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A REVIEW ON HEPATOPROTECTIVE ACTIVITY OF PUNICA GRANATUM LINN

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ABSTRACT

This review article focuses on the hepatotoxic substance, chemicals, various reasons contributing to liver ailments causing fatal effects. It presents a number of drugs, herbal formulations and their mechanism in causing liver injuries. Alongside this article also proposed various plants, herbs, synthetic products which alters the toxic hazards caused to liver, one of which is Punica granatum (pomegranate).The chemical constituents present in punica such as polyphenols, alkaloids, flavonoids and their wide range of therapeutic effects mentioned here, further the role of antioxidant property of punica plays a vital role in hepatoprotective activity of Punica granatum.

KEYWORDS: Punica granatum, Alanine transaminase (ALT), Alanine phosphatase (ALP), Aspartate aminotransferase (AST), Superoxide Dismutase (SOD), Tumor Necrosis Factor (TNF alpha), Interleukins (IN's).

INTRODUCTION

Liver operates a wide variety of cycles such as the deamination, transamination, physiological reactions via producing urea, liver enzymes alter TCA cycle, Lipid metabolism and metabolism that is first pass metabolism of each drug taken orally takes place in liver. Continuous consumption of medicines leads to poisonous reactions in the liver to which alcohol consumption additionally helps also agents such as viruses, chemicals, alcohol, and

auto-immune ailments. Liver additionally carries out fat metabolism in which hepatocytes, the liver cells converts fats into energy and destroys extra amount of bilirubin produced by means of breakdown of old and worn-out RBCs.[2] Hence it's an important aspect to keep the liver healthy and fit, but by different conditions and factors it is prone to toxic substances of the environment, and abused by using negative drug habits, alcohol, and prescribed over the counter tablets which can subsequently lead to one-of-a-kind liver illness such as hepatitis, liver scarring, fibrosis. Alcohol consumption accounted for 3.3 million deaths in 2012, World Health Organization 2014. WHO 2014 Global popularity record on alcohol estimates that 50% of all death instances are by means of cirrhosis due to alcohol abuse.

Thus, damage to the liver due to liver ailments is a wide cause today.[1,3] India is recognized to have a giant burden of viral hepatitis. It impacts about 400 million humans globally and each year 6 to 10 million human beings are newly contaminated. About 1.4 million humans die every 12 months from hepatitis.

Fig. 1: Stages of liver damage.

- **Substances inflicting hepatotoxicity:**

1) Herbs and nutritional supplements

Herbs and nutrients as diet supplements are consumed for weight loss, diabetes, growth immunity, bodybuilding etc. About 40% of human beings now do not expose the use of natural dietary supplements and their products use .Sometimes natural drug supplements are additionally adulterated with prescription pills such as steroids, growth hormones, thyroid hormone for weight loss , phosphodiesterase inhibitors etc.[8,9]

E.g.: The latest study indicates that lipokinetix, a combination of chemical compounds

together with extract from a specific tea for the motive of weight loss by means of growing metabolism, causes hepatitis, stomachache and the person suffers after three months of use.

It includes ephedrine-like stimulants, a kind of thyroid hormone and tea extract. FDA is not involved in manufacturing of natural dietary supplements, as a result their purity is decided solely by their manufacturer.

Herbal substances lead to liver scarring ending up to liver failure, inflammation to biliary ducts, macro- and micro vesicular steatosis and vascular malformations. In addition, several reasons make hepatotoxic to natural plants: mistake in identifying the plant, the phase at which the plant contains highest medicinal value is not detected properly, improper storage conditions for native product, contamination during manufacturing and mislabeling of products .Additional reason is misunderstood composition of natural substances particularly in multi-compound products. Contamination of natural products due to heavy metals, biopesticides, herbicides, various chemicals, even microorganisms make the substances toxic in nature.

Accordingly, more than a hundred plant preparations have been screened as toxic to the liver. The main liver damage caused due to pyrrolizidine alkaloids is venous obstructive disease called sinusoidal obstruction syndrome (SOS). Pyrarolizidine alkaloids accounts for a large number of cases upto 8000 cases globally. Marketed formulations causing DILI (Drug Induced Liver Injury) consist of OxyE-LITE used for weight reduction and body building consists of substances (dimethylamylamine, aegeline), Hydroxy-cut prohibited in market (containing inexperienced tea, ephedra) leads to increase in liver toxicity and cardiovascular risk.[10 ,11]

2) Drugs causing hepatotoxicity

Table 1: Table causing hepatotoxicity.

Sr. No.	Drugs	Toxic effects on liver
1	Rifampicin	Induces oxidative stress by free radicals Formation. Alters the membrane permeability.
2	Isoniazid	Inhibits Glutathione levels, generates Reactive Oxygen Species, binds to liver macromolecules and cause damage.
3	Acetaminophen	Reduces the amount of the antioxidant enzyme Superoxide dismutase (SOD), deplets glutathione.
4	Pyrogallol	It shows auto-oxidation property contributing to 8 Oxidative stress.
5	Diclofenac	T-cells induced liver injury by inflammatory response

6	Statins, Lovastatins	Functional abnormalities in liver.
7	Amiodarone	Disturbs the lysosomal/ mitochondrial dysfunctions Damages lipid bilayers of hepatocytes
8	Oral contraceptives	Hepatic adenomas, carcinoma, cholestasis Risk of gallstones formation.
9	Antibiotics: Ciprofloxacin, Erythromycin etc.	Idiosyncratic drug reactions in the liver

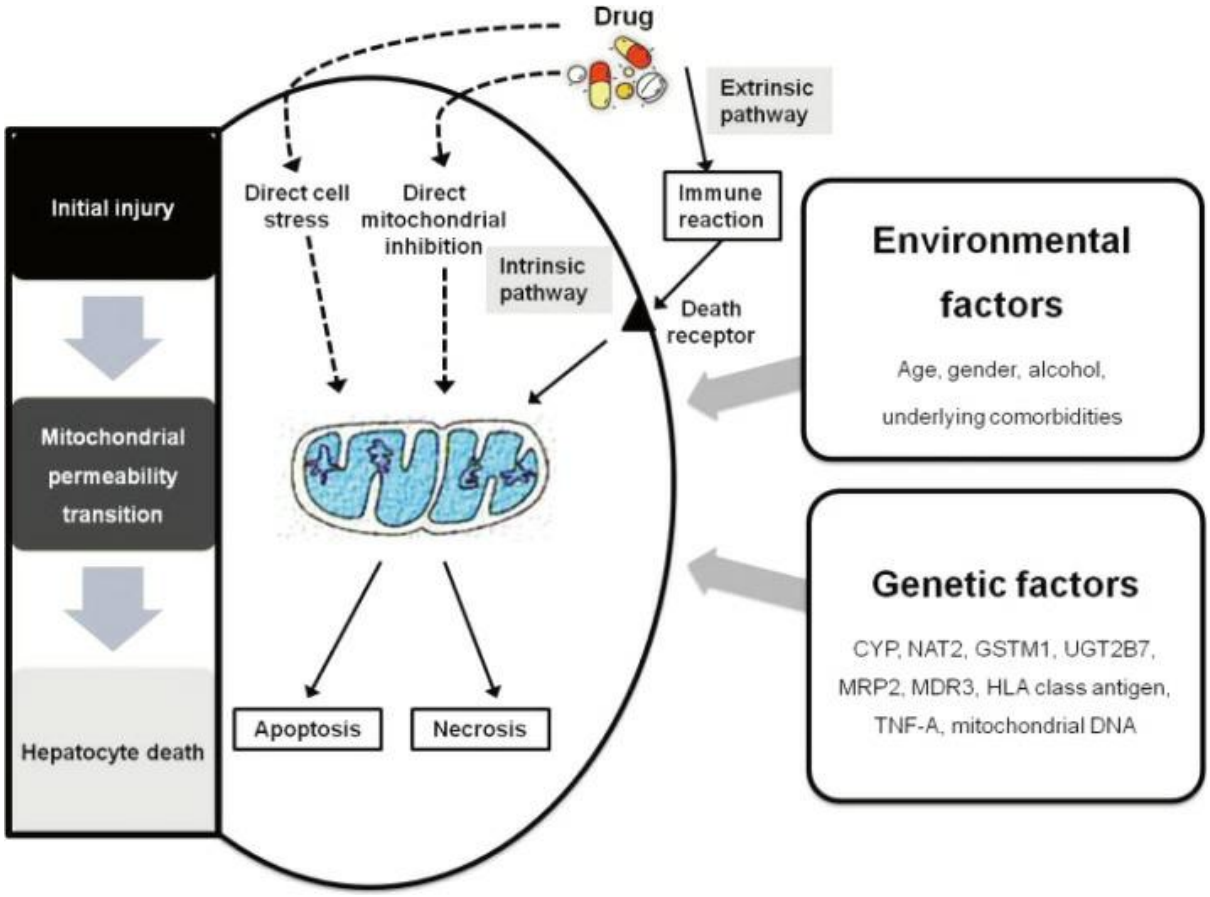

Fig. 2: Mechanism of liver injury by drugs and herbal products.

- **Herbal plants extracts and drug treatments used for liver safety:**[30,32,33,35,36]

Majority of liver disorders are treated using plant-based treatments. According to the World Health Organization (WHO), a maximum of 80 percent of the global population depends on medicinal plants for primary sources of health benefits. The WHO has mentioned that around 21,000 plant life are used for medicinal purposes. In India more than 87 flowers are used of which 33 plants have sole multi elements and are patented.

Figure 3: Pomegranate.

Table no. 2: Herbal plants used in hepatoprotection.

Plant name	Active constituents	Liver protective effect
Silymarin	Silybin, Silybinin, Isosilybin, Silydianin	Increase glutathione levels to combat antioxidant effects.
Ginseng	Ginsenosides Rc, Rd, and Rg_3	Suppresses the formation of inflammatory cytokinin's like TNF alpha, INs.
Green tea	Polyphenols, catechins, flavonoids	Strong antioxidant effect, degrades the free radicals.
Astaxanthin	It is a carotenoid	Raises antioxidant enzyme superoxide dismutase (SOD) and Glutathione amount.
Licorice	Glycyrrhizic acid, beta–Glycyrrhetic acid.	Suppresses TNF alpha and coagulates free radicals, Anti- apoptotic effect.
Turmeric	curcumin	Reduce TBARs levels and oxidative stress.
Garlic	Allicin, DADS, DATS	Anti-inflammatory Anti-oxidant effects
Danshen	Salvia, miltiorrhiza, tanshinol, salvianolic acid	Anti- fibrogenesis, Aids in lipid metabolism.
Ginkgo biloba	Flavonoids (kaempferol, quercetin), Ginkgolides A,B,C.	Regulates serum liver enzymes levels , reduces lipid oxidation.
Withania Somnifera	Withaferin A	Anti-fibrotic agent free radicals scavenger property.

- **Pomegranate**

Pomegranate is a deciduous shrub locality with Iran and one of the biggest producers in the world. It is also developed in neighboring countries from central Asia to Himalaya, Middle east followed by the Eyalet of Anatolia and Mediterranean Sea. Now its cultivation is spread

worldwide into countries such as India, Spain, America, Morocco, and Greece. Kandahar is famous for its superior quality of pomegranate in Afghanistan. Pomegranate is grown in varied climatic conditions and is suited for all types of soil. The favorable conditions include deep sandy clay soil and long hot summers for enhanced quality of fruit. It is a non-climatic plant and hence collection is done when fruit is fully ripening. Pomegranate requires 4 - 5 year to reach bearing stage and harvesting should be done only after immediate maturation stage, less or over developed fruit affects quality. The fruits can be picked after 120 - 130 days of fruit set.[47,48] Besides being used as a fruit, Punica granatum L, now not only has the attention of the public, but its food business and therapeutic properties are also gaining research interest. As a result, broad research studies have already been started in this subject. However, there isn't enough research on medicinal uses of its parts such as Flowers, leaves, newly formed barks, bark of young shoots and roots, fruit peel, and pomegranate sauce have been anciently used.

- **Assessment role of punica in hepatoprotection**

Several studies have been carried out in experimental animal models of mice to conclude the hepatoprotective activity of Punica granatum.

Hepatotoxic agents which are commonly known for their hazardous effects on liver such as Carbon tetrachloride (CCl_4) and D- galactosamine (D-GalN) are used to produce toxic effects on liver; CCl_4 elevates the liver enzymes Alanine transaminase (ALT), Alanine phosphatase (ALP), Aspartate aminotransferase (AST) and bilirubin along with protein levels of liver. Likewise, D- GalN shows toxic effects by inhibiting uridine nucleotides and RNA synthesis further leading to cell necrosis. Various studies and articles proposed that the administration of Punica granatum leaf or peel extracts to CCl_4 or D-GalN induced toxic mice in dose range of 250-500 mg /kg body weight regulates the elevated enzymes ALT, ALP, AST, protein levels to normal range thus counteracting the effect of toxic CCl_4 and D_GalN. Punica granatum possesses strong hepatoprotective effects, antioxidant and anti-inflammatory effects. It has high proportions of polyphenols, flavonoids (kaempferol, quercetin, luteolin), Anthocyanins (delphinidin, cyanidin, pelargonidin). Juice consists of polyphenols (0.2-1%), seeds contain high amount of tannins such as ellagic acids, punicalin, gallic acid. The polyphenols are known as strong antioxidants so they reduce the oxidative stress in liver by free radicals formation leading to liver injury. Also, flavonoids quercetin and rutin are scavengers of reactive oxygen species (ROS). Punica extract balances the glutathione,

catalase , peroxidase and SOD levels in the liver which are auto anti-oxidant of the body. The mechanism by which Punica granatum reduces the oxidative stress is that it has electron donor activity. Punica granatum donates the electrons to the free radicals generated in oxidative stress thus counter act and reduces their injuries to the liver. Thus, this antioxidant mechanism of P granatum makes it active in hepatoprotection. Also, its anti-inflammatory property inhibits the production of inflammatory modulators of the body such as cytokinin's, TNF alpha, IN's stopping further damage to liver.

Pomegranate fruit contains therapeutic properties, including anti-inflammatory and antimicrobial effects. The risk of breast and skin carcinomas is reduced by the use of pomegranate seed oil. The phenolic components are in large amounts in the fruit part with principle antioxidant action, on the other hand the seed oil contains Phyto estrogenic chemicals. Pomegranate fruit and bark are used to treat intestinal parasites, dysentery, and diarrhea. The juice and seeds are used as a throat and heart tonic. It's used to treat hemorrhoids and stop nose and gum leaks. The edible part of the fruit has tannins, vitamins sugars, acids, essential minerals starch and flavon compounds. In Ayurvedic medicine system, the pomegranate is mentioned as "a pharmacy unto itself" and is used to fight against parasites, often called, a "blood tonic," and to heal aphthae, diarrhea, and ulcers. P. granatum is also therapeutic for diabetes treatment in the Unani system of medicine practiced in the Middle East and India.

Recent studies on P granatum shows that it also possesses cardio protective properties due to presence of tannins, ellagic acid, ellagitannins and also daily intake of Pomegranate juice reduces hypertension and formation of atherosclerosis plaque. Currently studies are being carried out on therapeutic effects of P granatum on COVID 19 virus.

In vitro studies suggest that P granatum may inhibit the replication of COVID 19 virus.

In future the potency of P granatum may be checked against protein synthesis, replication of COVID 19 virus, mild to high cough, lung damage, deprived oxygen levels, complete blood count alterations caused by COVID 19 virus.

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