WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 2, 155-165. Review Article ISSN 2277– 7105

REVIEW ON: HEPATOTOXICITY AND HEPATOPROTECTIVE AGENTS

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Article Received on
22 November 2022,
Revised on 12 Dec. 2022,
Accepted on 02 Jan. 2023
DOI: 10.20959/wjpr20232-26881

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ABSTRACT

The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ. Other chemical agents, such as those used in laboratories and industries, natural chemicals (e.g., microcystins) and herbal remedies can also induce hepatotoxicity. Chemicals that cause liver injury are called hepatotoxins. Hepatoprotective drugs means the drugs that are prevent the liver disease. A number of synthetic hepatoprotective drugs are available in practice, however their effectiveness does not hold true with the entire range of population suffering from this disorder. Moreover, the side effects and the drug interactions are major restrictions in its clinical utility. On the other hand, drugs having toxic effect on the liver are better known as hepatotoxic drugs. Mono and poly-herbal preparations have been used in various liver disorders. According to one estimate, more than 700 mono and poly-herbal preparations in the form of decoction, tincture, tablets and capsules from more than 100 plants are in clinical use. The most commonly used parameters to assess the hepatoprotective activity are morphological e.g. Liver weight and volume, biochemical estimations, such as measurement of transaminase activity, SGPT, SCOT, alkaline phosphatase, serum bilirubin, total serum proteins, albumin, globulin and prothrombin time, functional parameters, pentobarbitone and hexobarbitone sleeping time and finally histopathological study regarding presence of necrosis, fatty degeneration and cirrhosis. In this review, we will briefly discuss hepatotoxicity and hepatoprotective agents.

KEYWORDS: Liver, Hepatotoxic, hepatoprotective, herbal formulations.

INTRODUCTION

Liver is the largest internal organ in our body performing more than 5000 separate bodily functions- from cleansing the blood of toxins to converting food into nutrients to controlling our hormone levels. It detoxifies various metabolites, synthesizes proteins, & produces biochemicals necessary for digestion. Most people never give their Liver a thought until something goes wrong. Yet, Liver disease is on rise. In fact, there are many types of Liver diseases that can be caused by various damages from drugs or chemicals, obesity, diabetic, or an attack from your own immune system. Hepatotoxicity has now become the most serious liver disorder, which accounts for about 15% of the world's burden of diseases. Hepatotoxicity, or liver damage, is caused by hepatotoxins, which may source from chemicals, dietary supplements, pharmaceutical drugs, and medicinal plants.

The main causes of liver damage are

- The major cause in India is alcohol addicts. It is suspected that more than half of the cases of hepatotoxicity are caused by alcohol.
- Chemicals like CCl4, phosphorous, Aflatoxins, Chlorinated Hydrocarbon, etc.
- Drugs i.e. DILI (Drug-Induced Liver Injury)
- Autoimmune Disorders
- Infections like Viral Hepatitis

MECHANISM OF HEPATOTOXICITY

- Most of the hepatotoxic chemicals damage liver cells mainly by inducing lipid per oxidation & other oxidative damages in liver.
- By forming the reactive free oxygen radicals which directly induces hepatotoxicity
- Increasing the apoptosis
- Reducing glutathione stores (an antioxidant of Human body).

MARKERS OF HEPATOTOXICITY

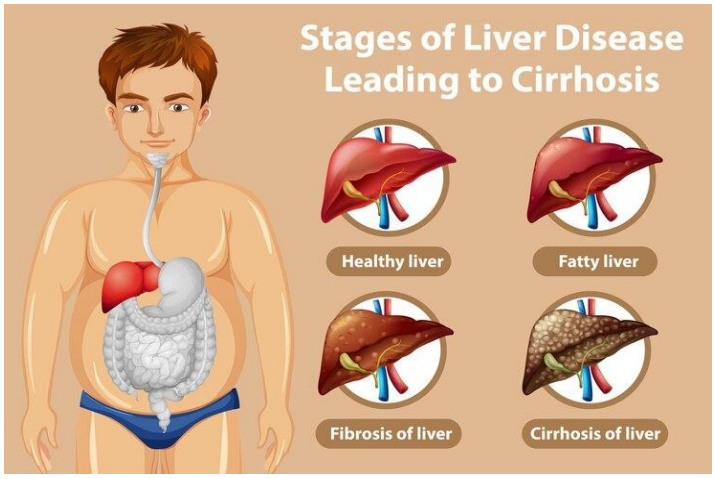
- AST- Aspartate Serum Transferase
- ALT- Alanine Amino Transferase
- ALP- Alkaline Phosphatase
- LDH- Lactate Dehydrogenase
- TB- Total Bilirubin
- TP- Total Protein
- TG- Triglycerides

- GGT- Gamma-glutamyl Transferase

A number of hepatoprotective agents are available in practice. However, their effectiveness doesn't hold true with the entire range of population suffering from the disorder.

MECHANISM OF ACTION

The mechanism of hepatoprotection by these compounds is generally by exerting multiple effects.[13] The herbal drugs used for the management of the chronic liver disease can regulate and strengthen the liver, gastrointestinal, and immune system.[24] The regulation of the gastrointestinal system may improve the general well-being of the patients, and the improvement of constipation may prevent the absorption of harmful substances and indirectly decrease ascites.[25] The protection of liver cells against toxic materials including drugs, lipid per-oxidation, and free radical injury may decrease inflammation, improve liver blood flow, and ultimately help in reduction in ascites and blood pressure.[26] They can suppress CYP2E1 enzyme that converts many drugs to their toxic metabolites.[27] They can protect the normal structure of mitochondrial membrane and enhance the activity of ATPase in mitochondria, thereby modulating the balance of liver energy metabolism.[28] They also possess anti-inflammatory and antiprotozoal activities. Immune dysfunction is a component of liver disease, and thus, immunomodulation by herbal therapy (withaferin-A) prevents oxidative stress and inflammation and strengthens the detoxifying power of liver cells.[29] Antiviral properties of picroliv, ellagic acid, phylanthin, and hypophylanthin are reported.[30] Moreover, Herbal drugs can promote protein synthesis in hepatocytes or decrease formation of leukotrienes, prostaglandins, and TNF-a by Kupffer cells.[31] Drugs like picroliv (iridoid glycoside) can cause liver tissue regeneration, and ellagic acid can prevent liver fibrosis.[31, 32] Anticholestatic and choleretic effects of silymarin and andrographolide are well established.[20] Further, nuclear factor-kappa B-mediated inhibition of inflammatory cytokines and chemokines had been shown with silymarin, picroliv, curcumin, and ellagic acid.[33–36] Moreover, cyclo- oxygenase-2-mediated inflammatory response had been shown to be inhibited by curcumin and inducible nitric oxide synthase inhibition with silymarin and curcumin.[34, 35] The pro-inflammatory cytokines and chemokines had been exhaustively studied with curcumin by Nanji and coworkers.[36] Silymarin and picroliv had been shown to inhibit TNF-a-mediated apoptosis.[37–39] All these effects strengthen the liver and regulate body metabolism and ultimately inhibit further liver cell damage in the favor of their regeneration.[40]

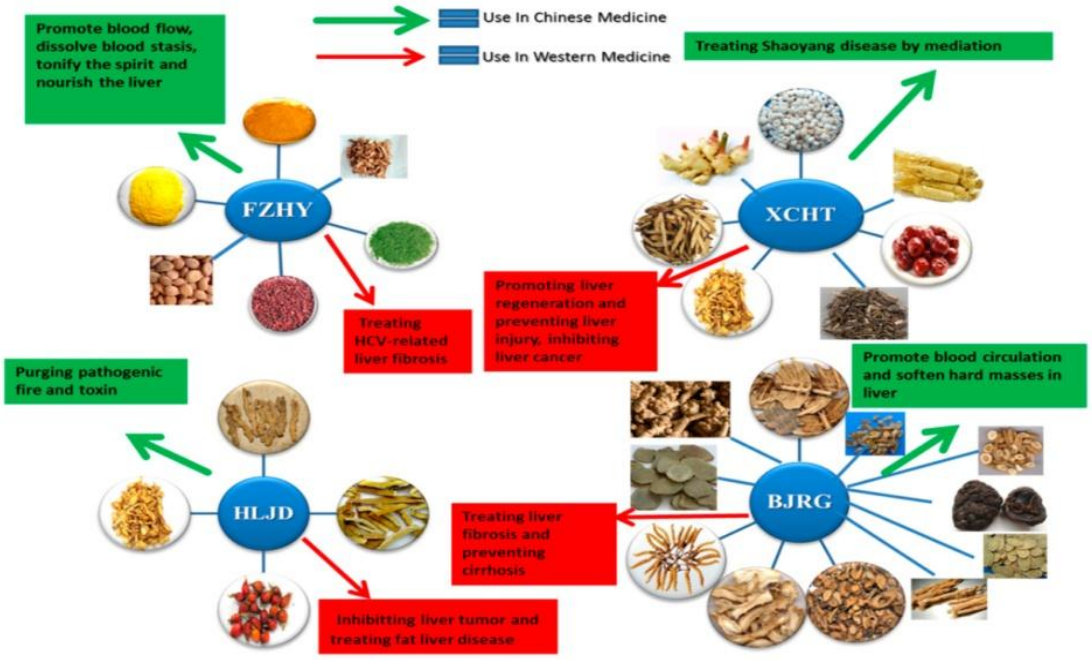


(Fig 1.)

(Fig.2)

HERBAL FORMULATIONS

Numerous medicinal plants and their formulations are used to treat liver disorders in ethno medicine practice as well as traditional system of medicine in India. There are about 600 commercial herbal formulations available in market all over the world, which are claimed to have hepatoprotective activity (Bedi et al., 2016). In India, about 40 anti- hepatotoxic, patented, polyherbal formulations representing a variety of combination of 93 medicinal plants from 44 families are available (Sharma et al., 1991). More than 700 mono and poly-herbal hepatoprotective preparations from more than 100 plants are in clinical use in the form of decoction, tincture, tablets and capsules. Recent global increase in the utilization of herbal drugs has also been reported in the literature (Girish et al., 2009).



(Fig .3)

Eastern countries have been using herbal drugs to treat liver diseases since ancient time (Rajaratnam et al., 2014). In ancient India (Vedic period) and China (Xia dynasty), records on use of herbal medicines track back to 2100 BC. The first written reports date back to 600 B.C. with the Charka Samhita of India and the early notes of the Eastern Zhou dynasty of China around 400 B.C (Onyije and Avwioro, 2012). Ayurveda, an indigenous system of medicine in India, has a long tradition of treating liver disorders with plant drugs. Minimizing side effects and increasing therapeutic efficacy of medicines is the basic need of today. Alternative system of medicine like Ayurveda, Unani etc. has been proved to be effective with minimum side effects. With rich diversity of plants, over 45,000 diverse plant species are found in India out of which about 15,000-20,000 plants have medicinal and therapeutic properties. Of these, only about 7,000- 7,500 are being used by traditional practitioners (Bedi et al., 2016). As per WHO report, around three quarters of the world's population uses herbs and other traditional medicines to cure various diseases, including liver disorders (Chaudhury and Refei, 2001). The medicinal plant such as Guduchi (Sharma and Pandey, 2010), *Elephantopus scaber* (Ho et al., 2012), *Aquilegia vulgaris* (Adamska et al., 2003), *Strychnos potatorum* (Sanmugapriya & Venkataraman, 2006), *Tridax procumbens* (Ravikumar et al., 2006), *Picrorhiza kurroa* (Mohd et al., 2012), *Silybum marianum* (Hermenean et al., 2015), *Andrographis paniculata* (Nasir et al., 2013), *Azadirachta indica* (Johnson et al., 2015) and *Glycyrrhiza glabra* (Sharma and Agrawal, 2014) has proven hepatoprotective properties and are used to treat liver disorders. Guduchi (*Tinospora sp.) is one of the most versatile*

rejuvenating shrubs, also known as 'Giloya' in Indian vernacular, and is reported to have many therapeutic applications (Pandey et al., 2012). Guduchi, as it is most commonly called, has been described as "one which protects the body" (Gawhare, 2013).

Some of the plant constituents possessing hepatoprotective activity (Handa et. al., 1986).

Plant constituents	Plant Name
Andrographolide	*Andrographis paniculata*
Catechin	*Anacardium occidentale*
Curcumin	*Curcuma longa*
Fumaric acid	Sida cordifolia
Glycyrrhizin	*Glycyrrhiza glabra*
Picrolive	*Picrorhiza kurroa*
Saikosaponins	*Bupleurum falcatus*
Silybin	*Silybum marianum*

List of few plants with hepatoprotective property against toxic chemical induced liver damage in experimental animals.

Plants	References
Acacia catechu	Jayasekhar *et. al*. (1997)
Azadirachta indica	Chattopadhyay *et. al*. (1994)
Andrographis paniculata	Handa and Sharma (1990)
Cappris spinosa	Gadgoll and Mishra (1995)
Carissa carandas	Hegde and Joshi (2009)
Daucus carota	Bishayee *et. al.* (1995)
Eclipta alba	Saxena *et. al.* (1993)
Ocium sanctum	Chattopadhyay *et. al*. (1992)
Phyllanthus emblica	Gulati *et. al.* (1994)
Phyllanthus debilis	Shah *et. al.*,2002
Picrorhiza kurroa	Dwivedi *et al.*,1991
Ricinus communis	Reddy *et. al.*,1993

CONCLUSION

The liver is of vital importance in intermediary metabolism, in the detoxification and in the elimination of toxic substances. Since the liver has considerable functional reserve, damage to the organ may not affect its activity. The maintenance of a healthy liver is vital to overall health of the human beings. Since the liver is involved in almost all biochemical processes and there are many different diseases that will affect it. The liver is often abused by environmental toxins, which are eating habits, alcohol and overdose of certain drugs which can damage and weaken the liver and eventually lead to many diseases. Therapies developed along the principles of Western medicine are often limited in efficacy, carry the risk of

adverse effects, and are often too costly, especially for the developing world. Therefore, treating liver diseases with plant-derived compounds, which are accessible and do not require laborious pharmaceutical synthesis seems highlyattractive.

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