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Herbal Medicine - A Review Article

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Abstract: ***Herbal and dietary supplements are generally used all over the World. There is a tendency or act for under reporting their intake by patients and the dimension or extent of their use is acknowledged by Physicians. Herbal hepatotoxicity is not uncommonly encountered, but the precise incidence and characteristic sign or symptoms of an illness have not been well characterized.***

Keywords: Phytomedicines, Hepatotoxicity, Ayurveda, Flavonoids, Phenols, Alkaloids and Tannins

1. Aim

To review the causes and diagnosis of herbal hepatotoxicity. This review will mainly focus on single constituents or herb and mixtures of herbs marketed under a single label.

2. Overview

Herbal medicine is also called botanical medicine or phytomedicine or alternative or traditional medicine. It is describes to use a, roots, leaves, seeds, berries, bark, or flowers of plants for medicinal purposes. The use traditional medicine has a long tradition outside of allopathic medicine. It is becoming more mainstream as improvements in analysis and quality control along with advances in clinical research show the value of herbal medicine in the treating and preventing disease. Plants had been in use for medicinal purposes of medicine quite long before recorded history.

Ayurveda is a medical system fore-mostly practiced in India that has been known for nearly 5000 years. This comprises diet and herbal remedies, while emphasizing the body, mind and spirit in disease prevention and treatment. Ancient Chinese and Egyptian papyrus writings describe medicinal uses for plants as early as 3,000 BC.

Indigenous cultures (such as African, even Native American) used herbs in their healing rituals, while others developed traditional medical systems in which herbal therapies were used. An herb is a plant or plant part used for its scent, flavor, or therapeutic properties. Herbal medicines are one type of dietary supplement. They are sold as capsules, powders, teas, extracts, tablets and fresh or dried plants. People use herbal medicines to try to maintain or improve their health.

Maximum people trust that products or food supplement labeled "natural" are always safe and good for health. Botanical medicines do not have to go through the testing that drugs do. Some herbs, such as *Comfrey* and Ephedra, can cause serious harm. Some herbs can interact with drug –called as drug interaction. They analyze or discuss research previously published by scientist and academicians rather than reporting novel research results. Review article comes in the form of systematic reviews and literature reviews and are a form of secondary literature.

Systematic reviews determine an objective list of criteria, and find all previously published original research papers that meet the criteria. They then compare the results presented in these papers. Literature reviews, by contrast, impart a summary of what the authors believe are the best and most relevant prior publications. The concept of "review article" is separate from the concept of peer-reviewed literature. It is possible for a review to be peer-reviewed, and it is possible for a review to be non-peer-reviewed. Natural Products Chemistry & Research is an Open Access journal and aims to publish most complete and reliable source of information on the discoveries and current developments in the mode of original articles, review articles, case reports, short communications, etc. in all areas of the field and making them freely available through online without any restrictions or any other subscriptions to researchers worldwide.

3. Introduction

Herbal medicine is also called botanical medicine or phytomedicine. An herb is a plant or plant part used for its therapeutic, scent or flavor properties. Herbal medicines are one type of dietary supplement. They are sold as tablets, capsules, powders, teas, extracts, and fresh or dried plants. The herbal medicines are used to maintain or improve the health.

It is describes to using a, roots, leaves, seeds, berries, bark, or flowers of plants for medicinal purposes (Jennifer Bret, 2007). The use of phytomedicines has a long tradition outside of conventional system of medicine (Hasan SS *et al*, 2009).

It is becoming more mainstream as improvements in quality control and analysis along with advances in clinical research and expressed the significance of plants medicine for curing and inhibiting the diseases

Ayurveda is a medical system which is practiced in India andhas been known for about 5000 years. This comprises food supplements and herbal therapy, while emphasizing the body, mind and spirit for curing and preventing the diseases. Ancient Egyptian papyrus and Chinese writings describe medicinal uses of herbsas early as 3,000 BC.

Botanical remedy has been burgeoningly used for the curing various diseases all over the World instead of their unproven therapeutic ability through systematic investigations. In the US, herbal and food supplements represent a $180 billion

market and their use was reported by 18.9% population in 2004, and this had doubled from the previous decade (Eisenberg DM *et al*, 1998). Approximately 50% of patients admitted that they did not disclose to doctors regarding the use of plant and food supplements. The list of the commonly used botanical preparations for various conditions, such as *Echinacea*, garlic, *Ginko biloba*, ginseng, grape seed extract, green tea, St. John's wort, and *Aloe vera*. Notably, the use of herbal food supplements specifically common in individuals with chronic diseases, as was reported by 30–60% of patients who ingested silymarin (milk thistle) particularly for liver diseases (Gordon, A.2006). Theoretically such population is more susceptible for toxicity of liver as well as more likely to develop severe hepatic adverse consequences

Botanical Products and Their Regulations

Plants products used for curing disease exist as both crude and commercial preparations. Crude plant products of leaves, seeds,roots or teas) are oftenly used in developing countries. Sometimes they are formulated as a mixture (i.e. Chinese and Thai herbal medicine, and Indian ayurvedic medicine in which all components are not known and may have toxic adulterants, like corticosteroids, non steroidal, anti-inflammatory drugs, and metal like arsenic, lead, mercury. In developed countries where commercial phytoproducts in the form of capsules, tablets are more generally used. They oftenly vary in content and concentration of chemical constituents come from different manufacturers. Even with standardization of the known active molecules or constituents flavonoids, phenols, alkaloids, tannins and have variations in bioavailability and pharmacological activity in humans (Masuda, T, 1999).These herbal supplements are expected to adhere to the regulations of the food Supplement and Health Education Act (DSHEA) of 1994, and the Final Rule for Current Good Manufacturing Practices for Dietary Supplements of 2007 in US. These regulations require for The manufacturers are need to determine the safety of botanical products before they are release into the market and also define the food ingredients like amino acids, minerals, vitamins, metabolite and any other concentrate. The manufacturers are also require to provide accurate and pure food products. Moreover the manufacturers are bound to register their products before their distribution in to the market. Thus US Food and Drug Administration (FDA) must have authority to review and approve herbal products for their effectiveness and safety

4. Causes

The prevalent of herbal product use and occurrence of liver toxicity by plants are not known exactly. Current regulations for herbal products do not mandate systematic surveillance or reporting of adverse effect by the manufacturer to the FDA. Hence, the data regarding herbal hepatotoxicity are derived largely from anecdotal reports, retrospective databases and, more recently, from prospective registries of drug-induced liver injury. Notably, few of these drug-induced liver injury reports have excluded patients with herbal hepatotoxicity. Herbal products are involved to cause hepatotoxicity in 2–11% of patients with drug induced liver injury, and in 5–10% of patients with drug-induced acute liver failure (ALF), although a single-center experience has involved HDS in upto 70% of patients with acute liver failure according to available data of drug-induced liver injury group from the Europe and US. These numbers show the intensity of herbal toxicity of liver in clinical practice.

Moreover, traditional plant medications are used on large scale in various countries such as Asia, China, Central America, Africa and even India. Whereas toxicity of liver produced by phytomedicines encountered in various above cited parts of World. The data of Drug induced liver injury are collected from Singapore and Korea do support the prevalence of herbal toxicity of liver which is approximately72% and 74% respectively. Astonishingly, the data of herbal drug induced liver injury gather from India was very low that is 1.3%, where the use of herbal remedies and ayurvedic compounds are quite common. Although the precise and concise logic remained unclear, so ayurvedic practitioners predicted that botanical compounds are commonly taken in India after the development of an illness like hepatitis whereas the contamination by heavy metal during treatment result in involvement of a non-hepatic organ which may overlook hepatitis.(Table 1)

Table 1: Herbal and food supplement Liver toxicity: Prevalence and clinical features among drug-induced liver injury in different reports.

Reference	Countries and patient characteristics	Prevalence of HDS hepatotoxicity	Clinical features and prognosis of cases identified as HDS hepatotoxicity
1.Andrade *et al*	Spain (1994–2004)	2%	89%- hepatocellular
	N = 446; DILI		11%- cholestasis
	Multi-center, prospective		56%- needed hospitalization
			11% death
2.Chalasani *et al*	USA (2003–2008)	9%	63%- hepatocellular
	N = 300-DILI		17%- cholestasis
	Multi-center, prospective		21%-Mixed Injury
			41- needed hospitalization
			6%-ALT-
			9%-Chronic DILI
3.Devarbhavi *et al*	India (1997–2008)	1.3%	50% -mortality
	N = 313; DILI		
	Single-center, retrospective		
4.Estes *et al.*	USA (2001–2002)		

	N = 20- ALF		
	Single-center, retrospective	50%	60%- underwent LT
5.Ibunez et al	Spain (1993–1998)	11%	64%-hepatocellular injury
	N = 103- DILI		18% -Cholestasis
	Population-based, prospective		18%-Mixed injury
6.Reuben *et al*.	USA (1998-2007)		90%- hepatocellular injury
	N=133-ALF from drug		21%-Spontaneous recovery
	Multi-center, Prospective	10%	29%-death
			50%-underwent- LT
7.Russo *et al*.[	USA (1990-2002)	5.1%	All underwent LT
	N= 270-ALF from drug		
	Retrospective,UNOS data		
8.Suk et al	Korea(2005-2007)		77%- hepatocellular injury
	N=371-DILI	73% (40%-herb,14%-dietary supplement, 19%-folk remedies)	11%- Cholestasis
	Multi-center, prospective		1.5-death
			10% -mixed injury
9.Wai et al	Singapore(2004-2006)	71%	72%-hepatocellular injury
	N=31-DILI		20- Cholestasis
	Multi-center, prospective		6%-mixed injury

ALF, acute liver failure; DILI, drug-induced liver injury; HDS, herbal and dietary supplement; LT, liver transplantation; UNOS, United Network for Organ Sharing. Herbal Products associated with Hepatotoxicity

Ayurvedic herbal products

Ayurvedic medicine is the science of a plant- derived system of curing and applicable to a no. of diseases. It generally comprises of large no. of herbs but sometime metals may also be used because of practice of 'Rasa Shastra' which refers to combining of herbs with minerals, metals, and gems). In 2005, approx. 20% of both USA and Indian-manufactured Ayurvedic medicines are known to possess certain quantity of mercury or lead. Although cases of heavy metal poisoning associated with Ayurvedic medicine have been continuously reported and this form of treatment is still utilized by more than I billion population of rural India and worldwide by the South Asian diaspora and others. A very little has been reported in the literature that herbal medicine caused hepatotoxicity instead of being used widely. Severe hepatitis has been documented in a woman who had treated herself for 9 months with various Indian Ayurvedic herbal products for her vitiligo, in which the key implicated ingredient was believed to be *Psoralea corylifolia*.*Centella asiatica* (Gotu kola, Mandukaparni, Kannada), an ayurvedic medicine used mainly for leprosy, has been reported to be associated with granulomatous hepatitis and cirrhosis. Additionally, in the European RCT of Ayurvedic herbal combination, Liv.52 which possess capers, wild chicory, arjuna, black nightshade, yarrow,*Cassia occidentalis* and others, for the treatment of alcoholic cirrhosis (*N* = 188), no effect on survival was seen in Child class A/B patients, but substantially increased liver-related mortality was observed in those with Child class C (2-year survival: 40% vs. 81% in those who adhered to treatment, *P* = 0.02), suggesting a potential detrimental effect of this Ayurvedic preparation.

Cassia occidentalis

C*assia occidentalis* Linn. belongs to Family Caesalpiniaceae is a common weed scattered from the foothills of Himalayas to West Bengal, South India, Burma, and Sri Lanka (Gupta, 2003) and regarded as 'Edible weeds of Agriculture or 'Famine food'. It possess diuretic, tonic, febrifugal, purgative, whooping cough and cough properties. It is used to treat sore eyes, rheumatism, typhoid, asthma, foul breath, gout, cholera, jaundice, tumors, hematuria and disorder of hemoglobin and is also reported to cure leprosy. For diabetes an infusion of the bark of *Cassia occidentalis* is given (Verma *et al*., 2010).A decoction is made from 15 leaves each of *Cassia occidentalis*, *Glycosmis pentaphylla* and *Vitex negundo* and used for bathing the new born baby to make the baby immune to skin diseases (Yadav *et al*., 2010).

In folklore medicine, seed powder (half a tea spoon) of *Cassia occidentalis* is used to cure fever while two table spoons of leave juice mixed with honey cures cough. For intestinal gas, half a cup of leave decoction is taken twice daily and paste of leave is applied for treating skin diseases (Manikandaselvi *et al*., 2016). *Cassia occidentalis* is widely consumed by the local people as a substitute for coffee. It is an ingredient in Himoliv, a polyherbal Ayurvedic formulation. It is also present in other polyherbal formulation like Liv.52 tablet and syrup which are extensively used for Hepatitis A (Tona *et al*., 2004) in conventional medicine. However, seeds are toxic as toxicity is attributed to various anthraquinones and their derivatives and alkaloids, but the specific toxins have not been identified. Data on human toxicity are extremely scarce. The case-fatality rate in acute severe poisoning is 75-80 per cent in children. This syndrome is characterized by vomiting started first, usually early in the morning followed by fever, altered sensorium, abnormal body movements and signs of extreme irritability and agitation (biting, scratching clothes and body and grimacing with protruding and moving tongue/lips)within 24 hours. Histopathologically, involvement of the brain appears to be secondary to massive hepatic necrosis. Although liver enzymes are markedly raised, serum bilirubin level is usually normal and most children are non-icteric. Low serum and CSF glucose levels are frequent features and serum ammonia levels are raised in two-third cases. All these point towards acute and severe liver cell necrosis, inflammatory reactions, cholestasis etc.

Germander

The blossoms of Germander (*Teucrium chamaedrys*), a plant found in Europe and the Middle East, have been used for thousands of years for a variety of disorders, like diabetes dyspepsia, obesity gout, hypertension,. This is present in the form of capsules, tea and as an addition to liquor. Many

reports (mostly from France) of liver injury have been documented, and these include presentations as acute, chronic hepatitis and as ALF. Most cases of hepatotoxicity occurred after 2 months of intake at the manufacturer's recommended doses (600–1600 mg/day). Symptoms were nonspecific abdominal pain, anorexia jaundice, nausea) and followed by a marked increase of ALT. After withdrawal, jaundice was generally disappeared within 8 weeks; however, the development of cirrhosis and relapse following accidental exposure have also been anecdotally reported. Germander is known to have glycosides, flavonoids, saponins and furan-containing diterpenoids. Furan-containing diterpenoids are well-known to be cytotoxic and carcinogenic. In rat studies, these constituents are oxidized by cytochrome P450 3A4 to reactive metabolites that bind to proteins, deplete cellular glutathione and protein thiols, and ultimately induce membrane disruption and hepatocyte apoptosis.

Green tea (*Camellia sinensis*)

Green tea is very famous worldwide and is also a frequent ingredient in various dietary supplements used predominantly for loss of weight. Several reports of hepatotoxicity, including ALF, following the ingestion of numerous and different green tea preparations have been published since 1999. A review of no. of published reports suggests a causal association between green tea and liver damage. Majority of cases were judged as 'possible' according to the CIOMS score and a positive rechallenge occurred in 8 cases. Patterns of liver injury were hepatocellular in most cases, but cholestasis and a mixed pattern were also observed. Liver histology examination revealed inflammatory reactions, cholestasis, occasional steatosis and necrosis. In addition, a case with features mimicking AIH (elevation of ALT, hyperglobulinemia, transient presence of anti-smooth-muscle antibodies and necro-inflammation with interface hepatitis on liver histology) following green tea infusion has also been described. The mechanism of hepatotoxicity is incompletely understood, but components responsible are perhaps gallic acid and catechins their esters, particularly epigallocatechin-3-gallate, which, under certain conditions such as fasting, can induce reactive oxygen species formation, and affect mitochondrial membrane potential. Although there is reason to be concerned regarding green tea-induced liver injury, a systematic review of 34 such cases (27 were categorized as possible causality and 7 as probable causality) performed by the US Pharmacopoeia has not uncovered a major safety issue and therefore a warning on the label of the product has not been implemented.

While there is concern of hepatotoxicity, significant amount of data from both experimental and clinical studies have suggested the role of green tea in hepato-protection and cancer prevention, as well as in 'optimizing' general health. Although heterogeneity among studies exists, a systematic review of 10 studies, including 4 RCTs, showed a significant protective role of green tea against various liver diseases whether the potential risk of hepatotoxicity from green tea outweighs their benefits remains unclear.

Ephedra sinica

Ephedra sinica is used as a nasal decongestant and bronchodilator; it also helps to reduce body weight. In a meta-analysis, it was noted to promote modest short-term weight loss (not sufficient data regarding long-term weight loss and the contribution from athletic performance), but was associated with increased rate of psychiatric and autonomic system issues, heart palpitations and gastrointestinal symptoms. Liver damage cause hepatitis, ALF, and as fulminant exacerbation of AIH, has been described in association of *Ephedra sinica* with ingestion, as well as with the use of multiple different commercial weight-loss herbal products containing *Ephedra sinica*.

Kava

Kava (*Piper methysticum*) is an indigenous to the Hawaii, Polynesia, Melanesia and some parts of Micronesia. The extract of rhizome is generally used to prepare a traditional beverage for recreational and social purposes. The food supplements possessing kava are promoted as a constituent to relieve tension, anxiety, stress, menopause and sleeplessness symptoms in Western countries. Its efficacy for the treatment of anxiety is sustained by a Cochrane meta-analysis. Many reports of severe toxicity of liver have been explained in the Europe and US and some of which have been confirmed by quantitative, structured and liver-specific causality assessment methods.

The pattern of damage was both cholestasis and hepatocellular in 36 cases of kava toxicity of liver; many of the patients were women, the cumulative dose and latency were highly variable, and ALF developed in 9 patients and 8 of whom underwent hepatotoxicity. The FDA started to advise consumers regarding the risk of severe injury liver associated with the use of kava-containing food supplements in the year 2002. The products kava have been banned from the markets of some countries in Europe, although they are still found in the Canada, US, Australia, New Zealand and South Pacific Islands.

The mechanism of hepatotoxicity has not been clearly explained.Moreover, no. of potential hepatotoxic constituents (i.e. pipermethystine, flavokavain B and mould hepatotoxins) and co-factors (i.e. alterations in hepatic microsomal cytochrome P450, cyclooxygenase inhibition, P-glycoprotein and glutathione) have been extensively reviewed by Teschke, Rolf, 2009. The author suggested that kava toxicity of liver is partly preventable by quality control, prescription adherence and avoidance of co-medications, because it take place primarily due to daily overdose (exceeding 250 mg of kava lactones), chronic dosing whereas the use of the kava leave, may possess the hepatotoxic alkaloid pipermethysticin, and adulterated raw material of kava .

***Atractylis gummifera* and *Callilepsis laureola* (Impila)**

Atractylis gummifera is a thistle located in the Mediterranean regions, where more than 26 *Atractylis gummifera*secrete a whitish glue-like substance often used by children as chewing gum, and also used as an antiemetic, abortifacient antipyretic and a diuretic. It is well-known toxic which is due to the presence of atractyloside and carboxyatractyloside, if taken for long time. These two

diterpenoid glucosides are capable of inhibiting mitochondrial oxidative phosphorylation by interacting with a mitochondrial protein, the adenine nucleotide translocator. Number of cases of renal and liver injury are reported which are related with intake of *A. gummifera* and they frequently involved children. This may also cause adverse effect if it is applied cutaneously. The onset of adverse effect usually commences within few hours after intake, and is characterized by vomiting, headache abdominal pain, diarrhoea, and convulsion and anxiety, which then often leads to acute failure of kidneys and liver, neurovegetative conditions and death. Compounds such as verapamil, or dithiothreitol could protect against the toxic effects of atractyloside by blocking ADP-ATP conversion through inhibition of P450 cytochrome, but only if administered before atractyloside exposure *in-vitro* experiment. New therapeutic efforts are being under way to develop polyclonal antibodies against the toxic components of *A. gummifera*.

Plants dietary supplements

Many medicinal plants products, including Noni juice (*Morinda citrifolia*), Cascara (*Cascara sagrada*), mistletoe (*Viscus album*), skullcap (*Scutellaria*), valerian (*Valeriana officinalis*), *Aloe vera*, Margosa oil (*Antelaea azadirachta, Azadirachta indica*), and food supplements, like vitamin A is also accountable to cause toxicity of liver.

Herb–Drug Interactions

Some herbs can interact with particular conventional or western medicines by no. of mechanisms which lead to damage or toxic effect such as renal toxicity, hepatotoxicity, abnormal bleeding, and cardiovascular collapse and even graft rejection. Many herbs have been identified as substrates, inhibitors or inducers of various cytochrome P450 enzymes, such as flavonoids, garlic, pepper, licorice, terpenoids, St. John's wort and anthraquinones. For example, St. John's wort is a potent inducer of CYP3A4, mediated by activation of the pregnane X receptor, which can then potentiate the intrinsic hepatotoxicity of other substances, such as germander and acetaminophen, by way of an increased conversion to toxic metabolites. It also increases plasma clearance of a number of drugs, such as cyclosporine and protease inhibitors, which can complicate the management of post-transplant immune-suppression as well as HIV and hepatitis C therapy. In addition, administration of St. John's wort significantly increased the systemic exposure and toxicity of methotrexate in a rat model. Several herbs, including Dong quai, garlic, papaya, tamarind, feverfew, and *Gingko biloba*, have been associated with an increased risk of bleeding in patients who are on warfarin or aspirin. Other herb–drug interactions may result in hepatotoxicity or significantly affect practice are summarised in Table 2.

Table 2: Herb– conventional drug interactions related to hepatology.

S.No.	Medication	Herb	Interactions and potential consequences
1.	Cyclosporin	Grape fruit juice	CYP3A4------induce toxic risk
		St.Johns wort	CYP3A4-------induce toxic risk
2.	Warfarin and aspirin	Danshen	Increase INR----- bleeding risk
		Dongqui	Increase INR------ bleeding risk
		Garlic	Increase INR---- bleeding risk
		Papaya	Increase INR -------- bleeding risk
		Tamarind	Increase aspirin level ---- bleeding risk
		Feverfew	Platelets dysfunction ------- bleeding risk
		Gingko biloba	Platelets dysfunction ------- bleeding risk
		Gingeng	Decreased INR ------- Clotting risk
		St.Johns wort	Decrease INR -------- Clotting risk
3.	CYP3A4	Pyrrolizidines	CYP3A4 induce------ hepatotoxicity
		Germander	CYP3A4 induce-------- hepatotoxicity
4.	Methotrexate	Echinaceca	Increased hepatotoxicity
		St.Johns wort	Increased methotrexate level and toxicity
5.	Prednisolone	Ginseng	Additive effect
		Glycyrrhizin	Reduced clearance---- hypokalemia
6.	Protease inhibitor	Garlic	CYP3A4-----induced optimal antiviral activity
		St.Johns wort	CYP3A4-----induced optimal antiviral activity
7.	Benzodiazepines	Kava	Increased sedative effect
8.	Spironolactone	Glycyrrhizin	Mineralocorticoid-----Low spironolactone level

5. Conclusion

Usually botanical products/supplements continue to be used on large scale all over the globe, plants hepatotoxicity shall continue to be observed. Such cascades are not necessarily unique to herbal medications as they can be seen with prescription medications such as antibiotics, anticonvulsants etc. It is therefore imperative that the recognition and reporting of herbal hepatotoxicity be held to the same standards as prescription medications.

The damage of liver is mostly hepatocellular, but mixed and cholestatic patterns can also take place. The adverse effects may ranges from mild injury to ALF in addition to evolution to chronicity. The diagnosis of botanical toxicity of liver relies on an appropriate knowledge of the available literature on toxicity of liver with the spectrum of herbal preparations intaken. The advances in the understanding of the frequency, the pathogenesis, the clinical manifestations and outcomes are required to be able to ameliorate the safety of plants medicine.

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