

Herbs and Supplements for Liver Toxicity: A Review on Mode of Action of Herbs and Supplements on Liver Toxicity

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Abstract

Liver diseases is a dynamic pathological condition which can be slowed down in its initial phases without proper clinical management of fibrosis Progressive liver damage may lead to cirrhosis and ultimately to liver failure or primary liver cancer which are irreversible conditions.

In order to cure fibrotic damage to liver, its early stages should be the center of attention. Some supplements and complementary and alternative medicine (CAM) deserve specific mention, because of their already recognized natural way of healing and long lasting curative effects.

Dietary supplements (DS) are extensive very consumed worldwide despite unproven efficacy. the true incidence of DS-induced liver injury (DSILI) is unknown, but is probably under diagnosed duo to the general belief of safety of these products, the present review is a systematic account of some herbs and supplements on both dual effects on liver (protective: Toxic), much additional work is still needed to explore molecular pathways to discover potential applications of these alternative medicines.

Key Words: Herbs – Supplements for liver toxicity.

Introduction

THE liver is a critical organ in the human body that is responsible for an array of functions that help support metabolism, immunity, digestion, detoxification, vitamin storage among other functions. it comprises around 2% of an adult, s body weight, the liver is a unique organ duo to its dual blood supply from the portal vein (approximately 75%) and the hepatic artery (approximately 25%), [1] the liver plays a role in nearly every organ system in the body, it interacts with the endocrine and gastrointestinal systems by aiding in digestion and metabolism. The liver is the storage location of fat-soluble vitamins and handles cholesterol homostasis [2,3]. It stores iron and copper. It plays a role in hematology with clotting factor and protein

synthesis. The liver plays a role in heme breakdown into unconjugated bilirubin and conjugates it. It plays a role in sex hormone metabolism and produces carrier proteins that are important in reproduction and development. kuffer cells and pit cells play an important role in the body's immunologic system. Liver also play a central role in detoxification and transforming chemicals [4], it is in away exposed to their harmful effects increasing its susceptibility to disease, therefore, it may not be surprising to that over 10% of the world population suffers from liver diseases. Most common of these conditions are the hepatitis, hepatic steatosis (fatty liver), fibrosis, cirrhosis, alcoholic and drug induced diseases [5].

Synthetic drugs used to treat liver ailments have often proved life threatening and therefore, the preference is being shifted to complementary and alteration medicines (CAM), which are either natural products or their derivatives, the very basis of this preference is their safety and long lasting therapeutic potential. As a result, the source of nearly half of the agents used to treat liver diseases now come from natural products [5].

Available evidence further indicated that bioactive compounds derived from medical herbs may be potential hepatoprotective agents. 65% of patients in Europe and US depend on herbal remedies for treatment of liver disease, however, their preparation, search, and extraction is an exhausted for all liver ailments [6,7].

Clinical characterization and a tubal listing of dietary supplements:

Herbals and dietary supplements (HDS), are used to maintain or improve health. Regulation of herbal products may vary between different countries [8]. In European Union, the concepts of traditional herbal medicines and traditional plant food

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supplements are defined under different legal frameworks [9].

Dietary supplements (DS) are extensively very consumed worldwide. Despite unproven efficacy the true incidence of DS-induced liver injury is unknown but is probably under diagnosed due to the general belief of safety of these products [8].

An herbal product is considered a medicinal product when presented as having properties for treating or preventing disease in human beings, or when it has a pharmacological-immunological or metabolic action. Some herbs along with their ingredients demonstrating molecular mechanisms are summarized in Table (1).

Table (1): Active ingredients of some herbs with molecular mechanisms mode of Action.

Plant extract	Active part	Pharmacology	Molecular-action
Silymarin [10,11] and silychrisin	Flavonoid	Antioxidant	α -SMA regulate
Nelumbo nucifera [12] (Arme pavine)	Alkaloid	Antiinflammation	α -SMA TNF- α
Rhubarb [13] Rhein Chinese herb	Anthraquinone	Anti-microbial-anti cancer-chronic liver	Anti-angiogenesis, inhibite TBG- β 1
Plumbago [14] Zeylanica L	Naphthoquinone	Anti-inflammation anti-oxidant-anti cancer	Antiangiogenesis TNF- α MMP-1 ECM-degrade
Glycirrhiza [15,16] glabra	Glycyrrhizic Acid	Anti-mutagenic Anti-viral Anti-oxidant	NrF-2 express of type 1, 11, collagen
Panax-ginseng [17]	Roots	Anti-cancer- anti inflammation-anti-diabetic-neuro-protêt	TNF- α -IL-1B
Green tea [18] Camellia sinenseis	Epigallocatechin-3-Gallate	Fibrosis cancer-stress	MMP-2 NF-k β

TNF: Tumor necrosis factor. IL-6: Interleukines. NF-k β : Nuclear factor kappa β lymphocyte. MMP: Matrix metalloproteinase.

Herbal induced liver injury-HDS-DILI:

An herb may be considered a medical product or a dietary supplements (DS) depend on medical claims of a therapeutic indication [8].

However, herbal dietary supplements HDS are not as safe as many people believe, these products can induce adverse effects including liver injury, moreover, occurrence of HDS-related liver toxicity ranges from 2% to 16% of all identified cases of

hepatotoxicity included in different drug-induced liver injury (DILI), an even higher prevalence of HDS-DILIL can be found in Asian countries, where there is a wide spread consumption of HDS, 73% in Korea, 71% in Singapore, and 40% in china [19-21]. Counts of adverse events and system organ class (SOC) [22]. That were found significant based on proportional reporting ratio (PRR) showed in Table (2).

Table (2): Herbs and their adverse effects.

Herb name	System organ class (SOC)	Adverse effect	PRR
Avena sativa (Oats)	Skin	Tissue disorder	9.32
Cannabis sativa (Marijuana)	Nervous	Psychaiatric disorder	4.77
Digital purpurea (Foxglove)	Cardiac	Cardiac disorder	8.5
Humulus lupulus (Hops)	Nervous	Psychiatric disorder	6.53
Silybum marianum (milk thistle)	Liver	Hepatobiliary disorders	3.45
Taraxacum officinale (Dandelion)	Liver	Hepatobiliary disorder	3.67
Allium sativum (Garlic)	Blood	Blood pressure increased	3
Camellia sinensis (Tea)	Heart	Heart rate increased	3.21
Cannabis sativa (marijuana)	Many	Suicide attempt	4.2
		Aggression	7.1
		Loss of consciousness	3.58
		Toxicity of varous organ	8.81
		Drug withdrawal syndrome	5.43
Curcuma longa (Turmeric)		Fatigue	3.36
Glycine max (soy bean)	Liver	ATL, AST, increased	9
Hypericum perforatum (st jhons Wort)	Abdominal	Par aesthesis	8

PRR: Proportional reporting ratio.

Reported cases of dietary supplements induced liver injury:

This point aimed to make description of potentially hepatotoxic DS as well as review the severity of DSILI. Herbal dietary supplement, HDS, related to hepatotoxicity is classified into two different groups: Herbal-induced liver injury and dietary supplement induced liver injury (DSILI). The definition of dietary supplement, DS, is different: One consumed it as an aid to improve nutritional status, as example to lose weight. The other defines DS as any product intended to supplement, but not substitute the diet. DS may contain one or more

ingredients including vitamins, minerals, herbs, botanicals, amino acids or extracts. Although herbals and DS sometimes overlap.

From the substances that considered as dietary supplements associated with liver injury are: Usnic acid, vitamin A, Garcinia cambogia, ma huang, 1, 3-dimethylamylamine [8]. Also herbalife products considered as DS: Such as hydroxycut, lipokinetix, oxy Elite pro, and anabolic steroids. Table (3) summarize information retrieved from original cases and cases from DILI registries associated with aforementioned DS.

Table (3): Complication of dietary supplements related to liver injury.

DS-name	Ingredient	DS-medical Indication	Liver injury	Test
- Anabolic androgenic-steroid (AAS) Stanozole-metha Sterone	- Testosterone, [24,25] synthesis of derivatives	- Muscle building breast-cancer anemia	- NAFLD hepatic Adenoma, hepato cellular, peliosis	- 24X ALT, AST
- Green tea [26] Camellia sinensis Epigallocatechin	- Methyl xanthine, alkaloid, gallate or its Metabolites	- Popular drink	- Hepatotoxic liver-damage	- 25-95 X ALT AST, Bilirubin 45>ULN
- Linoleic acid [27]	- Poly unsaturated Fatty acid Omega-6	- Improve-insuline sensitivity, reduce-fat, stimulate immune response	- Hepatocellular	- 100 X ALT, AST
- Usnic acid [28] (in-lichens) Alectoria Cladonia Lecanora Ramalina Evernia	- Lipokientix Norephedrine Caffeine Yohimbine Diiodothyronine	- Anti-microbial anti-inflammation anti-oxidant anti-piretic analgic	- Hepatocyte death acute liver failure	- 20X ALT, AST
- Herbalife products [29]	- Cosmetic Products	- Weight loss	- Hepatocellular Cirrhosis	- Auto-anti bodies
- Hydroxycut [30]	- Garcinia Cambogia, Cissus, Quadrangularis, Caffeine, Ma huang (ephedra)	- Weight loss muscle build	- Hepatocellular liver cholestasis	- Increase ALT, AST
- Oxyelite pro [31]	- 1,3dimethylamyl- amine (DMAA)	- Weight control muscle build	- Auto-immune gallbladder	- High ALT
- Vitamin A [32]	- Phytochemicals	- Improve immune night-blindness	- Liver profile cholestasis Non-cirrhotic Fibrosis	- Histological Assessment

Herb-drug adverse event similarities:

In order to determine the severity and extend of adverse events associated with herb as well as their respective potential to cause harm, a comparison with prescription drugs was carried out. The evaluation of hierarchical relationships among drug

herbs based on their respective adverse event profiles using the maximum parsimony criterion revealed characteristically distinguishable grouping. Selected examples are shown in the following figure. Drugs with similar mechanism of action and indications were grouped together. Warfarin

and acenocoumarol, anticoagulants targeting vitamin K epoxide reductase. Non-steroidal anti-inflammatory drugs Celecoxib, Rofecoxib, and Valdecoxib (targeting COX-1 and COX-2) were also grouped together as having similar adverse events. In addition, Aspirin and Clopidogrel, although having different targets but similar indications of use and adverse reactions [33]. Based on adverse drug reactions, Aripiprazole, ziprasidone, Risperidone and Quetiapine are grouped together [33]. Drugs indicated for attention deficit hyperactivity disorder and narcolepsy showed clear grouping with related mechanism of increasing levels of neurotransmitters (dopamine) [22].

Herbs-Drugs related names	
Herbs-Names	Drug-Names
Anmiata coaius	Rose Bengal Sodium 1 131
Aralia elata	Chlorpheniramine
Myroxyion balsamum	Sesameoil
Nicotiana tabaum	Alminoprofen
Echinacea purpurea	Diethylamine salicylate
Glycine Max	Sultamicillin

Discussion

Herbal supplements are used worldwide for reasons such as treating numerous ailments, performance enhancements or for health maintenance [22].

Dietary supplements which included botanical products and over-the counter (OTC) products submit serious adverse reports, however, there is limited information regarding potential adverse reactions and associated with herbal treatments [33]. The lack of safety and efficacy information for herbs may play a role in hindering possible progress in identifying and assessing safety of potential therapeutic candidates for alleviating symptoms associate with disease. there have been recommendation for including herbal in national pharmacovigilance system [34]. However, the lack of standardized labels can make systematic analyses infeasible, for example, information pharmacovigilance systems needs to include the identity of herbs instead on just brand names.

Complementary an alternative medicine (CAM) is used in medical treatment but it is not the component of main stream medicine system. Extensive use of CAM is highlighted among people with chronic diseases.

Using search term such as dietary supplements combined with the following, drugs-induced liver

-injury/herb-induced-liver -injury/hepatotoxicity/liver damage, search will focus on language case reports, case serious, and clinical reviews. All reports crucial entities case reports, including cases with sufficient information published in other languages.

At the end, using a scalable approach for mapping and resolution of herb names allowed data -driven-exploration of potential adverse-events from sources that have remained isolated, the result from this review is high light several herb-associates safety issues, providing motivation of subsequent in depth analysis including scope of severity of potential safety issues with supplements use.

DS-ILI is challenging duo to the further these products are not regulated in the same way as prescription drugs are, and subsequently lack uniform criteria for manufacturing and authentication of this product [8].

Probably, underreporting is even higher with DS than with DILI given that consumers and health care parturition are not always aware of possible adverse events of the supplements [35].

References

- 1- SI-TAYEB K., LEMAIGRE F.P. and DUNCAN S.A.: Organogenesis and development of the liver. *Dev. Cell.*, 16; (18): 178-89, 2010.
- 2- SAXENA R., THEISE N.D. and CRAWFORD J.M.: Microanatomy of the human liver-exploring the hidden interface. *Hepatology*, 30 (6): 1339-46, 1999.
- 3- UZMA L. and RIAZ A.: Herbal remedies for liver fibrosis: *J. Tradit Complement Med.*, 8 (30): 352-360, 2018.
- 4- MUSTAFA M.E., MANSOOR M.M., MOHAMED A. and BABKER A.A.A.: Evaluation of platelets count and coagulation parameters among patients with liver disease. *World J. Pharm. Res.*, 368: 360 -368, 2015.
- 5- ZHANG A., SUN H. and WANG X.: Recent advances in natural products from plants for treatment of liver diseases. *Eur. J. Med. Chem.*, 63: 570-577, 2013.
- 6- AHMED A. and AHMED R.: Resveratrol mitigate structural changes and hepatic stellate cell activation. *Chem. Biol. Interac.*, 221: 1-12, 2014.
- 7- AHMED A. and AHMED R.: Understanding the mechanism of hepatic fibrosis and potential therapeutic approaches. *Saudi J. Gastroenterol.*, 18: 155-167, 2012.
- 8- MIREN G.C., MERCEDES R.D., AIDA O.A., INMACULADA M.C. and RAUL J.A.: Hepatotoxicity by dietary supplements. *International J. of Molecular Sciences*. Doi:10.3308, 2016.
- 9- SERAFINI M., STANZIONE A., FODDAI S., ANTON R. and DELMULLE L.: The European role on traditional herbal medicinal products and traditional plant food supplements. *J. Clin. Gastroenterol.*, 46: 593-594, 2012.

- 10- VAKNIN Y., HADAS R., SCHAFFERMAN D., MURKHOVSKY L. and BASHHAN N.: The potential of milk thistle, as a source of edible sprouts rich in antioxidants. *Int. J. Food Sci. Nutr.*, 20: 1-8, 2007.
- 11- TSAI J.H., LIU J.Y. and WU T.T.: Effects of silymarin on the resolution of liver fibrosis induced by carbon tetrachlorid in rats. *J. Vir. Hep.*, 15: 508- 514, 2008.
- 12- WENG T.C., SHEN C.C., CHIU Y.T., LIN Y.L. and HUANG Y.T.: Effects of artemepavine against hepatic fibrosis induced by thioacetamide in rats. *Phyt. Res.*, 26: 344-353, 2012.
- 13- HE Z.H., ZHOU R. and HE M.F.: *Phytomedicine*, 18: 470-478, 2011.
- 14- WEI Y., ZHAO T. and ZHANG Z.: Plumbagin inhibits leptin- induced proliferation of hepatic stellats cells. *Trop. J. Pharm. Res.*, 12: 691-698, 2013.
- 15- LUO Y., ZHU M.L., SUN X.F. and LIANG Z.Q.: Preparation of water-soluble sodium salt of glycyrrhetic acid and 11-deoxy glycyrrhetic acid and research on anti-inflammatory effect. *Prac. Pharm. Clin. Remed.*, 11: 182-184, 2008.
- 16- VAN ROSSUM T.G. and De MAN R.A.: Glycyrrhizin as a potential treatment for chronic hepatitis C. *Aliment Pharmacol. Ther.*, 12: 199-205, 1998.
- 17- HOU Y.L., TSAI Y.H., LIN Y.H. and CHAO J.C.: Ginseng extract and ginsenoside Rb1 attenuate carbon tetrachlorid-induced liver fibrosis in rats. *BMC Compl Altern Med.*, 14: 415, 2014.
- 18- ZHEN M.C., WANG Q. and HUANG X.H.: Green tea polyphenol epigallocatechin -3- gallate inhibits oxidative damage and preventive effects on carbon tetrachloride-induced hepatic fibrosis. *J. Nutri Biochem.*, 18: 795-805, 2007.
- 19- SUK K.T., KIM D.J., KIM C.H., et al.: A prospective nationwide study of drug -induced liver injury in korea. *Am. J. Gastroenterol.*, 107: 1380-1387, 2012.
- 20- WAI C.T., TAN B.H., et. al.: Drug -induced liver injury at Asian center: A prospective study. *Liver Int.*, 27: 465-474, 2007.
- 21- ZHOU Y., YANG L., LIAO Z., HE X. and GUO H.: Epidemiology of drug-induced liver injury in china: *Eur. J. Gastroenterol. Hepatol.*, 25: 825-829, 2013.
- 22- VIVEKANAND S., LUIZ F.F.G. and INDRA N.S.: *Bioinformatics and Biology Insights*, 14: 1-11, 2020.
- 23- SMITH D.A. and PERRY P.J.: The efficacy of ergogenic agents in athletic competition part 1 *Ann. Pharmacother.*, 26: 520-528, 1992.
- 24- SCHWINGEL P.A., COTRIM H.P., et al.: Recreational anabolic-androgenic steroid use associated with liver injuries among Brazilian young men. *Subst Use. Misuse.*, 50: 1490-1498, 2015.
- 25- CHOI S.K., JIN J.S., CHO S.G., CHOI S.J., et al.: Spontaneous liver rupture in a payient with peliosis hepatis. *World J. Gastroenterol.*, 15: 5493-5497, 2009.
- 26- JIN X., ZHENG R.H. and LI Y.M.: Green tea consumption and liver disease. *Liver Int.*, 28: 990-996, 2008.
- 27- BILAL M., PATEL Y., BURKITT M. and BABICH M.: Linoleic acid induced acute hepatitis. *Case Rep. Hepatol.*, 2015.
- 28- FAVREAU J.T., RYU M.L., et al.: Severe hepatotoxicity associate with Lipokinex. *Ann. Intern. Med.*, 136: 590-595, 2002.
- 29- STICKEL F., DROZ S., et al.: Herba life nutrition supplement. *J. Hepatol.*, 50: 111-117, 2009.
- 30- FONG T.L., KLONTZ K.C., et al.: Hepatotoxicity due to hydroxycut. *Am. J. Gastroenterol.*, 105: 1561-1566, 2010.
- 31- KLONZTZ K.C., DEBACK H.J., et al.: The role of adverse event reporting in the FDA response to multi state outbreak of liver disease associate with a dietary supplement. *Public Health Rep.*, 130: 526-532, 2015.
- 32- KOWALSKI T.E., et al.: Vitamin A hepatotoxicity. *Am. J. Med.*, 97: 523-528, 1994.
- 33- IZZO A.A., HOON K.M., RADHAKRISHNAN R. and WILLIAMSON E.M.: Adverse events and drug interaction of herbal remedies. *Phytother Res.*, 30: 691-700, 2016.
- 34- HARPAZ R., et al.: Noval data -mining methodologies for adverse drug event discovery and analysis. *Clin. Pharmacol. Ther.*, 91: 1010-1021, 2012.
- 35- DANAN G. and BENICHO C.: Identifying herbal adverse events from spontaneous reporting systems using taxonomic name resolution approach. Application to drug -induced liver injury. *J. Clin. Epidemiol.*, 46: 1323-1330, 1993.

الأعشاب والمكملات الغذائية وتأثيرها الضار على الكبد

أمراض الكبد تعتبر حالات فسيولوجية يمكن تقليلها من البداية وضرر الكبد المتقدم ممكن أن يؤدي إلى تليف أو فشل كبدي وهذه حالة غير قابلة للعلاج.

علاج ضرر الكبد المتقدم يكون على مراحل خاضعة للاهتمام بعض المكملات الغذائية والعلاج البديل (CAM) تقوم بدور في هذا العلاج

المكملات الغذائية تستهلك حول العالم بالرغم من عدم ثبوت كفايتها للعلاج وبعض هذه المكملات يسبب ضرر للكبد بما يسمى (DILI-DS) وهذا يخضع للعديد من الأبحاث في هذا المقال مراجعة لكثير من هذه المكملات الغذائية وتأثيرها الضار والصحي على الكبد وتحليل لبعض منها على أمراض الكبد.