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Ayurvedic Intervention for Hepatobiliary Disorders: Current Scenario and Future Prospect

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Abstract

Hepatobiliary diseases include a heterogeneous group of diseases of the liver and biliary system affecting more than 50% population ranging from Non-alcoholic fatty liver diseases, gall stone, hepatitis to hepato-cellular carcinoma. Ayurveda has been using to treat several liver ailments, but its efficiency is poorly documented by means of scientific studies. High number of Aurveda liver tonics has been prescribing for chronic liver diseases and G.I. disorders. Thirteen classical Ayurveda formulations and eight medicinal plants mostly used by Ayurveda were reviewed along with scientific studies. Arogyavardhini vati is highest prescribing medicine in liver disorders. Haridra, Katuki, chireeta, punnanava, kiratatikta, Bhumi amalaki are commonest single herb used by the herbalist and Ayurveda physician in the treatment of Jaundice and other liver disorders. Many grey areas of hepato billiary disorders can be addressed through scientific research in Ayurveda.

Keywords: Hepato–biliary diseases; Kamala; Kumbha kamala; Halimaka Pandu; Jalodara; Yakritdalha dara; Yakritpliha dara; Yakrit kshaya; Pittaasmari (cholithiasis); Argyavardhini vati; Phalatrikadi kwatha

Introduction

Ayurveda is traditionally skillful and treating liver diseases since centuries and the drug toxicity appears to be less as compared to conventional medicine. Currently available medical therapies for liver disorders have more systemic toxicity therefore physicians hesitate to administrate modern medicine for long term use [1]. Clinical and animal research in this century has confirmed the efficacy of several medicinal plants and herbo-mineral compounds described in Ayurveda in the treatment of liver disease, it may be cause for patients with chronic liver disease seek primary or adjunctive herbal treatment and it is a common occurrence observed all over the globe [2]. Hepato biliary diseases are the serious ailments and the medical treatment scenario is worsened day by day for lack of proven precise therapeutic regimens. There are many plants and their extracts that have been shown to possess hepato-protective activities [3]. There are more than three hundred herbo-mineral preparations in Indian system of medicine for the treatment of jaundice and chronic liver diseases. More than 50% people of our country relay on Ayurveda and herbal medicine for liver diseases. Undoubtly Ayurveda herbs and products having defined biochemical active component can protect liver from oxidative stress, promote virus elimination, block fibrogenesis, anti-inflammatory, immune-modulating, liver regenerating and inhibit tumour growth *in vitro* and *in vivo* studies [4-6]. A number of Ayurveda liver preparatory medicines are available in market but their efficacy were commended by various authors for lack of evidence and proper medication [7,9]. Some Ayurveda drugs are reported as hepatotoxic also [10]. The efficacy and safety of currently available treatments is still unsatisfactory, much effort has been spent searching a better treatment strategies in AYUSH system.

Hepatobiliary disease includes a heterogeneous group of diseases of the liver and biliary system caused by viral, bacterial, and parasitic infections, neoplasia, toxic chemicals, alcohol consumption, poor nutrition, metabolic disorders, and cardiac failure. The hepatic disorders includes from viral hepatitis, other inflammatory liver diseases, liver damage due to alcohol and toxin, neoplasia of liver, cystic liver diseases, vascular liver disorders and amyloidal liver disease [11]. Biliary system also constitutes a diverse spectrum of diseases affects the gall bladder and bile duct, often presenting with similar clinical signs and symptoms of liver diseases. Bile is produced by the liver and is channeled by the biliary ductal system into the intestinal tract for the emulsification and absorption of fats. Biliary disease is caused by abnormalities in bile composition, biliary anatomy, or function. The exact incidence of hepato biliary disorders are not found but it affecting more than 50% population ranging from Nonalcoholic fatty liver diseases, gall stone, hepatitis to hepato cellular carcinoma. In about 80% of patients, gallstones are clinically silent. Approximately 20% of patients develop symptoms over 15-20 years, that is, about 1% per year, and almost all become symptomatic before complications develop. About 20,000 deaths found every year due to liver disorders. Hepatotoxicity from drugs and chemicals is the commonest form of iatrogenic diseases. Inorganic compounds producing hepatotoxicity are Arsenic, Phosphorus, Copper and Iron. Some Organic agents including certain naturally occurring plant toxins such as Pyrrolizidine alkaloids, mycotoxins and bacterial toxins have known hepato toxicity effect [12,13]. Jaundice is the commonest presentation of patients with liver and biliary disease [14]. The cause can be established in most cases by simple non-invasive tests, but many patients will require referral to a specialist for management. Liver function tests routinely combine markers of function (albumin and bilirubin) with markers of liver damage (alanine transaminase, alkaline phosphatase, and ã-glutamyl transferase). Abnormalities in liver enzyme activities give useful information about the nature of the liver insult like a predominant rise in alanine transaminase activity (normally contained within the hepatocytes) suggests a hepatic process. Serum transaminase activity is not usually raised in patients with obstructive jaundice, although in patients with common duct stones and cholangitis a mixed picture of raised biliary and hepatic enzyme activity is often seen [15]. Ultrasonography is the most cost-efficient,

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sensitive, and accurate method for screening of most of the liver diseases. Unfortunately, conventional and synthetic drugs used in the treatment of hepato biliary diseases are inadequate and sometimes can have serious side effects.

Ayurveda Literature in Hepato Biliary Disorders

Ayurveda is a whole medical system that is based on various theories about health and illness and on ways to prevent, manage, or treat health problems. The liver is a well-known organ for Ayurveda. In Vedas, "Takima" or "Yakna" words are used for liver. The synonyms words like-Kalakhanda, Jyotisthana, Yakritkhanda, Yakritpinda, Raktadhara and Raktashaya are found in the ancient literature for liver. Yakrit comes from Sanskrit word i.e., yat (conversion) and krit (to do). It is also narrated as yakrit sabita (liver is sun) in vedic literature from the liver can be manifested as allergies, high cholesterol, hypoglycemia, constipation, digestive problems, or fatigue. If the imbalance continues for a long time, serious diseases of the liver, including hepatitis, cirrhosis, jaundice and cancer, could develop. Ayurveda mostly nomenclature the diseases as per functional abnormities but yakrit roga, grahani, and hrud roga are named as per morphological and anatomical abnormalities.

Ayurveda classics like-Caraka Samhita, Susruta Samhita, Astanga Hrudaya, Gada Nigraha, Bhavaprakash, Madhava nidana, Chikitasa manjari, etc. had described the hepato biliary diseases either in kamala (Jaundice) or in Udara roga (abdominal disorders) context. A significant number of liver diseases are described in Ayurveda like-Kamala, Kumbha kamala, halimaka Pandu, Jalodara (Ascitis), Yakritdalhadara (heptomegaly), Yakritpliha dara, Yakrit kshaya (cirrhosis of liver), Pittasmari (cholithiasis) etc. Ayurveda physician relay the treatment of Udara roga (abdominal disorder) to treat hepato biliary disorders [16]. Panchakarma Intervention is advisable in Shakha srita kamala. Virechan (medicated purgation) is the best among all sodhana procedures. A number of classical formulation for liver diseses like-Arogya vardhini vati, lokanath rasa, yakrutdari lauha, rohitaka lauha, yakrit plihadari lauha, yakrit plihadara churna, kumaya sava, PatolaKaturohinyadi kashayam, Rohitakarista, punnanvadi kasaya, kokilashyadi kasaya, etc. [17]. More than sixty percent of jaundice patients of our country have the first choice to visit to traditional healers for their treatment. Seeff et al. found that 41% of outpatients with diagnosis of liver disease have history of use herbal medicine [18,19]. The medicinal plants having rechana (purgative), mutrala (diuretics), vata samaka, agnivardhaka (carminative), ama, meda and kapha nasak qualities are preferable for hepato biliary disorders. Picroliv-*Picrorrhiza kurroa*, Andrographiloid-Andrographis paniculata, Phyllanthin-Phyllanthus niruri, Wed elolactone-Eclipta alba, Glycyrrhizin-Glycyrrhiza glabra. Curcuminoids–Curcuma longa are the Ayurvedic herbs showed potential hepato protective activities in animal model. These herbs generally have strong antioxidative potential and cause induction of antioxidant enzymes like superoxide dismutase, reduced glutathione and catalase. The mechanisms of hepato-protection include stimulation of heme oxygenase-1 activity, inhibition of nitric oxide production, hepatocyte apoptosis and nuclear factor-κB activation [20]. Saman grita like Panchagabya grita, Rohitaka grita, Panchakola grita, Amalaki grita are described in Ayurveda for treatment of liver diseases. Virechana (Medicated purgation) is the treatment of choice in liver disorder specially Jalodara [21]. Vardhama pippali yoga is said to be effective in hepatic cirrhosis which was varied by clinical study [22].

Ayurveda Products/Herbs for Hepato Billiary Disorders

Arogyavardhini vati

It is a classical polyherbo-mineral formulation mentioned in Ayurvedic formulary. It has been used for centuries with excellent efficacy and safety in treatment of jaundice, liver disorders, and various skin disorders. It consists of Terminalia chebula (Haritaki) Terminalia bellerica (Bibitaka), Emblica oficinalis (Amalaki), Aspalitum (Silajatu-Suddha), Commipora wightill (Guggulu Shuddha), Ricinus communis (Eranda), *Picrorrhiza kurroa* (Katuka) leaf juice of Azadiracta indica (Nimba) andmetals including Shuddha Rasa (purified mercury), Shuddha Gandhaka (purified sulphur), Laua Bhasma (irom compound in ash form), Abhraka Bhasma (mica in ash form), and Tamra Bhasma (copper compounds in ash form), Abhraka Bhasma (mica in ash form), and Tamra Bhasma (copper compounds in ash form), Abhraka Bhasma (mica in ash form), and Tamra Bhasma (copper compounds in ash form). An experimental study clearly demonstrated the protective effect of well-known Arogyavardhini vati against CCI4 induced hepatotoxicity in rats [23,24] it has proven anti-oxidant properties. It is safe in use although contains copper and mercury. Argyavardinivati along with left juice of Bhumyamlaki (*Phyllanthus frataruns* L.) and Triphla churna have a significant role to clearing of HBSAg and normalise Liver Transminase in Hepatitis B infected patient within 45 days [25]. Argya vardhini vati has good therapeutic utilities in nonalcoholic liver disorders also.

Bruhat lokanath rasa

It is a herbo-mineral compound used in the treatment of spleenomegaly, liver diseases, jaundice, oedema and inflammatory conditions. It contains suddha parada, Gandhaka, abhrabhasma, lauha bhasma, tambra bhasma, varatika bhasma described rasendra sara samgraha in context of pliha chikitasa. It contains heavy metals like-mercury, copper, so long term use can be monitored. It can be used in liver cancer although evidence is not sufficient [26].

Mohamrutunjaya lauha (BR-Yakrit pliha adhikara)

It is the drug of choice in cirrhosis of liver along with other liver disorders. It is preparation of iron, mercury along with arsenic effective in anaemia, relapsing fever and enlarges of spleen and liver [27].

Sarbeswar lauha (BR-Yakrit pliha adhikara)

It is also an excellent unexplored preparation of Bhaisaya ratnabali used in spleeno-hepatomegaly.

Navjeeban rasa

It can increase the functional efficiency of liver, increase enzyme efficiency and increase serum albumin. Thus arouses appetite and built up the body strong [28].

Rudra rasa

Roudra Rasa is a novel Herbo-mineral product of Ayurveda mentioned to treat Arbuda. This product is evaluated clinically and has shown highly encouraging results in the management of liver and other G.I. cancer [29].

Yakrit plihari loha

It is used in the Ayurvedic treatment of all types of ascites, fever, edema, jaundice, bloating, anemia, anorexia, indigestion [30].

Phala trikadi kwatha

Phalatrikadi kvatha contains eight drugs which are having predominately Kamalahara properties like–Pitta-Kapha Shamaka, Yakriduttejaka, Shothahara, Pandurogahara, recana, dipana etc. Kvatha of Triphala (Amalaki, Haritaki and Bibhitaki), Amrita, Vasa, Tikta (Katuka), Bhunimba, and Nimba tvaka taken with Honey relieves Kamala and Pandu. This formulation used for fatty liver [31,32].

Yakrit plihantak churna

Yakrit Plihantak Churna is most effective herbal remedy to treat jaundice, liver damage, fatty liver, liver cirrhosis, etc. [33].

Amalaki grita

Administration of medicated ghee in chronic diseases is the one of the treatment principle of Ayurveda. Amalaki grita is administrated to chronic liver diseases a patient who has good appetite. It has hepatoprotective property [34].

Panchagabya grita

It has wide range of application in Ayurveda. It is used in Kamala. It is hepato protective and antioxidant [35,36].

Rahitaka grita

It is good formulation in chronic diseases. It has chemo protective action [37].

Liv 52

Liv 52 brought a revolution in the biomedical and clinical research in liver diseases. It has 24 clinical papers and 92 experimental studies on liver disorders. It is the highest selling Ayurveda product in India and marketed in 25 countries. Liv 52 has significant effect on the prevention and treatment of viral hepatitis, prophylaxis of adverse effect of chemotherapy in tuberculosis, liver cirrhosis, alcoholic hepatitis etc. [38,39].

Andrographis paniculata (Kirata tikta)

A. paniculata plant extract could repair the hepatic injury and/or restore the cellular permeability, and reducing the toxic effect of ethanol induced liver toxicity and preventing enzymes leakage into the blood circulation. A recent study showed that andrographolide attenuated concanavalin A-induced liver injury and inhibited hepatocyte apoptosis. It has been reported to be efficacious in chronic hepatitis B viral infection [40,41].

Curcuma longa (Haridra)

The pharmacological properties of curcumin were reviewed recently and focused mainly on its anticancer properties. However, its beneficial activity on liver diseases. Curcumin attenuates liver injury induced by ethanol, thioacetamide, iron overdose, cholestasis and acute, subchronic and chronic carbon tetrachloride (CCl(4)) intoxication; moreover, it reverses CCl(4) cirrhosis to some extent. The pleiotropic activities of curcumin derive from its complex chemistry as well as its ability to influence multiple signaling pathways, including survival pathways such as those regulated by NF-kB, Akt, and growth factors; cytoprotective pathways dependent on Nrf2; and metastatic and angiogenic pathways [42-44].

Eclipta alba

Eclipta alba (EA) extract was studied on paracetamol induced hepatic damage in mice. Treatment with 50% ethanol extract of *E. alba* (100 and 250 mg/100 g body weight) was found to protect the mice from hepato-toxic action of paracetamol as evidenced by significant reduction in the elevated serum transaminase levels. Histopathological studies showed marked reduction in fatty degeneration and centrizonal necrosis, in animals receiving different doses of *E. alba* along with paracetamol as compared to the control group [45].

Glycyrrhiza glabra

The active component of Glycyrrhiza glabra (glyccyrrhizic acid, saponin, triterpene) play an important role in arresting production of inflammatory cytokine and protect liver. It also reduces the hepatotoxicity [46].

Picrorrhiza kurroa (Katuki)

Numerous animal studies demonstrated the active constituents of Picrorrhiza kurroa effective in preventing liver toxicity and improve hepatic glycogen preservation. It is effective in hepatis B infection and promising effect on bilirubin, SGOT, SGPT. It has also cytotoxic activities against human breast, liver and prostate carcinoma cell line. It also promotes liver regenerating activities by restoring cytochrome [47,48].

Phyllanthus niruri

Some species of *Phyllanthus* were found to exhibit hepatoprotective activity against drugs or toxins and this property was majorly attributed to phyllanthin and hypophyllanthin. Hepatoprotective activity of five different species of *Phyllanthus*, namely, *Phyllanthus* amarus, *Phyllanthus* fraternus, *Phyllanthus aderaspatensis*, *Phyllanthus urinaria*, and *Phyllanthus Rotundifolius*. The mechanism of action appears to be related to the suppressive effect of Phyllanthus extract on HBsAg secretion and HBsAg mRNA expression and the inhibition of hepatitis B virus polymerase activity. Water extract of P. urinaria induces apoptosis by DNA fragmentation and increased caspase-3 activity, reduces the viability of numerous cancer cells lines probably by telomerase suppression activity, and reduces the angiogenesis as suppressing MMP-2 secretion and inhibiting MMP-2 activity through zinc chelation [49-52].

Swertia chirayita

Swertia chirayita has multiple uses for several liver disorders. It is used for hepatitis, malaria, hepato-toxic disorder, hepatitis, fatty liver, hepato cellular carcinoma. The crude and purified extract significantly inhabited cell proliferation and tissue adopsis [53-55].

Tinospora cordifolia (guduchi)

This plant prevented fibrous changes and promoted regeneration of parenchyma tissue. It as membrane stabilising effect and modulation of kuffer cell activities [56].

Current Practice and Research

Primary Ayurveda treatment in jaundice is mostly seen in rural India and adjuvant Ayurveda treatment along with allopathic medicine is found urburn areas of India. Chronic liver diseases like viral hepatitis, non alcoholic fatty liver disease (NAFLD), cirrhosis of liver, hepato cellular carcinoma are the most common type diseases found in Ayurveda hospital and clinic. Arogyavardhini vati is highest prescribing medicine in liver disorders. Katuki, chireeta, punnanava, kiratatikta, bhumi amalaki are commonest single herb used by the herbalist in the treatment of Jaundice. Some of the Ayurveda formulations like-

phaltrikadi kwatha and Lokanath Rasa, Rudra Rasa are still in practice in Nonalcoholic Fatty Liver Disease (NAFLD), viral hepatitis B and hepato cellular carcinoma survival. Yogaraj Gugulu and Varunadi Kasaya are the best medication for solitary cholilithiasis as dyslipidimia is the major laying factors [57]. Administration of medicated ghee is limited in liver disorders. Curently it only used in haemolytic jaundice patient whose appetite is good.

There is no doubt that certain herbal products contain chemically defined components that can protect the liver from oxidative injury, promote virus elimination, block fibrogenesis, or inhibit tumor growth. Although additive effects may be lost, the active molecules must be isolated and tested in suitable culture and animal experiments and finally in randomized, placebo-controlled studies to enable rational clinical use of the agents. It is very interesting to note that institutional qualified Ayurveda doctors and Ayurveda teaching and research institutes have less numbers of hepato biliary patients compared to the traditional practitioners and herbalist in rural areas of our country. It arise the question whether institutional qualified Ayurveda doctors and Ayurveda teaching and research institutes have not accepted by people or they are not competent enough to reach the confidence of people. Lack of awareness creation and evidence based practices are the key component to be addressed properly for future development. Central council for research in Ayurveda Sciences (CCRAS) is the apex body Under Ayush ministry of our country engaged to create evidence in Ayurveda practices. Recently CCRAS has renamed NRIADD, Bhubaneswar to Central Ayurveda Research Institute for hepato billiary disorders and invited research projects on different prevalent diseases of hepato billiary system. Many grey areas of hepato billiary disorders can be address through these research such as Safe and effective Ayurveda medicine for NAFLD, Alcoholic liver disorders, antiviral activities of Ayurveda formulations, Sero converting medication in hepatitis B, Ayurveda drug causing hepato-toxicity, survival outcome of hepato cellular carcinoma, anti-fibrotic, anti-cirrhotic agent and regenerative potential for chronic liver diseases from Ayurveda liver protective, new hepato protective herbs leads from folk lore claims, modern medicine & Ayurveda drug interaction and hepato toxicity etc. Ayurveda is used to treat several liver ailments, but its efficiency is poorly documented by our physician and hence debated and many times critisied by modern medicine practitioners commonly claiming effective therapies. Hepato biliary diseases has an interesting philosophical background with a long history, but it received increasing scepticism due to the lack of evidence based efficiency as shown by high quality trials. Hepatotoxicity and drug interactions are commonly published with some Ayurveda medications. Some scientist criticise its efficacy as placebo effect and explained by modulation of nuro-endo immune system. Sometimes Ayurvedic compounds in India are often taken after the development of hepatitis like illness and the high rate of heavy metal contamination in the remedies result in a more dominant non hepatic organ involvement. Key issues of presently available classical ayurveda medicine and newly developed herbal medicines will have to focus on questions as to whether the benefit risk balance is appropriate and on monitoring safety and efficacy on liver diseases.

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