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ANALYTICAL REVIEW OF HEPATOPROTECTIVE DRUGS MENTIONED IN BHAVAPRAKASHA NIGHANTU

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ABSTRACT

Liver is one of the vital organs and largest gland of the human body occupied in right hypochondriac region. It plays vital role for metabolism of absorbed nutrient materials, secretion of bile and bile pigments, synthesis of plasma proteins, storage of Vitamin-A, glycogen etc. and detoxification of xenobiotics. Due to its active participation in detoxification of xenobiotics, drugs, alcohol etc. liver is more prone to injuries. Similarly, liver infections by different types of Hepatitis viruses, autoimmune and genetic disorders are also seen in liver. The global crude annual incidence rate for Liver disease is 14 per 100000 populations and recent reports have shown that 10% of world population is affected with liver diseases. According to the WHO fact sheets on hepatitis, 60,000 persons die of the acute and chronic hepatitis B annually. There are various drugs in contemporary system of medicine for liver diseases but those synthetic drugs becoming toxic to liver itself. Hence drugs from herbal origin are becoming popular and acceptable worldwide. Lots of herbal, herbomineral and drugs of animal origin have been mentioned in classical Ayurvedic literature in treatment of Yakrit Vikaras (Liver disorders). Bhavaprakasha Nighantu is one of major Ayurvedic lexicons of 16th century known as Materia-Medica of Ayurveda, has also mentioned drugs for various types of liver disorders. Out of 426 drugs, total 16 drugs are mentioned as Kamalahara or Yakrit Vikarahara (Hepatoprotective). The purpose of this study is to enlist the drugs useful in liver disorders from Bhavaprakasha Nighantu and critically analyze according to the studies done upon them.

Key words: Liver diseases, Xenobiotics, Hepatitis, Bhavaprkasha Nighantu,Yakrit Vikarahara, Kamalahara.

INTRODUCTION

Liver is one of the vital organs and largest gland of the human body occupied in right hypochondriac region. It weighs about 1200 to 1600 gm, roughly 2% in adult and 5% in infant. It plays vital role for metabolization of absorbed nutrient materials, secretion of bile and bile pigments, synthesis of plasma proteins, storage of vitamin-A, glycogen etc. and detoxification of xenobiotics. Due to its active participation in detoxification of xenobiotics, drugs, alcohol etc. liver is more prone to injuries. Similarly, infections by Hepatitis virus-A, B, C, D, and E, autoimmune and genetic disorders are also associated to liver.[1] Hepatic disease (Liver disease) is a term for a collection of conditions, diseases and infections that affect the cellular or tissue's structures or functions of the liver.[2] Liver disease causes various patho-physiological changes like cirrhosis, nonalcoholic hepatic steatosis, hepatitis, biliary cirrhosis, alcoholic hepatitis, liver cancer etc. The global crude annual incidence rate for Liver disease is 14 per 100000 population, while standardized annual incidence rate is 8.1 per 100000 and recent reports have shown that 10% of world population is affected with liver diseases.[3,4] According to the WHO fact sheets on hepatitis, 60,000 persons die of the acute and chronic hepatitis B annually and more than 170 million population worldwide have long term infection with Hepatitis-C.[5] Liver diseases can be broadly categorized under three subheadings i.e. Alcoholic Liver disorders, Non-Alcoholic Liver disorders and Genetic Liver disorders. Liver injuries or Hepatic toxicity can occur by several mechanisms like 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] There are a number of drugs or therapies available for the treatment of hepatic disorders, but still there is a need for the novel drug discovery because of various adverse reactions and expensiveness. Hence drugs from herbal origin are becoming popular and acceptable worldwide.

Liver diseases in Ayurveda can be correlated with Yakrit Vikaras. The specific descriptions about Yakrit Vikaras (Hepatic disorders) are not mentioned in Ayurveda classics but various diseases related with Yakrit (Liver) are mentioned. Yakriddalyudara[6] (Distended abdomen due to Hepatomegaly), Kamala (Jaundice), Kumbh Kamala[7] (Deep- seated Jaundice), Hallimaka, Lagharaka,[8] Panaki[9] (Chronic and complicated Jaundice) are the common Vikaras (disorders) of Yakrita(Liver). Among Yakrit Vikaras, Kamala has been given more preference in Ayurveda classics. Kamala is a disease in which all likes and dislikes disappear.[10] It is characterized by yellowish discoloration of eye balls, skin, face, nail and urine associated with constitutional features like loss of appetite and weakness.[11] Kumbh Kamala, Hallimaka, Lagharaka and Panaki are further complications of Kamala when it is not treated properly and person affected with Kamala further indulges Ahara (Food items) and Vihara (general behavior or activities) which vitiate Pitta. Kamala is further classified as Sakhashrita Kamala and Koshthashrita Kamala,[7] which can be correlated with obstructive and non obstructive Jaundice. Kamala itself mentioned in Pandu Roga Chikitsa-Sthana in Charaka Samhita as a result of further aggravation of Pitta in Pandu Rogi (anaemic patient). Another main disease related with Yakrit (liver) is Yakriddalyudara (distended abdomen due to hepatomegaly) which is mentioned in Udara Roga Chikitsa with Pleehodara which is one of the type of Udara Roga (Diseases

related with abdominal cavity) mentioned by Acharyas. In Udara Roga Chikitsa Acharya has opined that almost all treatment of Pleehodara (distended abdomen due to spleenomegaly) could be applied to Yakriddalyudara also, which lies in Dakshina Parshwa (right hypochondrium).[12]

For such type of diseases lots of drugs are mentioned in Brihatrayee (the great lexicons of Ayurveda- Charaka Samhita, Sushruta Samhita and Ashtanga Hridaya) and Laghutrayee (Madhava Nidana, Sharangdhara Samhita and Bhavaprakasha Nighantu) as Kamalahara, Yakrit Vikarahara (hepatoprotective), Yakridvridhihara (drugs useful in hepatomegaly), Pleehahara, Pleehaghna (drugs used in spleenic disorders) etc. Bhavaprakasha Nighantu is important lexicon of Ayurveda written by Bhava Mishara in 16th Century AD. It is a materia-medica of Indian medicine. In Bhavaprakasha Nighantu 426 drugs are mentioned in 22 different Vargas[13] (Categories) containing herbs, grains, cereals, fruits, minerals, water, honey, alcohols, different type of milk products and urine of different types of animal. Among those the drugs useful for Yakrit Vikaras (liver disorders) are mentioned as Kamalahara, Yakridvikarahara and Pleehahara.

Most of the drugs mentioned as Kamalahara, Yakridvikarahara and Pleehara are established as Hepatoprotective agents by various experimental and clinical studies. So out of total Vargas an attempt is done to sort out and enlist those drugs which are mentioned as Kamalahara, Kamalajeet, Yakridvikarahara, Yakrit Rogahara, Pleehara, Pleehaghna and their efficacy as Hepatoprotective is reviewed by reviewing various research studies done on them.

Hepatoprotective drugs in Bhavaprakash Nighantu

Among 426 drugs dealt in Bhavaprakasha Nighantu 16 drugs are mentioned as Kamalahara/Yakrit Vikarahara (Hepatoprotective), 23 drugs are mentioned as Pleehahara and 23 drugs are mentioned as Panduhara (anti-anaemic or haematinic).[14] Most of these drugs contain several phytochemicals, which possess strong antioxidant activities. Basically, these antioxidant phytochemicals are responsible for hepatoprotective activity. The antioxidant phytochemicals which act as hepatoprotective agents are flavonoids, terpenoids, polyphenols (Ellagic acid, Gallic acid, Tannins), alkaloids, saponins, vitamins, carotenoids, minerals (copper, manganese, zinc etc.), enzymes (superoxide dismutase, catalase, glutathione, peroxidase), polysaccharides, saponins, lignins, xanthones and pigments etc.[15]

Pharmacological screening for Hepatoprotective activity is mostly done on experimental models like alcohol induced, CCl4 (carbon tetrachloride), paracetamol, isoniazid, rifampicin, 2-AAF(2acetylaminofluorine), lead and arsenic induced hepatotoxicity in rats at different dose with variant time duration.

Table 1: Plants detail for Kamalahara (Hepatoprotective) Drugs in Bhavaprakasha Nighantu

S.N.	Sanskrit Name	Botanical name	Family	Dosha Karma (Action on Dosha)	Related Karma (action)	Reference of Varga and Shloka(verse) no.
1.	Haritaki	*Terminalia chebula*	Combretaceae	Tridoshahara	Kamalahara, Pleeha and Yakrit Rogahara	Haritkyadi Varga- 22
2.	Vanshalochana	*Bambusa arundinacea*	Poaceae	Kapha-pittashamaka	Kamalahara	Haritkyadi Varga- 117
3.	Guduchi	*Tinospora cordifolia*	Menispermaceae	Tridosha-shamaka	Kamalahara	Guduchyadi Varga- 10 Shaka Varga- 42
4.	Eranda Phala	*Ricinus communis*	Euphorbiaceae	Kapha-vatashamaka	Yakrit-Pleehahara, Udara-rogahara	Guduchyadi Varga-65-66
5.	Indravaruni	*Citrullus colocynthis*	Cucurbitaceae	Kapha-pittahara	Kamala- Pleehahara	Guduchyadi Varga-203-205
6.	Mahendravaruni	*Trichosanthus palmate*	Cucurbitaceae	Kapha-pittahara	Kamala- Pleehahara	Guduchyadi Varga-203-205
7.	Sharpunkha	*Tephrosia purpurea*	Papillionaceae	Kapha-Vatashamak, Prabhava-Pleehaghna	Yakrit- Pleehahara	Guduchyadi Varga-210
8.	Kumari	*Aloe vera*	Liliaceae	Kapha-Pittahara	Pleeha and Yakrit – vriddhihara	Guduchyadi Varga-230
9.	Dronapushpi	*Leucas cephalotes*	Lamiaceae	Kapha-Vatashamaka, Pittashodhaka	Kamalajeet	Guduchyadi Varga-65-66 ShakaVarga-34
10.	Kakodumbara	*Ficus hispida*	Moraceae	Kapha- Pittashamaka	Kamalahara	Vatadi Varga- 10
11.	Kutshalmali	*Ceiaba pentandra*	Bombacaceae	Kapha- Vatahara	Pleeha- Yakrit Rogahara	Vatadi Varga- 59
12.	Draksha	*Vitis vinifera*	Vitaceae	Vata-pittakashamak	Kamalahara	Amradiphala Varga- 112

Table 2: Drugs other than Herbs mentioned as Kamalahara (Hepatoprotective) in Bhavaprakasha Nighantu

S.No.	Sanskrit Name	English Name	Doshkarma	Related Karma	Reference of Varga and Shloka no.
1.	Navina Ghrita	Newly prepared Ghee	-	Kamalahara	Ghrita Varga- 18
2.	Go- Mutra	Cow's urine	Kapha-Vatanashaka. Pittakara	Kamalahara	Mutra Varga- 2
3.	Kanta Lauha	Magnetic iron ore	-	Kamalahara	Dhatwadi Varga- 49
4.	Hingula	Cinnabar	Kapha-Pittashamaka	Kamalahara	Dhatwadi Varga- 105

Table 3: List of Herbs mentioned as Pleehahara/Pleehaghna (Drugs useful in spleenomegaly or spleenic disorders) in Bhavaprakasha Nighantu

S. N.	Sanskrit Name	Botanical name	Family	Dosha Karma (action on Dosha)	Related Karma (action)	Reference of Varga and Shloka no.
1.	Pippali/Pippali Moola	*Piper longum*	Piperaceae	Kapha-Vatasahamaka	Pleehahara/ Pleehaghna	Haritkyadi Varga- 55,65
2.	Panchakola	-	-	Kapha-Vatashamaka	Pleehaghna	Haritkyadi Varga- 73
3.	Yavani	*Trachyspermum ammi*	Apiaceae	Vata- Shleshmahara	Pleehapranut	Haritkyadi Varga- 77
4.	Tumbaru	*Zanthoxylum alatum*	Rutaceae	Vata- Shleshmahara	Pleeharoga-Nashaka	Haritkyadi Varga– 115
5.	Pashanabheda	*Bergenia ligulata* (*Saxifraga ligulata*)	Saxifragaceae	Tridosha-shamaka*	Pleehahanti	Haritkyadi Varga– 185
6.	Arka	*Calotropis procera*	Asclepiadaceae	Vatashamaka	Pleehahara	Guduchyadi Varga-69
7.	Sehunda	*Euphorbia neriifolia*	Euphorbiaceae	Kapha-Vatashamak	Pleehahara	Guduchyadi Varga-79
8.	Sobhanjana	*Moringa oleifera*	Moringaceae	Kapha-Vatahara	Pleehahara	Guduchyadi Varga- 107 Shaka Varga- 50
9.	Mundi	*Sphaeranthus indicus*	Asteraceae	Tridosha-shamaka*	Pleehahara	Guduchyadi Varga- 218
10.	Rohitaka	*Tecomella undulata*	Bignoniaceae	Kapha- Pittashamaka	Pleehaghati	Vatadi Varga- 35
11.	Amlavetasa	*Garcinia pedunculata*	Cluseaceae	Kapha-Vatahara	Pleeha-Roganashaka	Aamraphaladi Varga-145
12.	Vastuka/ Sugandha Vastuka	*Chenopodium album/ Chenopodium ambrosioides*	Chenopodiaceae	Tridoshahara*	Pleehahara	Shaka Varga-7
13.	Surankanda	*Amorphophallus campanulatus*	Araceae	Kapha-shamaka	Pleeha-vinashanam	Shaka Varga-92
14.	Hastikarna	*Leea macrophylla*	Vitaceae	VataKapha-shamaka	Pleehapaha	Shaka Varga-109

Table 4: Number of Kamalahara (Hepatoprotective) drugs according to Varga

S.No.	Name of Varga	Number of Drugs
1.	Haritkyadi Varga	2
2.	Guduchyadi Varga	7
3.	Vatadi Varga	2
4.	Amradiphala Varga	1

Table 5: Number of Pleehara Dravya (Drugs used in spleenic disorders) according to Varga

S.No.	Name of Varga	Number of Drugs
1.	Haritkyadi Varga	5
2.	Guduchyadi Varga	4
3.	Vatadi Varga	1
4.	Amraphaladi Varga	1
5.	Shaka Varga	3

Table 6: Number of Kamalahara Dravya (Hepatoprotective) according to Doshaghnata

S.No.	Doshkarma	Number of Drugs
1.	Tridoshahara/ Tridoshashamaka	2
2.	Vatapittashamaka	1
3.	Vatakaphashamaka/Kaphavatashamaka	4
4.	Kaphapittashamaka/ Pittashleshmahara	5
5.	Vatashamaka	-
6.	Pittashamaka	-
7.	Kaphashamaka	-

Table 7: Number of Pleehahara Dravya (Drugs used in spleenic disorders) according to Doshaghnata

S.No.	Doshakarma	Number of Drugs
1.	Tridoshahara/ Tridoshashamaka	3
2.	Vatapittashamaka	-
3.	Vatakaphashamaka/Kaphavatashamaka	8
4.	Kaphapittashamaka/ Pittashleshmahara	1
5.	Vatashamaka	1
6.	Pittashamaka	-
7.	Kaphashamaka	1

Enumeration of Drugs with their experimental/clinical study references and interpretation

Haritaki - Haritaki (*Terminalia chebula* Retz.) is the commonest drugs used in Ayurveda practices. It is a one of the content of famous formulation Trifala Churna. Acharya has mentioned 7 types of Haritaki for different purposes. It has Lavana varjit Kashaya Pradhana Pancha rasa and Tridoshahara action as Prabhava (potency).[14] Tannin, Chebulic acid, Chebulinic acid, Gallic acids, Chebulagic acid, Anthrocine glycoside etc. are the major phytoconstituents.[16] A study " Hepatoprotective Effects of *Terminalia chebula* Fruit Extract against 2-AAF–Induced Hepatic Damage in Albino Mice: Role of MDR1 and COX-2" has shown that administration of fruit extract of *Terminalia chebula* inhibited the expression of MDR1(multidrug resistance-1) by preventing ROS (reactive oxygen species) generation and COX-2 (cyclo-oxygenase-2) expression through AKT1 and MAPK (mitogen-activated protein kinase) signaling pathway and prevent the possible neoplastic transformation leading to hepato-carcinoma. The

study has established *Terminalia chebula* as potent Hepatoprotective.[17]

Vanshalochana- Vanshalochana is a segregated and condensed material found in hollow internodes of plant *Bambusa arundinacea* of Poaceae family. The major phytoconstituents are Silica 90.56%, Potash 1.10% Peroxide of Iron 0.90%, Alumina 0.40% etc.[18] It is mentioned as Kamalahara in Bhavaprakash Nighantu, but no study has been carried out to establish this claim.

Guduchi- Guduchi (*Tinospora cordifolia*) is a large glabrous climber with succulent, corky and grooved stems having sub-deltoid or cordate shaped leaves. The major phytoconstituents are Giloin, Tinosporide, Cordifolide, Tinosporon, Cordifol, Hepatocosanol, β-sitosterol etc. Stems and leaves are used for various diseases like Madhumeha (Diabetes mellitus), Kamala (Jaundice), Fever etc.[16] Use of Stem is mentioned in Guduchyadi Varga in Bhavaprkasha Nighantu while uses of leaves are mentioned in Shaka Varga. 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.[19]

Erandaphala- Eranda (*Ricinus communis*) is erect, herbaceous above and woody below, cylindrical branched shrub having large petiole and palmate shaped leaves.[16] Roots, root bark, seed etc. are commonly used in Ayurveda practices. In Bhavaprakasha Nighantu Erandaphala (Fruits of *Ricinus communis*) is mentioned as effective in liver and spleenic disorders (Yakrita-Pleehahara). As per study, it is established that ethanolic extract of *Ricinus communis* had the ability to restore and regenerate the hepatocytes due to the presence of bioactive molecule rodoxanthine.[20]

Indravaruni- Indravaruni (*Citrullus colocynthis*) is a perennial twinner or climber having hairy stem and deeply lobed leaves. Fruits, roots and leaves are used for medicinal purpose. It has purgative, hypoglycaemic, antipyretic, diuretic, antihistaminic and antimicrobial actions.[21] In Bhavaprakasha Nighantu it is also mentioned as Kamalahara (hepatoprotective). As per study, it is proved that *Citrullus colocynthis* extract, fractions and isolated compound could inhibit CCl4 induced hepatitis by regulating various biochemical parameters such as SGPT, SGOT, ALP and BL (Bilirubin). From its extract, Cucurbitacin B and Colocynthin are derived from Toluene fraction which showed promising hepatoprotective activity in CCl4 model at 50 mg/kg dose level.[22]

Mahendravaruni- Mahendravaruni (*Trichosanthes palmate*) is large branched, tendril climber of family cucurbitaceae having palmately 3-5 lobed leaves. The fruits consist cucurbitane, hexanorcucurbitane and octanorcucurbitane glycosides.[23] It's hepatoprotective effect is not evaluated but its antioxidant effect is established,[24] due to its antioxidant properties, it may be effective as hepatoprotective.

Sharpunkha- Sharpunkha (*Tephrosia purpurea*) is a copiously branched sub-erect herb having imparapinnate leaves and leaflets are narrow oblanceolate. Flowers are red or purple in color, found all over the India. Whole plant is used for medicinal purposes. It is generally used as anti-inflammatory, anthelmintic, diuretics, depurative etc. Specially root is used in hepatospleenomegaly.[25] It's hepatoprotective effect is established by various studies. A study "Hepatoprotective activity of *Tephrosia purpurea* against arsenic induced toxicity in rats" showed hepatoprotective effect by decreasing lipid peroxidation and incresing GSH (glutathione).[26]

Kumari- Kumari (*Aloe vera*) is a perennial herb having short stem and shallow root system. Leaves are fleshy, sessile and tapering, cuspidate apex and horny prickles on the margin. Leaf pulp, juice and aloin are used for anthelmintic, carminative, stomachic, emmenagogue and ophthalmic diseases. It is also used for dysmenorrhoea and hepatopathy.[27]As per study; it is significantly effective in acute viral hepatitis.[28]

Dronpushpi- Dronpushpi (*Leucas cephalotes)* is an erect or diffuse branched herb having quadrangular stem, leaves sub-sessile, linear, or linear lanceolate, flowers white, terminal or axillary whorls. The used parts of plant are leaves and flowers. It is used as anthelmintic, anti-inflammatory, antipyretic, antibacterial, depurative etc.[29] It is mentioned as Kamalajeet (subsides jaundice) in Bhavaprakasha Nighantu. As per study, it has significant hepatoprotective effect in rifampicin and isoniazid induced hepatotoxicity in rat. Alcoholic extract of *L. cephalotes* has significant hepatoprotective effect mainly due to increase in superoxide dismutase, glutathione and Catalase level and decrease in SGPT (serum glutamate-pyruvate transaminase), SGOT (serum glutamic oxaloacetic transaminase), Alkaline phosphatase, bilirubin and other biomarkers.[30]

Kakodumbara- Kakodumbara (*Ficus hispida*) is a moderate sized weak tree of family Moraceae. Leaves are opposite, long, scabrid surfaces, pubescent, 3-5 ribbed. Barks and fruits are used as anti-dysentric, anti-inflammatory, haemostatic, glactogogue etc. It is useful in leucoderma, jaundice, epistaxis, intermittent fever etc.[31]As per study, the methanolic extract of leaves of *Ficus hispida was* evaluated for hepatoprotective activity against paracetamol induced hepatotoxicity in rats, and it was observed that it showed significant effect by lowering serum levels of SGOT, SGPT, ALP and bilirubin at the dose of 400mg/kg. These observations were supplemented by histopathological examination of liver sections.[32]

Kutshalmali- Kutshalmali (*Ceiba pentandra*) is a medium to tall sized deciduous tree of family Bombacaceae. Trunk is prickly at young and becomes smooth when it becomes older. Branches are arranged in whorl. Roots are diuretic, aphrodisiac, antipyretic and tonic, used in gonorrhea, dysuria, intermittent fever etc. Bark is diuretic, emetic, purgative and useful in hepatopathy, abdominal compliance, tumors etc.[33] As per study, ethyl acetate fraction of methanol extract of stem bark of *Ceiba pentandra* in dose of 400 mg/kg showed significant hepatoprotective effects against paracetamol induced liver damage in rats. A significant ($P < 0.05$) reduction in serum enzymes GOT (ALT), aspartate aminotransferase (AST), GPT, alkaline phosphatase (ALP), total bilirubin content were noticed. The ethyl acetate fraction of stem bark of *Ceiba pentandra* was found to contain tannin, C-glycoside, phenolic compounds, flavonoid, reducing sugar and triterpenes, which were able to maintain normal functional status of the liver.[34]

Draksha- Draksha (*Vitis vinifera*) is a deciduous tendril climber. Dried fruits are refrigerant, laxative, emollient, intellect promoting, cardiotonic, haematinic, expectorant etc. It is useful in anaemia, cough, fever, haemoptysis, jaundice, skin diseases etc. Leaves, stems, roots and flowers are also used in various other conditions.[35] As per study, ethanolic extract of the root of *Vitis vinifera* at an oral dose of 200 mg/kg exhibited a significant hepatoprotective effect by lowering the serum levels

of SGPT, SGOT, alkaline phosphatase and total bilirubin in rats with liver damage induced by carbon tetrachloride. These observations were supplemented by histopathological examination of liver.[36] Leaves and seeds are also established as potent hepatoprotective.[37,38]

Pippali- Pippali (*Piper longum*) is a slender aromatic climber of Piperaceae family. Roots and dried spikes are used as medicine. The roots are useful in gout, lumbago, dyspepsia, stomachalgia, spleenopathy etc. Similarly, dried spikes are used as stomachic, aphrodisiac, carminative, expectorant etc.[39] The major phytoconstituents are Piperine, Piplartine, Pipernonaline etc[16]. In Bhavaprakasha Nighantu, Pippali and Pippali Mool are mentioned as Pleehahara/Pleehaghna. Pippali is also useful in liver disorders. As per study, *Piper longum* milk extract (200 mg/day p.o. for 21 days), showed significant hepatoprotective effect in CCl4 induced hepatic damage in rats. There were extensive necrosis, inflammation and infiltration by lymphocytes due to intoxication of CCl4 and in the *Piper longum* treated group the areas of regeneration were seen around the necrotic focus. The antihepatotoxicity effect is due to increase in SOD and decrease in lipid peroxidation.[40]

Yavani- Yavani (*Trachyspermum ammi*) is a annual herb of Apiaceae family. The used part of Yavani is fruit, which acts as stimulant, antispasmodic and carminative and is commonly used as an important remedial agent for flatulence, dyspepsia, diarrhea, abdominal tumors, abdominal pains, piles, and bronchial problems. Further, studies have revealed that it contains various phytochemical constituents mainly carbohydrates, glycosides, saponins, phenolic compounds, volatile oil (thymol, γ-terpinene, para-cymene, and α- and β-pinene), protein, fat, fiber and mineral containing calcium, phosphorous, iron and nicotinic acid.[41] As per study, the hexanolic extract of *Trachyspermum ammi* (dose of 250mg/kg s.c.) showed significant hepatoprotective effect in CCl4 induced hepatotoxicity in rats. Hepatic regeneration occurred following administration of the hexanolic extract of *Trachyspermum ammi*. [42]

Tumbaru- Tumbaru (*Zanthoxylum alatum*) is a small tree of family Rutaceae with dense glabrous foliage and straight prickles on stems having imparipinnately compound leaves. Barks and fruits are commonly used in Ayurveda practices. It is commonly used in flatulence, helminthiasis, diarrhea, hepatopathy, spleenopathy, skin diseases, cough, asthma, diabetes, etc.[43] 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 of *Zanthoxylum alatum* revealed the presence of isoquinoline alkaloid, berberine, flavonoids and phenolic compounds, which are responsible for their hepatoprotective activities.[44]

Pashanabheda- Pashanabheda (*Saxifraga ligulata/ Bergenia ligulata*) is highly branched perennial herb up to 60-180 cm in height. Root is red in color, stem short thick, fleshy and leaves are ovate, sessile, rounded apex, fringed with short hairs. Root contains C-glycosides called bergenin, gallic acid etc. It has diuretic, anti-inflammatory, haemostatic and cardiotonic actions.[16] As per study carried in CCl4 induced hepatotoxicity in albino rats, ethanolic extract of the roots of *Bergenia ligulata* were administered in dose of 500 mg/kg b.w, p.o/ day, significantly decreased in the levels of Serum Glutamate Pyruvate Transaminase (SGPT), Serum Glutamate Oxaloacetate Transaminase (SGOT), Serum Alkaline Phosphatase (ALP) and total bilirubin showed its efficacy as hepatoprotective in comparison with Liv-52.[45]

Arka- Arka (*Calotropis procera*) is a shrub in which young parts clothed with white cotton like tomentum. Leaves are sub-sessile opposite decussate, umbellate cymes inflorescence and fruit is etaerio of follicles type. Calotropin, α- amyrin, β- amyrin etc. are the major phytoconstituents. Pharmacological actions related to Arka are stomachic, purgative, emetic, expectorant, digestive, anthelmintic etc.[16] The various parts i.e. leaves, flowers, root bark are proven significant hepatoprotective in different models of hepatotoxicity.[46-48] As per study, the methanol extract of root bark of *Calotropis procera* exhibited a significant hepatoprotective effect in a dose dependent manner. The probable mode of action may be due to modification of reduced levels of glutathione, superoxide dismutase, catalase activity and malondialdehyde equivalent, an index of lipid peroxidation of the liver against CCl4 induced hepato-oxidative stress in albino rats.[49]

Sehunda- Sehunda (*Euphorbia neriifolia*) is a small armed tree with whorled fleshy branches, branchlets are thick, broad, winged, with spiny stipules, leaves sub-sessile and small. Roots and latex are used for different pharmacological actions. Roots are anodyne, purgative, digestive, stomachic etc. while juice or latex are anti-inflammatory, deobstruent and strong purgative.[16] In Bhavaprakasha Nighantu Sehunda is mentioned as Pleehahara and its hepatoprotective activity is established by various experimental studies. As per study done in paracetamol induced hepatotoxicity in rats, methanolic extract of *Euphorbia neriifolia* was administered orally at the doses of 200 and 400 mg/kg daily for 16 days and it was observed that the toxic effect of paracetamol was controlled significantly by restoration of the biochemical parameters, such as, SGPT, SGOT, ALP, total protein and total bilirubin. Histological study of liver section showed presence of normal hepatic cords and absence of necrosis and fatty infiltration. The hepatoprotective effect is basically due to reduced glutathione content, superoxide dismutase and catalase activity.[50]

Shobhanjana- Shobhanjana (*Moringa oleifera*) is a middle sized graceful tree with corky grey bark and easily breakable branches. Leaves are tripinnately compound having slender rachis thickened and articulated at the base. Roots, bark, leaves and seeds are useful for various pharmacological actions. Roots are carminative, anodyne, anthelmintic, diuretic etc. Bark is used in ascites and in fungal infection. Leaves are useful in scurvy, wounds, tumors etc. Seeds are useful in neuralgia, inflammation, intermittent fever and ophthalmopathy.[51] The hepatoprotective effect was studied in CCl4 treated rats, in the study, hepatotoxic rats were treated with ethanol extract of *Moringa oleifera* for a period of 60 days at three doses levels; 100, 200 and 400 mg/kg body weight/day, orally. The hepatoprotective effects were studied by assaying the serum marker enzymes like SGOT, SGPT, GGT, LDH, ALP, ACP, total bilirubin, total protein and albumin in serum. Concomitantly the activities of LPO (lipid peroxidation), SOD, CAT, GSH, and GPx (Glutathione peroxidase) were also assayed. In CCl4 treated rats all parameters are significantly altered, which were significantly recovered towards an almost normal level in rats co-administered with *Moringa oleifera* extract in a dose-dependent manner. The results of study suggested that the antioxidant and hepatoprotective activities of *Moringa oleifera* leaves are possibly related to the free radical scavenging activity which might be due to the presence of phytoconstituents like total phenolics, flavonoids in the extract

and/or the purified compounds β-sitosterol, quercetin and kaempferol, isolated from the ethanol extract.[52]

Mundi- Mundi (*Sphaeranthus indicus*) is a spreading aromatic herb having hairy stems and branches. Stems are winged, flowers are purple or pink colored. Juice of plant is useful in hemicranias, jaundice, gastropathy etc. Roots are diuretic, expectorant, stomachic and useful in fever, leprosy, diabetes, dyspepsia etc.[53] As per study, *Sphaeranthus amaranthoides* whole plant has significant hepatoprotective activity against paracetamol induced hepatotoxicity in rats. In the study, administration of ethanol extract at 400 mg/kg.b.wt. showed significant (P<0.001) reduction in elevated serum enzyme levels like SGPT, SGOT, ALT, and total bilirubin as compared to paracetamol induced group. Administration of paracetamol induced liver toxicity by decreasing the liver glutathione level and increased the MDA (Malondialdehyde) level, while ethanol extract at 400 mg/kg significantly increased glutathione content and decreased the MDA level indicating the hepatoprotective role.[54]

Rohitaka- Rohitaka (*Tecomella undulata*) is a small deciduous tree of Bignoniaceae family. Leaves are simple, opposite, oblong-lanceolate with wavy margin and obtuse apex. Flowers look like flower of pomegranate, yellow orange coloured. It's used parts are bark and seed. It is found in dry areas of India like Gujarat, Rajasthan. The major phytoconstituents are Teomin, β-sitosterols, mixture of n-hepatocosane and n-nonacosane and others. It contains iridoid glucoside- tecoside, tecomelloside etc.[55]It is mentioned as Pleehaghna in Bhavaprakasha Nighantu. It's hepatoprotective effect is well established. As per study done in alcohol and paracetamol induced hepatotoxicity in rat, it is observed that supplementation of *T. undulata* extract restored the depleted SOD, CAT GSH and GPx contents near normalcy and also brought down to elevated levels of AST, ALT ALP, GGT (gamma-glutamyl transferase**)** and total bilirubin. These biochemical restorations are mainly due to the inhibitory effects on cytochrome P450 and/ or glucuronidation.[56]

Amlavetasa- Amlavetasa is a controversial plant. The botanical source of Amalvetasa should be considered as *Garcinia pedunculata*.[57] In Bhavaprakasha Nighaantu Amlavetasa is mentioned as Pleeharoganashaka. It may also be useful for liver disorders. As per study, pre-treatment with aqueous extract of fruits of *Garcinia pedunculata* at a dose of 400 mg/kg as a suspension with 0.5% gum-acacia prevented the paracetamol-induced hepatotoxicity by decreasing in serum transaminases, alkaline phosphatase and histopathological changes. Based on the above observation it can be concluded that *Garcinia pedunculata* pretreatment exhibited significant hepatoprotective activity against Paracetamol-induced hepatotoxicity in rats.[58]

Vastuka/ Sugandhavastuka- Vastuka and Sugandh Vastuka are *Chenopodium album* and *Chenopodium ambrosioides* respectively. Both are annual herbs found throughout India. Whole plants are used as digestive, carminative, laxative, diuretic, aphrodisiac and tonic. These are useful in peptic ulcers, helminthiasis, dyspepsia, seminal weakness, spleenopathy, haemorrhoids, ophthalmopathy etc.[59] As per study, acetone and methanol extract of *Chenopodium album* (400mg/kg, oral) showed significant hepatoprotective effect in paracetamol induced hepatic injury in rat.[60] Where as *Chenopodium ambrosioides* acts as antioxidant.[61]

Surankanda- Surankanda (*Amorphophallus campanulatus*) is a tuberous herb, commonly cultivated throughout India. Tuber is large globose, depressed, dark brown in colour. Leaves are long petioled having paler blotches; leaflets are obovate or oblong, spadix inflorescence. It's used part is tuber, which is used as analgesic, uterine tonic, lipolitic, stomachic and it is best in case of Arsha (Haemorrhoids) according to classics.[16] It is mentioned as Pleehavinashanam, that means kills the diseases related to Spleen. It's hepatoprotective effect is also established. As per study, ethanolic and aqueous extracts of *Amorphophallus campanulatus* at a dose of 500 mg/kg were administered orally once daily against carbon tetrachloride (CCl4) induced hepatic damage in rats and the study concluded that the elevated serum enzymatic levels were significantly restored towards normalization by the extracts.[62]

Hastikarna- Hastikarna (*Leea macrophylla*) is herb with tuberous roots. Leaves are simple, ovate-cordate. Flowers are white and in corymbose cymes. Fruit is berry depressed-globose, black in color. In Bhavaprakasha Nighantu it is mentioned as Pleehapaham (cures spleenic diseases). It's hepatoprotective activity is also established by various studies. As per study done in CCl4 induced hepatotoxicity in rat, it's methanolic extract is used in test group, different fractions of *Leea macrophylla* showed very potent 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging effect, FeCl3 reducing effect, superoxide scavenging effect, and iron chelating effect. CCl4 increased the biomarker enzymatic profiles, which is reduced by methanolic extract of *Leea macrophylla*. It partially restored the lipid profiles, total protein, CK-MB and histopathologically showed the treated liver towards restoration. [63]

Table 8: **Interpretation of drugs as hepatoprotective (Yakrita Vikarahara)**

Name of Drug	Doshkarma (action on Dosha)	Karma (action)	Major Phytoconstituent	Mechanism of action
Terminalia chebula	Tridoshahara	Kamalahara, Anulomana, Doshasamshodhaka	Chebulagic acid [16]	preventing ROS generation and COX-2 expression[17]
Tinospora cordifolia	Tridosha-shamaka	Pittasaraka Kamalahara	Giloyin	increasing SOD and CAT.[19]
Ricinus communis	Kaphavata-shamaka	Pittashamaka due to madhura vipaka, Taila is Virechaka	rodoxanthine [20]	Increasing GSH, Regenaration of Necrosed part.[20]
Citrullus colocynthis	Kapha-pittahara	Kamalahara, Yakriduttejaka, Rechaka	Cucurbitin-B,[22] Colocynthin	Reduces Lipid peroxidation, increases GSH.[22]
Tephrosia purpurea	Kapha-vata shamaka	Yakritpleehahara, Pittasarka	Tephrorins A and B, tephrosone[26]	decreasing lipid peroxidation and incresing GSH. [26]
Aloe vera	Kapha-pittahara	Yakrit-doshahara, Yakriduttejaka*	Anthraquinone[16]	Dicreases S.bilirubin, ALT, AST, ALP[28]
Leucas cephalotes	Kapha-vata shamaka Pittashodhaka	Kamalajeet . Pittasaraka*	LeucasdinsA,B,C [16]	Increase in superoxide dismutase, glutathione and catalase level.[30]

Ficus hispida	Kapha-Pittashamaka	Kamalahara. Pittasaraka*	leaf extract contains steroids and triterpenoids.[32] Barks contains tannins, saponins, glycosides.[16]	Reducing Lipid peroxidation, increases GSH[32]
Ceiaba pentandra	Kapha- Vatahara	Pleeha- Yakrit Rogahara	tannin, C-glycoside, phenolic compounds, flavonoid, reducing sugar and triterpenes.[34]	Inhibitory effects on cytochrome and increases glutathione.[34]
Vitis vinifera	Vata-pittakashamaka	Kamalahara. Anulomana*	Fruit contains moisture(74-79%), sugars(15-20%), acids(0.5-1.25%), tannin, tartaric acid, citric etc.[64]	Enhances synthesis of Total protein and albumin which accelerates regeneration and protection of hepatocytes.[36]
Piper longum	Kapha-vatashamaka	Yakritrogahara Yakriduttejaka	Piperine, Piplartine [16]	Increases SOD and decreases lipid peroxidation. [40]
Trachyspermum ammi	Vata- Shleshmahara	Pleehapranut. Vata-anuloman.*	carbohydrates, glycosides, saponins, phenolic compounds, volatile oil (thymol, γ-terpinene, para-cymene, and α- and β-pinene) etc.[41]	increases glutathione and decreases lipid peroxidation.[42]
Zanthoxylum alatum	Vata- Shleshmahara	Pleeharoga- Nashaka. Yakriduttejaka.*	Fruit- Amino acids, glutmatic acids etc. Fruit oil- Citral, xanthoxylene. Seed oil- limonene, β-phellandrene etc. Bark- β-sitosterols, berberine etc.[65]	increases the levels of antioxidant enzymes: superoxide dismutase, catalase and glutathione and act as significant hepatoprotective.[44]
Saxifraga ligulata	Tridosha-shamaka*	Pleehahanti.	Root contains C- glycosides called Bergenin, gallic acid etc.[16]	Not clear.
Calotropis procera	Vatashamaka	Pleehahara. Pittasaraka.*	Calotropin, α- amyrin, β- amyrin[16]	acted by modifying the levels of reduced glutathione, superoxide-dimutase, catalase activity and malondialdehyde equivalent, an index of lipid peroxidation of the liver.[49]
Euphorbia neriifolia	Kapha-Vatashamak	Pleehahara. Tikshna Virechka.*	Cycloartenal, euphol, Neriifolione, Nerifoliol etc.[66]	Reduces glutathione content, superoxide dismutase and catalase activity. [50]
Moringa oleifera	Kapha-Vatahara	Pleehahara. Saraka .*	Moringine, Moringinine,[67] total phenolics, flavonoids in the extract and/or the purified compounds β-sitosterol, quercetin and kaempferol, isolated from the ethanol extract.[52]	possibly related to the free radical scavenging activity which might be due to the presence of phytoconstituents. [52]
Sphaeranthus indicus	Tridosha-shamaka*	Pleehahara. Yakriduttejaka, Anulomaka	Isoflavane glycoside-5, eugenol, β-caryophyllene , sphaerene etc.[54]	increases glutathione content and decreased the MDA level.[54]
Tecomella undulata	Kapha-pittashamaka	Kamalahara, Pittasravaka	Tecomelloside,[55] Rutin [56]	Inhibitory effects on cytochrome P-450 , promotion of its glucuronidation .[56]
Garcinia pedunculata	Kapha- Vatahara	Pleeha- Roganashaka, Anulomana, Bhedana.*	Fruits contains Garcinol, Peduncalol, Mallic acid, Citric acid. Leaves contain β-sitosterol,friedelin etc.[57]	reduces glutathione content.[58]
Chenopodium album	Tridoshahara*	Pleehahara	flavonoids, tannin, Phenolo ic compound, saponin and alkaloids [60]	hepatoprotective activity because of its Flavonoid bearing capacity.[60]
Amorphophallus campanulatus	Kaphashamaka	Pleeha-vinashanam. Yakriduttejaka, Anulomana.*	β-sitosterol, betulimic acid etc. in plant, protein, fat, carbohydrates, Vitamins, calcium etc. in corm.[68]	mechanism of this activity may be due to free radical scavenging potential caused by the presence of flavonoids in the extracts.[62]
Leea macrophylla	Vata-Kaphashamaka	Pleehapaha.	Starch, Proteins, Reducing sugars, Tannins, Saponins, Fats, and Alkaloids.[69]	2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging effect, FeCl3 reducing effect, superoxide scavenging effect, and iron chelating effect.[63]

*Sharma. P.V. Dravya-Guna Vigyan. Vol. 2. Varanasi: Chaukhambha Bharati Academy, Reprint 1998

DISCUSSION

Among 426 drugs, 12 herbs from 4 Vargas are mentioned as Kamalahara (drugs which cure Jaundice or Hepatoprotective). Except herbs, Navneeta, Ghrita, Kanta Lauha and Hingula are also mentioned as Kamalahara. 14 herbs are specially mentioned as Pleehahara (drugs that cure splenic disorders). Among those, maximum number of drugs are from Guduchyadi varga and most of the drugs which act as Kamalahara having Kapha-Pittashamaka (which alleviates Kapha and Pitta), while drugs mentioned as Pleehahara are Vatakaphashamaka (which alleviates Vata and Kapha). Panchakola is only compound formulation in the list mentioned as Pleehahara. Almost all herbs mentioned as Kamalahara and Pleehahara in the table except Vanshalochana, are proven as hepatoprotective by experimental studies. Hepatoprotective effect of *Trichosanthes palmate* is not studied separately but it's anti-oxidant effect is established, by which we can consider it's beneficence in liver diseases. As Charaka opined in Chikitsa sthan 13th chapter (Charaka Samhita) in Udara chikitsa that the drugs which are mentioned for Pleehodara (distended abdomen due to splenomegaly), most of them are useful for Yakriddalyudara (distended abdomen due to hepatomegaly), which is also proved by experimental studies.

The drugs mentioned in the lists are beneficial in various types of liver diseases, acting as Antihepatotoxins agents, Hepatotropic agents or Hepatoprotective agents. Anti-hepatotoxins agents are drugs which antagonize the effects of any hepatotoxins. Hepatotropic agents are those drugs which generally support or promote the healing process of the liver and Hepatoprotective agents are those drugs which prevent various types of liver affections. Generally any hepatoprotective agent can act as an anti hepatotoxic or hepatotropic agent but the vice versa is always not true.[70] *Citrullus colocynthis* can be considered as Anti- hepatotoxic agents, *Ricinus communis* as Hepatotropic and *Terminalia chebula* as one example of Hepatoprotective agents. But in practice these activities cannot be easily distinguished from each other.

Kamala is the commonest disease of Yakrit (liver) mentioned in classics. Various Yakrit Vikaras are mentioned in Ayurvedic classics like Yaokriddalyodara, Kamala, Kumbhaka, Hallimaka, etc. All of them are interrelated and can be correlated with hepatomegaly, ascites, jaundice etc. in contemporary science. There are various types of liver diseases broadly classified as Acute Parenchymal diseases, Chronic Liver diseases, Autoimmune, Genetic, Neoplasm, Drug-induced and Diseases due to Hepatobilliary obstruction. There are various biological, physical and chemical agents act as hepatotoxins and produce liver diseases. Hepatotoxins act mainly due to inducing lipid per oxidative damage, forming free oxygen radicals, increasing apoptosis and reducing glutathione in liver. Hepatoprotective drugs are the drugs which prevent liver diseases. Large numbers of drugs obtained from plants are endowed with hepatoprotective claims either directly or indirectly. Hepatoprotective effects of herbal drugs are studied against various toxic chemicals like Paracetamol, CCl4, alcohol, β-Galactosamine, Thioacetamide, Nimusalide, Isoniazid, Rifampicin, Arsenic, etc. at different dose with variant time duration which may be *in-vitro* or *in-vivo*.

The Hepatoprotective mechanisms are included as an increase in antioxidant level / decrease in oxidants (ROS formation), inhibition of cytochrome P-450, increase and decrease level of liver enzymes, reduced peroxidation / lipid peroxidation and increase in level of glutathione. Several phytomolecules including flavonoids, alkaloids, glycosides and saponins obtained from various plant sources have been reported as potent hepatoprotective agents.

According to Ayurveda concept, Yakrit is moola of Raktavahasrotas. Rakta and Pitta has Ashraya Ashrayee (substratum and subsistence) relationship so mostly Yakrit Vikaras (liver diseases) are occurred due to vitiation of Pitta, so most of the drugs mentioned for Yakrit Vikara (Liver diseases) or Kamala are Kapha- Pittashamaka either due to Tikta (bitterness), Kashaya (astringent) Rasas or Madhura Vipaka or Sheeta Veerya. Kamalahara or hepatoprotective activities of those drugs are basically due to Pittashamaka or Yakriduttejaka (chloretic) or Pitta- saraka (cholagogue) or Anuloman or Rechaka (laxative or purgative) properties. Virechana karma (purgation) is known to be best in the cases of Pittaja Vikara (diseases due to vitiation of pitta), so they are considered to be beneficial in Kamala. The Deepana (drugs which kindle gastric fire) and virechaka (laxatives/purgatives) drugs used for the management of chronic liver disease can regulate and strengthen the liver and gastrointestinal system or may prevent the absorption of harmful substances and indirectly decreases ascites.

Plant secondary metabolic compounds with the cholagogue and choleretic action are important therapeutic agents for the treatment of cholestasis and hepatobiliary disorders, which may be substantiated with Pittarechaka and Yakridutejaka karma.

CONCLUSION

Yakrit is a major vital organ having different important functions and prone to various type of disorders due to various biological, physical, chemical and genetic factors. The drugs used for Yakrit Vikara are basically Pittashamaka, Pittasamshodaka in nature. The herbs described in Bhavaprakasha Nighantu as Kamalahara, Yakrit Vikarahara, Pleehahara/Pleehaghna are established as Hepatoprotective, Anti-hepatotoxic and Hepatotropic by various experimental and clinical studies. The herbs mainly produce hepatoprotective action by anti-oxidant properties as well as increasing glutathione, reducing lipid peroxidation and inhibiting Cytochrome P450. Pittarechaka and Yakridotejaka drugs are effective by their cholagogue and choleretic activity. These drugs could be taken for higher studies in term of clinical validation in future.

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