Indigenous Herbal Recipes for Treatment of Liver Cirrhosis

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Abstract

Hepatic fibrosis and its end-stage sequelae of cirrhosis and liver cancer are major causes of morbidity and mortality throughout the world and their prevalence is rising, largely due to the increasing impact of chronic viral hepatitis and non-alcoholic steatohepatitis (NASH). Therapies currently available are only to manage patients suffering from or progressing to liver cirrhosis. In Western medicine the lack of treatments to target the arrest or reverse the progression of disease hampered the clinicians to successfully treat these patients with established cirrhosis. This review focused on the Hepatic fibrosis and importance herbal medicines for prevention and treatment of chronic liver diseases.

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1. Introduction

The use of medicinal plants for treatment of various diseases has been practiced for centuries in the Asian continent. It is thought that indigenous medical practice of Sri Lanka was introduced from India long ago. However, historical evidence indicates that a traditional system of veterinary medicine existed even 5000 years ago during the time of King Rawana. The Indian ayurvedic system came to Sri Lanka, especially with the advent of Buddhism around 2600 years ago, where a group of "Ayurvedic" specialists accompanied "Mahinda Thero" when he came to "Mihintale". On the other hand, Siddha system of medicine came to Sri Lanka with the Hindu Tamil migrants and Uani system came with the Muslim merchants who came to Sri Lanka. Thus, indigenous medical practices of Sri Lanka became a mixture of all these systems, but still the traditional system of medicine is being practiced. The practice of indigenous medicine in Sri Lanka was reaching the peak during 337 to 365 A.D. at the time of king "Buddadasa". However, with the invasion of the western power the practice of indigenous medicine was gradually declined but is still being practiced in isolated pockets in remote areas of the country.

In the monographs of indigenous medical practices valuable information on diagnosis, rationales of the treatment with prognosis are described for various diseases, including respiratory, urogenital, nervous, musculoskeletal, gastro-intestinal disorders as well as external disease conditions such as wounds, broken bones/horns, skin diseases. According to the indigenous medical practice, a part or whole of a single plant or mixture of various parts of plants including flowers, rhizomes, stems, fruits, roots, tubers, leaves, stem-barks, seeds are used to make various herbal preparations including decoctions, juices, powders, oil extracts. The unique feature in indigenous veterinary medicine is that, for the same disorder the type and part of plants and their proportions used can vary with the locality/region or with the practitioner. The herbal recipes are usually combined with tattooing and do inchantment (a formula of prayer addressed to a deity or devil).

2. Hepatic Fibrosis and Historical Perspective

Hepatic fibrosis and its end-stage sequelae of cirrhosis and liver cancer are major causes of morbidity and mortality throughout the world and their prevalence is rising, largely due to the increasing impact of chronic viral hepatitis and non-alcoholic steatohepatitis (NASH). It is hoped better disease prevention and more effective antiviral therapies will help reduce this disease burden. However, there remains a major need both to understand the mechanisms involved in hepatic fibrosis in order to design treatments that prevent liver scarring, and to develop better therapies for the treatment of cirrhosis and its complications.

Liver fibrosis results from chronic damage to the liver in conjunction with the accumulation of extra cellular matrix (ECM) proteins, which is a characteristic of most types of chronic liver diseases. The main causes of liver fibrosis include chronic HCV infection, alcohol abuse, and nonalcoholic steatohepatitis (NASH). The accumulation of ECM proteins distorts the hepatic architecture by forming a fibrous scar, and the subsequent development of nodules of regenerating hepatocytes defines cirrhosis. Cirrhosis produces hepatocellular dysfunction and increased intrahepatic resistance to blood flow, which result in hepatic insufficiency and portal hypertension, respectively. Hepatic fibrosis was historically thought to be a passive and irreversible process due to the collapse of the hepatic parenchyma and its substitution with a collagen-rich tissue.

Currently, it is considered a model of the wound-healing response to chronic liver injury. Early clinical reports in the 1970s suggested that advanced liver fibrosis is potentially reversible. However, liver fibrosis received little attention until the 1980s, when hepatic stellate cells (HSCs), formerly known as lipocytes, Ito cells, or perisinusoidal cells, were identified as the main collagen-producing cells in the liver. This cell type undergoes a dramatic phenotypic activation in chronic liver diseases with the acquisition of fibrogenic properties. Methods to obtain HSCs from both rodent and human livers were rapidly standardized in the 1980s and prolonged culture of HSCs on plastic was widely accepted as a model for the study of activated HSCs and the key signals that modulate HSCs’ fibrogenic actions were delineated. Experimental models for studying liver fibrogenesis in rats and in transgenic mice were developed, which corroborated the cell culture studies and led to the identification of key fibrogenic mediators.
At the clinical level, the natural history of liver fibrosis, from early changes to liver cirrhosis, was delineated in patients with chronic HCV infection. Rapid and slower fibrosers were identified, and genetic and environmental factors influencing fibrosis progression were partially uncovered. Since the demonstration, in the 1990s, that even advanced liver fibrosis is reversible, researchers have been stimulated to identify antifibrotic therapies. Biotechnology and pharmaceutical companies are increasingly interested in developing antifibrotic programs, and clinical trials are currently underway. However, the most effective therapy for treating hepatic fibrosis to date is still to remove the causative agent.

A number of drugs are able to reduce the accumulation of scar tissue in experimental models of chronic liver injury. Recently, NASH has been recognized as a major cause of liver fibrosis. First described by Ludwig et al. it is considered part of the spectrum of nonalcoholic fatty liver disease. These range from steatosis to cirrhosis and can eventually lead to hepatocellular carcinoma. NASH is a component of the metabolic syndrome, which is characterized by obesity, type II diabetes mellitus, and dyslipidemia, with insulin resistance as a common feature. As the prevalence of obesity is rapidly increasing, a rise in the prevalence of NASH is anticipated. Three systems that have been attracted much attention in liver fibrosis and portal hypertension to date includes endothelin system, sympathetic adrenergic system and the renin angiotensin system (RAS). However, the RAS blockers and agonists have been shown to be the most promising drugs, and the testing of these compounds in human liver diseases await the data generated from experimental animal models.

3. The Rennin Angiotensin System and Hepatic Fibrosis

Authors’ group has played a leading role in establishing that angiotensin (Ang) II, a key effector peptide of the renin angiotensin system (RAS), plays a central role in the pathogenesis of hepatic fibrosis and its complications. This work has stimulated major interest in the potential therapeutic role of RAS blockade in liver disease. In addition to establishing the central role of Ang II, authors have shown that there is an alternate, angiotensin converting enzyme 2 (ACE2) dependent arm of the RAS which is activated in both experimental and human chronic liver disease and opposes many of the vasoconstrictive and profibrotic effects of Ang II and may contribute to vasodilatation in cirrhosis.

The demonstration that stellate cells, key effectors of hepatic fibrosis, contract, proliferate, and produce profibrotic cytokines and collagen I in response to Ang II suggested that this peptide stimulates fibrogenesis via its direct effect on these cells. Studies using RAS inhibitors showed that the RAS plays a major role in the pathogenesis of hepatic fibrosis. These findings are now supported by a range of subsequent studies which have shown that angiotensin converting enzyme (ACE) inhibitors and Ang II type 1 receptor (AT1) blockers attenuate liver fibrosis and down-regulate key inflammatory and profibrotic cytokines.

4. The ACE2/Ang-(1-7)/Mas Axis in Chronic Liver Disease

The classical view of the RAS is of a linear cascade in which ACE is a key enzyme, converting Ang I to the potent vasoconstrictor and profibrotic cytokine Ang II, which acts via the AT1 receptor. It is now known that there is an alternate arm of the RAS in which ACE2, a homologue of ACE, degrades Ang II and generates Ang-(1-7), which in contrast to Ang II, has vasodilatory, anti-growth and anti-proliferative actions. These effects are mediated in part by the Mas receptor, a G protein-coupled receptor (GPCR). This ACE2/Ang-(1-7)/Mas axis is thought to intrinsically regulate the RAS system by reducing Ang II levels and producing Ang-(1-7), thus counterbalancing the potentially harmful effects of Ang II (Figure 1). Infusion of Ang-(1-7) into cirrhotic rats ameliorates fibrosis induced by bile duct ligation.
5. Herbal Treatments for Liver Fibrosis

Herbal medicines have been used in the treatment of liver diseases for a long time in different parts of the world including China, India, Iran, Japan, Mexico, Sri Lanka, and several other countries. Diagnosis and treatment of liver fibrosis with integrative Chinese Medicine is well established. Several reports have demonstrated a prophylactic and therapeutic role of Chinese Medicine herbal formulas on liver fibrosis. “BJ-JN” is a traditional Chinese formulation and has an anti-oxidant activity and inhibitory activity on the activation of hepatic stellate cells (HSCs) in rats with hepatic fibrosis induced by CCl4, and a significant reduction in the proliferation of HSCs in vitro, leading to a significant reduction in collagen secretion.

The regulation of ‘redox’ state within the tissue by “Yinchenhao Decoction” and “Huangqi Decoction” has been suggested as a potential mechanism by which they counter hepatic fibrosis in rats. Thus, whilst “Yinchenhao Decoction” is responsible for elimination of hepatic lipid peroxide levels, “Huangqi Decoction” appears to enhance anti-oxidative ability of the tissue. Moreover, “Yi Guan Jian” acts against hepatocyte apoptosis and HSC activation, resulting in a diminished hepatic fibrosis. The “TCM 319” is also a Chinese Medicine formula consisting of six Chinese herb extracts attenuated hepatic fibrosis induced by CCl4 in rats. The anti-fibrotic effect of TCM 319 recipe has been shown to be associated with down-regulation of gene expression of tissue inhibitor of matrix metalloproteinase 1 (TIMP-1), platelet derived growth factor (PDGF-B) and PDGF-Rbeta, which were accompanied by reduced protein expression of PDGF-Rbeta and transforming growth factor-beta 1 (TGF-beta1).

Treatment with “BushenRougan Recipe” (BSRGR), another traditional Chinese herbal medicine, decreases the expression of collagen type I and connective tissue growth factor (CTGF) mRNAs in rats with hepatic fibrosis. Furthermore, “Dan-shao-hua-xian” capsules, preparations of traditional Chinese medicine enhance the expression of PPAR-gamma but decrease that of TNF-alpha and NF-kappaB in the fibrotic liver of rats induced by CCl4 administration. Furthermore “Danshensu”, “Baicalin”, “Astragalus” and “Panaxnotoginsengsaponins (PNS)” four other Chinese herb products have been shown to ameliorate hepatic fibrosis in rats by mechanisms that exert inhibitory action on proliferation and expression of type I and type III collagen by HSCs. Collectively, these findings suggest that Chinese herbal preparations can block the progression of hepatic fibrosis and have both prophylactic and therapeutic potential in the treatment of cirrhosis.

The protective effect of “Liv-52” an Iranian herbal preparation on liver cirrhosis has been reported. These protective effects were associated with anti-inflammatory, anti-oxidative and immunomodulating properties of the components in the herbal preparation. It has also been reported that methanol extract of aerial parts of Leucophyllum frutescens, a Mexican plant, is hepatoprotective. The observations by Chinese, Iranian and Mexican investigators are supported by a Japanese study in which a traditional Japanese medicines “Hochu-ekki-to” and “Ninjin-youei-to” have been demonstrated to be effective as anti-fibrotic agents, and may exert their action by...
inhibiting pro-fibrotic cytokine production, resulting in the suppression of collagen synthesis and secretion into extracellular matrix in the liver\textsuperscript{39}. In support of these findings there are several indigenous Sri Lankan herbal preparations that are available for the treatment of end stage cirrhosis\textsuperscript{3–5}. Few such recipes are given in Appendix A.

Drugs currently available are only to manage patients suffering from liver cirrhosis and its complications such as variceal bleeding associated with portal hypertension. In Western medicine the lack of treatments to target the arrest or reverse the progression of disease hampered the clinicians to successfully treat these patients with established cirrhosis. At present, the use of herbal medicines for prevention and treatment of chronic liver diseases is in the focus of attention for both the physicians and the patients; the reasons for such shift towards the use of herbals include a considerable cost of conventional drugs, adverse drug reactions, and their inefficacy\textsuperscript{38}. A successfully treated case of severe acute hepatitis with severe liver dysfunction in a 45-year-old well-nourished, healthy man with “Inchinko”, a Chinese herbal medicine has been described and its hepatoprotective and choleric effects were identified\textsuperscript{40}. These therapies include several stages of treatment depending on the condition of the patient\textsuperscript{3–5}. Therefore, extensive research should be carried out to investigate the therapeutic efficacy of indigenous herbal recipes in progressive liver fibrosis.

6. Conclusions

Identification of the active ingredients of herbal recipes will help to develop therapeutic strategies to arrest the progression of liver injury into liver cirrhosis. A reduction in fibrosis will be expected to improve portal hypertension, a life threatening complication of cirrhosis and thus, they can be efficiently utilized to reduce the death rate due to the end-stage liver cirrhosis and portal hypertension.

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Appendix A. Some herbal recipes available for complete cure of liver disease in indigenous Sri Lankamedicine

A.1. Recipe 1

The rhizome of *Zingiber officinale*, the seeds of *Coriandrum sativum*, the fruit of *Solanum virginianum* the roots of *Solanum melongina*, the heartwood of *Polyalthia longifolia*: 11g each, add 0.8 L of water boiled down to 0.1 L on slow fire. Use after adding Rock salt and the seed powder of *Piper longum*.

A.2. Recipe 2

The fruits of *Terminalia chebula* and *Phyllanthus emblica*, the seeds of *Piper longum* and *Coriandrum sativum*, and Rock salt equal amounts, roast and grind. Boil infusion of below ingredients: the rhizome of *Zingiber officinale*, the seeds of *Coriandrum sativum*, the fruit of *Solanum virginianum*; equal amounts of each ingredient. Mix and add some sugar.

A.3. Recipe 3

The rhizome of *Zingiber officinale*, the seeds of *Piper longum*, *Piper nigrum*, *Coriandrum sativum*, *Nigella sativa*, *Cuminum cyminum*, *Brassica juncea*, *Elettaria cardamomum*, the bark of *Cinnamomum verum*, *Kokoona zeylanica*, the leaves of *Cinamomum tamala*, *Picrorhiza kurrooa*, the aril and kernel of *Myristica fragrans*, the immature nut of *Syzygium aromaticum*, the flowers of *Messua ferrea*, Carbon, Rock salt, impure Sodium chloride, Black salt, Yawakaralunu; take equal amounts, roast, grind and give with warm water.
A.4. Recipe 4

The seeds of *Holarrhena antidysenterica*, *Macrotyloma uniflorum*, the cotyledons of *Caesalpinia bonduc*, *Lagenandra lancefolia*, the fruits of *Terminalia chebula*, the gum of *Ferula assafoetida*, the rhizome of *Acorus calamus*, the roots of *Aristolochia indica*, the seeds of *Macrotyloma uniflorum*, Rock salt; Take equal amounts. Roast, grind and dissolve powder in hot water. Add the fruit juice of *Citrus aurantifolia* and gingerly oil.

A.5. Recipe 5

The rhizome of *Zingiber officinale*, *Cucuma longa*, the seeds of *Piper nigrum*, *Piper longum*, *Elettaria cardamomum*, *Coriandrum sativum*, *Cuminum cyminum*, *Nigella sativa* and *Holarrhena antidysenterica*, *Macrotyloma uniflorum*, *Citrus aurantifolia*, *Caesalpinia bonduc*, *Fe rula assafoetida*, *Holarrhena antidysenterica*, *Macrotyloma uniflorum*, *Acorus gramineus*, the tubers of *Languas galanga*; equal amounts, roast, grind and add to warm water.

References


