IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

"Herbal Guardians Of The Liver: A Comprehensive Review"

Dr. Anilkumar Aher, Shreya Gurgude, Aishwarya Halde, Samyak Jadhav, Yash Kadu
Department of Pharmacognosy, MVP's College of Pharmacy, Nashik
Maharashtra (422002), India

Abstract: The liver is an important organ for metabolism and removing harmful substances from the body. However, liver injury and dysfunction are major issues for healthcare, the pharmaceutical industry, and regulatory agencies. The liver can be harmed by various toxic substances, including certain antibiotics, chemotherapy drugs, environmental toxins like carbon tetrachloride and thioacetamide, excessive alcohol, and microbial infections. Current treatments often involve synthetic drugs that may worsen liver damage. Therefore, herbal medicines are gaining interest as potential alternatives for liver disease treatment. These remedies have been used for centuries, and this review aims to provide an overview of effective plant-based phytochemicals tested in liver damage models. The goal is to identify natural compounds that can protect and promote liver health.

Index Terms –Hepatoprotective, survey, Marketed product, Kalmegh, Milk Thistle, Jewel Orchid, Neem.

INTRODUCTION

The liver is an important organ that does many jobs in the body, but it is also prone to damage from various sources. This includes harmful substances, infections, metabolic issues, blood flow problems, and cancer. Liver disease is a major global health issue, causing around two million deaths yearly, which is about 4% of all deaths. Factors such as exposure to toxic substances, heavy drinking, and infections can harm the liver, damaging its cells and leading to serious health problems that affect people's lives and can be life-threatening.

Mechanisms of Hepatotoxic agents:

Hepatotoxins are divided into two main types: Intrinsic and Idiosyncratic. Intrinsic hepatotoxins, like Carbon tetrachloride, Thioacetamide, and Acetaminophen, damage the liver in a predictable way that depends on the dose, with a consistent delay before damage occurs. In contrast, Idiosyncratic hepatotoxins, such as Halothane and some Antibiotics, harm a small percentage of people exposed to them, and this damage does not depend on the dose. The time between exposure and damage can vary widely, and these toxins are often hard to study because their effects cannot be easily reproduced in animal experiments.

Well known hepatotoxins include:

1. Carbon tetrachloride (CCl4)

Liver damage resulting from Carbon tetrachloride (CCl4) occurs through a complicated process that involves oxidative stress, lipid peroxidation, and inflammation. The CYP2E1 enzyme within the liver metabolizes CCl4, creating toxic trichloromethyl and trichloromethyl peroxide radicals. These reactive radicals attach to unsaturated fatty acids found in the membranes of hepatocytes, mitochondria, and the endoplasmic reticulum, initiating a series of lipid peroxidation reactions that eventually cause hepatocyte injury and death.

Acute CCl4 poisoning leads to a notable surge in pro-inflammatory mediators such as TNF-α, IL-1β, IL-6, NO, and Lipocalin 2-NGAL, while simultaneously reducing the levels of the anti-inflammatory cytokine IL-10. This disparity fosters the onset of liver inflammation. The free radicals and reactive oxygen species (ROS) produced by CCl4 damage activate multiple liver cell types, including Kupffer cells, stellate cells, and

sinusoidal endothelial cells. These activated cells secrete pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, PGE2, and eicosanoids, which further intensify hepatocyte damage.

NGAL (Lipocalin-2) serves as a biomarker for liver inflammation that is associated with the severity of liver injury. Injured hepatocytes release NGAL, which stimulates Kupffer cells to produce chemokines that recruit neutrophils and monocytes to the inflammation site, enhancing the inflammatory response and tissue injury. The pathogenesis of CCl4-induced liver damage encompasses a complex interaction of pro-inflammatory and anti-inflammatory mediators. TNF-α is crucial in aggravating nitrosative stress by inducing iNOS and releasing NO. Conversely, IL-10 exerts a protective effect by inhibiting pro-inflammatory mediators and alleviating liver inflammation. CCl4 exposure results in a notable rise in liver enzyme activities, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and sorbitol dehydrogenase (SDH), due to damage to cellular and subcellular membranes, resulting in their leakage into the systemic circulation.

2. Acetaminophen

A particular analgesic and antipyretic medication can lead to serious liver damage when consumed in high doses, resulting in necrosis of liver cells. In standard therapeutic doses, the drug is mainly metabolized into glucuronic or sulfated derivatives for elimination. A minor portion of the drug is transformed into intermediate reactive compounds which are detoxified through conjugation with glutathione. However, when taken in excessive quantities, the surplus is oxidized by the cytochrome P450 enzyme (primarily the CYP2E1 isoform), producing a harmful intermediate known as N-acetyl-P-benzoquinone imine (NAPQI). Typically, NAPQI is quickly conjugated with glutathione and removed from the body. However, when NAPQI levels surpass the available glutathione, a covalent bond forms between the metabolite and proteins, resulting in adduct formation, mitochondrial dysfunction, and oxidative stress. This ultimately leads to liver cell necrosis or death. The mechanism underlying the liver damage caused by the medication involves a complex interplay of metabolic processes and cellular mechanisms. Understanding this mechanism is vital for creating strategies to prevent and treat drug-induced liver damage.

3. Ethanol

The liver is especially susceptible to the harmful effects of Ethanol. The main mechanism of injury is linked to the metabolic breakdown of Ethanol by a particular enzyme, which initiates a sequence of oxidative stress and produces Reactive Oxygen Species. This consequently results in an increase in Lipid peroxidation, leading to changes in the composition of phospholipids within the cellular membrane. As a result, the structure and integrity of the membrane are compromised, resulting in higher levels of a specific enzyme in the bloodstream. Additionally, Ethanol has been demonstrated to hinder the functioning of an essential Antioxidant enzyme, by diminishing the activity of other enzymes that are important for reducing oxidative stress. The reduction in Antioxidant enzyme activity is believed to stem from the damaging effects of free radicals generated during Ethanol metabolism. Alternatively, it is plausible that a byproduct of Ethanol oxidation could directly affect these enzymes, further contributing to observed liver damage. Overall, the relationship between Ethanol metabolism, oxidative stress, and Antioxidant defenses is intricate, and additional research is necessary to completely comprehend the mechanisms behind Ethanol-induced liver damage.

4. D-Galactosamine

The harm inflicted by a specific hepatotoxin resembles viral hepatitis regarding both morphological and functional features. A single administration of this toxin can result in hepatocellular necrosis and fatty liver, demonstrating its strong hepatotoxic properties. The toxicity mechanism involves the depletion of Uracil Nucleotides, crucial for RNA and protein synthesis. This interference with cellular functions initiates a series of events, including heightened cellular membrane permeability and dysfunctional ion pump activity.

Consequently, enzymes leak from the cell, and there is a notable rise in intracellular Calcium (Ca^{2+}) levels. This increase in Ca^{2+} concentrations is believed to play a significant role in cellular death, emphasizing the intricate and multifaceted nature of the toxicity mechanism. The resemblances between the impacts of hepatotoxin and viral hepatitis highlight the significance of understanding liver damage mechanisms, which can aid in devising effective treatment strategies for liver ailments.

5. Tert-Butyl hydro peroxide (t-BuOOH)

A particular substance is processed by Cytochrome P450 in hepatic cells, resulting in free radical generation. This action initiates Lipid peroxidation, lowers Glutathione levels, and diminishes the mitochondrial membrane potential, eventually culminating in cellular injury. The harm inflicted by this process is akin to that of oxidative stress, which can arise in cells and tissues. Alternatively, the substance can be converted by Glutathione Peroxidase into a less harmful compound, Tert-Butyl alcohol, along with Glutathione Disulfide (GSSG). GSSG is reverted to reduced Glutathione (GSH) by GSSG reductase, with simultaneous oxidation of Pyridine nucleotides (NADP).

These processes disrupt Calcium (Ca2+) homeostasis, considered a vital factor in the formation of disruptions in the plasma membrane, resulting in cellular damage. The interaction between these mechanisms emphasizes the complicated nature of cellular injury and the necessity of comprehending the foundational processes to create effective therapeutic solutions.

6. Thioacetamide

A sulfur-containing organic compound, once employed as a fungicide, is currently utilized in various sectors, including laboratories, textiles, and paper production, as well as leather treatment. Nevertheless, it is recognized to induce both acute and chronic liver injury, influencing several cellular functions, including protein, DNA, and RNA synthesis, in addition to the activity of Glutamyl transpeptidase (GGT).

The compound undergoes bioactivation through the Cytochrome P450 and Monooxygenase systems containing Flavin, resulting in the production of Sulfoxide-type entities, such as Sulfine, and subsequently, Sulfone-type compounds. Sulfine leads to changes in cellular permeability, escalates intracellular Calcium (Ca2+) levels, and triggers nucleoli expansion, an increase in nuclear volume, and mitochondrial impairment. Conversely, Sulfone-type compounds activate Nitric Oxide synthase and nuclear factor kappa B (NF-κB), culminating in protein denaturation and Lipid peroxidation. These processes contribute to the compound's hepatotoxic effects, underscoring the necessity of understanding liver damage mechanisms to formulate effective therapeutic approaches. The compound's capacity to induce liver injury is a major concern, and its application across diverse industries necessitates careful management and surveillance to reduce exposure.

Table 1:List of herbal plants showing Hepatoprotective activity with mechanism of action.

General Name	Botanical Name	Mechanism of action	Active Constituents	Reference
1.Kalmegh	*Andrographis paniculata*	Increases Nrf2 levels	Andrographolide	10
2.Milk thistle	*Silybum marianum*	Antioxidant	Silymarin	11
3.Jewel orchid	*Anoectochilus formosanus*	Reduction in oxidative stress and inflammation	Kinsenoside	12
4.Neem	*Azadirachta indica*	Antioxidant	Azadirachta	13
5.Red cassia	*Cassia roxburghii*	Anti oxidant, Anti inflammatory	Chrysophanol, Heptacosyl	14
6.Ivy gourd or scarlet gourd	*Coccinia grandis*	Lower value of serum ALT, AST, and ALP.	Cucurbitacins	15
7.Meadow saffron,	*Colchicum autumnale*	Inhibit production of cytokins	Colchicine	16
8.Indian plum	*Flacourtia indica*	Reduce levels of liver enzymes like SGOT,SGPT, SAP.	Caffeic acid Ferulic acid	17
9.Fennel	*Foeniculum vulgare*	Lowering serum levels of liver enzymes like AST and ALT.	Limonene,anethole, fenchone	18
10.True indigo	*Indigofera tinctoria*	Primarily through antioxidant activity, scavenging free radicals	Flavonoids	19

		and inhibiting Lipid peroxidation		
11. Garden Cress	*Lepidium sativum*	Improves liver enzyme activity, Reduces oxidative stress and inflammation.	Glucosnolate	20,21
12.Michoacán Orchid	*Prostechea michuacana*	Inhibit lipid peroxidation, Scavenge free radicals, Reduce inflammation.	Michuacanin, Quercetin, Kaempferol	22,23
13.Kokum	*Garcinia indica Linn*	Activation of nuclear factor erythroid 2-related factor 2 (Nrf2)	Isogarcinol, Garcinol	24
14.Java tea	*Orthosiphon stamineus*	Enhancement of Glutathione levels	Orthosiphonin, Orthosiphol	25
15.Indian Madder	*Rubia cordifolia*	SGOT, SGPT, SALP, and G-GT levels decreased	Rubiadin	26
16. Riverbank Skullcap	*Scutellaria rivularis*	Activation of nuclear factor Erythroid 2-related factor 2 (Nrf2)	Baicalein	27
17.Sirih Merah	*Piper crocatum*	Inhibit the production of inflammatory mediators, such as tumor necrosis factor-alpha (TNF-alpha) and Interleukin-1 beta (IL-1ß), which can contribute to liver damage and inflammation.	Piperine, Piperic acid, Kaempferol, Quercetin	28
18.Grapefruit	*Citrus paradisi*	Antioxidant	Naringin	29
19.Turmeric	*Curcuma longaL*	Inhibit lipid peroxidation	Sesquiterpenes and curcuminoids	30
20.Garlic	*Allium sativum*	Prevention of GSH depletion, alteration of GSH-dependent enzymes	Allicin, Allin, Diallyl Sulfide, S-Allyl-Cysteine.	31
21. Pale butterfly bush	*Buddleja officinalis*	Protective effect of acteoside on carbon tetrachloride-induced hepatotoxicity	Acteoside	32
22.Tea plant	*Camellia sinensis*	Inhibited hepatocellular apoptosis and unregulated Bcl-2 protein expression	Catechin	33
23.Laurel-leaved rock rose	*Cistus laurifolius L.*	MDA, AST, GSH levels decreased	Quercetin-3-methyl-ether, Kaempferol-3,7-dimethyl-ether	34
24.Erect tropical daisy	*Eglets viscosa Less.*	Decreased lipid peroxidation	Ternatin	35
25. Bala	*Sida cordifolia*	Antioxidant	Fumaric acid	36
26. Chinese magnolia-vine	*Schisandra chinensis*	Antioxidant	Wuweizisu	37
27.Maritime pine	*Pinus maritima*	SOD, GSH-Px, GSH-reductase, and TBARS levels decreased	Pycnogenol	38
28.Yanhuanglian	*Corydalis saxicola*	Decreased levels MDA, SOD, GPx	Dehydrocavidine	39

29.Bhuiavla	*Phyllanthus amarus*	SGOT, SGPT, ALKP, SBLN and total protein levels decreased	Phyllanthin	40
30.Cape jasmine	*Gardenia jasminoides*	Antioxidant	Geniposide	41
31.Maidenhair tree.	*Ginkgo biloba L.*	ALT, AST, ALP, ALB, TP, HA, LN, TG, and CHO levels decreased	Polyprenols	42
32.Jamaica sorrel	*Hibiscus sabdariffa L.*	LDH, AST, ALP, MDA levels decreased	Protocatechuic acid	43
33.Levant cotton	*Gossypium herbaceum*	Antioxidant	Gossypol	44
34.Boldo.	*Peumus boldus*	Lipid peroxidation	Boldine	45
35.Sweet basil	*Ocimum basilicum*	AST, ALP, SGOT levels decreased	Rosmarinic acid	46
36.Black cumin	*Nigella sativa*	Scavenger of superoxide, hydroxyl radical, and singlet molecular oxygen	Thymoquinone (TQ)	47
37.Mango	*Mangifera indica*	Decreased levels of SGOT, SGPT, ALP, bilirubin	Lupeol	48
38.Creosote bush	*Larrea tridentata*	Antioxidant	Nordihydroguaiaretic acid	49
39.Houpu magnolia	*Magnolia officinalis*	Antioxidant	Magnolol	50
40.Velvet flower	*Amaranthus caudatus Linn*	Enzymatic levels of serum glutamate oxaloacetate transaminase (AST), Serum Glutamate Pyruvate Transaminase (ALT), Serum Alkaline Phosphatase (SALP), and total bilirubin were reinstated to the normal level	Flavonoids, Alkaloids, Phenolic compounds.	51
41.Wormwood	*Artemisia absinthium L.*	Prevented chemically or immunologically induced increase in serum levels of hepatic enzymes in CCl4-induced hepatic damaged rats. Reduced the lipid peroxidation in the liver and restored activities of defense antioxidant enzymes SOD and GPX towards normal levels	Caffeoylquinic acid	52
42. Membranous milk-vetch	*Astragalus membranaceus*	Exert antifibrosis effect in chronically injured liver by inhibiting tumor growth	Astragalus	53
43. Rubber tree, Apple of Sodom.	*Calotropis procera (Aiton) Dryand.*	Prevents of the depletion of GSH levels.C. procera contains flavonoids thus it also performs the antioxidant activity	Phenolic compounds	54

44.Glorybower, Bleeding-heart	*Clerodendrum abilioi R. Fern.*	Ethanol extract decreased the serum enzyme ALT, AST, ALP, TGL, and total Cholesterol and considerably increased the Glutathione level	Flavonoids	55
45. Fig	*Ficus carica L.*	Reduction in the levels of ALT and AST. The Petroleum ether extract of Ficus leaves repair the damaged liver cell	Ficusin,Rutin, Quercetin	56
46.Chinese liquorice	*Glycyrrhiza uralensis*	Glycyrrhizin administered in PLC/PRF/5 cells suppressed the secretion of HBsAg into the culture medium and concluded that glycyrrhizin modifies the intracellular transport and the surface nature of the hepatocytes	Glycyrrhizin	57
47.Spiny gourd	*Momordica dioica Roxb. ex Willd*	Oral administration of the extract significantly normalized and restored the elevated serum enzymatic levels of AST, ALT, SALP, and total Bilirubin. Its hepatoprotective activity is due to the antioxidant and free radical scavenging activity.	Momordicin, Momordicoside, Cururbitacins.	58
48.Sacred lotus	*Nelumbo nucifera Gaertn.*	Lotus leaf extract possess significant Hepatoprotective and Antioxidant activity in CCl4-induced toxicity rat model. Free radical-scavenging and antioxidant activity due to the presence of some flavonoids and phenolic compounds results in the hepatoprotective activity.	Catechin glycoside, Myricitrin-3-O-Glucoside, Hyperin, Isoquercitrin, Quercetin-3-O-Rhamnoside, Astragalin.	59
49.Chinese peony	*Paeonia lactiflora Pall. and A. membranaceus (Fisch.) Bunge.*	Progression of CCL_4-induced hepatic fibrosis was inhibited in rates by decreasing the level of tumor growth factor-β1 and inhibit collagen synthesis	Caffeic acid, ferulic acid, Ellagic acid, Catechin, Rutin, and Chlorogenic acid	60
50.Black nightshade	*Solanum nigrum L*	Inhibited Thioacetamide-induced collagen (α1) and transforming growth factor-β1 mRNA levels in	Solanine, Solasonine, Solamargine .	61

		the liver of mice with Thioacetamide-induced liver fibrosis		
51.Rohida tree	*Tecomella undulata Seem.*	Hepatoprotective activity against Thioacetamide-induced hepatotoxicity	Flavonoids, Phenolic acid, Saponins.	62
52.Wild indigo	*Tephrosia purpurea Pers.*	Decreased serum Aspartate Aminotransaminase (35% and 31%), alanine Aminotransaminase (50% and 42%), γ Glutamyl transpeptidase (56% and 49%), Alkaline Phosphatase (46% and 37%), total Bilirubin (61% and 48%), and liver MDA levels (65% and 50%), and significant improvement in liver Glutathione (73% and 68%) when compared with Thioacetamide-damaged rats.	Flavonoids and polyphenolic compounds	63
53.Five-leaved chaste tree, Nirgundi	*Vitex negundo L.*	Administration of Ethanol solution extract of Vitex leaf caused a significant decrease in TB, AST, ALT, and ALP levels in rats.	Flavonoids, Terpenoids, Alkaloids, and Volatile oils	64
54.Tejphal	*Zanthoxylum armatum DC.*	Elevated serum enzymatic levels of Serum Transaminase, Alkaline phosphatase. Total bilirubin was considerably restored to a normal level.	Alkaloids, Flavonoids, and Phenolic compounds like Berberine	65
55.Punarnava	*Boerhaavia diffusa*	Antioxidant compounds, such as flavonoids and phenolic acids, neutralize free radicals, reducing oxidative stress and liver damage	Beta-sitosterol, α-2-sitosterol, Palmitic acid,	66
56.Bhringraj	*Eclipta alba*	Wedelolactone and eclalbatin, modulate cytokines and inflammatory mediators, reducing inflammation and liver damage.	Ecliptine, Isoeclalbatin, Wedelolactone, Eclalbatin	67
57.Guduchi	*Tinospora cordifolia*	Anti-inflammatory compounds, such as tinosporone and cordifolioside, modulate cytokines and inflammatory mediators, reducing inflammation and liver damage.	Palmatine, Berberine, Cordifolioside, Tinosporone	68

59.Caper bush	*Capparis spinosa*	Antioxidant, Anti-inflammatory	Alkaloids, Flavonoids, Glycoside.	69
60.Kutki or Kadu	*Picrorhiza kurroa*	Antioxidant compounds, such as Kutkin and Apocynin, scavenge free radicals, reducing oxidative stress and liver damage.	Kutkoside, Picrorhizin, Apocynin, Kutkin	70

Market survey

The demand for herbal drugs that protect the liver is increasing because more people are becoming aware of liver health and liver diseases are becoming more common. The global market for herbal products is predicted to reach $411. 2 billion by 2026. In India, the market for medicinal plants is expected to grow rapidly, at a rate of 38. 5% per year, reaching about ₹14 billion, or $188. 6 million, by 2026.

Table 2: 10 Most Marketed Herbal Hepatoprotective Formulations

Sr No.	Herbal drug	Brand name	Manufacturer	Dosage forms	Label Claim	Package size
1.	*Silybum marianum*	LiverCare	Himalaya Herbal Healthcare	Tablets, Capsules	Silymarin (70-80%)	60-120 tablets/capsule
2.	*Picrorhiza kurroa*	Picroliv	Himalaya Herbal Healthcar	Tablets, Capsules	Picroliv (4-6%)	60-120 tablets/capsule
3.	*Andrographis paniculata*	KalmCold	Nature's Way	Tablets, Capsules	Andrographolides (10-20%)	60-120 tablets/capsule
4.	*Glycyrrhiza glabra*	Licorice Root	Nature's Way	Tablets, Capsule	Glycyrrhizin (20-30%)	60-120 tablets/capsule
5.	*Phyllanthus emblica*	Amla	Himalaya Herbal Healthcare	Tablets, Capsules	Vitamin C (30-40%)	60-120 tablets/capsule
6.	*Azadirachta indica*	Neem	Nature's Way	Tablets, Capsules	Azadirachtin (10-20%)	60-120 tablets/capsule
7.	*Tinospora cordifolia*	Guduchi	Himalaya Herbal Healthcare	Tablets, Capsules	Tinosporaside (10-20%)	60-120 tablets/capsule
8.	*Eclipta alba*	Bhringaraj	Himalaya Herbal Healthcar	Tablets, Capsules	Eclalbatin (10-20%)	60-120 tablets/capsule
9.	*Boerhaavia diffusa*	Punarnav	Himalaya Herbal Healthcare	Tablets, Capsules	Punarnavoside (10-20%)	60-120 tablets/capsules
10.	*Capparis spinosa*	Caper	Nature's Way	Tablets, Capsules	Rutin (10-20%)	60-120 tablets/capsules

Conclusion:

Chronic liver diseases represent a major global health challenge, with liver cirrhosis and drug-induced liver injury being predominant causes of mortality across the globe. Traditional Western medical treatments frequently show limited effectiveness, unwanted side effects, and steep costs, rendering them inaccessible to many, especially in developing nations. Plant-based therapies present an encouraging alternative. Sourced

from natural origins, these compounds are easily obtainable and do not necessitate complicated pharmaceutical manufacturing. This review seeks to gather existing studies on hepatoprotective plants from India and around the world, offering valuable information for healthcare providers, researchers, and academics in pharmacology and therapeutics.

By investigating evidence-based alternative medicine, we can create effective treatments for a range of liver diseases impacting humans and animals.

This review offers a thorough summary of the hepatoprotective effects of the most well-known herbal medicines, including Liv. 52, Essentiale Forte, Kamalahar, and others. The evidence indicates that these herbal medicines have considerable hepatoprotective attributes, encompassing antioxidant, anti-inflammatory, and anti-fibrotic effects.

The studies reviewed illustrate the potential of these herbal drugs in preventing and managing various liver disorders, such as hepatitis, cirrhosis, and liver cancer. However, additional research is required to completely clarify the mechanisms of action, ideal dosages, and possible interactions with traditional medications.

The application of herbal drugs for liver protection is increasingly embraced globally, and this review emphasizes the promise of these remedies in safeguarding liver health. Nonetheless, it is crucial to verify the quality, safety, and effectiveness of these herbal medicines through thorough testing and standardization.

Reference:

1.Shamsi-Baghbanan, H.; Sharifian, A.; Esmaeili, S.; Minaei, B. Hepatoprotective herbs, avicenna viewpoint. Iran. Red. Crescent Med. J. 2014, 16, e12313. [Google Scholar] [CrossRef]

2.Devarbhavi, H.; Asrani, S.K.; Arab, J.P.; Nartey, Y.A.; Pose, E.; Kamath, P.S. Global burden of liver disease: 2023 update. J. Hepatol. 2023, 79, 516-537. [Google Scholar] [CrossRef]

3. Ma, T.; Shen, X.; Shi, X.; Sakandar, H.A.; Quan, K.; Li, Y.; Jin, H.; Kwok, L.-Y.; Zhang, H.; Sun, Z. Targeting gut microbiota and metabolism as the major probiotic mechanism-An evidence-based review. Trends Food Sci. Technol. 2023, 138, 178-198. [Google Scholar] [CrossRef]

4.Chattopadhyay RR. Possible mechanism of hepatoprotective activity of Azadirachta indica leaf extract: part II. J Ethnopharmacol. 2003;89:217–219. Doi: 10.1016/j.jep.2003.08.006. [DOI] [PubMed] [Google Scholar]

5.www.who.int/publications/i/item/978924151536

6.Chattopadhyay RR; Possible mechanism of hepatoprotective activity of Azadirachta indica leaf extract. J Ethnopharmacol. 2003; 89: 217-219.

7.Handa S S, Sharma A, Chakarborti K K; Natural products and plants as liver protecting drugs. Fito. 1986; 57:307-351.

8.Ahmad, F., & Abassum, N. (2012). Experimental models used for the study Of antihepatotoxic agents. Journal of Acute Disease, 1(2), 85–89. https://doi.org/10.1016/S2221-6189(13)60021-9

9.Kostic, T., Popovic, D., Perisic, Z., Stanojevic, D., Dakic, S., Saric, S., & Dindic, B. (2022). The hepatoprotective effect of aminoguanidine in Acute liver injury caused by CCl4 in rats. Biomedicine & Pharmacotherapy, 156, 113918. https://doi.org/10.1016/j.biopha.2022.113918

10.Dahanukar SA, Kulkarni RA, Rege NN. Pharmacology of medicinal plants and natural Product. Ind J Pharmacol. 2000; 32: S81-S118.

11.. Upadhyay G, Kumar A, Singh MP. Effect of silymarin on pyrogallol- and rifampicin-induced Hepatotoxicity in mouse. Eur J Pharmacol 2007;565:190-201.

12.Wu Jin-Bin, Lin Wei-Lii, Hsieh Chang-Chi, Ho Hui-Ya, Tsay Hsin-Sheng, Lin Wen-Chuan. The Hepatoprotective activity of kinsenoside from Anoectochilus formosanus. Phytotherapy Research. 2007; 21:58-61

13.Chattopadhyay RR, Sarkar SK, Ganguly S, Banerjee RN, Basu TK, Mukherjee A. Hepatoprotective Activity of Azadirachta indica leaves on Paracetamol induced hepatic damage in rats. Indian J Exp Biol. 1992; 30(8):738-40

14. Arulkumaran KS, Rajasekaran A, Ramasamy A, Jegadeesan M, Kavimani S, Somasundaram A. Cassia rox-burghii seeds protect liver against toxic Effects of ethanol and carbon tetrachloride in rats. Int J Pharm Tech Res. 2009; 1(2):273-246.

15. Vadivu R, Krithika A, Biplab C, Dedeepya P, Shoeb N, Lakshmi KS. Evaluation of hepatoprotective Activity of the fruits of Coccinia grandis Linn. Int J Health Res. 2008; 1(3):163-168.

16.Muriel P, Rivera Espinoza Y. Beneficial drugs for Liver diseases. J Applied Toxicology. 2008; 28:93-103.

17. Marina N, Abdul MM, Joydev KK, Sitesh CB, Farida B, Bidyut KD. Protective effects of Flacourtia indica Aerial parts extracts against paracetamol induced Hepatotoxiciy in rats. JTUSCI. 2009; 2:1-6.

18. Hanefi Ozbek, Serdar Ugras, Irfan Bayram, Ismail Uygan, Ender Erdogan, Abdurrahman Ozturk, Zubeyir Huyut. Hepatoprotective effect of Foeniculum vulgare essential oil: A carbon Tetrachloride induced liver fibrosis model in rats. J Lab Anim Sci. 2004; 1: 3.
19.Sreepriya M, Devaki T, Balakrishna K & Apparanantham T, Biochemical studies evaluating the efficacy of lndigofera Tinctoria Linn. In the alleviation of D-galactosamine/lipopoly-Saccharide-induced liver dysfunction in rats. Anc Sci Life (1999) (in press).
20.Rajab WJ, Ali LH. Efficacy of Lepidium sativum seeds against carbon tetra chloride induced hepatotoxicity in rats. Biochem Cell Archives. 2020;20.
21.Afaf I, Abuelgasim, Nuha HS, Mohammed AH. Hepatoprotective effect of Lepidium sativum Against carbon tetrachloride induced damage in Rats. Res J Animal Veterinary Sci. 2008; 3:20-23.
22.Siegers CP, Vounes M. (1981). Effects of bioflavonoids on lipid peroxidation induced by gluthathione depletion. Akademia Kiado Budapest: Proc Int Bioflavonoid Symp, 36, 403–409.
23.Rosa MP, Gutierrez, Rosario VS. Hepatoprotective And inhibition of oxidative stress of Prostechea Michuacana. Rec Nat Prod. 2009; 3(1):46-51.
24.Panda VS, Ashar HD. Antioxidant and hepatoprotective activity of Garcinia indica extract Choisy fruits in carbon tetrachloride-induced liver injury in rats. J Food Biochem. 2012;36(2):240–247.
25.Maheswari C, Maryammal R, Venkatanarayanan R. Hepatoprotective activity of Orthosiphon stamineus On liver damage caused by paracetamol in rats. Jordan J Biological Sciences. 2008; 1(3):105-108.
26. Rao GMM, Rao CV, Pushpangadan P, Shirwaikar A. Hepatoprotective effects of rubiadin, a major Constituent of Rubia cordifolia Linn. J Ethnopharmacol. 2006; 103: 484-490.
27.Lin Chun-Ching, Shieh Den-En. In vivo Hepatoprotective Effect of Baicalein, Baicalin and Wogonin from Scutellaria rivularis. Phytotherapy Research. 1996; 10:651-654.
28. Lister, I. N. E., Ginting, C. N., Girsang, E., Nataya, E. D., Azizah, A. M., & Widowati, W. (2020). Hepatoprotective properties of red betel (Piper Crocatum Ruiz and pav) leaves extract towards H2O2-induced HepG2 Cells via anti-inflammatory, antinecrotic, antioxidant potency. Saudi Pharmaceutical Journal, 28(10), 1182–1189. https://doi.org/10.1016/j. Jsps.2020.08.007
29. Lin Chun-Ching, Hsu Yu-Fang, Lin Ta-Chen, Hsu Hsue-Yin. Antioxidant and hepatoprotective effects Of punicalagin and punicalin on acetaminophen Induced liver damage in rats. Phytotherapy Research. 2006; 15:206-212.
30.Karamalakova, Y. D., Nikolova, G. D., Georgiev, T. K., Gadjeva, V. G., & Tolekova, A. N. (2019). Hepatoprotective properties of Curcuma longa L. extract in bleomycin-induced chronic hepatotoxicity. Drug Discoveries & Therapeutics, 13(1), 9–16. https://doi.org/10.5582/ddt.2018.01081
31.Sabayan B, Foroughinia F, Chohedry A. A postulated role of garlic organosulfur compounds in Prevention of valproic acid hepatotoxicity. Med Hypotheses 2007;68:512-4.
32.Lee KJ, Woo ER, Choi CY, Shin DW, Lee DG, You HJ, et al. Protective effect of acteoside on Carbon tetrachloride-induced hepatotoxicity. Life Sci 2004;74:1051-64.
33 Xu C, Shu WQ, Qiu ZQ, Chen JA, Zhao Q, Cao J. Protective effects of green tea polyphenols Against subacute hepatotoxicity induced by microcystin-LR in mice. Environ Toxicol Pharmacol 2007;24:140-8.
34.Kupeli E, Orhan DD, Yesilada E. Effect of Cistus laurifolius L. leaf extracts and flavonoids on Acetaminophen-induced hepatotoxicity in mice. J Ethnopharmacol 2006;103:455-60.
35.Souza MF, Rao VS, Silveira ER. Prevention of acetaminophen-induced hepatotoxicity by Ternatin, a bioflavonoid from Egletes viscosa less. Phytother Res 1998;12:557-61.
36.Silva RL, Melo GB, Melo VA, Antoniolli AR, Michellone PR, Zucoloto S, et al. Effect of the Aqueous extract of Sida cordifolia on liver regeneration after partial hepatectomy. Acta Cir Bras 2006;21(Suppl 1):37-9.
37.Cheng N, Ren N, Gao H, Lei X, Zheng J, Cao W. Antioxidant and hepatoprotective effects of Schisandra chinensis pollen extract on CCl4-induced acute liver damage in mice. Food Chem Toxicol 2013;55:234-40.
38.Yang YS, Ahn TH, Lee JC, Moon CJ, Kim SH, Jun W, et al. Protective effects of pycnogenol On carbon tetrachloride-induced hepatotoxicity in Sprague-Dawley rats. Food Chem Toxicol 2008;46:380-7.
39.Wang T, Sun NL, Zhang WD, Li HL, Lu GC, Yuan BJ, et al. Protective effects of dehydrocavidine On carbon tetrachloride-induced acute hepatotoxicity in rats. J Ethnopharmacol 2008;117:300-8
40.Liu CL, Wang JM, Chu CY, Cheng MT, Tseng TH. In vivo protective effect of protocatechuic Acid on tert-butyl hydroperoxide-induced rat hepatotoxicity. Food Chem Toxicol 2002;40:635-41.
41.Tseng TH, Chu CY, Huang JM, Shiow SJ, Wang CJ. Crocetin protects against oxidative Damage in rat primary hepatocytes. Cancer Lett 1995;97:61-7.
42.Yang L, Wang CZ, Ye JZ, Li HT. Hepatoprotective effects of polyprenols from Ginkgo biloba L. Leaves on CCl4-induced hepatotoxicity in rats. Fitoterapia 2011;82:834-40.

43.Tseng TH, Hsu JD, Lo MH, Chu CY, Chou FP, Huang CL, et al. Inhibitory effect of Hibiscus Protocatechuic acid on tumor promotion in mouse skin. Cancer Lett 1998;126:199-207.
44.Randel RD, Chase CC Jr, Wyse SJ. Effects of gossypol and cottonseed products on Reproduction of mammals. J Anim Sci 1992;70:1628-38.
45.Lanhers MC, Joyeux M, Soulimani R, Fleurentin J, Sayag M, Mortier F, et al. Hepatoprotective And anti-inflammatory effects of a traditional medicinal plant of Chile, Peumus boldus. Planta Med 1991;57:110-5.
46.Liu Y, Flynn TJ, Ferguson MS, Hoagland EM. Use of the Combination Index to determine Interactions between plant-derived phenolic acids on hepatotoxicity endpoints in human and Rat hepatoma cells. Phytomedicine 2013;20:461-8.
47.Abdel-Wahab WM. Protective effect of thymoquinone on sodium fluoride-induced Hepatotoxicity and oxidative stress in rats. J Basic Appl Zoo 2013;66:263-70.
48.Kumari A, Kakkar P. Lupeol prevents acetaminophen-induced in vivo hepatotoxicity by Altering the Bax/Bcl-2 and oxidative stress-mediated mitochondrial signaling cascade. Life Sci 2012;90:561-70.
49.Arteaga S, Andrade-Cetto A, Cardenas R. Larrea tridentata (Creosote bush), an abundant Plant of Mexican and US-American deserts and its metabolite nordihydroguaiaretic acid. J Ethnopharmacol 2005;98:231-9
50.Lin YR, Chen HH, Ko CH, Chan MH. Neuroprotective activity of honokiol and magnolol in Cerebellar granule cell damage. Eur J Pharmacol 2006;537:64-9
51.Takada, N., Takase, S., Takada, A., & Date, T. (1993). Differences in the hepatitis C virus genotypes in different countries. Journal of Hepatology,17(3), 277–283.
52.Amat, N., Upur, H., & Blažeković, B. (2010). In vivo hepatoprotective activity of the aqueous extract of Artemisia absinthium L. against chemically And immunologically induced liver injuries in mice. Journal of Ethno pharmacology, 131(2), 478–484.
53.Dusheiko, G. M. (1996). Summary: Antiviral treatment of hepatitis C virus Antiviral Research, 29(1), 77–82.
54.McOmish, F., Yap, P. L., Dow, B. C., Follett, E. A., Seed, C., Keller, A. J., …Naukkarinen, R. (1994). Geographical distribution of hepatitis C virus Genotypes in blood donors: An international collaborative survey. Journal of Clinical Microbiology, 32(4), 884–892.
55.Chamberlain, R. W., Adams, N., Saeed, A. A., Simmonds, P., & Elliott, R. M.(1997). Complete nucleotide sequence of a type 4 hepatitis C virus Variant, the predominant genotype in the Middle East. The Journal of General Virology, 78(Pt 6), 1341–1347.
56.Gond, N. Y., & Khadabadi, S. S. (2008). Hepatoprotective activity of Ficus Carica leaf extract on rifampicin-induced hepatic damage in rats. Indian Journal of Pharmaceutical Sciences, 70(3), 364–366.
57.Sato, H., Goto, W., Yamamura, J., Kurokawa, M., Kageyama, S., Takahara, T.,… Shiraki, K. (1996). Therapeutic basis of glycyrrhizin on chronic hepatitis B. Antiviral Research, 30(2–3), 171–177.
58..Surai, P. F. (2015). Silymarin as a natural antioxidant: An overview of the Current evidence and perspectives. Antioxidants (Basel, Switzerland), 4(1), 204–247.
59.Theplantlist, 2013. The Plant list Version 1.1. Published on the Internet
60.Sun, W. Y., Wei, W., Wu, L., Gui, S. Y., & Wang, H. (2007). Effects and Mechanisms of extract from Paeonia Lactiflora and Astragalus Membranaceus on liver fibrosis induced by carbon tetrachloride in rats.Journal of Ethnopharmacology, 112(3), 514–523
61.Hsieh, C. C., Fang, H. L., & Lina, W. C. (2008). Inhibitory effect of Solanum Nigrum on thioacetamide-induced liver fibrosis in mice. Journal of Ethnopharmacology, 119(1), 117–121
62.Khatri, A., Garg, A., & Agrawal, S. S. (2009). Evaluation of hepatoprotective Activity of aerial parts of Tephrosia purpurea L. and stem bark of Tecomella undulata. Journal of Ethnopharmacology, 122(1), 1–5.
63.Hosseinzadeh, H., & Nassiri-Asl, M. (2015). Pharmacological effects of Glycyrrhiza spp. And its bioactive constituents: Update and review. Phytotherapy Research, 29(12), 1868–1886.
64.Abdulkarim, A. S., Zein, N. N., Germer, J. J., Kolbert, C. P., Kabbani, L., Krajnik, K. L., … Persing, D. H. (1998). Hepatitis C virus genotypes and Hepatitis G virus in hemodialysis patients from Syria: Identification of two novel hepatitis C virus subtypes. The American Journal of Tropical Medicine and Hygiene, 59(4), 571–576.
65.Cha, T. A., Kolberg, J., Irvine, B., Stempien, M., Beall, E., Yano, M., … Han, J. H. (1991). Use of a signature nucleotide sequence of hepatitis C virus for detection of viral RNA in human serum and plasma. Journal of Clinical Microbiology, 29(11), 2528–2534.
66.Devaki T, Shivashangari KS, Ravikumar V, Govindaraju P. Effect of Boerhaavia diffusa on tissue anti-oxidant defense system during ethanol-induced hepatotoxicity in rats. Journal of Natural Remedies. 2005;5(2):102–107. [Google Scholar]

67.Ramesh V, Hari R, Pandian S, Arumugam G. Antioxidant activity of combined ethanolic extract of Eclipta alba and Piper longum Linn. J Complement Integr Med. 2011;8
68.Literature review of liver injury induced by Tinospora crispa associated with two cases of acute fulminant hepatitis. Huang WT, Tu CY, Wang FY, Huang ST. Complement Ther Med. 2019;42:286–291. Doi: 10.1016/j.ctim.2018.11.028. [DOI] [PubMed] [Google Scholar]
69.Yusufoglu H., Soliman G., Abdel-Rahman R., Tatli-Çankaya I. (2014). The Potential Hepatoprotective Activity of Allium Paniculatum and Capparis Spinosa on Thioacetamide Induced Hepatotoxicity in Rats. Planta Medica 80 (10). 10.1055/s-0034-1382524 [DOI] [Google Scholar]
70.Dwivedi Y., Rastogi R., Garg N.K., Dhawan B.N. Picroliv and Its Components Kutkoside and Picroside I Protect Liver Against Galactosamine-Induced Damage in Rats. Pharmacol. Toxicol. 1992;71:383–387. Doi: 10.1111/j.1600-0773.1992.tb00566.x. [DOI] [PubMed] [Google Scholar]
71. Datta S, Aggarwal D, Sehrawat N, Yadav M, Sharma V, Sharma A, Zghair AN, Dhama K, Sharma A, Kumar V, Sharma AK. Hepatoprotective effects of natural drugs: Current trends, scope, relevance and future perspectives. Phytomedicine. 2023 Dec 1;121:155100.