Liver injury: Light and Dark Side of Herbal Formulations

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Abstract

Global burden of liver diseases responsible for more than two million deaths annually, that presents a significant health concern worldwide. The practice of natural products or herbal formulations to treat ailments started with the evolution of human civilization. Traditional herbs are tremendous remedies for the treatment of liver diseases and WHO reported that majority of the population in Asian and African content using natural formulations for liver disorders like fatty liver diseases. Due to the unavailability of regulatory agencies guidelines and standard bylaws to maintain the quality, safety and efficacy of herbal medicines especially in the underdeveloped as well as developing countries, many herbal formulations making companies advertise that herbal medicines do not induce any adverse effect and even a number of people are attracted by these companies and using herbal medicines. There are several reasons such as self-treatment, improper intake, sub-standard product, unqualified practitioners are the reasons for toxicity of herbal formulations. This review summarizes the dark and light side of herbal formulations in liver injury.

Keywords: Herbal formulations, Liver injury, adverse effect

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Introduction

For survival, the cells in the living organism are driven biochemical reactions termed as metabolism (Dwivedi and Jena, 2018). The liver is the principle metabolic machinery that processes the foods, absorbed from the...
intestine and subsequent delivery of processed nutrients to the target organs in the body. Liver serves as the first line of defense to detoxify toxic agents that absorbed from the stomach and intestine. In the process of detoxification of some compounds, it undergoes to harmful stress that leads to the malfunctioning or alterations in the normal metabolic processes and eventually results into liver failure and other severe problems including death (Núñez, 2006). The etiologies for the liver disease could be hepatotoxic drugs, alcohol consumption, microbial infection, lifestyle and dietary habits (Dwivedi and Jena, 2020). Approximately, 900 drugs have been reported to cause liver injury in the patient, some of which exerts minimal/low toxic effect, while others are highly toxic at high doses such as acetaminophen, anti-tubercular drugs (Friedman et al., 2003). Hepatotoxicity of a drug is the most common reason for a drug to be withdrawn from market. New chemicals entities, for which clinical trials are being conducted and fail in the trial due to hepatotoxicity. Approximately, half of the all acute liver failures and overall, 5% of all hospital admissions are reported to linked with drug-induced hepatotoxicity (Dey et al., 2013). Now a days, the prevalence of non-alcoholic fatty liver disease (NAFLD) is 25-30% in general population, whereas, it is much higher in the individual with obesity, diabetes and hyperlipidemia. NAFLD in an umbrella term, which covers the spectrum of the liver diseases ranging from simple fatty liver to non-alcoholic steatohepatitis, which can subsequently lead to liver fibrosis, liver cirrhosis and primary liver cancer hepatocellular carcinoma. According to the recent report of WHO, there are an estimated 325 million individuals globally, living with hepatitis B and/or C, and there are several other viral strain hepatitis A, D and E, which all causes the viral hepatitis (WHO, 2020). Alcoholic liver disease also raised a significant health concern, which represents 5.3% of all deaths globally and there are 3.3 million individuals dies every year due to alcohol abuse (WHO, 2018). The alcohol abuse is a causative factor in more than 200 type of illness and pathological state (Dwivedi et al., 2020). Furthermore, liver fibrosis is common event in all types of chronic liver diseases that could lead to end-stage of liver disease, liver cirrhosis, responsible for more than two million deaths annually, worldwide (Dwivedi and Jena, 2019b). In addition, HCC is the end-stage of viral hepatitis and all other type of chronic liver diseases that responsible for an increasing number of cancer-related mortality, which is the second leading cause of cancer death in East Asia and sub-Saharan Africa (Patwa et al., 2020). Besides the above-mentioned liver diseases, there are several other hepatic diseases such as autoimmune hepatitis, hereditary or congenital biliary atresia, hemochromatosis, Wilson’s disease, Gilbert’s syndrome, alpha 1-antitrypsin deficiency and glycogen storage diseases, which are also responsible for significant number of mortalities worldwide (Kumar et al., 2019).
Mechanism and pattern of liver injury

Drugs are removed from the market due to the late side effect of drugs, which are hepatotoxic in nature (Jangra et al., 2016). Liver is closely related with the metabolism of the substances from intestine via hepatic portal vein, which increases the vulnerability of liver to injurious stimuli and other toxic substances. A number of chemicals reported to induce liver injury by increasing reactive oxygen species and lipid peroxidation and by decreasing reduced glutathione level. When, the number of oxidant factors enhanced and the antioxidant substances of cell depleted, it is termed as oxidative stress. It has been reported that persistence of oxidative stress could lead to initiation and perpetuation of pro-inflammatory reaction by inducing direct or indirect release of inflammatory mediators. The pro-inflammatory and inflammatory substances further promote the inflammation in the other type of hepatic cells as well as other in other organs at systemic level (Dwivedi and Jena, 2019a). Most of the harmful chemicals interfere with the organelle function such as damage to mitochondria and thereby impairing the production of energy needed to carry out the metabolism. Mitochondrial dysfunction leads to the generation of excessive amount of reactive oxygen species, which subsequently injure the other hepatic cell as well as other organs (Dwivedi and Jena, 2020). Some other substances reported to interact with microsomal enzyme system such as activation of cytochrome P450 CYP2E1, which play a major role in toxicant metabolism such as alcohol, thioacetamide and etc. Injury to the liver parenchymal cells bile ducts results the accumulation of bile acids/salts in the liver, which further damage the liver (Abou Seif, 2016).

Besides, above-mentioned events, an interplay among the certain molecular pathways such as induction of nitric oxide synthase, NF-κB, inflammatory interleukins and etc. plays a critical role in the induction of molecular injury at molecular level (Dwivedi and Jena, 2020).

Hepatic damage occurs either due to enhanced oxidant factors or reduced antioxidant substances levels that leads to the cellular necrosis, apoptosis and DNA damage to hepatic cells. After damage to plasma membrane of parenchymal cell which is known as hepatocyte, is a released as transaminases (alanine aminotransferase; ALT and aspartate aminotransferase; AST) enzymes to systemic circulation and measurement of these enzymes in blood plasma/serum are considered as a very well-established end-point clinical diagnostic marker for liver injury (Navarro et al., 2017). In addition to these enzymes, there are several other plasma/serum markers such as γ-glutamyl transferase (GGT), bilirubin (total, direct and indirect), alkaline phosphatase (ALP), triglycerides and cholesterol evaluated to establish the liver injury. The criteria for liver injury is considered after a rise in
either (a) more than three-fold change in upper limit of normal ALT level (b) more than two-fold change in upper limit of normal ALP level, or (c) more than three-fold change in upper limit of normal total bilirubin level (Mumoli et al., 2006).

Natural system of therapy used the herbs, started nearly 5000 years ago by the Sumerians, who first described medicinal uses of herbs for illness (Navarro et al., 2017). Furthermore, the ancient civilization in China and India described about the medicinal properties of herbs in 2100 BC. Later, nearly 1000 BC, in the ancient civilization of Egypt has demonstrated about the use of castor oil, opium, indigo, coriander, mint, garlic and other herbs for medicinal purposes (Navarro et al., 2017). In 600 BC, the first written document was Charaka Samhita of India. Later, a systematic early report about the medicinal purposes was Eastern Zhou dynasty of China in 400 BC.

**Light side of plant products and herbal formulation**

Traditional herbs are tremendous remedies for the treatment of liver diseases (Abou Seif, 2016). In the recent decades, there has been a significant change in a global strategy from synthetic to natural product formulation. Popularity of natural remedies has exponentially increasing and at least one fourth of the patients having liver disease use herbal formulations (Choubey et al., 2019). The WHO estimates that majority of the population in Asian and African content using natural formulations for primary healthcare (Abou Seif, 2016). Presently, the dietary alterations result in liver disorders like fatty liver diseases (Rahman et al., 2019). The plant diversity in India is reported to be nearly 45,000 plants, out of which approximately 15,000-20,000 possess curative and therapeutic properties (Sahu Chittaranjan et al., 2020). The old system of herbal medicines known for its relative convenience, easy accessibility, safety and efficacy, reduced side-effect, natural way of healing and long-lasting curative effect. The protocols depicting treatment with herbal formulations are integrative in nature and are reported to exhibits most appropriate therapies meeting the need of a particular patient. Approximately, half of the herbal formulations used for the treatment of liver diseases, are semisynthetic or congeners of natural product and its derivatives (Sahu et al., 2020).

The aerial parts of *Andrographis paniculata* (*A. paniculata*) herb most widely used in India for its hepatoprotective properties. Due to the presence of several flavonoids, polyphenols and glycosides in whole herb extract, it has been reported to decrease lipid peroxidation as well as to enhance the antioxidant substances (Subramaniam et al., 2015). Several other beneficial properties such as antibacterial, antimalarial,
antiviral, cardioprotective, antioxidant, anti-inflammatory, antidiabetic and also antitumor activities have been well reported for in the literature (Abou Seif, 2016).

Silymarin (*Silybum marianum*; milk thistle) has been another widely used natural herb for gastrointestinal disease of biliary tract and liver. Its thistle possesses several bioactive phytoconstituents flavonolignans, such as silybin, silychristin and silydianin, which commonly known as silymarin (Shaarawy et al., 2009). Silybin is the major constituents, which contribute 75% of bioactive constituents. Silymarin is present in the whole herb but mainly condensed in its seeds and fruit. Due to the certain beneficial properties such as antioxidant and anti-inflammatory, it increases the detoxification of toxins and replenishes the antioxidant substances in the cell. Rasool et al, reported that silymarin exhibits hepatoprotection against certain liver toxicant such as ethanol, carbon tetrachloride, acetaminophen and D-galatosamine in different animal models of liver injury (Rasool et al., 2017).

*Camellia sinensis* (green tea) leaves contain several beneficial bioactive polyphenol constituents such as epigallocatechin, epicatechin, catechin, tannins and caffeine, increases the defense mechanism in the cells against pathogens and other toxic chemicals (Wang and Goodman, 1999). It is widely known to possess antiaging, antioxidant and free radical scavenging activities and catechin polyphenols have therapeutic value in the prevention and treatment of several illness and disorders (Ostrowska and Skrzydlewska, 2006; Pandey et al., 2020). It exhibits hepatoprotective properties and has been reported to improve liver function by decreasing the generation of reactive oxygen species and by maintaining the total antioxidant capacity of the cells (Lodhi et al., 2014).

Ginger (*Zingiber officinale*) is one of the most commonly used food spices, globally. It is an important herb in Ayurvedic, Chinese and Unani system of medicine for the treatment of rheumatism, asthma, nervous diseases, gingivitis, constipation, stroke, toothache, catarrh and diabetes (Wang and Wang, 2005; Tapsell et al., 2006). Ginger extract at different doses improved the bromobenzene-induced alterations by decreasing the free radicals and by increasing the antioxidant enzymes in the liver of rats (El-Sharaky et al., 2009). Hozayen and AbouSeif reported that ginger root extract exhibits protective effect against aspartame-induced hepatic alteration by improving the levels of blood transaminases, ALP, γ-GT, bilirubin, albumin, serum total protein, tumor necrosis factor (TNF), α-fetoprotein, LDH activity, antioxidant enzymes and lipid peroxidation (Hozayen and Abouseif, 2015). Curcumin is also present in ginger that is very known for its antioxidant as well as anti-inflammatory activities and protects endothelial cells against oxidative stress (Motterlini et al., 2000).
Pumpkin (Cucurbita pepo L.) is a plant commonly used as functional food and its seed reported to have rich source of unsaturated fatty acids, fibers and antioxidants, which all exhibits liver protective and antiatherogenic properties. Pumpkin seed oil possesses beneficial unsaturated fatty acids such as palmitic, stearic, oleic and linoleic acids. It has been reported that, treatment with pumpkin oil mediates liver protection by exhibiting antioxidant and enhanced detoxification activities (Abou Seif, 2014).

**Dark side of plant products and herbal formulation**

Natural products are considered to be free from adverse side effect, as these are being derived from natural sources. However, this conception is not always true. Due to the unavailability of regulatory agencies guidelines and standard bylaws to maintain the quality, safety and efficacy of herbal medicines especially in the underdeveloped as well as developing countries, many herbal formulations making companies advertise that herbal medicines do not induce any adverse effect and even a number of people are attracted by these companies and using herbal medicines. A number of communities still dependent on using herbal formulations for several illness in Asian and African continent and some of the people taking herbal formulations along with the regular allopathic medicine for hypertension and diabetes, this could also lead to the potential drug interaction, which results in failure of multiple organ failure and even death (Jangra et al., 2020).

The toxic effect of herbal medicine occurs due to several reasons such as self-treatment, improper intake, substandard product and unqualified practitioner.

**Self-treatment, a reason for toxicity of herbal formulations**

Herbal formulations are freely available without prescription in the markets, even in the departmental store and these are advertised as a marvelous cure along with no adverse effect for any said diseases. The individual or patients who need to go for a long-term allopathic treatment are attracted by these advertisement as well as local non-allopathic medicine practitioners that the herbal products are very safe and these could be continued as a routine medicine for long-term. A very famous proverb, “Prevention is better than cure”, following this byword, the individuals who are conscious about their health, they also start taking herbal medicines to remain fit and healthy and as a result, a number of individuals/communities are appealed towards self-treating herbalformulations (Fatima and Nayeem, 2016).
Improper intake, a reason for toxicity of herbal formulations

Allopathic drugs launched for the treatment of public after series of preclinical toxicity testing and extensive clinical trials and these drugs are ensured for its quality, safety and efficacy. Further, all of these drugs have fixed dose depending on the patient’s weight and age. Furthermore, the adverse/side-effect and contraindication has been provided along with allopathic medicines. No any above-mentioned procedure followed for the approval, marketing and treatment in case of herbal formulations/medicine. Even, some of these herbal formulations are marketed as a food or dietary supplement, but there is no indication of about the proper dose such as in units or mg of dose, ml of syrups. Normally, in case of herbal formulations, same dose is applied for children, adults and old individual. Also, there is non-availability of treatment course, which could be in months or years may toxic in long-term use. Hence, the above-mentioned factors are taken into consideration which may lead to improper intake(Barrett et al., 1999).

Sub-standard product, a reason for toxicity of herbal formulations

Due to the absence of regulatory guidelines and standards available for quality, safety and efficacy, there are several of sub-standard herbal formulations sold in the market. Some of these formulations may contain high or less amount and even, absence of bioactive constituents. There are some other concerns such as wrong selection of herb, use of adulterant/another herb species by the collector, improper processing and storage of these herb results in the loss of efficacy of herbal formulations. Most of the times, the label on these formulations do not disclose or improper details about the ingredient present in it(Jennifer, 2002).

Unqualified practitioners, a reason for toxicity of herbal formulations

It is most common problem in underdeveloped as well as developing country, where there is lack of qualified practitioners prescribing herbal formulations. In the present time, there are several coursed offered by different universities related to the complementary and alternative medicine, that producing a qualified herbal medicine practitioner. Half of the herbal formulations practitioners around the globe are unqualified for this profession, who generally continued this tradition form their fathers and forefathers(Fatima and Nayeem, 2016).
Green tea induced hepatotoxicity

In the recent decade, green tea has drawn the attention of human population, who are health conscious. Due to its said anti-aging properties, it has widely been used by the old- and middle-aged individuals. It is most commonly consumed beverages by billions of individuals around the globe. Green tea extract is very well known to possess beneficial medicinal properties that obtained from the leaves of the *Camellia sinensis* herb. The extract has been claimed that it has several beneficial properties such as weight-loss, enhancing metabolism and fat burning. The claims were made on the basis of study performed in vitro, which revealed that concentrated extract possess antioxidant activity, increase the activities of several metabolic pathway and inhibits the lipogenesis thereby exhibiting the above-mentioned effects (Wolfraam et al., 2006). However, human studies on the green tea did not revealed the activities on weight loss, although a small number of studies showed the weight losing effect (Hsu et al., 2008). Some prospective clinical trial did not show effect on weight loss as well as did not reveal any adverse/side-effect.

It was very astonishing to see the first reports related to the case of acute hepatitis of individual taking green tea (Bonkovsky, 2006). There are at least 50 reports available in literature of green tea, which are related to the instances of acute liver injury with jaundice (Mazzanti et al., 2009, 2015). In 2008, United States Pharmacopeia reported 34 cases of hepatic injury associated with the intake of green tea (Sarma et al., 2008). In a prospective clinical trial US Drug-Induced Liver Injury Network (DILIN), related to herbal and dietary supplement linked liver injury, there were 97 products containing catechin or green tea, were obtained from market for testing; of which 49 products have catechins, an bioactive constituent of green tea (Navarro et al., 2013).

Green tea related acute hepatitis was reported within 1-3 months of using products. This illness was self-limited. However, fatal cases were also reported in 10% patients, who observed with acute liver injury and jaundice. The etiologies of the hepatic injury due to green tea is not known but high doses catechins in green tea exhibited liver toxicity in rodents. Green tea contains 30-50% of epigallocatechin gallate (Lambert et al., 2010). In the literature of green tea linked liver toxicity, dose of epigallocatechin gallate less than 12 mg/kg/day did not show to be excessive, whereas it exhibited toxicity at 30-90 mg/kg/day. The above-mentioned findings suggested that the hepatic injury from green tea is purely a type of idiosyncratic reaction.
However, specific constituents or its metabolite present in herbal formulations exhibiting liver toxicity due to the absence of the reports describing the presence of chemicals and their purity. However, there are also the possibilities of contamination with other herbal sources.

Conclusions

Herbal formulation seems to possess promising potential to treat acute as well as chronic liver injury. However, standardization of herbal formulations to reduced the marketing of sub-standard product, is the need of hour. The practice of dispensing herbal formulations must be done by the qualified practitioners. Further the practice of self-treatment must be stopped, which will be very helpful in eliminating improper intake. For herbal formulations, there is an immediate need of conducting systemic, randomized and placebo-controlled trial. There is a need of regulatory agency, which need to regulate the contents in herbal formulation.

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