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AN INSIGHT ON DRUG-INDUCED HEPATOTOXICITY W.R.T. GARAVISHA AND IT'S AYURVEDIC MANAGEMENT

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ABSTRACT

Liver is a vital organ involved in metabolism of nutrients, detoxification of drugs and xenobiotics by Drug Metabolizing Enzymes to maintain homeostasis. Liver insufficiency and drug induced hepatotoxicity are the major causes of liver disease and death worldwide. In Ayurveda, Garavisha are explained as artificial poisons prepared by mixing various substances, that takes time to get metabolised and produce toxicity in the long run. This may be prevented and managed by the usage of Yakrit Rogahara, Kamalahara, Yakrit Vriddhihara Dravyas which act as hepatoprotective agents. In this paper, an attempt is made to co-relate drug-induced hepatotoxicity to Garavisha, along with the description of a few classes of allopathic drugs, their mechanisms, and a few examples of Ayurvedic Audbhida (Ekamulika Dravyas) and Parthiva/Bhauma Dravya like Dhatu Bhasmas having hepatoprotective action.

KEYWORDS: Drug-induced Hepatotoxicity, Garavisha, Yakrit rogahara, Hepatoprotective, Dhatu Bhasma.

INTRODUCTION

Liver is a multifunctional organ situated in the right hypochondriac region. It performs varieties of biological and metabolic functions in the body. It has a vital role in the metabolism of absorbed nutrients, secretion of bile and bile pigments, synthesis of plasma proteins and mainly detoxification of xenobiotics Drug Metabolizing Enzymes.[1] Drug-induced hepatotoxicity is an acute or chronic liver injury secondary to drugs.[2] Liver insufficiency and drug induced hepatotoxicity are a major causes of liver disease and death worldwide. The Hepatotoxicity can occur by several mechanisms such as Cytochrome P450 activation, lipid peroxidation, Glutathione inhibition, induction of nitric acid synthesis, mitochondrial dysfunction, activation of pro-inflammatory mediators and bile acid-induced liver cell death, etc.[3]

Visha is defined as a substance which when enters in the body, vitiates Dosha-Dhatus and produces ill effects or death of an individual. According to Ayurveda Samhitas, it has three types- Sthavara, Jangama and Gara visha. Sthavar visha is of plant origin. Jangam visha is of animal origin. Gara visha (Artificial Poison) is the type of Samyogaja visha (Unnatural poison or chemically prepared poison) which is prepared by the combination of either poisonous or non-poisonous substances. According to Chakrapani commentary Garavisha is termed as Nirvisha Dravya Samyog Krut. In classical review direct reference of drug induced hepatotoxicity is not found but it may be considered that, this form of toxicity may be included in Gara visha (Kritrim visha).[4] Liver disorders are considered as Yakrit-vikara in ayurveda. For such disorders, the Acharyas have mentioned various groups of drugs in the Brihatrayee and Laghutrayee under different groups such as Yakrit-Vikarahara Gana, Kamalahara Gana, Yakrit-Vriddhihara gana, etc. Various Rasa Dravyas are also mentioned in the Rasa Granthas which are said to be hepatoprotective These drugs have been proven to show hepatoprotective, hepatotropic effect in the body, thereby, restoring the liver health.[5]

Hence, in this paper, an attempt is made to co-relate drug-induced hepatotoxicity to Garavisha, along with the citing of a few classes of allopathic drugs and their mechanisms in causing drug-induced hepatotoxicity, and description about a few Ayurvedic Herbs and Dhatu Bhasma having hepatoprotective action which may be taken for further evaluation in term of clinical validation in future.

MATERIALS AND METHODS

Various printed materials, online journals, research articles were referred, and the matter was arranged systematically.

Drug-Induced Hepatotoxicity

Liver has a significant function of xenobiotic metabolism in which exogeneous lipophilic xenobiotics are converted to hydrophilic compounds via biochemical processes catalysed by cytochrome P_{450} enzyme systems. The metabolic products obtained are then actively transported by hepatocyte transporter proteins into the plasma or bile for excretion by the kidney or gastrointestinal tract. However, sometimes, these xenobiotics produce reactive or toxic metabolites or electrophiles that bind covalently to hepatocytes, resulting to changes in protein conformation, DNA mutation or induce lipid peroxidation respectively, thereby leading to hypersensitivity reaction or liver necrosis. This is known as drug-induced injury or chemical injury.[6]

Classification of Drug-Induced Liver injury (DILI) or hepatotoxicity

DILI is commonly classified into intrinsic and idiosyncratic hepatotoxicity. Intrinsic hepatotoxicity is regarded as dose-dependent and predictable above an approximate threshold dose, whereas idiosyncratic hepatotoxicity occurs without obvious dose-dependency and in an unpredictable fashion.

Grossly, the hepatotoxic reactions are of three types- Hepatocellular (which consist of hepatocellular necrosis), Cholestatic (with or without inflammation), and mixed or miscellaneous.

Mechanism of Drug- induced hepatotoxicity

A major cause of hepatotoxic reactions may be drug-induced intrahepatic cholestasis. The vital roles of ROS in the cellular damage are widely investigated and it has been suggested that the covalent binding of ROS as well as reactive intermediates to macromolecules could likely contribute to the severe harmful drug reactions. There are several studies that suggest the generation of reactive metabolites and free radicals from hepatotoxic drugs. Membrane lipid peroxidation is directly related to the depletion of tissue GSH (an intracellular antioxidant) leading to the altered functional integrity of these structures and if the damage is severe, it could be fatal. Membrane lipid peroxidation may lead to alteration in membrane fluidity and permeability, enhanced rates of protein degradation, and ultimately cell death. The assumption is upheld by the way that oxidative damage to erythrocytes causes loss of membrane capacity by enhancing lipid peroxidation (LPO) and modifying the erythrocyte antioxidant framework. The concentration of intracellular GSH, therefore, is the key determinant of membrane integrity and the extent of toxicant-induced hepatic cell injury.

Specific Class of Drugs and their role in Hepatoxicity-

1. Analgesics

- **Paracetamol –** It is a commonly used analgesic and antipyretic which contains acetaminophen as the active ingredient, which has been shown to be well-tolerated in the prescribed dose but in the event of overdose, liver damage occurs. This is because, acetaminophen metabolism catalysed by cytochrome P_{450} enzymes in the liver produces N-acetyl-p-benzoquinemine(NAPBQI)- a highly reactive (toxic) intermediate metabolite. During acetaminophen's overdose, a high concentration of the toxic metabolite is produced, and thus overwhelms the detoxification process, leading to hepatocellular necrosis.[7]

2. NSAIDS (non-steroidal anti-inflammatory drugs)

- **Diclofenac -** Diclofenac is glucuronylated and subjected to cytochrome p450-mediated reactions that result in bioactive products. Both reactive metabolites and immune mechanisms mediate toxicity. Decreased prostaglandin synthesis due to cyclooxygenase (COX) inhibition may also enhance injury. Chronic diclofenac administration may result in elevated ALT levels in the first four–six months of therapy, but severe toxicity has also been reported.[8]
- **Methotrexate –** Use of high-dosage methotrexate or for prolonged duration may result in hepatoxicity which may further lead to fibrosis and cirrhosis. The mechanism includes oxidative stress which increase the generation of reactive oxygen (ROS) and nitrogen species, inhibits cytosolic NADP-dependent dehydrogenase and NADP malic enzyme, which reduce the levels of glutathione, superoxide dismutase, catalase and finally reducing the effectivity of the antioxidant defence system protecting the cell against ROS. The altered balance between ROS production and antioxidant defences leads to oxidative stress.

3. Anti-tubercular drugs

- **Rifampicin-** Rifampicin is a potent inducer of cytochrome P450 action and enhances the covalent binding of reactive metabolites of acetyl hydrazine to the macromolecules of hepatocytes leading to hepatic cell damage. Prolonged exposure significantly could be a reason for the increased level of lipid peroxidation. Anti-tubercular drugs increase intracellular calcium concentration. Additionally, CYP2E1 activation and fatty acid accumulation in the liver either due to excessive supply of lipids to the liver or interference with lipid deposition, has been documented in the anti-tubercular drug-induced liver disorders.[9]

4. Anti-retroviral drugs

The therapeutic action of highly antiretroviral drugs (HAART) used in the management of human immunodeficiency virus (HIV) under various pathways and their adverse effects are localised in the hepatic cells. They cause hepatic mitochondrial dysfunction or acute mitotoxic effect or oxidative stress depending on the drug used.[10]

Ayurvedic Concept of Garavisha (Chronic toxicity)

Garavisha is considered as Kritima Visha(artificial poison) which is a Samyogaja Visha prepared by combinations of various substances(poisonous or non-poisonous). It exerts toxic effects after an interval of sometime and as such does not kill the patient instantly. In the classics, Gara Visha is said as kalantara-avipaki, meaning, it takes time to get metabolised and produce chronic toxicity. The line of treatment includes Shodhana particularly Vamana, followed by Suvarna Prashana, treatment of Mandagni, and various Agadapana. The main emphasis is laid on eliminating the toxins from the body through detoxification process and restoring the normalcy by the judicial use of pacifying medications followed by rejuvenation process.

Drug-Indued Hepatotoxicity w.r.t Garavisha

Various experimental and clinical trials on humans and animals have explained the hepatotoxicity resulting due to prolonged or overdose usage of certain pharmaceuticals. Garavisha explained in the ayurvedic classics are said to show chronic toxicity due to intake of combination of various poisonous or non-poisonous substances which are artificially prepared, for a long duration of time. This concept of Garavisha may be co-related with drug-induced hepatoxicity as the latter is known to be caused due to intake of artificially prepared drug, taken as a single drug or in combination, for prolonged duration or in overdosage. The concept of Kalantara-avipaki in terms of drug-induced hepatotoxicity may be substantiated as both garavisha and the pharmaceutical drug takes some interval of time to get metabolised in the body and show chronic toxicity.

List of a few Ekamulika Dravyas acting as Hepatoprotective agents

- **Haritaki (Terminalia *chebula*) –** Haritaki is one among the triphala, which is the most used drug in the ayurvedic practice. It has Lavanavarjita Pancharasa and is Tridoshahara. Kamalahara, Anulomaka, Doshasamshodhaka, etc are a few Karmas of it. Haritaki has chebulagic acid as its major phytoconstituent. A study has shown that administration of Haritaki fruit extract inhibited the expression of MDR1(multidrug resistance -1) by preventing ROS(reactive oxygen species) generation and COX-2(cyclo-oxygenase-2) expression. This may prevent the neoplastic changes leading to hepatocarcinoma. Hence, Haritaki is an efficient hepatoprotective drug.[11]
- **Katuki (*Picrorhiza kurroa*) –** Katuki is said to have Tikta Rasa (bitter), Laghu and Ruksha Guna, Sheeta Virya and Katu Vipaka. It is Kapha-Pittahara. Katuki is Yakrit-uttejakara, Deepaniya, Kamalarogahara, Yakritvikarahara. It has been reported that flavonoids, triterpenes, alkaloids, and coumarins may be responsible for their hepatoprotective, hypolipidemic and antioxidant effects. Picrorhiza extract prevents Liver cell damage by prevention of uncontrolled propagation of free radicals. It was found that picroside-I and kutkoside inhibited the non-enzymatic generation of O2-anions, oxidative malonaldehyde (MDA) and scavenged superoxide (O2) anions. The extract helps hepatocytes to repair their intracellular glutathione stores after any type of injury or infection.[12]
- **Guduchi (*Tinospora cordifolia*) –** Guduchi is commonly used in Ayurvedic practice. It is having Kashaya and Tikta Rasa, Laghu and Snigdha Guna, Madhura Vipaka, Ushna Virya. Hence, it is Doshatrayahara. The major phytoconstituents are Giloin, Tinosporide, Cordifolide, Tinosporon, Cordifol, Hepatocosanol, etc. The Kamalahara (hepatoprotective) action is established by various experimental and clinical studies. As per study done, administration of aqueous stem extract and aqueous leaves extract along with the lead nitrate increased the activities of SOD (superoxide dismutase) and CAT (catalase) and decreased the levels of AST (Aspartate aminotransferase), ALT (Alanine aminotransferase), ALP (Alkaline phosphatase), and ACP (Acid phosphatase) enzymes in mice and acted as potent Hepatoprotective.[13]
- **Bhringaraja (*Eclipta alba*) –** Bhringaraja is a wonder herb useful in various ailments. It has Katu, Tikta Rasa, Laghu and Ruksha Guna, Ushna Virya and Katu Vipaka. It is said to be Kapha-vatahara in nature. The experimental study conducted by Naik et al., on albino rat models treated with high fatty diet to investigate the hepatoprotective activity of E. alba (Bhringaraja) demonstrated that phytochemical constituents such as Wedelolactone, demethylwedelolactone, and saponins are associated with hepatoprotectivity. It was found that these phytochemicals significantly reduced the fat deposition, mononuclear infiltration, and necrotic foci. Regeneration of hepatocytes in the liver was also stimulated by these phytochemical constituents. In another study, paracetamol was used to induce hepatotoxicity in the models. Alcoholic and aqueous extracts were comparatively investigated. It was found that alcoholic extract of E. alba has more potent hepatoprotective activity.[13]
- **Tumbaru (*Zanthoxyllum alatum*) -** Barks and fruits of Tumbaru are commonly used in Ayurveda practices. It has Katu and Tikta Rasa, Laghu, Teekshna and Ruksha Guna, Ushna Virya and Katu Vipaka. It is Vata-kaphahara. Also, Tumbaru is Yakrit-uttejaka and Pleeha Rogahara. As per study done in CCl4 induced hepatotoxicity in rats, ethanolic extracts of bark of *Zanthoxylum alatum* at doses of 100, 200, and 400mg/kg were administered orally once daily for 7 days, significantly increased the levels of antioxidant enzymes: superoxide dismutase, catalase and glutathione and act as significant hepatoprotective by lowering biomarkers of hepatotoxicity like SGPT, SGOT, ALT, Bilirubin etc. Phytochemical analysis revealed the presence of isoquinoline alkaloid, berberine, flavonoids and phenolic compounds, which are responsible for their hepatoprotective activities.[14]

Dhatu Bhasma in Liver Disorders

Not only the Audbhida Dravyas but also the Parthiva/Bhauma Dravyas such as the Dhatus (Metals) in their Bhasma(incinerated) form have shown their action on Yakrit (Liver) by its Guna-Karma and Prabhava.

- **Tamra Bhasma**- Ashuddha Tamra Patras are subjected Shodhana, Marana and Amriteekarana to obtained Shuddha Tamra Bhasma which possesses Tikta, Kashaya, Amla Rasa; Snigdha, Laghu Guna; Ushna Veerya and Madhura Vipaka. It is indicated in various Vyadhis such as Visha, Yakrit Vikara, Pandu, Sthoulya, Netra roga, etc along with the Roganusara Anupana (Adjuvents).[15] Rasagranthas mentions the dosage as 1/8 – ½ Ratti.[16] Tamra Bhasma along with Trikatu Churna and Madhu(Honey) for 1 week is indicated in case of Yakrit-Vriddhi.[17] Tamra Bhasma mainly acts on Yakrit-Visheshata Pittashaya. Due to its Saraka guna, it induces the Srava/Sarana of Dosha and clears the Avarana.It has its action over Pleeha-Yakrit Vriddhi, Arbuda, Granthi, etc. Acts on Kapha, Rasa, Rakta, Mamsa Dhatu, Yakrit, Pleeha, Grahani, Pakvashaya, etc. It is Atyanta Teekshna, Ugra, Ushna, Pittasravi. Hence it needs to be used along with other Aushadha along with the observance of Pathya-Apathya.[18]
- **Loha Bhasma**- Ashuddha Loha Patras are purified, incinerated and obtained in its Bhasma form which possesses Tikta, Kashaya Rasa; Ruksha, Guru, Lekhana Guna; Sheeta/Ushna Veerya and Madhura Vipaka. Karma includes Lekhana, Vrishya, Rasayana, Chakshushya, Medhya, Varnya, Yogavahi, etc.[19] Loha Bhasma has meticulous benefits in Pandu, Shula, Arshas, Kamala, Yakrit-Pleeha Roga, Hridroga, Amavata, etc Vyadhis along with suitable adjuvents. The dosage is ¼-2 Ratti.[20] In Case of Yakrit-pleehavriddhi Loha+Tamra Bhasma can be taken together. Loha Bhasma due to its Prabhava acts on Rakta Dhatu, and aids in enhancing the Guna-Karma-Pramana of Rakta in Sharira. Also removes Nistejata of Rakta. It mainly acts on Tridosha, Rakta, Mamsa, Sarva Dhatu, Hridaya, Yakrit, Pleeha.[21]
- **Mandura Bhasma**- When iron is heated red hot and hit with heavy hammers in factories and in blacksmith's workshop, the 'rust' at the surface of the iron falls off to the ground. After a few years, this rust is obtained as solidified iron-rust, which is identified as 'Loha Mala' or 'Mandura'. Mandura Bhasma is Vrishya, Sheeta Guṇa Yukta. It is Ruchikaraka and Agnideepaka, Pittahara. It is indicated in Pandu roga, Kamal roga, Shosha roga, Shotha roga, Halimaka roga and Pleeha vriddhi.[22] 1/ 4 ratti to 2 ratti is the dosage.[23] It is Sheetala, Soumya, Kashaya Guna Yukta and acts on Rakta and Raktanu in Sharira. Mandura Bhasma increases the Hb%, this in turn acts on Hridaya, gives it Bala and Dasha Dhamanis and regulates the Rasa-Rakta Gamana in these Dhamanis thereby reduces Shotha and Pandu, Kumbha-Kamala. In case of Yakrit-Pleeha Vriddhi in Baala, it reduces the Vriddhi and does Bala Vardhana. Mainly acts on Pitta, Rakta, Mamsa, Majja, Yakrit, Pleeha, Phupphusa, Hridaya, Agnyashaya.[24]

DISCUSSION

Pharmaceuticals primarily serve as therapeutic agents in the management of various disorders, but over-dependency or illicit consumption of drugs results in hepatotoxicity which confers a detrimental effect on liver. Various ayurvedic drugs are said to be potential sources for new therapeutic agents that could be used in the prevention of hepatic injuries. Several Phyto molecules including flavonoids, alkaloids, glycosides and saponins obtained from various plant sources have been reported as potent hepatoprotective agents in experimental liver-injury cell and animal models. The basis behind the protection provided by the natural herbs is hypothesized to be their antioxidant property through which they remove the free radicals from the cellular environment and therefore provide protection against ROS mediated damage to membrane lipids and macromolecules. The protective potential of herbs is also contributed by its interaction with various CYP isoforms, its capability to increase GSH biosynthesis, level of Phase II/antioxidant enzymes and to inhibit the entry of toxins to the cells.

Acharyas have said Garavisha as kalantara-avipaki and has chronic toxicity. Though there is no direct reference of drug-induced hepatotoxicity in the ayurvedic classics, it may be co-related with garavisha as prolonged usage or overdosage of certain drugs have shown hepatoxic effects which may be similar to the concept of garavisha. Hence in this condition, Yakrit Rogahara Dravyas, Kamalahara Dravyas and Yakrit-uttejaka Dravyas may show significant effect.

Yakrit being the Moola of Raktavahasrotas, Rakta and Pitta have Ashraya Ashrayee relationship. Hence most of the Yakrit Vikaras (liver diseases) have Pitta and Rakta Dushti(vitiation). Kamalahara or hepatoprotective action of drugs mentioned under Yakrit-vikarahara or Kamalahara are basically due to Pittashamaka or Yakriduttejaka (chloretic) or Pitta- saraka (cholagogue) or Anuloman or Rechaka (laxative or purgative) properties. Multiple experimental studies suggest that various Dhatu Bhasmas have shown hepatoprotective activity by acting on Drug- induced elevation of levels of SGOT, SGPT and alkaline phosphate etc. These Bhasma act by their Guna-Karma and Prabhava. They are said have meticulous potency as they are subjected to Shodhana, Marana, Amriteekarana, etc procedures along with other herbal drugs.

CONCLUSION

Yakrit or liver is a major vital organ having various functions and prone to various type of disorders due to different biological, physical, chemical and genetic factors. Drug-induced hepatotoxicity may be co-related with garavisha which is chronic toxicity. It is important to recognize and remove the offending agent as quickly as possible to prevent the progression to chronic liver disease or fulminant hepatic failure. The expanding prevalence and effectiveness of Ayurveda in the

treatment of various disorders led the investigators to look into their potential in countering drug-induced liver toxicity. Hence, these drugs may be taken for further evaluation in term of clinical validation in future.

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