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# Herbal Hepatotoxicity: A Review on Phytochemical Induced Liver Injury

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**ABSTRACT**

Liver plays a key role in the metabolism and excretion of xenobiotics which makes it highly susceptible to their adverse and toxic effects. Drugs of synthetic origin are found to be major reason of liver toxicity but some herbs also contributes in same fashion. Various herbal medicines with a history of efficacy are effectively used by humans. However, owing to the presence of different phytoconstituents, which are found to be hepatotoxic, it is needed to focus on such phytochemicals. This review emphasizes some crucial aspects of phytoconstituents that produces hepatotoxicity and possible mechanism responsible for it.

## INTRODUCTION

Hepatotoxicity implies chemical-driven liver damage and the chemicals that cause liver injury are called hepatotoxins. Liver plays a vital role in bio-transformation and sometimes clearing of chemicals that are susceptible to the toxicity. Certain medicinal agents in overdoses and sometimes even at therapeutic ranges may injure the liver. Other chemical agents, such as those used in laboratories and industries, herbal remedies can also cause injury to liver cell. Most of the drugs have been implicated in causing liver damage and is the most common reason for a drug to be withdrawn from the market (Singh *et al.,* 2012). Hepatotoxicity and drug-induced liver injury of drugs of different origin is one of leading cause of compound failures, highlighting the need for drug screening assays such as stem cell-derived hepatocyte-like cells that are capable of detecting toxicity early in the drug development process (Singh *et al.,* 2012, Yildirimman *et al.,* 2011). The diseases and disorders of liver is a worldwide problem in the absence of reliable liver protective drugs in allopathic medical practices (Gurusamy *et al.,* 2009). According to the office for National Statistics in the United Kingdom, liver disease is now the fifth most common cause of death (Williams, 2006).

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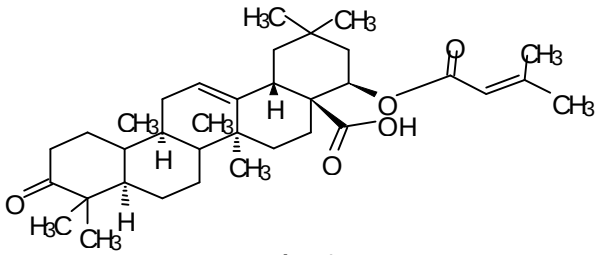
## PHYTOCONSTITUENTS OF HEPATOTOXIC POTENTIAL

***Lanata Camra* Linn**

*Family: Verbenaceae* (Garcia *et al.,* 2010).

Chemical constituents: The two major components of *Lanata camra* leaves are lantadene A and lantadene B that have ability to produce liver toxicity (Singh *et al.,* 1999, Singh *et al.,* 2003).




Lantadene A

**Mechanism of action**

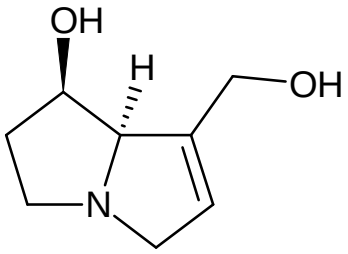
The lantana toxins after absorption, transported to the liver in portal blood. The toxins resemble cholesterol and absorption of cholesterol is known to be facilitated by esterification with cholesterol esterase, whether the lantana toxins are absorbed in native form or after modification is unknown. It has been revealed that the bile canalicular membrane is primary site of injury by the lanata toxins. Biotransformation and disposition of lantadenes in guinea pig as laboratory animal model has been investigated that showed that lantadenes could not be detected in liver, bile, gall bladder, blood and urine samples. Lantadene A, lantadene B and their reduced derivates reduced lantadene A (RLA) and reduced lantadene B (RLB) and two unidentified metabolites could be detected in the contents of lower GIT and faeces.

The intrahepatic cholestasis in lantana poisoning causes photosensitization due to retention of phylloerythrin which is normally excreted in bile and jaundice due to accumulation of bilirubin, as a result of inhibition of bile secretion (Sharma and Dawra, 1984, Sharma *et al.,* 1983, Sharma *et al.,* 1980, Sharma *et al.,* 1981, Singh *et al.,* 2011).

***Senecio vulgaris* L.**

*Family: Compositae*

Chemical Constituent: Retrorsine




Retrorsine

**Mechanism of action**

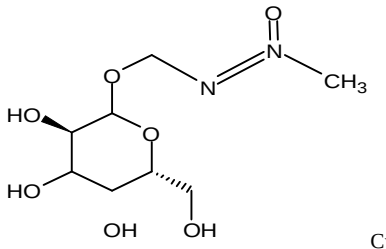
Previous study reveals that pyrrolizidine alkaloid retrorsine inhibits the incorporation of labelled amino acids into rat liver and plasma proteins in vivo. Retrorsine induced inhibition was greater and detected earlier than with aflatoxin. Both toxins affected the liver ribosomal aggregates by increasing the proportion of monomers plus dimers. The effect of retrorsine was greater than that of aflatoxin and the main site of inhibition is the ribosomes. Both toxins alter the incorporation of orotate into liver nuclear RNA (Villa-Trevino and Leaver, 1968, McIntosh *et al.,* 1976).

It also exhibits toxicity to the aminopyrine-N-demethylase enzyme system (Eastman and Segall, 1980). Retrorsine is metabolised to a reactive pyrrole by a cytochrome P450 enzyme which is a alkylating agents which can cross-link DNA thus inhibiting mitosis and protein synthesis, and can produce membrane lipid peroxidation in isolated rat hepatocytes (Morris *et al.,* 1994).

***Cycas revoluta***

*Family: Cycadaceae*

Chemical constituent: Cycasin




Cycasin

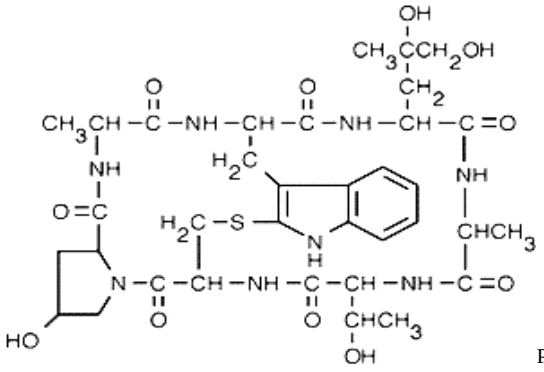
**Mechanism of action**

Cycad sago palm is extremely poisonous to animals and almost all parts of the plant are toxic. The seeds contain the highest level of the toxin called cycasin. The cycasin has ability to causes gastrointestinal irritation and in high doses leads to liver failure (Bigoniya *et al.,* 2009, Nishida *et al.,* 1956, Nishida *et al.,* 1955, Zarchin *et al.,* 2011). The chemical structure of cycasin is methylazoxymethanol-β-D-glucoside and is hepatotoxic and carcinogenic. Enzymatic hydrolysis of cycasin produces the aglycone which is mutagenic in nature (Laqueu, 1968, Morgan and Hoffmann, 1983).

***Amanita Phalloides***

*Family: Amanitaceae*

Chemical constituent: Phalloidin, Amanitins




Phalloidin

**Mechanism of action**

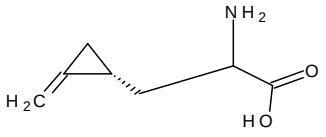
Phalloidin selectively inhibits biliary secretion and also induces a cytolytic lesion, but not a fatty liver, as in alpha-amanitin intoxication. Phalloidin causes severe liver damage characterized by marked cholestasis, which is due in part to irreversible polymerization of actin filaments, resulting in a rapid accumulation of polymerized microfilaments, which mainly occurs in the cytoplasmic region close to the canalicular plasma membrane. This further leads to reduction in canalicular contractility, loss of integrity in tight junctions, impaired vesicular trafficking and increased paracellular permeability all leading to a reduction in bile flow, the accumulation of biliary components and eventually to necrosis of liver cells. Thus, a common finding after intoxication by phalloidin is an elevation of serumbiochemical

markers of cholestasis and liver damage, such as alkaline phosphatase, transaminases and bilirubin (Pringle *et al.,* 2009, Herraez *et al.,* 2009, Santi *et al.,* 2012).

***Blighia sapida* (Ackee)**

*Family: Sapindaceae*

Chemical constituent: Two major components are Hypoglycin A and Hypoglycin B




Hypoglycin A

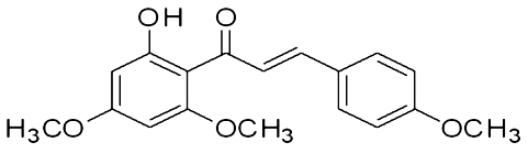
**Mechanism of action**

The unripened or inedible portions of the fruit contain the toxins hypoglycin A and hypoglycin B. Hypoglycin A is found in both the seeds and the arils, while hypoglycin B is found only in the seeds. Hypoglycin is converted in the body to Methylenecyclopropyl acetic acid (MCPA) which is toxic. The MCPA inhibits numerous enzymes involved in the breakdown of acyl-CoA compounds. Hypoglycin binds irreversibly to coenzyme A, carnitine and carnitine acyltransferases I and II reducing their bioavailability and consequently inhibiting β-oxidation of fatty acids. The β-oxidation normally provides the body ATP, NADH, and acetyl CoA which is used as supplement for the energy production by glycolysis. Inhibition of β-oxidation leads to depletion of glucose stores leading to hypoglycemia and clinically, this condition is called Jamaican vomiting sickness (Sherratt, 1986, Gaillard *et al.,* 2011, Blake *et al.,* 2006).

***Piper methysticum* (Kava)**

*Family: Piperaceae*

Chemical constituent: Three major components are Flavokavain A, Flavokavain B and Pipermethystine




Flavokavain A

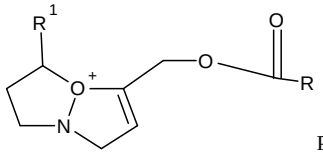
**Mechanism of action**

Flavokavain B, found in the plant's rhizome which may contribute to toxic effects. It is also known that some of the kava pyrones have ability to block several subtypes of the enzyme cytochrome P450. The pipermethystine is also known to induce hepatoxicity in humans. They also increases activities of cytochrome P450 (CYP) isoforms including CYP1A2 that are responsible for the metabolic activation of potent carcinogenic environmental toxins such as aflatoxins, benzo[a]pyrene and others (Yamazaki *et al.,* 2008, Teschk *et al.,* 2011, Whittaker *et al.,* 2008, Lude *et al.,* 2008, Behl *et al.,* 2011, Teschke *et al.,* 2009) which causes injury to liver cells.

***Comfrey***

*Family: Symphytum*

Chemical constituent: Pyrrolizidine




Pyrrolizidine

**Mechanism of action**

Pyrrolizidine is generally considered unsafe with numerous toxicological effects in animals and humans. Along with essential nutrients, comfrey also contains pyrrolizidine alkaloids (Rode et al, 2002). Pyrrolizidine alkaloids causes obstructions of the veins in the liver, known as hepatic veno-occlusion (Rode *et al.,* 2002, Roitman, 1981). Hepatotoxicity is also related to host susceptibility, total ingested dose and route of exposure (Ridker and McDermott, 1989). Numerous hepatotoxic Pyrrolizidine alkaloids with differing toxicities have been identified in the plant, including symphytine, echimidine, intermedine, symviridine, and lasiocarpine (retronecine mono and diester alkaloids). Roots contain 100-fold higher alkaloid content than the aerial portions (Rode *et al.,* 2002, Roitman, 1981, Ridker and McDermott, 1989). The rat study showed loss of perivenular hepatocytes with extravasation of red blood cells into perivenular spaces and into the perisinusoidal space of Disse. The livers were found to be enlarged, increased in consistency and finely nodular in appearance. Oxidative stress is one of the mechanism by which Pyrrolizidine alkaloids exhibits liver injury (Chojkier, 2003, Yee and Roth, 2010).

**Table. 1** : Some hepatotoxicity producing plant, their constituents and mechanisms.

| Plant | Constituent | Mechanism | References |
|---|---|---|---|
| *Lanata camra* Linn. (verbenaceae) | Lantadene A and Lantadene B | Inhibition of bile secretion | Garcia et al., 2010, Singh et al., 1999,Singh et al., 2003, Sharma and Dawra, 1984, Sharma et al., 1983, Sharma et al., 1980, Sharma et al., 1981, Singh et al., 2011 |
| *Senecio vulgaris* L. (Compositae) | Retrorsine | Causes liver ribosomal aggregates | Villa-Trevino and Leaver, 1968, McIntosh et al., 1976, Eastman and Segall, 1980, Morris et al., 1994 |
| *Cycas revoluta* (Cycadaceae) | Cycasin | Produces toxic intermediate by enzyme p450 | Bigoniya et al., 2009, Nishida et al., 1956, Nishida et al., 1955, Zarchin et al., 2011 |
| *Amanita Phalloides* (Amanitaceae) | Phalloidin | Inhibition of biliary secretion | Pringle et al., 2009, Herraez et al., 2009, Santi et al., 2012 |
| *Blighia sapida* (Ackee) (Sapindaceae) | Hypoglycin A , Hypoglycin B | Inhibits several enzymes involved in the breakdown of acyl COA compounds | Sherratt, 1986, Gaillard et al., 2011, Blake et al., 2006 |
| *Piper methysticum* (Kava) (Piperaceae) | Piperidine alkaloids Flavokavain A, Flavokavain B | Block several subtypes of the enzyme cytochrome p450 | Yamazaki et al., 2008, Teschk et al., 2011,Whittaker et al., 2008, Lude et al., 2008, Behl et al., 2011,Teschke et al., 2009 |
| *Comfrey* (Symphytum) | Pyrrolizidine | It produces hepatic veno-occlusion | Rode et al., 2002, Roitman, 1981, Ridker and McDermott, 1989, Chojkier, 2003, Yee and Roth, 2010 |

## CONCLUSIONS

Although synthetic drugs are potential cause of liver toxicity, consumption of some phytoconstituents also leads to toxicity of liver cells. Drugs of herbal origin are considered to be safe and do not exhibit any undesirable effects. Focusing on such phytochemicals and its cytotoxic mechanism might be valuable in determining role of these chemicals in normal and altered body physiology. It is needed to study molecular basis of potent hepatotoxic phytoconstituents like Pyrrolizidine alkaloids which are generally present in food.

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