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ROLE OF AYURVEDA IN DRUG INDUCED RENAL AND HEPATIC DISORDERS

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ABSTRACT

Hepatotoxicity and Nephrotoxicity is one of the most common liver and renal problem in present era respectively and occurs when body is exposed to a drug or toxins. Exposure to chemical agents like aminoglycosides, NSAID, ethelene glycol, carbon tetrachloride, sodium oxalate and heavy metals such as lead, mercury, cadmium and arsenic induces nephro and hepatotoxicity. Medicinal plants may serve as a vital source of potentially and liver problems. Many herbs have been proven to be effectual as hepatoprotective and nephroprotective agents while many more are claimed to be nephro and hepatoprotective but there is lack of any such scientific evidence to support such claims. Siylmarin a flavonol ligan mixture extract from the silybum marianum (milk thistle) is a popular remedy for hepatic diseases. Several hundreds of plants have been examined for use in a wide variety of liver and renal disorders. **Silymarin- Silybum *marianum* , Picroliv- *Picrorrhiza kurroa(katuki)*, Andrographiloid- *Andrographis paniculata (bhunimb)* ,Phyllanthin- *Phyllanthus niruri (bhumyamlaki)*, Wedelolactone- *Eclipta alba (bhringraj)*, Glycyrrhizin – *Glycyrrhiza glabra (yashtimadhu)*, Curcuminoids – *Curcumalonga (haridra)***.The present review is aimed to elucidate the list of hepato and nephroprotective medicinal plants which are scientifically proved in treating renal and hepatic disorders[1]

Keywords: Ayurveda, *katuki*, *bhunimb*, *bhumyamlaki*,*bhringraj*,*yashtimadhu*,*haridra*

INTRODUCTION

Drugs are an important cause of liver injury. More than 900 drugs, toxins have been reported to cause liver injury. Drug induced hepatic injury is the most common reason cited for withdrawal of an approved drug. The manifestation of drug induced hepatotoxicity is highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure.

In India, approximately 5000 cases of acute liver failure occur annually and drugs account for over 50% of them(39% are due to acetaminophen,13% are idiosyncratic reaction due to other medication) The hepatic injury have remained a challenge to medical profession, since many of them may ultimately lead to irreversible changes. Ayurvedic herbals and herbo mineral drugs can play an effective role in treating certain liver disorders including hepatic injury.

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Among the several medicinal plants, *katuki, kalmegh, amalaki, yashtimadhu, sarpunkha* has shown better result

DRUGS THAT MAY CAUSE LIVER DYSFUNCTION OR DAMAGE

The liver is the principal organ that is capable of converting drugs into forms that can be readily eliminated from the body. Given the diversity in use today and the complex burden they impose upon the liver, it is not surprising that a broad spectrum of adverse drug's effects on liver functions and structures has been documented. The reactions range from mild and transient changes in the results of liver function tests to complete liver failure with death of the host. Many drugs may affect the liver adversely in more than one way, as cited below in several listings. The use of the following drugs requires careful monitoring of their effects on the liver during the entire course of treatment.

This list is just a general guideline. Many drugs affect the liver to one degree or another and we can't list all of them here; new drugs are always being approved for general use. Read the accompanying literature with your prescriptions and always consult with your doctor or pharmacist about any new medication if you have liver disease![2]

Drugs that may cause **ACUTE DOSE-DEPENDENT LIVER DAMAGE** (resembling acute viral hepatitis)

- acetaminophen
- salicylates (doses over 2 grams daily)

Drugs that may cause **ACUTE DOSE-INDEPENDENT LIVER DAMAGE** (resembling acute viral hepatitis)

. acebutolol . indomethacin .phenylbutazone . allopurinol . isoniazid . phenytoin . atenolol . ketoconazole . piroxicam carbamazepine		. labetalol . probenecid . cimetidine . maprotiline pyrazinamide .dantrolene .metoprolol .quinidine . diclofenac . mianserin		. quinine . diltiazem . naproxen . ranitidine . enflurane . para-aminosalicylic acid . sulfonamides . ethambutol . penicillins . sulindac		. ethionamide . phenelzine . tricyclic antidepressants . halothane . phenindione . valproic acid . ibuprofen . phenobarbital . verapamil

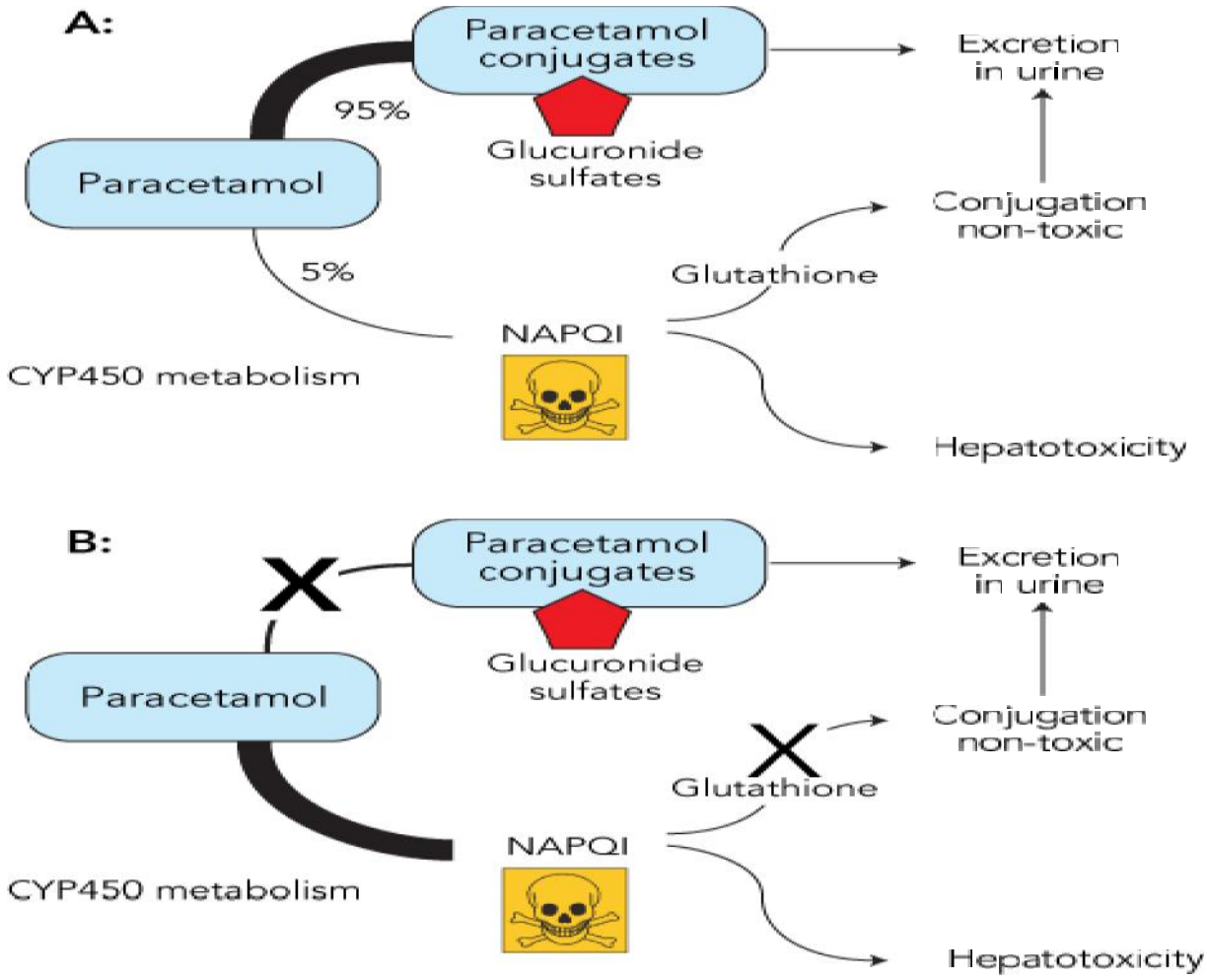
MECHANISM OF PARACETAMOL INDUCED HEPATOTOXICITY

When paracetamol is taken in standard doses in healthy individuals, more than 90% is conjugated to form inactive metabolites, which are then excreted in urine. A small proportion of the paracetamol is metabolised by the cyp450 system to N-acetyl-p-benzoquinone imine (NAPQI), which, if allowed to accumulate, is toxic to the liver. Normally NAPQI is conjugated with glutathione and the harmless products excreted in the urine. Prolonged starvation can severely deplete the cosubstrates required for paracetamol conjugation and reduce glutathione stores, so that even therapeutic doses of the drug can result in the accumulation of toxic amounts of NAPQI. Regular and prolonged treatment with paracetamol may be particularly in fasting patients, as ongoing metabolism of the drug leads to further consumption of already depleted glutathione stores. Alcohol and other drugs capable of inducing CYP450 predispose patients to paracetamol

toxicity by increasing the production of NAPQI. In addition, chronic alcohol misuse leads to depletion of glutathione.

RISK FACTORS FOR DEVELOPING HEPATIC TOXICITY UNDER THESE CIRCUMSTANCES INCLUDE-

1. Prolonged fasting
2. Regular excessive alcohol intake
3. Concurrent use of drugs that induce CYP450, especially CYP4502E.
4. Elderly patients with renal and cardi-opulmonary insufficiency may also be at increased risk



DIGRAMATIC PRESENTATION OF HEPATOTOXICITY INDUCED BY PARACETAMOL

ROLE OF AYURVEDA IN HEPATO-TOXICITY-

The hepatic injury has remained a challenge to medical profession, since many of them may ultimately lead to irreversible changes. Ayurvedic herbals and herbo mineral drugs can play an effective role in treating certain liver disorders including hepatic injury. Among the several medicinal plants, *katuki, kalmegh , amalaki, yashtimadhu, sarpunkha* have shown better result. In these I am try-ing to explain the effective role of *katuki, kalmegha* in the treatment of hepatotoxicity through this paper.[3]

KATUKI-

Botanical name-*Picrorhiza Kurroa*

Family-Scrophulariaceae

Picrorhiza kurroa is a herb from Ayurved that is commonly called katuki or kutaki. It

contains 'bitter principle' which is mixture of two molecule, the iroid glycosides known as picroside1 and picroside2 (picroside2 also called kutkoside) and the mixture overall is then called kutkin or picroliv.

The hepatoprotective action of picrorhiza kurroa is not fully understood but may be attributed to picrorhiza's ability to inhibit the generation of oxygen anions and to scavenge free radicals.picrorhiza's antioxidant effect has been shown to be similar to that of superoxidase dismutase, metal- ion chelators and xanthine oxidase inhibitors. In rats having liver injury after giving acetaminophen, picrorhiza restored depleted glutathione levels, thereby enhancing detoxification and antioxidation and helping maintain a normal oxidation-reduction balance.

In this same animal model picrorhiza also demonstrated an anti-lipid peroxidative effect. Like silymarin, picrorhiza has been shown to stimulate liver regeneration in rats, possibly via stimulation of nucleic acid and protein synthesis[4]

KALMEGH

BOTANICAL NAME-*Andrographis panniculata*

FAMILY-Acanthaceae

Andrographis panniculata a plant widely used as a traditional herbal medicine in many countries has drawn attention of the researcher in recent years.

It major constituents are Diterpenoids and Flavonoids. The antihepatotoxic effect of Andrographis panniculata is due to extract and derivative compound, such as andrographolide, the major active compound. Neoandrographolid shows anti-inflammatory and anti hepatotoxic properties.14-Deoxy-11,12 didehydroandrographolid and 14-deoxyandrographolid have immunostimulatory , anti-atherosclerotic and anti-hepatotoxic activities

The hepatoprotective activities of Kalmegh include-

(1) Inhibiting carbon tetrachloride (CCl_4), tert-butylhydroperoxide (t-BHP)-induced hepatic toxicity,

(2) Acting as cytochrome P450 enzymes (CYPs) inducers,

(3) Modulating glutathione (GSH) content,

(4) influence glutathione S-transferase (GSTP) activity and phosphatidylinositol-3-kinase pathway,

(5) Synergistic effect with anti-cancer drugs induced apoptosis contributing to the bioactivities of *A. paniculata* extracts and isolated bioactive compounds.[5]

NEPHROTOXICITY:-

Medicinal plants may serve as a vital source of potentially useful new compounds for the development of effective therapy to combat a variety of kidney problems. Many herbs have been proven to be effectual as nephroprotective agents while many more are claimed to be nephroprotective but there is lack of any such scientific evidence to support such claims. Developing a satisfactory herbal therapy to treat severe renal disorders requires systematic investigation of properties like acute renal failure, nephritic syndrome and chronic interstitial nephritis. Herbal medicines possess curative properties due to the presence of their chemical components. The present review is aimed to elucidate the list of nephroprotective medicinal plants, which are scientifically proved in treating renal disorders.

Agents Which Causes Nephrotoxicity

Drugs, diagnostic agents & chemical are well known to be nephrotoxic. The following are some of the important nephrotoxic agents7.

A) Heavy metal: Mercury, arsenic, lead, bismuth

B) **Antineoplastic agents**

Alkylating agents: Cisplatin, cyclophosphamide

Nitrosoureas: Streptozotocin, Carmustine, Lomustine & Semustine

Antimetabolites: High dose Methotrexate, Cytosine Arabinose, high dose 6-thioguanine, 5-flurouracil

Antitumor antibiotics: Mitomycin, Mithramycin, Doxorubicin

Biologic agents: Recombinant leukocyte and interferon

C) Antimicrobial agents: Tetracycline, Acyclovir, Pentamidine, Sulphadiazine, Trimethoprin, Rifampicin, Amphotericin B

D) Aminoglycosides: Gentamycin, Amikacin, Kanamycin, Streptomycin

E) Miscellaneous

Radiocontrast agents: Non-steroidal anti-inflammatory agents (NSAID's): Ibuprofen, Indomethacin, Aspirin etc.[6]

SOME NEPHROPROTECTIVE PLANTS:-

BOTANICAL NAME	FAMILY	USEFUL PART	CHEMICAL CONSTITUENT	SCREENING METHOD
Aerva lanata[7]	amaranthacae	Whole plant	Botulin,β-sitosterol, Amyrin, Hentriacontane, Campesterol, Stigma sterol, Kaempferol, Propionic acid, β-carboline-I, Aervoside and Aervolanine	Gentamycin induced
Crataeva nurvula[8]	capparidaceae	Fruit	Kaemferol-3-O-a-D-glucoside, Quercitin-3-O-a-D-glucoside, Flavanoids, Glucosinolates	Gentamycin induced
Strychnos potatorum [9]	Loganiaceae	Seed	Flavanoids, Phenols, Saponins, Alkaloids, Steroids, Tannins, Glycosides, and Lignins	Gentamycin induced
Carica papaya[10]	Caricaceae	Seed	Flavanoids, Phenols, Alkaloids, Protein, Sterols, Terpenoids, Carbohydrates, Steroids, Tannins, Glycosides, Terpins and Saponins	Cisplatin induced
Ficus religiosa L[11]	Moraceae	Latex	Flavonoids, Amino acids and Tannins.	Cisplatin induced

PASANABHEDA

BOTANICAL NAME- *Aerva lanata*

FAMILY- Amaranthaceae.

Aerva lanata is also called as Pasanabheda, Chaya, Gorakhganja belongs to the family Amaranthaceae. The *Aerva lanata* plant is

reported to have α-amyrin, campesterol, β-sitosterol, its palmitate, chrysin and flavonoid glucosides. Canthin-6-one and β-carboline alkaloids were isolated from *Aerva lanata*. Four new alkaloids viz., aervine, methylaervine, aervoside and aervolanine were isolated. The plant was reported for various activities such as diuretic, hepato protective, antidiabetic, antimicrobial, anthelmintic and demulcent activity. *Aerva lanata* also shows its effect on cisplatin and gentamycin model of acute renal failure.

The ethanolic extract of the entire plant of *Aerva lanata* was studied for its nephroprotective activity in cisplatin and gentamicin induced acute renal injury in albino rats of either sex. In the curative regimen, the extract at dose levels of 75, 150 and 300 mg/kg showed dose-dependent reduction in the elevated blood urea and serum creatinine and normalized the histopathological changes in cisplatin model. In the gentamicin model the rats in the preventive regimen also showed good response to the ethanol extract at 300 mg/kg. The results suggest that the ethanolic extract of *Aerva lanata* possesses marked nephroprotective activity with minimal toxicity and could offer a promising role in the treatment of acute renal failure caused by nephrotoxins like cisplatin and gentamicin70

VARUNA

BOTANICAL NAME- *Crataeva nurvala*

FAMILY- Capparidaceae

Crataeva nurvala Buch-Ham belongs to the Family Capparidaceae commonly known as Varuna, is an evergreen tree indigenous to India71. Moreover, pharmacological study reveals the potentiality of *Crataeva nurvala* extract and its active principle, particularly lupeol as diuretic, anti-inflammatory, anti-oxidant, cardio-protective, hepatoprotective, lithonotriptic, anti-rheumatic, anti-periodic, contraceptive, anti-protozoal, rubifacient and vesicant72.

The alcoholic extract of *Crataeva nurvala* 250 and 500 mg/kg for 10 days showed protective activity against cisplatin 5 mg/kg induced nephrotoxicicty. The results suggested, that the alcoholic extract has significantly altered the dysfunction of renal proximal tubule cells by decreasing the concentration of blood urea nitrogen, creatinine, lipid peroxidation, glutathione and catalase73

DISSCUSSION AND CONCLUSION

HEPATOTOXICITY

The hepatic injury have remained a challenge to medical profession since many of them may ultimately lead to irreversible changes.ayurvedic herbal herbo –mineral drug can play an effective role in treating certain liver disorders including hepatic injury(hepatotoxicity).among several medicinal plants such as katuki ,amlaki, yasthimadhu, kalmegh, sarpunkha has shown better result with respect to hepatotoxicity. The bio chemical parameters-serum bilirubin ,alkaline phosphatase, SGOT, SGPT have also recorded statically significanct improve with these plants.

NEPHROTOXICITY

From this study, it is clear that the medicinal plants play a prominent role against various diseases. A variety of medicinal plants such as Pashanbhed, Varun, Shigru, Punarnava and plants extracts have been reported for its significant nephroprotective activity in animal models. The nephroprotective activity is probably due to the presence of Flavanoids in all the few medicinal plants. The results of this study indicate that extracts of leaves and plants of some medicinal plants have good potentials for use in kidney damage.

The present review study give evidential explore mechanism of action of medicinal plants against experimentally induced nephrotoxicity. Hence, the review of the study is concluded that the herbal drug possesses nephroprotective activity and it has been proven by different animal models which gives many links to develop the future trials.

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