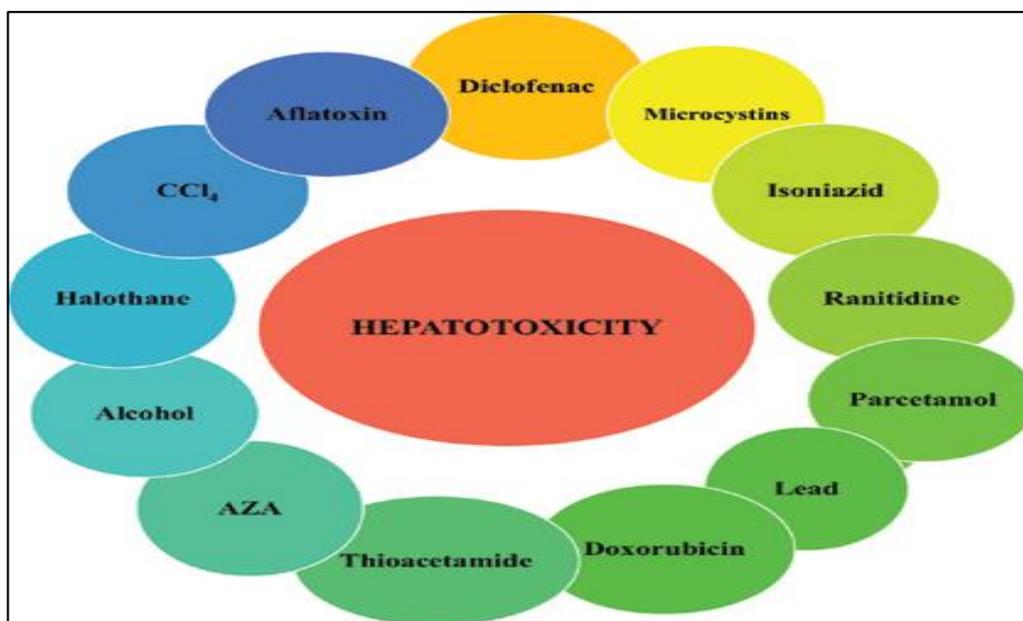


Figure 1- Hepatotoxic drugs [26]

### 2.3 Hepatotoxicity induced by anti-tubercular drugs

The first line anti-tubercular drugs (Rifampicin, Isoniazid and Pyrazinamide) are common hepatotoxic drugs. Rifampicin-induced cytochrome P450 enzyme-induction results in increased production of the toxic metabolites from acetyl hydrazine (AcHz). Rifampicin also increases the metabolism of INH to isonicotinic acid and hydrazine, both of which are hepatotoxic. Human genetic studies have shown that cytochrome P4502E1 (CYP2E1) is involved in anti-tubercular drug hepatotoxicity. The CYP2E1 c1/c1 genotype is associated with a higher CYP2E1 activity and may lead to a higher production of hepatotoxins [24].

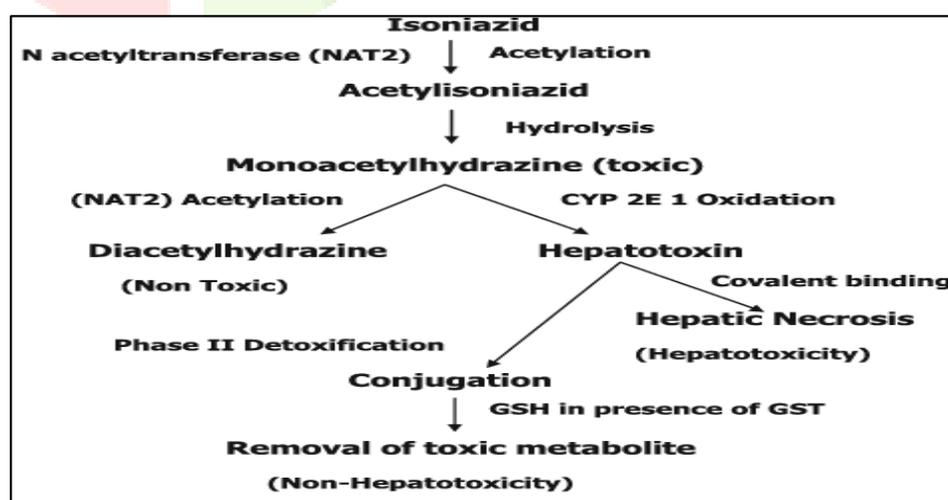


Figure 2- Hepatotoxicity by isoniazid

## 2.4 Hepatotoxicity induced by Paracetamol

Acetaminophen, also known as APAP (in the United States), paracetamol (in Europe and other areas of the world) or N-acetyl-p-aminophenol, is one of the most commonly utilized compounds worldwide. Its use as an anti-pyretic or analgesic drug has been predominant since 1955.

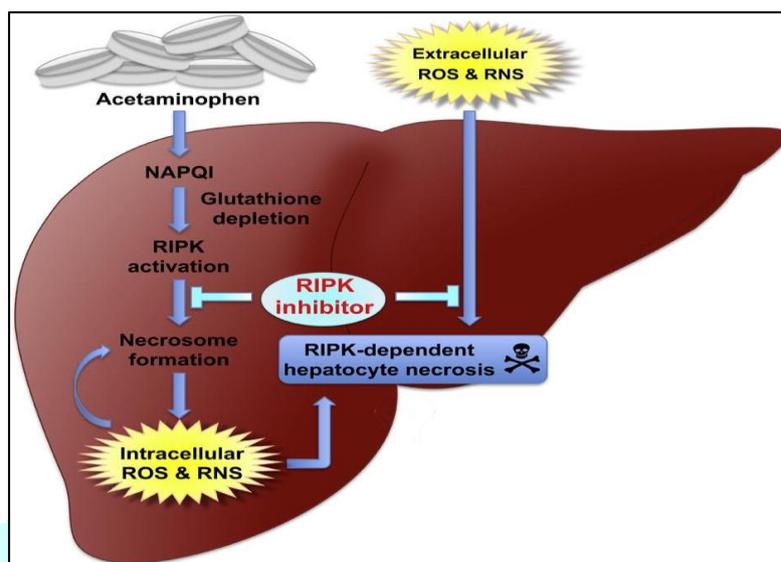


Figure 3- Hepatotoxicity by Paracetamol [14].

APAP hepatotoxicity occurs through formation of the noxious NAPQI metabolite, which is present in excessive quantities, as augmented by features of glutathione (GSH) depletion, oxidative stress and mitochondrial dysfunction leading to depletion in adenosine triphosphate (ATP) stores [7].

## 2.5 Hepatotoxicity by CCl<sub>4</sub>

The ccl4 damages the cells mainly by two methods. The first method includes the covalent binding of reactive species to cellular components and another mechanism includes interaction of free radical intermediates with oxygen which increases the lipid peroxidation. This gives rise to destruction of lipids, particularly unsaturated phospholipids, resulting in damage to intracellular membrane [18].

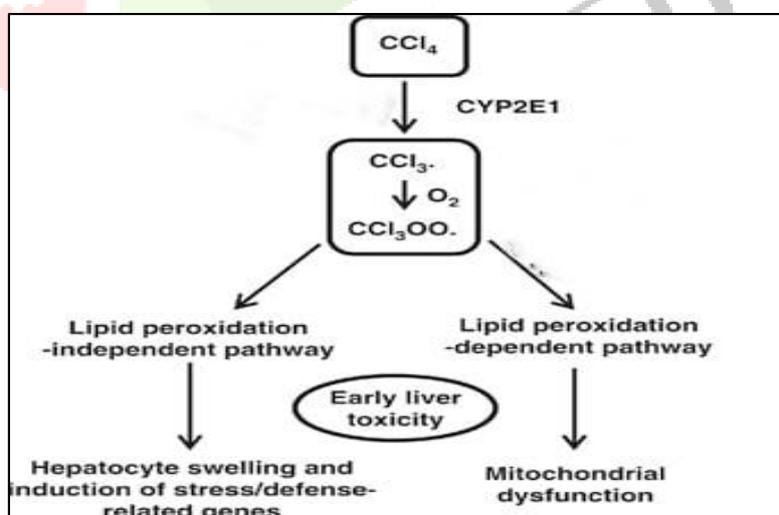


Figure 4-Hepatotoxicity by Carbon tetrachloride [2].

## 2.6 Hepatotoxicity by Thioacetamide

Thioacetamide in our body converts to sulfine and sulfene. Sulfine is responsible for the enlargement of nucleoli, increase in nuclear volume and intracellular concentration of  $\text{Ca}^{++}$ , change in cell permeability and inhibits mitochondrial activity. Sulfene is responsible for the release of nitric oxide synthase, centrilobular necrosis, protein denaturation and lipid peroxidation. Furthermore, it impairs the urea cycle [36].

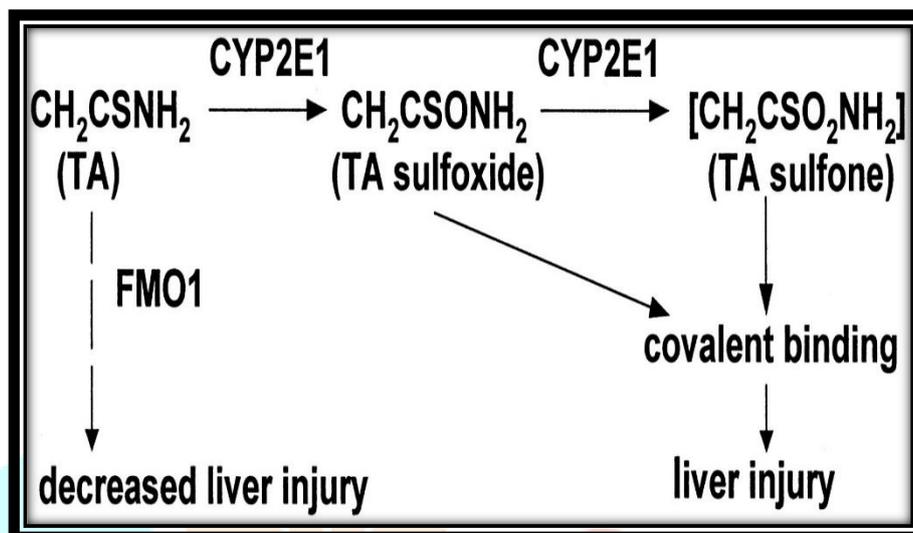


Figure 5-Hepatotoxicity by Thioacetamide

## III. Herbal or Medicinal Plants:

Herbal medicines have been defined as “preparations manufactured industrially consisting of active ingredients which are purely and naturally original, not chemically altered plant substances, and are responsible for the overall therapeutic effect of the product [4]. Medicinal Plants plays an important role in human fitness care. Approximately 80 % of world population is predicted on using conventional medicine that predominately based on plant materials. Herbal drugs are more broadly used than allopathic drugs as hepatoprotectives because they are less expensive, higher cultural acceptability, higher compatibility with the human body [10].

The use of plants for healing purposes predates human history and forms the origin of much modern medicine. Clinical, pharmacological, and chemical studies of these traditional medicines, which were derived predominantly from plants, were the basis of most early medicines such as aspirin (willow bark), digitoxin (from foxglove), morphine (from the opium poppy), quinine (from cinchona bark), and pilocarpine (Jaborandi) Herbal medicine is still the mainstay of about 75 - 80% of the world population, mainly in the developing countries, for primary health care [25].

## IV. List of Herbal Plants used as Hepatoprotective agents

Sr. No.	Botanical Name of Plant	Hepatoprotective Part	Hepatoprotective Component	Origin	Biochemical Test
1	Aphanamixis polystachya	Leaf root and bark	Aphanamixoid A	Indomalaysi, Western Ghats-South and central Sahyadris	efficacy against liver damage, marker enzymes like; ASAT ALAT, LDH
2	Andrographis paniculata	Leaf	Andrographolid e	Southern and Southeastern Asia	Effective against CCl <sub>4</sub> , paracetamol, ethanol-induced elevation levels of SGPT, SGOT, ALP, DB and LDH.
3	Acacia catechu	Leaf	Ethanollic and aqueous extracts from leaves	Caribbean, Pacific and America	Reduce serum marker enzyme like (SGOT), SGPT, ALP and improve serum lipid profiling
4	Asteracantha longifolia L.	Leaved axial flower, root and seed	Andrographolid e	India and Shri Lanka	Inhibit APAP induced liver damager marker enzyme and Methanol extract of seed showed Inhibition of hepatocarcinogenesis in Wistar rats with increase in GPx, CAT and ODC
5	Aegle marmelos	Leaf, Bark	Eugenol	India	Reduce liver injury marker enzyme like AST ALT ALP etc
6	Adhatoda vasica	Leaf	Leaf extract	Asia	Reduce serum marker enzymes
7	Azadirachta indica	Leaf, root and stem bark	juice extract	India, Pakistan and Bangladesh growing in tropical and semi-tropical regions.	significant reversal in serum levels of SGOT, glutamic pyruvic transaminase, alkaline phosphatase (ALP), total bilirubin (TBL) and histological changes in liver induced by CCl <sub>4</sub> .

8	Baliosermmontanum	roots, leaves and seeds	Aqueous leaf extract	Nepal, Burma, Malaya and India	significant reduction in serum enzyme such as $\gamma$ -glutamyl transpeptidase and lipid peroxidase, ALT AST and increase in reduced glutathione (GSH) also histopathological improvement
9	Boerhaavia Diffusa	Root	rotenoids, boeravinone E and boeravinone B	India, the Pacific, and southern United States.	Protection against majority all serum parameter and aqueous form is more has more activity than powder form
10	Butea monosperma	Dried flowers	Water extract	Indian Subcontinent and Southeast Asia,	marked reduction in the levels of activated Erk1/2 and SAPK/JNK
11	Cajanus indica	Leaves	Methanol, n-hexane, Aqueous extract of the leaves	Indian subcontinent, eastern Africa and Central America.	significant reduction in serum enzyme
12	Cassia fistula	Fruit pulp	Leaves Fruit pulp extract	South Asia	significantly and dose-dependently decreased the liver damager marker enzyme activities
13	Ephedra foliate	whole plant	Crude extract, Ethanolic Extracts	Middle East and central Asia	significant in all parameters studied, except SGPT level and disappearance of fatty deposition and necrosis.
14	Fumaria indica	whole plant	alkaloid protopine	native to Europe, Africa and Asia, most diverse in the Mediterranean region	changes in serum enzymes (SGOT, SGPT, ALP) and metabolites bilirubin, reduced glutathione (GSH) and lipid peroxidation (MDA content)
15	Hibiscus sabdariffa	dried flowers	Dried flower extract	native to tropical Africa but cultivated and widely	reduced the elevated levels of LDH, GOT, GPT, and MDA and increased the reduced activities of SOD and GSH-Px in a dose-dependent manner

16	Halenia elliptica	aerial parts	methanolic extract	China	significant decrease in ALT, AST, ALP, and total bilirubin levels
17	Hygrophila auriculata	Roots	aqueous extract	India, Sri Lanka, Burma, Malaysia	Inhibit the enhanced ALT AST ALP and serum enzyme
18	Phyllanthus niruri	Leaves	aqueous and methanol extracts and protein,	Amazon, China, Southern India,	normalize level of all liver biochemical parameters total antioxidant capacity, lipid peroxidation, and oxidative stress enzyme levels and also protective role against liver cirrhosis
19	Silybum marianum	seeds and roots	Silymarin	Southern Europe, Asia	Inhibit the enhanced ALT AST ALP and platelet counts
20	Terminalia arjuna	Bark	aqueous extract Flavonoids	Southern Europe, Asia	potential therapeutic value against Isoniazid induced hepatic damage

Table 1 - Hepatoprotective plants [19]

## V. Silymarin as Standard Drug

### Plant Profile

<b>Kingdom</b>	Plantae
<b>Order</b>	Asterales
<b>Family</b>	Asteraceae
<b>Tribe</b>	Cynareae
<b>Genus</b>	Silybum
<b>Species</b>	<i>S. marianum</i>

Table 2: Botanical Name:Silybum marianum Gaertn



Figure 6: Silybum marianum

## Pharmacokinetics-

Silymarin isn't soluble in water and is typically administered in an encapsulated form [37]. Silymarin is absorbed when given orally. Peak plasma concentration is achieved in 6-8 h. The oral absorption of silymarin is just about 23-47%, leading to low bioavailability of the compound; it's administered as a standard extract (70-80% silymarin). After oral administration the recovery in bile ranges from 2-3%. Silybin and also the other components of silymarin are rapidly conjugated with sulfate and glucuronic acid within the liver and excreted through the bile.[38-41] The poor water solubility and bioavailability of silymarin led to the event of enhanced formulations; e.g., silipide (Siliphos), a complex of silymarin and phosphatidylcholine that is ten times more bioavailable than silymarin;[42] an inclusion complex formed between silymarin and  $\beta$ -cyclodextrin, which is approximately 18 times more soluble than silymarin.[43] There have been reports of silybin glycosides that have better solubility and stronger hepatoprotective activity.[44]

## Toxicity

Studies on the acute toxicity of silymarin after intravenous infusion have been carried out in mice, rats, rabbits, and dogs. The LD50 values were 400 mg/kg (mice), 385 mg/kg (rats), and 140 mg/kg (rabbits and dogs). Depending on the infusion rate these values vary. With slow infusion (over 2-3 h) the LD50 was 2 g/kg in rats and after oral administration it was 10 g/kg. Intravenous bolus dose of silymarin as the hemisuccinate sodium salt has also been used to carry out acute toxicity studies in beagle dogs, rabbits, Wistar rats, and NMRI mice. The LD50 was 1050 mg/kg (male mice), 970 mg/kg (female mice), 825 mg/kg (male rats), 920 mg/kg (female rats), and 300 mg/kg (rabbits, dogs). [45] These data demonstrate that the acute toxicity of silymarin is very low. Similarly, its subacute and chronic toxicity are also very low. [46,47]

## Mechanism of Action

Silymarin's hepatoprotective effects are purportedly accomplished via several mechanisms; these include:

- Antioxidation[48,49]
- Inhibition of lipid peroxidation[50]
- Stimulation of ribosomal RNA polymerase and subsequent protein synthesis, leading to enhanced hepatocyte regeneration[51]
- Enhanced liver detoxification via inhibition of phase I detoxification[52,53]
- Enhanced glucuronidation and protection from glutathione depletion[54]
- Anti-inflammatory effects, including inhibition of leukotriene and prostaglandin synthesis, Kupffer cell inhibition, mast cell stabilization, and inhibition of neutrophil migration[55]
- Slowing or even reversing of fibrosis by reduction of the conversion of hepatic stellate cells into myofibroblasts[56]
- Anticarcinogenesis by inhibition of cyclin-dependent kinases and arrest of cancer cell growth

- Silymarin is also found to have immunomodulatory effects on the diseased liver [57,58]

## Conclusion

From this study, it is concluded that herbal plants play a major role against various diseases. Many herbal plants and plant extracts have effective hepatoprotective activity. Flavonoids, alkaloids, terpenoids, glycosides and steroids are responsible for the hepatoprotective effect of numerous plants. The result of this study indicate that extracts of leaves and whole plant extract of huge medicinal plants have good potentials for use in hepatic disease.

## References :-

1. Adam Kowalczyk, Martyna Przychodna , Sylwia Sopata, Agnieszka Bodalska and Izabela Fecka; Thymol and Thyme Essential Oil—New Insights into Selected Therapeutic Applications; 2020.
2. Alain Fautrel, *et al.*, French Institute of Health and Medical Research Carbon tetrachloride-mediated lipid peroxidation induces early mitochondrial alterations in mouse liver; Laboratory Investigation, 2012.
3. Anna Bertolini, Ivo P. van de Peppel, Frank A.J.A. Bodewes, Han Moshage, Alberto Fantin, Fabio Farinati, Romina Fiorotto, Johan W. Jonker, Mario Strazzabosco, Henkjan J. Verkade, Giulia Peseri; Abnormal liver function tests in COVID-19 patients: relevance and potential pathogenesis; 2020.
4. Azhar H. Alostad, Douglas T. Stenke and Ellen I. Schafheutle; Herbal Medicine Classification: Policy Recommendations; Frontiers in Medicine; 2020.
5. Can Alejandra Paniagua, Amariles Pedro; Hepatotoxicity by Drugs; <http://dx.doi.org/10.5772/intechopen.72005>, 2018.
6. Dilipkumar Pal, Chandan Kumar Sahu, Arindam Halder; Bhasma: The ancient Indian nanomedicine; Journal of Advanced Pharmaceutical Technology & Research; 2014.
7. Eric Yoon, Arooj Babar, Moaz Choudhary, Matthew Kutner and Nikolaos Pysopoulo; Acetaminophen-Induced Hepatotoxicity: a Comprehensive Update; Journal of Clinical and Translational Hepatology, 2016.
8. G. Kavita, K. Santosh, and S. Reeta, "Evaluation of antibacterial activity of aerial parts of *Thymus serpyllum* L.," Journal of Pharmacy Research, 2011.
9. Hartmut Jaeschke, Gregory J. Gores, Arthur I. Cederbaum, Jack A. Hinson, Dominique Pessayre and John J. Lemasters; Mechanisms of Hepatotoxicity; Toxicological Sciences, 2002.
10. Hassan Towseef, et al, Hepatoprotective Activity of Some Medicinal Plants: A Review; "International Research Journal of Pharmacy" 2019. <https://www.industryarc.com/Report/16155/liver-disease-treatment-market.html>
11. [https://www.who.int/health-topics/hepatitis#tab=tab\\_1`](https://www.who.int/health-topics/hepatitis#tab=tab_1)
12. Jian Sun, Alessio Aghemo, Alejandro Forner, Luca Valenti; COVID-19 and liver disease; Liver International. 2020.
13. Kavita Gulati, Mohd Rafi Reshi, Nishant Rai and Arunabha Ray; Hepatotoxicity: Its Mechanisms, Experimental Evaluation and Protective Strategies; American Journal of Pharmacology; 2018.
14. Kenji Takemoto, *et al*; Necrostatin-1 protects against reactive oxygen species (ROS)-induced hepatotoxicity in acetaminophen-induced acute liver failure, 2014.
15. Liver Disease Treatment Market – Forecast (2022 - 2027) <https://www.worldgastroenterology.org/publications/e-wgn/e-wgn-expert-point-of-view-articles-collection/global-burden-of-liver-disease-a-true-burden-on-health-sciences-and-economies>.

16. Luo K Elaine and Newman Tim; “The Liver: Structure, function, disease”; “Medical News Today”2018.
17. Mansoorali K.P., Prakash T., Kotresha D., Prabhu K. and Rao Rama N.; Cerebroprotective effect of *Eclipta alba* against global model of cerebral ischemia induced oxidative stress in rats; ScienceDirect; 2012.
18. Meinrad Boll, Lutz W. D. Weber, Eberhard Becker and Andreas Stampfl; “Mechanism of Carbon Tetrachloride-Induced Hepatotoxicity”; Hepatocellular Damage by Reactive Carbon Tetrachloride Metabolites,2001.
19. Mishra Savita, Aeri Vidhu and Katare Deepshikha Pande, Hepatoprotective Medication for Liver Injury; ResearchGate; 2014.
20. Mohsen Naghavi, Catherine Bisignano, Kevin Ikuta; The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017; The Lancet Gastroenterology & Hepatology, January 2020.
21. Mohsen Naghavi, Catherine Bisignano, Kevin Ikuta; The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017; The Lancet Gastroenterology & Hepatology, January 2020.
22. N. Diklic, “Lamiaceae,” in ‘ Flora Srbije VI, M. Josifovic, Ed., pp. ‘ 339–527, 1974.
23. Ozougwu, C Jevas; “Physiology of Liver”; “International Journal of Research in Pharmacy and Biosciences” 2017.
24. Pandit Aashish, Sachdeva Tarun and Bafna Pallavi; Drug-Induced Hepatotoxicity: A Review; Journal of Applied Pharmaceutical Science 02 (05); 2012.
25. Qazi Majaz A, Molvi Khurshid; Herbal Medicine: A Comprehensive Review; ResearchGate; 2016.
26. Roohi Mohi-ud-din, Reyaz Hassan Mir, Gifty Sawhney, Mohd Akbar Dar and Zulfiqar Ali Bhat; Possible Pathways of Hepatotoxicity Caused by Chemical Agents ,2019.
27. Rownak Jahan, Abdullah Al-Nahain, Snehal Majumde and Mohammed Rahmatullah; Ethnopharmacological Significance of *Eclipta alba* (L.) Hassk. (Asteraceae); 2014.
28. S Vetriselvan, U Subasini, Victor Rajamanickam C, Thirumurugu S; Hepatoprotective activity of *Andrographis paniculata* in ethanol induced hepatotoxicity in albino Wistar rats; International Journal of Comprehensive Pharmacy; 2011.
29. S. Sivakrishnan, “Liver diseases-an overview”;world journal of pharmacy and pharmaceutical sciences; 2019.
30. Sarin S.K, Maiwall Rakhi; World Gastroenterology Organisation, 2022
31. Sefidkon F., Dabiri M. and Mirmostafa S.A.; The Composition of *Thymus serpyllum* L. Oil; Journal of Essential Oil Research; 2004.
32. Slam, M.T.; Khalipha, A.B.R.; Bagchi, R.; Mondal, M.; Smrity, S.Z.; Uddin, S.J.; Shilpi, J.A.; Rouf, R. Anticancer Activity of Thymol: A Literature Based Review and Docking Study with Emphasis on its Anticancer Mechanisms. Iubmb Life 2019.
33. Snedana Jarit, Miroslava Mitrovit, And Pavle Pavlovit; Review of Ethnobotanical, Phytochemical and Pharmacological Study of *Thymus serpyllum* L., 2015.
34. Sumeet K. Asrani, Harshad Devarbhavi, John Eaton, Patrick S. Kamath; Burden of liver diseases in the world; Journal of Hepatology; january 01, 2019.
35. Sureshchandra, Vijay Barve, Vijay Srinivas, Sathya Sangeetha, K. Ravikumar, Kartikeyan R., Vaibhav Kulkarni, Ajith S. Kumar, S.N. Venugopal, B. S. Somashekhar, M.V. Sumanth, Noorunissa Begum, Sugandhi Rani, Surekha K.V., and Nikhil Desale; Envis center of medicinal plants; 2016.

36. Tasleem Akhtar and Nadeem Sheikh; An overview of thioacetamide-induced hepatotoxicity; Toxin Review, Informa Healthcare USA;2013.
37. Luper S. A review of plants used in the treatment of liver disease: Part 1. *Alternate Med Rev* 1998;3:410-21.
38. Pepping J. Milk thistle: *Silybum marianum*. *Am J Health Syst Pharm* 1999;56:1195-7.
39. Schandalik R, Gatti G, Perucca E. Pharmacokinetics of silybin in bile following administration of silipide and silymarin in cholecystectomy patients. *Arzneimittelforschung* 1992;42:964-8.
40. Tyler V. *Phytomedicines in Western Europe: their potential impact on herbal medicine in the United States*. *Herbalgram* 1994;30:24-30.
41. Morazzoni P, Montalbetti A, Malandrino S, Pifferi G. Comparative pharmacokinetics of silipide and silymarin in rats. *Eur J Drug Metabol Pharmacokinet* 1993;18:289-97.
42. Kidd P, Head K. A review of the bioavailability and clinical efficacy of milk thistle phytosome: A silybin-phosphatidylcholine complex (Siliphos). *Altern Med Rev* 2005;10:193-203.
43. Arcari M, Brambilla A, Brandt A, Caponi R, Corsi G, Di Rella M, et al. A new inclusion complex of silibinin and beta-cyclodextrins: in vitro dissolution kinetics and in vivo absorption in comparison with traditional formulations. *Boll Chim Farm* 1992;131:205-9.
44. Morazzoni P, Bombardelli E. *Silybum marianum* (cardus marianus). *Fitoterpia* 1994;66:3-42.
45. Desplaces A, Choppin J, Vogel G. The effects of silymarin on experimental phalloidine poisoning. *Arzneimittelforschung* 1975;25:89-96.
46. Morazzoni P, Bombardelli E. *Silybum marianum* (cardus marianus). *Fitoterpia* 1994;66:3-42.
47. Saller R, Meier R, Brignoli R. The use of silymarin in the treatment of liver diseases. *Drugs* 2001;61:2035-63.
48. Mirguez MP, Anundi I, Sainz-Pardo LA, Lindros KO. Hepatoprotective mechanism of silymarin: No evidence for involvement of cytochrome P450E1. *Chem Biol Interact* 1994;91:51-63.
49. Wagner H. Plant constituents with antihepatotoxic activity. In: Beal JL, Reinhard E, editors. *Natural Products as Medicinal Agents*. Stuttgart: Hippokrates-Verlag;1981.
50. Bosisio E, Benelli C, Pirola O. Effect of the flavonolignans of *Silybum marianum* L. on lipid peroxidation in rat liver microsomes and freshly isolated hepatocytes. *Pharmacol Res* 1992;25:147-54.
51. Sonnenbichler J, Zetl I. Biochemical effects of the flavonolignane silibinin on RNA, protein and DNA synthesis in rat livers. *Progr Clin Biol Res* 1986;213:319-31.
52. Baer-Dubowska W, Szafer H, Drajka-Kuzniak V. Inhibition of murine hepatic cytochrome P450 activities by natural and synthetic phenolic compounds. *Xenobiotica* 1998;28:735-43.
53. Halim AB, el-Ahmady O, Hassab-Allah S, Abdel-Galil F, Hafez Y, Darwish A. Biochemical effect of antioxidants on lipids and liver function in experimentally induced liver damage. *Ann Clin Biochem* 1997;34:656-63.
54. Saller R, Meier R, Brignoli R. The use of silymarin in the treatment of liver diseases. *Drugs* 2001;61:2035-63.
55. Saraswat B, Visen PKS, Patnaik GK, Dhawan BN. Effect of andrographolid against galactosamine-induced hepatotoxicity. *Fitoterpia* 1995;66:415-20.
56. Floersheim GL, Eberhard M, Tschumi P, Duckert F. Effects of penicillin and silymarin on liver enzymes and blood clotting factors in dogs given a boiled preparation of *Amanita phalloids*. *Toxicol Appl Pharmacol* 1978;46:455-62.
57. De La Puerta R, Martinez E, Bravo L, Ahumada MC. Effect of silymarin on different acute inflammation models on leukocyte migration. *J Pharm Pharmacol* 1996;48:968-70.
58. Dehmlow C, Erhard J, de Groot H. Inhibition of Kupffer cell functions as an explanation for the hepatoprotective properties of silibinin. *Hepatology* 1996;23:749-54.