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A Critical Review of Indian Medicinal Plants for Hepatocellular Carcinoma

Dr. Narendra Bhatt[1], Dr. Manasi Deshpande[2]
[1]Consultant Ayurveda – Research & Industry, CRIA Consultants Pvt. Ltd. 15, Bachubai Building, J.Bhatankar Marg, Parel, Mumbai 400 012,
[2]Professor and Head, Department of DravyagunaVigynan, Bharati Vidyapeeth [Deemed to be University] , College of Ayurved, Pune, 411043

***Corresponding author:** Dr. Manasi Deshpande

ABSTRACT: Progression of chronic liver disease to hepatocellular carcinoma is not uncommon in India. Approximately 22,000 new cases of primary liver cancer are reported annually in the country. HCC is very complex and unique when compared with other cancer types. Treatment such as surgical resection, ablation, and chemo-embolization is useful only to selected patients. Over all very low (4%) survival rate of HCC underlines the limitations in treatment options and marks it as cause of major health burden. At present, liver transplantation remains the only curative option for the patients of cirrhosis and end stage liver diseases.
The etiology and pathology of HCC is not clearly defined in detail in the Indian system of medicines. But tumors are discussed under the names various ASU terminology to designate basic common neoplasms, which can appear in any tissue or organ of the body. Both allopathic and ASU systems generally refer to neoplasms as the uncoordinated abnormal cell growth found within particular organs or body tissues.
The Indian systems of medicine are the oldest traditional medicinal systems offering treatments for chronic liver diseases and cirrhosis for centuries. A large number of single and compound drug formulations are documented to have benefit over chronic liver conditions as hepatic tonic. The therapeutic benefits offered by various ASU formulations in treatment of chronic liver diseases have however not much explored in treatment of HCC. Experiments on animals and cell cultures have shown that some potential plants can alleviate and prevent pathological changes in the liver.
The present paper is an attempt to list the plants with hepatoprotective and related beneficial effects which are used in Indian system of medicines. An attempt has been made to provide details on validation of certain potential plant drugs for anticancer and anti-metastatic properties against hepatocellular carcinoma.

KEY WORDS: Liver disorders, HCC, Hepatoprotective, Phytochemicals, Ayurveda, Indian Medicinal plants

INTRODUCTION

Liver is the fundamental organ for digestion and metabolism of medicines (1). Liver disease accounts for approximately two million deaths per year worldwide, one million due to complications of cirrhosis and one million due to viral hepatitis and hepatocellular carcinoma. Cirrhosis is currently the 11th most common cause of death globally and liver cancer is the 16th leading cause of death; combined, they account for 3.5% of all

deaths worldwide. Cirrhosis [Ch] is within the top 20 causes of disability-adjusted life years and years of life lost, accounting for 1.6% and 2.1% of the worldwide burden (2). Progression of chronic liver disease to Hepatocellular carcinoma [HCC] is not uncommon in India. Approximately 22,000 new cases of primary liver cancer are reported annually in the country. (3)

HISTORY

The natural history of HCC is variable. The concept of early cancer has been evolving during the last two decades. In many patients the tumour has a long-lasting subclinical incubation period and often grows as a solitary mass to a size at which it can be detected by ultrasound. In other patients, however, the onset of the tumour is multi-nodal with great variations in the growth rates. Prognostication of patients with HCC takes into account the size and number of tumour nodes and their relation to the portal veins, and the degree of liver impairment (4). Surveillance of patients with cirrhosis has led to an increasing number of cancers detected early in the form of small nodules that first appear as well-differentiated tumours and proliferate along with gradual dedifferentiation [5].

BACKGROUND AND METHODOLOGY

Various scientific research and review articles/papers are available on Liver diseases/ Liver disorders in ASU systems (6-16).Several reviews have provided major contributions to the current knowledge on the herbal medicines for treatment of various liver disorders. Published papers are reviewed to provide understanding of the use of herbal medicine against HCC.

A series of reviews undertaken by *Bhatt et al* specific to therapeutic approach and use of certain plants in various liver disorders including Cirrhosis and HCC based on principles of Indian System of Medicine [ISM], these reviews summarised the information about hepatoprotective herbal drugs used in traditional medicine for the treatment of liver diseases (12-16).

However, the therapeutic benefits offered by ISM in the treatment of chronic liver diseases as HCC has not been explored much. In this review, an attempt has been made to explore the potential plant drugs and mineral/metals from ISM for the treatment of Cirrhosis and Heapatocellular carcinoma.

LIVER DISORDERS IN INDIAN SYSTEM OF MEDICINE

Liver and its dysfunctions are well defined and described in ISM. In fact, the significance of liver in the context of blood as an important constituent of human biology is specific to all the systems of medicine. In ISM classics, the aetiology and pathology of Liver disorders are defined. According to Ayurved and Siddha, liver is an important organ actively involved in metabolic functions and location of *Pitta* [*ranjak pitta*] and *Rakta dhatu* [Blood]. Unani system is also considered liver as a source of *hararat-e-ghariziya* (innate heat) for body. When it does not function well, vitiation of *dosha*, derangement of temperament of humours may produce various types of Liver disorders. Similarly, few diseases, which are not treated in time, may cause damage to liver structure/ functions. The different types of liver diseases are largely classified according to the cause of the specific problem in the modern science (17-22).

HEPATOCELLULAR CARCINOMA

Liver cancer is the fourth most common cause of cancer-related deaths worldwide, and about 90% of primary liver cancers are Heapatocellular carcinoma (HCC) (23). Despite improvements in diagnosis and management of HCC, prognosis remains poor, with a 5-year survival rate less than 40% (24, 25).

Etiological/Causative Factors

A. Modern science-

HCC is an extremely complex condition and there are multiple factors involved in the aetiology of HCC. The aetiology of HCC, a variety of risk factors have been associated with the development, including hepatitis viruses, carcinogens, heredity diseases, metabolic syndrome, and fatty liver disease (26-28). The development of HCC is initiated by hepatic injury involving inflammation leading to necrosis of hepatocytes and regeneration. This chronic liver disease sequentially transitions to fibrosis, cirrhosis, and HCC (29-30). Inflammation, necrosis, fibrosis, and ongoing regeneration characterize the cirrhotic liver and contribute to HCC development.

B. Indian system of Medicine-

Causative factors

Following are the major causative factors responsible for the various types of liver disorders-

- Due to intake of excessively hot, saline, alkaline, dry, mutually contradictory and unclean food, sour and poisonous food and drinks, improper diet, and other regimens given to the patient after the administration of *Panchakarma* therapy,
- Suppression of the manifested natural urges, negligence of treatment of diseases, like anaemia, jaundice, hepatitis, spleen disorder and the consequential unctuousness in the body vitiation of the channels of circulation,
- Continued presence of product of improper digestion and metabolism in the body,
- Excessive accumulation of vitiated *doshas* it causes defective digestion and increase in waste products / morbid matter. [Fig.1]

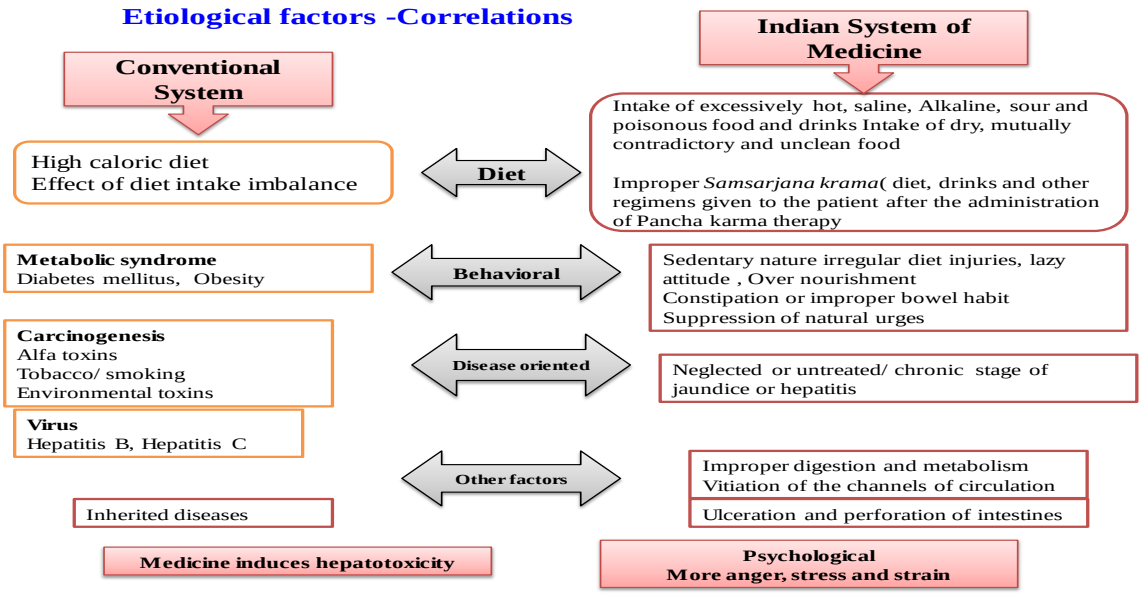


Figure 1. Correlation- Etiological factors- Conventional Medicine and ISM

Disease Process of Liver Disorders to HCC

A. Pathogenesis of Hepatocellular Carcinoma (31)

Chronic exposure of the liver to injury from viral hepatitis, alcohol abuse or NASH causes repeated hepatocyte damage and sets up a vicious cycle of cell death and regeneration which eventually results in cirrhosis. The resultant genomic instability leads to initiation of HCC. Step wise accumulation of multiple genetic events

including gene rearrangements, somatic mutations, copy number alterations, epigenetic changes and growth factor pathway alterations eventually lead to tumour progression and metastases [Fig.2].

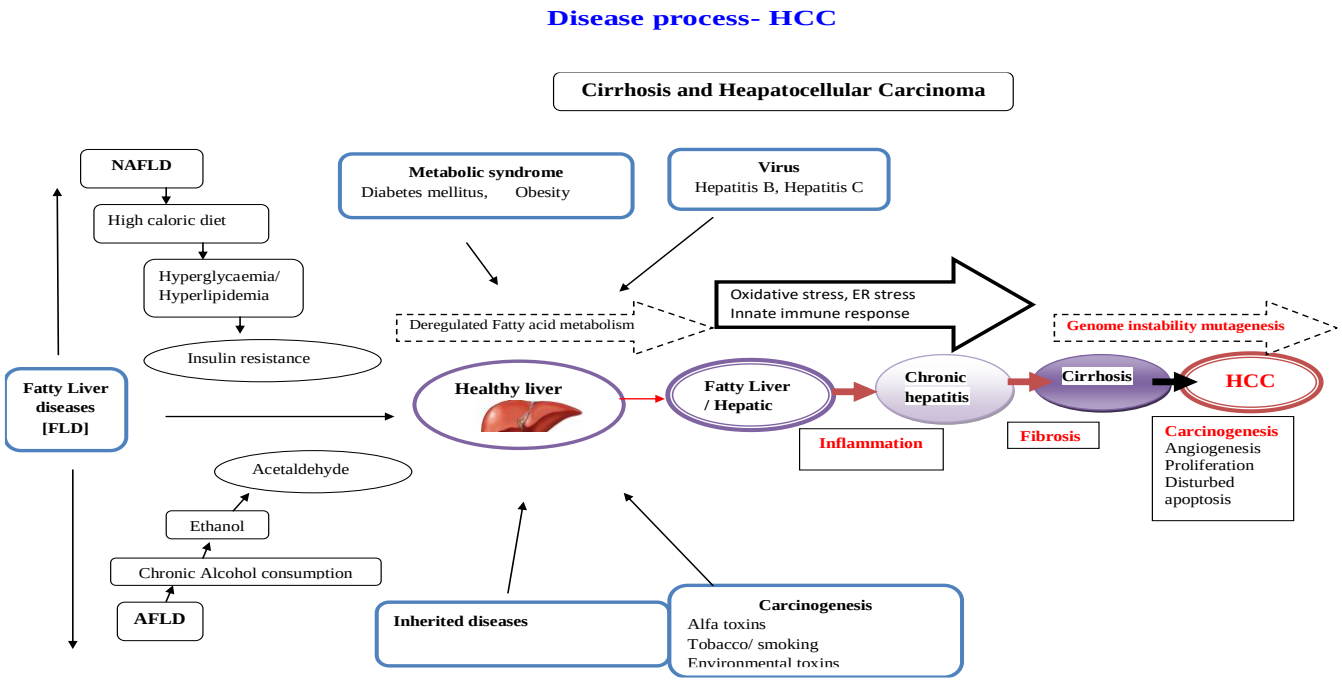


Figure 2. Disease Process of HCC- Conventional medicine

B. Disease process as per ISM (32-42)

The detail description of disease process occurring in liver as a result of HCC is not available in classical texts. So here try to through light to understand the pathological changes/ conditions may be responsible for HCC.

Vitiation of Raktavaha strotas

The *Strotas* are the empty passage, provenance from the root collocation acts as a carriage system for the supply of nutritional needs of the organism. *Raktavaha Strotas* from its origin can be comparing with the Haemopoietic system and liver and spleen is its root of origin. The liver and spleen perform a major role life cycle of RBC, its destruction and recycling of components.

Raktavah strotas gets vitiated due to above mentioned causative factors. Vitiation of raktavaha strotas can lead to derangement in stable *rakta dhatu*, also vitiate other channels & tissues and produce following symptoms -

Panduta- Anaemia
Pleeha- Enlargement of spleen
Kamala – Hepatitis / Jaundice
Jwar- Fever
Daha- Burning sensation
Asrugdara – Irregular or excessive menstruation
Guda-medhra-asya paka – Inflammation of anus, mouth (stomatitis), urethritis
Gulma – Localised abdominal lump/tumour / swelling
Raktapitta – It is an indisposition in which bleeding occurs from upper channels like nose, mouth etc or from lower channels like anus, urinary passage, genitals etc
Vyanga, Pipalavah, Tilakala –Pigmentation and melanin related like thin black patches, freckles warts/moles, chlosma etc.

Dadru – Ringworm
Charmadala – Pustules exudation and causing peeling of skin
Shwitra – Vitiligo/ Leukoderma
Pama – scabies
Kotha – Skin eruption
Asra Mandalam – Reddish circular skin eruption or patches

Vitiation of *Raktavaha strotas* leads to disorders of liver, spleen, skin. Some symptoms point out to direct involvement of liver in disease process like anaemia, jaundice etc. Symptoms like burning sensation, fever, *inflammation of anus, mouth (stomatitis), urethritis, Reddish circular skin eruption or patches* indicate inflammatory process in all parts of body while various types of skin disorders indicate vitiation of blood tissue leading to deterioration of immunity all over body.

Udar- rog- Distension or Enlargement of abdomen

Udara roga denotes generalized distension or enlargement of abdomen of any etiology. It is not only limited to ascites, accumulation of fluid in the peritoneal cavity but also includes gaseous distension, hepato-spleenomegaly of varied etiology, intestinal obstruction and intestinal perforation. Under this *Yakritodara/Pleehodara* (Hepatosplenomegaly) may be considered as reason for HCC.
The etiopathogenesis of *yakritodara* and *plihodara* are similar except the anatomical location. It is classified into *chyuta* (displacement) and *achyuta* (not displaced) *yakrut vriddhi* [enlargement of liver].
Due to vitiation of there will be progressive enlargement of the Liver/spleen becomes stony hard initially and on palpation feels like a tortoise back and if neglected the enlarging liver.

Abnormal growth/ Carcinoma

According to Ayurvedic texts, carcinoma is a disease resulting from the derangement of bodily systems due to dietary constituents. The nervous system (*Vata*), the venous system (*Pitta*) and the arterial system (*Kapha*) are three basics of Ayurveda and very important for normal body function. In malignant tumours all three systems get out of control and lose mutual coordination that causes tissue damage, excessive metabolic crisis resulting in proliferation. It differs according to each person's pathogens (exogenous) and constitutions (genetic, *bijadosa*).

Tumours are discussed under the various terminologies to designate basic common neoplasm, which can appear in any tissue or organ of the body. The description of several diseases having abnormal growth as an essential feature is described as -
Grathi –(knotty, hardened mass)-*Vata* and other *dosha* associated with *Kapha*, getting aggravated, vitiate the muscle, blood and fat tissues and produce a round, bulged and hard swelling, and known as *Granthi* [knotty, hardened mass]

Apachi –(expended glandular enlargements)-Fat tissues and *Kapha* getting increased, gives rise to expended glandular enlargements. This is static, round and broad, unctuous and has mild pain.

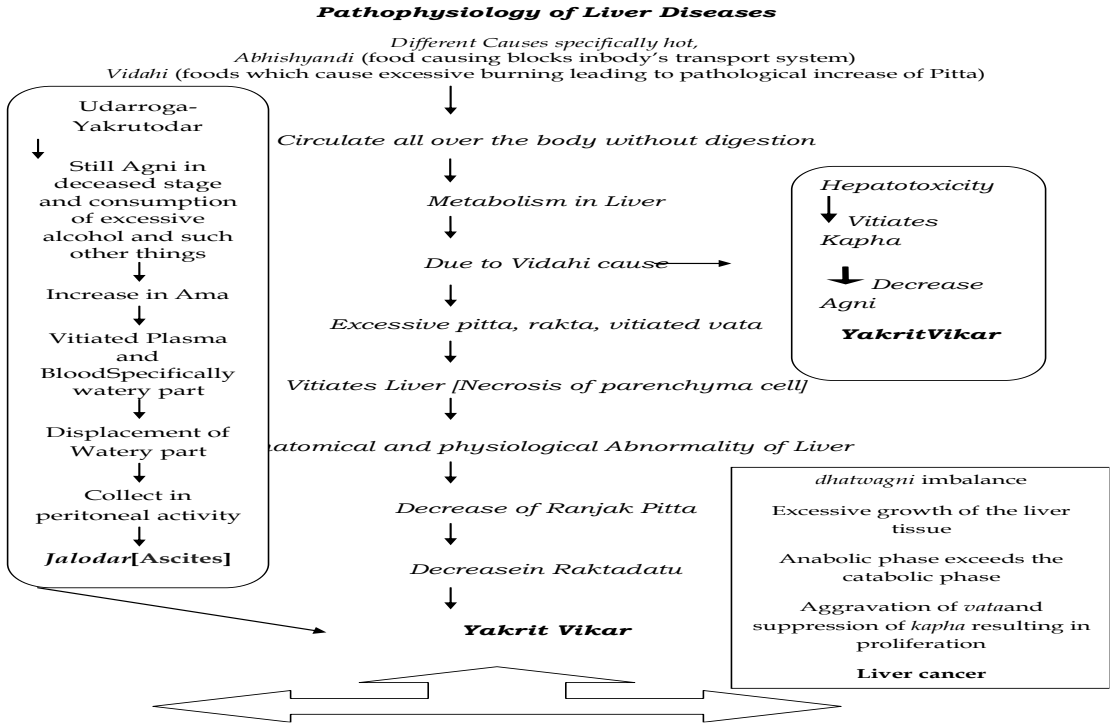
Arbuda-(deep rooted longitudinal rounded mass)-Aggravated *doshas* causing vitiation of muscle tissue, produce muscular swelling, anywhere in the body which is round, static with mild pain, big size, deep rooted, growing slowly and not ripping is called as *Arbuda.*

***Gulma* –(**composite enlargements)-The aggravated *vata* takes away either *kapha* or *pitta* or *rakta* from their place, forms a mass of growth in koshtha, and obstruct the channel of intestine and causes pain in the region of epigastria, umbilicus, hypogastria and in both the flanks.

***Vidradhi* –(**abscess of doubtful origin)-*Doshas* getting aggravated, vitiate the skin, blood, muscle, fat and bone tissue and become localised produce a troublesome swelling, slowly bulging up, rooted deep, painful, round called as *Vidradhi.*

Both allopathic and ASU systems generally refer to neoplasm as the uncoordinated abnormal cell growth found within particular organs or body tissues.

Figure 3 Disease Process- Liver diseases to HCC According to ISM



Correlation with contemporary science [31-42]

The yakrit vridhi is a pathological process by vitiation of dosa, decreased agni, production of ama, obstruction of srotas and altered the properties of dosa, dhatu by swabhava satmya viparyaya Various liver disorders are the pathological process by vitiation of dosha, decreased *agni* [digestive enzymes], production of *ama*[waste toxins], obstruction of channels and altered the properties of *dosa, dhatu*. This causes vitiation of *prana* (a variety of vata dosha), *agni* (digestive enzymes) and apana (another variety of vata, related to expulsion of faeces, flatus, urine etc) and obstruction to the upward and downward channels of circulation. Excess consumption of alcohol increased pitta and reduces watery part and vitiated vata to reduce the size of liver mass. Vitiated *pachak pitta* due to hot property effect the functions of *ranjk pitta*, increased *pitta* that evaporate the watery content and damage the architecture of Liver hence degeneration and dryness of Liver stated. Due to dry property vitiated *vata* further may change the parenchyma of liver leads to liver cirrhosis.

Excess intake of fat diet and progressively developed obesity, fatty dietary habit less physical exercise leads to increase blood lipid and vitiated fat metabolism, which produce more FFA, decrease the digestive power of fat tissues and all three *doshas* are aggravated and localized in liver. Due to increase in unctuous property

and decrease of hot property triggered to produce more *kapha* and FFA leads to liver enlargement, which may correlate as steatosis (pure NAFLD). Further accumulation of *FFA* with hepatic FFA produce hepatic inflammation in parenchyma change to hepatic stellate cells may relate to NASH (non-alcoholic steatohepatitis). Hepatic FFA directly block the *channels* and liver , therefore portal hypertension and cholagit resulted as blockage of intra and extra hepatic duct leads to accumulation of bile and Jaundice. Increased accumulated *pitta* due to hot and liquid properties triggered for fibrosis- [Proliferation- Vata responsible for faulty division of cell and Kapha for growth] may produce cirrhosis, HCC, or both(33,39,40)

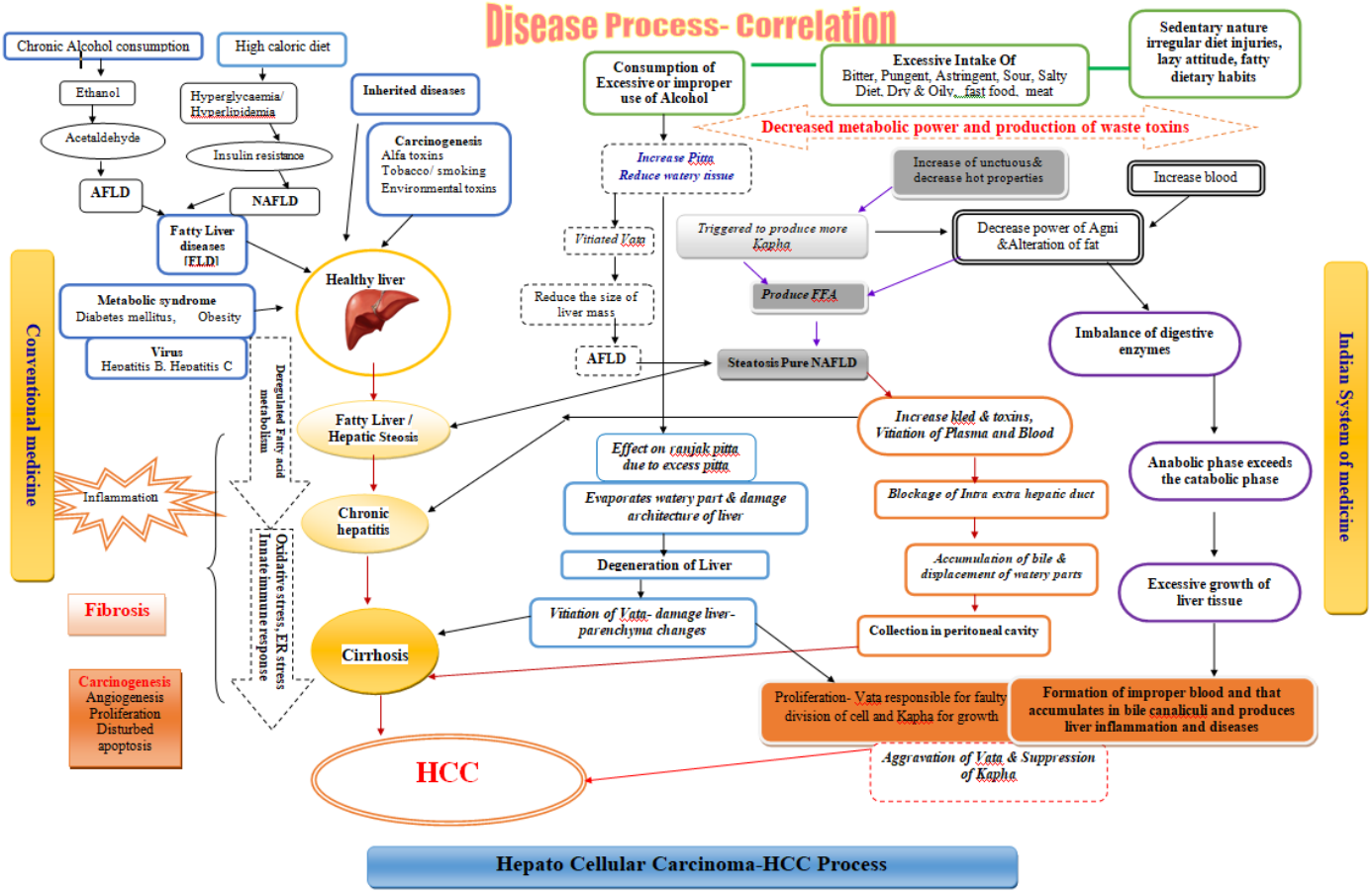


Figure 4. Correlation- HCC- Disease process

TREATMENT MODALITIES

Tumour status, liver function and general condition are three major determinants for selection of treatment modalities in modern medicine science (43-46).

The Indian systems of medicine are the oldest traditional medicinal systems of India. In ASU classical texts, specific treatment protocols for Cirrhosis and HCC are not mentioned. The fundamental principles of ISM are finding the cause of an illness and restoring the balance between the three major bodily systems by supplying deficient substances and by reducing the excessive ones [*Samanya Vishesh siddhant*- Principle of similarity-dissimilarity](17-22)

The ISM treatment for liver disease is depending on involvement of *dosha- dhatu- strotas* with proper diagnosis. Purification process using internal and external medications, which can eliminate pathogens, Curative therapy, pacifies pathogens, Correction of metabolic defects, Immunotherapy, Anti-cancerous drugs, Symptomatic treatment, Surgical treatment with herbal and mineral medicines (*Sastra chikitsa*) are the line of treatment.

Table 1. General Line of treatment in Modern medicine science and ISM

Modern Medicine	Indian system of Medicine
Tumor Resection	*Nidan parivarjan* [to avoid the known disease causing factors in diet and lifestyle of the patient] Restoration of balance (*prakritisthapani chikitsa*)
liver transplantation	Diet restrictions [*Pathyapathya*]- Life style management
Percutaneous Local Ablation: Radiofrequency Ablation and Percutaneous Ethanol Injection	Purification process (*shodhana chikitsa including panchakarma*) using internal and external medications
Transarterial Chemo-embolization	Curative therapy (*shamana chikitsa*) pacifies pathogens (*dosas*)
Yttrium-90—Labeled Microspheres Radio-embolization	Correction of metabolic defects (*dhatwagni chikitsa*)
Systemic Therapy- sorafenib, bevacizumab (Avastin, Genentech), ramucirumab, ABT-869, everolimus, and ARQ 197	Hepatoprotective (*vyadhipratyanika chikitsa*)
	Restoration of normal function (*rasayana chikitsa*)
	Spiritual therapy (*naishthiki chikitsa*)
	Surgery with herbal and mineral medicines (*Sastra chikitsa*) (considered only as a last resort)

Challenges

Challenges in HCC treatment occurs at various levels including at the level of screening, diagnosis, treatment, and at the level of acceptance of the proposed solution for HCC (47). The treatment suggested for Ch and HCC have limitations due to several medical and psychosocial reasons. The use of these methods is limited due to their side effects and the development of resistance to the available chemotherapy and their complexities (48).

Due to the limited treatment options to HCC, other than surgery and the poor prognosis of the disease, there is a critical need for additional therapies to enhance the survival or the quality of life. Complementary and alternative medicine (CAM) is considered as one way that may improve the anticancer drug efficacy and reduce their toxic effects (49). Many natural products are helpful in the co-treatment and prevention of HCC due to cost effectiveness, higher safety margins, long-lasting curative effects and few adverse effects.

Natural Remedies and Its Activities

The use of natural remedies for the treatment of liver diseases has a long history (50). Natural drugs like plants, minerals and animal drugs are more advisable. In Siddha medicine the use of metals and minerals are more predominant in comparison to other Indian traditional medicine systems.

A large number of single and compound drug formulations are documented to have benefit over chronic liver conditions. These formulations are mostly used as hepatic tonic on the basis of various pharmacological actions mainly as ***anti-inflammatory, rejuvenate, blood purifier, appetizer/digestive, scraping/drastic action***. The therapeutic benefits offered by various ASU formulations in treatment of chronic liver diseases have however not much explored in treatment of HCC. Experiments on animals and cell cultures have shown that some potential ASU plants can alleviate and prevent pathological changes in the liver. Considerable research works *in vitro* and *in vivo* as an anti-Heapatocellular carcinoma have been carried out with hepatoprotective, antioxidant, and immune properties.

The present paper is an attempt to list the plants with hepatoprotective and related beneficial effects which are used in ASU system of medicines. An attempt has been made to provide details on validation of certain ASU potential plant drugs for anticancer and anti-metastatic properties against Heapatocellular carcinoma.

Summary of Pre-Clinical and Safety Studies of Selected formulations, Plants & minerals -

Scientific evidence has been collected on preclinical efficacy of photochemical/extracts and some poly herbal formulations in various animal models as obtained through Google and PubMed searches. The information of pharmacological & safety study of some important formulations and plants are as follow-

Herbal ASU formulations

Review was taken by Bhatt et al suggested that more than 126 liver products described in various Ayurvedic classical texts, more than 150 products are prepared as proprietary medicines by pharmacies and 18 are patented. More than 106 medicinal plants are used for the preparation of various Liver products.

It is observed that maximum Ayurved classical products are used in liver disorders specifically in Jaundice, Hepatitis, Alcoholism, Cirrhosis and Ascites conditions. These products are the combination of herbs and minerals. The common classical products such as *Arogyavardhini Vati, Draksadiarkom, Gudapippali, Kumari Asava, Punarnava Mandoora, Udramrit Vati,* are used in various types of conditions related with Liver.

Arogyavardhini vati, it is a classical polyherbal-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. An experimental study clearly demonstrated the protective effect of well-known *Arogyavardhini vati* against CCL 4 induced hepatotoxicity in rats (51, 52) it has proven anti-oxidant properties. *Argyavardini vati* along with *Bhumyamlaki* leaves juice (*Phyllanthus frataruns L.*) and *Triphla powder* have a significant role to clearing of HBSAg and normalize Liver Transminase in Hepatitis B infected patient within 45 days (53). AVR has proven Hepatoprotective action against PCM-induced hepatotoxicity in rats (54). Safety of *Arogyavardhini Vati* on liver, kidney, and brain has been evaluated in earlier studies (55). There was a significant reduction of BMI in two treated cases treated by ***Arogyavardhini vati*** and ***Phalatrikadi kvatha*** in non-alcoholic fatty liver disease (56).

Phalatrikadi Kwatha (PTK) is an effective and beneficial formulation for management of Hepatitis B patient. Anti-oxidants properties of most of the drugs in PKT formulation i.e *Amalaki(Emblica officinalis Gaertn.), Haritaki (Terminalia chebula Retz.), Bibhitaki (Terminalia bellerica Roxb.), Amrita (Tinospora cordifolia Miers.), Vasa (Adhatoda vasica Nees.), Katuki(Picrorrhiza kurroa Royale ex Benth.), Bhunimba (Andrographis panniculata Nees.) and Nimba (Azadiracht aindica A. Juss.)* (57-61), they may help to protect the diseased liver due to free radical overload.

Vasaguduchyadi Kwatha is a compound formulation, indicated for the treatment of liver diseases, especially for *Kamala* (jaundice) and *Panduroga* (anemia).Results of acute toxicity study suggested that *Vasaguduchyadi Kwatha* are relatively safe up to the dose of 5 g/kg(62).

Punarnavastak kwath protects hepatocyte from CCl(4)-induced liver damages due to its antioxidant effect. An in vitro study on HepG2 cell lines also supports its protective effect (63).

Liv 52 is the important formulation used in liver diseases. Usage of Liv.52 can help regulate levels of enzymes, optimize assimilation, and improve the functional efficiency of the liver. It helps restore the functional efficiency of the liver by protecting the hepatic parenchyma and assist in promoting hepatocellular regeneration. It facilitates rapid elimination of acetaldehyde, the toxic intermediate metabolite of alcohol metabolism, and helps ensure protection from alcohol-induced hepatic damage. It helps diminish the lipotropic

activity in chronic alcoholism and prevents fatty infiltration of the liver. In pre-cirrhotic conditions, helps arrests the progress of the disease and prevents further liver damage (64).

Amlycure D.S. helps in regeneration & repair of hepatocytes by increasing the nucleic acid content – RNA, DNA & Protein. It accelerates repair & regeneration of liver cells by assures liver protection, acting as anti-oxidant, accelerates repair and regeneration of liver cells from alcohol educed liver damage by increasing the level of alcohol metabolizing enzymes. It protects liver from toxins, boosts immunity, promotes &enrich hepato-billiary secretions thus accelerates fat digestion and retards fat deposits in liver tissues, fights fatty liver condition (65).

The polyherbal *LIVT tablet* was prepared by using nine herbal extracts such as, *Boerhavia diffusa* (40 mg), *Tinospora cordifolia* (40 mg), *Eclipta alba*(20 mg), *Andrographis paniculata* (20 mg), *Picrorhiza kurroa* (20 mg), *Phyllanthus amarus* (20 mg), *Embelia ribes* (12 mg), *Cichorium intybus* (10 mg) and *Tecomella undulata* (10 mg). It was tested on D-galactosamine induced HepG2 cell toxicity model. MTT assay and demonstrated a significant hepatoprotective activity and could be used as an active herbal alternative for the treatment of liver ailments (66).

Other formulations like *Panchagavyaghrita, Rohitakaghrita, Panchakolaghrita, Amalakighrita* are described in Ayurveda for treatment of liver diseases. *Virechan*a (Medicated purgation) is the treatment of choice in liver disorders especially for ascites (67). *Vardhamapippali* yoga is effective in hepatic cirrhosis (68).

Jigrine a poly herbal Unani formulation containing aqueous extracts of 14 medicinal plants *Cichorium intybus L. [Chicory/Kasni], Tamarix dioica Roxb. [Tamarisk], Solanum nigrum L. [Makoh] Rheum emodii Wall [Revandchini], Rubia cordifolia L. [Majeeth], Vitex negundo L. [Sambhalu],Cassia occidentalis L. [Kasaundi], Foeniculum vulgare Mill. [Sonf],Cuscuta reflexa Roxb [Tukhme], Careya arborea Roxb. Wild [Baokhamba], Phyllanthu sniruri L. & Hook [Bhuiamla] Plantago major L. [Bartang], Rosa damascena Mill. [Gul-e-surkh], Solanum xanthocarpum Schrad.& H.Wendl. [Katheli]* is used for liver ailments. The study revealed hepatoprotective potential of *jigrine* post-treatment against thioacetamide induced hepatotoxicity in rats (69).

Qurs-e-Zarishk Sagheer (QZS) is a compound preparation demonstrated significant liver enzyme lowering effect in CCl4 induced hepatic injury indicating hepatoprotective effect (70).

Kabideen (Syrup) is a Unani poly herbal formulation indicating significant hepatoprotective effect against paracetamol induced hepatotoxicity in albino rats at a dose of 5.25 ml/kg body weight (71).

Shrbat-e- Deenar(SD) investigated against the CCl4 induced liver damage in rats. It showed a marked protection on alanine transaminase, aspartate transaminase, albumin and Urea, protective effect by restoring the level of lipid peroxidation, reduced glutathione and glucose-6- phosphatase. Histopathological study also showed recovery in the architecture of liver cells(72).

TSF, siddha formulation is a combination of seven botanicals includes *Sphagneticola calendulacea whole plant, Phyllanthus amarus whole plant, Terminalia chebula pericarp, Terminalia belerica fruit, Emblica officinalis fruit, Curcuma longa rhizome and Cuminum cyminum fruit*. Research suggested that TSF Significantly inhibited CCl4 induced hepatic fibrosis; due to spectrum of synergistically active photochemical (73).

Karisalai Karpam tablet is a *siddha* formulation containing seven plants proprietary medicine used to cure liver disorders such as jaundice, enlargement of liver and spleen, anaemia. It possesses the hepatoprotective property and antioxidant activity against paracetamol-induced liver damage, which provides a support for its use in treatment of liver disorders (74).

Potential Medicinal Plants

Various plants and formulations have been claimed to have hepatoprotective activity. Nearly 160 Phytoconstituents from 101 plants have been claimed to possess liver protecting activity. In India, more than

106 plants are used in various types of liver disorders, in 33 patented and proprietary multi-ingredient plant formulations.

It is observed that eighty-two, fifty-seven and thirty-four plants drugs are used in multiple Ayurved, Siddha and Unani formulations respectively (15, 41,42,75,76).

Meta-analysis studies have shown that ISM potential plants are beneficial in regulating the virus stimulated HCC and reducing the chemotherapy side effects. They could delay tumour progression, increase survival and life quality, and improve the quality of life due to synergistically efficient chemotherapy/ radiotherapy option.

Table 2: Most potential plant dugs for Liver disorders in ASU systems

Sr no.	Botanical name	Parts used	Attributes	Active constituents	Proposed mechanism of action
1.	*Aloe vera (L.) Burm.f. I Aloe barbadensis Mill.* *Liliaceae* Aloe	Leaf	*Bitter, Sweet, Heavy, Unctuous Sweet, Hot Balancing all doshas*	Alkaloids, tannins, flavonoids, saponins, glycosides, proteins, Amino acid, Steroids	***Crude extract-***decrease the MCF-7 cells, HeLa cells, Cell viability, Apoptosis induction, Cyclin D1, CYP1A1 , CYP1A2, increase Bax, p21 expression (77) ***Aloe-emodin***- Inhibited cell proliferation in human liver cancer cell lines (HepG2, Hep 3B) Kuo P-L (78), Aloe polysaccharide Exhibited resistance against liver cancer cell proliferation (79) *Aloe vera* attenuate APAP-induced hepatitis through the improvement of liver histopathology by decreased oxidative stress, reduced liver injury, and restored hepatic GSH (80). ***Barbaloin*** -C-glucoside of aloe emodin anthrone –preventing AAPH-induced hemolysis of erythrocytes, protected Ca^{2+}-ATPase and protein sulfhydryl groups on erythrocyte membranes against oxidative attack by tBHP/hemin (81) The extracts separately increased cytotoxicity against HepG2 cells in a time and dose dependent manners. Also, it apparently induced apoptosis through increase P53 and decrease Bcl-2 genes expression Lyophilized A. vera extract ***Lyophilized Aloe extract*** - increased Cytotoxicity against HepG2 cells in a time and dose dependent manners, induced apoptosis through increase P53 and decrease Bcl-2 genes expressions (82)

2.	*Allium sativum Liliaceae* Garlic	Bulb	*Sweet, Salty, Pungent, Bitter, Astringent, Oily, Heavy, Hot*	Sulfur-containing phytoconstituents such as alliin, allicin, ajoenes, vinyldithiins, and flavonoids such as quercetin	***Diallyl sulfide (DAS)*** -anti-inflammatory activity through the modulation of cytokines as it inhibits the activity NF-kB (83) ***A combination of vitamin C and DAS*** - as inhibition of circulatory TNF-α and IL-6 in DENA-induced HCC in rats [84)], increases the sensitivity to chemotherapy as cisplatin in the treatment of HCC (85) ***Allium sativum or garlic oil (GO)*** – against N-nitrosodiethylamine NDEA induced hepatocellular carcinoma; it may increase the antioxidant activity, the induction of apoptosis (86) ***SAC garlic derivative, S-allylcysteine (SAC)***- A series of in vitro experiments including MTT, colony-forming, wound-healing, invasion, apoptosis, cell cycle assays demonstrate the anti-proliferative and anti-metastatic effects (87)
3.	*Amoora rohituka (Roxb) Wight &Arn./ Tecoma undulata (Sm.) G.Don Bignoniaceae* Rohida Tree	Bark	*Pungent, Astringent Light, Dry, Cold, Pacify Kapha, Pitta*	Radermachol pentacyclic quinone, phytosterols, glycosides, tannins, phenolic	***Methanolic extract (TSB-7)*** - Hepatoprotective potential partially due to the presence of betulinic acid using hepg2 cells (88,89) ***Rohitaka ghrita*** -a significant hepatoprotective potential against paracetamol induced hepatocellular damage in rats, impaired the hepatic antioxidant system by increased lipid peroxidation; decreased glutathione, catalase levels and also Na^+K^+ATPase level(90)
4.	*Andrographic paniculata Nees. Acanthaceae* Green chireta	Whole plant	*Bitter, Light, Dry, Pungent, Hot Pacify Vatapitta*	Andrographolide, panaculoside, flavonoids, andrographonin, panicalin, neoandrographolide, apigenin 7-4-dimethyl ether,	***BHC (hexachlorocyclohexane)*** induced increase in the activities of enzymes gamma-Glutamyltrans peptidase, glutathione-S-transferase, lipidperoxidation indicating antioxidant, hepatoprotective activity (91,92), enhance the activity of hepatic enzyme, normalizes histopathological changes of malignant hepatic tissue induced by hexachlorocyclohexane (93), showed indirect & direct effects on tumor cells by inducing apoptosis, cancer cell necrosis, improving body's own immune system against tumor cells, inhibiting cell-cycle arrests and cancer cells proliferation (94) ***Ethanolic extract*** -a cytotoxic effect against diverse human cancer cell lines like PC-3 (prostate), HepG2 (hepatoma), colon 205

					(colonic) cancer cells and Jurkat (lymphocytic) [(95), ***Andrographolide***- reduce the replication of HCV markedly due to its ability to induce the p38 MAPK/Nrf2/HO-1 pathway, where, MAPK stands for mitogen activated protein kinase and HO-1 is heme oxygenase-1(96), It also causes activation of ROS-dependent c-Jun NH_2-terminal kinase (JNK) resulting in the activation of tumor suppressor p53, thereby increasing p53 phosphorylation and protein stabilization (97,98)
5.	*Berberis aristataDC./ Berberis lyceimRoyle Berberidaceae* Indian Barberry	Bark	*Bitter, Astringent Light, Dry Pungent, Hot Pacify Kapa, pitta*	Alkaloids, reducing sugar, Coumarin, saponins, Flavonoids, Steroids, Glycosides, Tannin, Polyphenol, terpenoids	***Water/ethanolic extract*** exhibited significant antiproliferative activity against the HepG2 cancer cell line with an IC_{50} value of 47 µg/mL. (99) ***Berberine*** - It down-regulates numerous hepatic pro-inflammatory genes such as IL-6, serum amyloid A3 (SAA3), NF-kB, TNF-α, decrease TNF-α and COX-2 expression in cyclophosphamide-induced hepatotoxicity in a rat model (100), anti-cancer activity on the human HCC cell lines through the induction of apoptosis and inhibition of tumor cell proliferation (101), induces both cell death and apoptosis in HepG2 cells. This is related to the down-regulation of CD147, which is highly expressed in HCC cells (102) Inhibit the human hepatocellular cancer cell growth through the induction of AMPK-mediated caspase-dependent mitochondrial pathway cell apoptosis in addition to suppressing p53(103). The expression of p53 was found to be up-regulated through suppression of MDM2, the inner p53 inhibitor, at the post-transcriptional level (104). ***The combination of berberine and vincristine*** - helpful effect against hepatoma cell lines through the potentiating of the pro-apoptotic effect of the single drug (105) Hepg2 cancer cell line ***via*** ppar gamma activation and cox2 inhibition - regulating prostaglandin e2 (pge2) signaling pathway(106)
6.	*Boerhavia diffusa* L.	Root	*Bitter, Sweet Light, Dry*	*b*-Sitosterol, a-2-sitosterol, palmi	Anti-inflammatory, hepatoprotective, and antioxidant effects and can be considered as an option in cases of HCcA (107- 110),

	Nyctaginaceae Hogweed		*Pungent Hot Pacify Kapha, Vata*	tic acid, tetracosanoic, hexacosonoic, stearic, arachidic acid, urosilic acid, Hentriacontane, b-Ecdysone, triacontanol	***Dehydrorotenoid boeravinone H***, isolated - prevents HCV entry and infection in cell culture (ex vivo(111)
7.	*Cichorium intybus* L. *Compositae* Chicory	*Whole plant*	*Bitter, Light, Dry Pungent, Hot, Pacify Kapha, Vata*	Sesquiterpene lactones, cichoric acid, pactin, fixed oil, choline, cichoriin, lactucin, intybin	***TAA***-induced hepatic damage, fibrosis, and cirrhosis by relieving oxidative stress and by interruption of the inflammatory pathway via AMPK/SIRT1/FXR signalling P (112), ***supplemented diet against*** nitrosamnine-induced- promising role for ameliorating the oxidative stress and hepatic injury induced by nitrosamine compounds (113) ***Seed extract (CI)*** - hepatic steatosis caused by early and late stage diabetes in rats (in vivo), and induced in HepG2 cells (in vitro) by BSA-oleic acid complex (OA) released glycerol from HepG2 cells, and targeted the first and the second hit phases of hepatic steatosis (114), Amelioration of diabetes- and oleic acid-induced non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) via modulation of PPARα and SREBP-1 (114), Synergistic effect and the role of chicory extract [inulin (IN)] as a chemo-sensitizer for cisplatin (CIS) treatment of HCC (115)
8.	*Cinnamomum zeylanicum Blume/ Cassia Lauraceae* Dalchini	*Bark*	*Bitter, Light, Dry, Pungent, Hot Pacify Kapha, Vata*	Proanthocyanidin compound, procyanidin B2	***Supplementation with cinnamon*** at a dosage of 0.2ml/100g BW/day daily orally in Diethylnitrosamine induced rats improves the histoarchitecture of hepatic cells with slight regeneration of tubular structure, restoration of nuclear shape with presence of dense glycogen granules(116). Ameliorate the toxicity of chemical toxins in liver, kidney, blood, brain, embryo, reproductive system, heart, spleen through antioxidant effect, modulation of CK-MB, LDH, TNF-α, IL-6, mitogen-activated protein kinase (MAPK), and nuclear factor-κb (NF-κb) signalling pathways (117). ***Oil***-reversed destructive actions -alpha-fetoprotein (AFP), liver enzymes, hepatic

					malondialdehyde (MDA), and p53 protein expression levels as well as genetic mutations in intron 5 of p53 gene in the form of Single-Nucleotide Polymorphisms (SNPs) and insertions increased GSH and SOD levels, revealed partial reversal of normal liver architecture (118).
9.	*Curcuma longa* L. *Zingiberaceae* *Turmeric*	Root tuber	*Pungent, Bitter, Light, Dry, Hot Pacify Kapha, Vata*	Curcumin, Bis-desmethoxycurcum Desmethoxy Curcuminin, etrahydro Curcumin, Alpha Curcumene, Ar-turmerone, Curcumol, DehydroCurdione Zingiberene	***Rhizome ethanolic extract*** -thioacetamide stimulated liver cirrhosis in rats through anti-inflammatory and antioxidant properties (119) ***Curcumin***- inhibited the migration as well as invasion of HCC-SK-Hep-1 cells, decreased the secretion of MMP-9, matrix metalloproteinase-9 (120), abrogated the invasion & migration of CBO140C12 cells (121), inhibited histone acetylation in Hep3B cells (122, 123), anti-proliferating effects in Bel7402, SGC7901 and HL60 cells (124), inhibited cell survival in Hepa1-6 cells with downregulated VEGF-A expression (125), attenuated cell growth in Huh7, Hep3B, HepG2, SK-Hep-1, QGY-7703 cells in which the G2/M arrest was previously abrogated (126), inhibited growth and produced dose-dependent damage in both the mitochondrial and nuclear DNA in HepG2 cells (127), produced mitochondrial hyperpolarization in HepG2 cells (128), inhibited the proliferation of HEP3B, SK-Hep-1 and SNU449 cells (129), ***Curcumin and its -diketone*** modified analogs inhibited proliferation in HA22T/VGH cells (130) , ***Curcumin as well as tetrahydrocurcumin*** attenuated the proliferative activity of HepG2 cells (131), ***Curcumin and its novel analog GL63*** inhibited growth in HepG2 cells (132), Curcumin, alone or in combination with cisplatin and doxorubicin synergistically exerted cell growth inhibitory effects in HA22T/VGH cells (133).

					Curcumin and turmeric extract- reduced GGT+ foci in AFB1-treated male Wistar rats(134), protected against DENA-induced hyperplasia in male Wistar rats (135), suppressed the DENA-induced hepatocellular carcinoma in male C3H/HeN mice (136), attenuated DENA-induced GGT+ foci and hepatocellular carcinoma in female Wistar rats (137), prevented the DENA-initiated and 2-AAFpromoted development of altered GGT+ /GST+ hepatic foci in male Wistar rats (138), significantly blocked the DENA-initiated and PB-promoted nodule incidence in male Wistar rats (139), suppressed the DHPN-induced liver adenoma formation in male BALB/c mice (140)
10.	Eclipta alba *f.* prostrata *(L.) Hassk. Compositeae/ Asteraceae* False Daisy	Whole plant	*Pungent, bitter Light, Dry, Pungent, HotPacify Kapha, Vata*	Coumestans, alkaloids, flavonoids, glycosides, polyacetylenes, triterpenoids, stigmasterol, β-terthienylmethanol, wedelolactone	***Juice*** inhibited cancer invasion and migration, without affecting cell adhesion (141). . ***Crude extracts, four fractions*** wedelolactone (I), eclalbasaponin I (II), luteolin (III) and luteolin-7-O-glucoside (IV) , and the isolated compounds- assessed using hepatoma cell smmc-7721-30% ethanol fraction and eclalbasaponin I dose-dependently inhibited the proliferation of hepatoma cell SMMC-7721 with IC50 values of 74.23 and 111.17 μg/ml(142), ***Hydro-alcoholic extract*** Inhibit the proliferation of liver (HepG2) in a dose-dependent manner (143) , Multidrug resistance reversal potential reversal agent using multidrug-resistant hepatocellular carcinoma cell line (DR-HepG2) (144) ***Coumestans-*** Galnandphalloidin-cytotoxicity in rat hepatocytes-antiheptotoxic activity, stimulatory effect on liver cell regeneration (145)
11.	*Emblica officinalis Gaertn / Phyllanthus emblica* Phyllanthaceae Indian gooseberry	Fruit	*Sour Light, Sweet Cold Pacify all dosha*	Gallic acid, ascorbic acid, ellagic acid, rutin, quercetin, and catechol	Anti-autophagy, anti-apoptosis, antioxidant and anti-inflammatory action (146,147)

12.	*Glycyrrhiza glabra* L. Fabaceae *Liquorice*	Root	*Sweet Heavy, Unctuous Sweet, ColdPacify Vata, Pitta*	Liquirtin, glycyrrhizin	Anti-tumor activities through inhibition of cellular proliferation, development and growth of cancer cells (148,149), reduce hepatic steatosis in transgenic mice expressing the full-length HCV poly-protein (150), an inhibitory effect on HCV core gene expression and HCV full-length viral particle both at protein and RNA level and have a synergistic effect with interferon (151). Inhibit HCC occurrence in DENA-treated mice (152)]. ***Extract*** - induced by DENA/CCl4 in rats and more potent than cisplatin alone or cisplatin combined with Glycyrrhiza glabra, not associated with side effects (153)
13.	*Nigella sativa* L. *Ranunculaceae* Black onion seeds	Seeds	*Pungent, Bitter, Light, Pungent, Hot Pacify Vata*	Thymoquinone, nigellone, alkaloids, terpenoids	***Ethanolic extract*** - cytotoxic effect against diverse cell lines such as Molt4, Hep G2 and LL/2(154)], a marked enhancement of DENA-induced histopathological variations of the hepatic tissue (155) ***Crude methanolic extract***- 50% cytotoxicity against Dalton's lymphoma ascites (DLA), Ehrlich ascites carcinoma (EAC) and Sarcoma-180 cells (S-180 cells) (156) , methanolic extract in HCC albino rat model showed modulation of glucoregulatory enzymes (157) ***Aqueous extract*** -antiproliferative activity and morphological changes like membrane damage and cell shrinkage in HepG2 cells, which lead to DNA damage, cell death and a decrease in cell proliferation (158) Inhibit tumor initiation, progression, an anti-inflammatory, immunomodulatory effect. - regulate signalling pathways like p53, iNOS and caspases (159)
14.	*Phyllanthus niruri Linn / Phyllanthus amarus Schumach. &Thonn Euphorbiaceae* Stonebreaker	Whole plant	*Bitter, Astringent, Sweet, Light, Dry, Sweet, Cold Pacify Kapa, pitta*	Flavonoids, alkaloids, terpenoids, lignans, polyphenols, tannins, coumarins and saponins,	Antitumor (160)], antiviral (161), antioxidant (162)], anti-inflammatory (163), radiation protection (164)- protect liver cancer by enhancing the immune function of the body ***Phyllanthin***- CCl4-induced toxicity in human hepatoma HepG2 cell line alleviated the changes induced by CCl4 in a concentration-dependent manner (165)

15.	*Picrorhiza Kurroa* Royleex Benth *Scrophulariaceae* *Katuki*	Rhizomes	*Bitter, Dry, Light Pungent, Cold, Kapha – pittahara*	Picroside I and II, kutkoside,	***Icrosides-I, II and III and kutkoside***- Lower the levels of hydroperoxides and lipid peroxidases, facilitate recovery of antioxidant to prevent the liver from oxidative impairment, hepatoprotective activity in alcohol-induced hepatotoxicity in rats (166). ***Picroli***v- protection against liver damage by CCl4 by acting as free radical scavenger and inhibitor of LPO of liver plasma membrane (167)
16.	*Piper Longum* L. *Piperaceae* *Long pepper*	Fruit	*Pungent, Light, Unctuous Sweet , Hot, Pacify Kapha, Vata*	Volatile oil, starch, proteins, alkaloids, saponins, carbohydrates	Significant protection against acetaminophen-induced hepatotoxicity in mice(168) Twenty HCC patients administrated an oral dose of 4 g curcumin, 40 mg piperine, and 500 mg taurine daily for three successive treatment cycles, each was a 30-day. The combined treatment was able to produce a significant decrease in the levels of serum IL-10, and miR-21 while it resulted in a non-significant up-regulation of serum miR-141 expression level (169).
17.	*Plumbago zeylanica* L. *Plumbaginaceae* *Chitrak*	Root	*Pungent, Light, Dry Pungent, Hot, Pacify KaphaVata*	Plumbagin, isozeylanone, zeylanone, elliptinone, droserone,	***Plumbagin***- mediates the production of ROS, regulates the PI3K/Akt and MAPK signaling pathways to promote apoptosis and autophagy, and shows significant therapeutic effects on HCC (170), Significant inhibition of metastasis liver cancer by introducing 1, 4-naph-thoquinone extract (171), Restrained hepatocellular carcinoma angiogenesis by stromal cell-derived factor (SDF-1)/CXCR4-CXCR7 axis (172), improve the resistance of hepatocellular carcinoma HepG2R cells to sorafenib by increasing the ROS level (173), inhibited the proliferation of SMMC-7721 cell line in a dose- and time-dependent manner and upregulated the expression levels of autophagy genes and related proteins (LC3, Beclin1, Atg7, and Atg5), increase the caspase-3 protein level and cleaving vimentin (174, 175) inhibit proliferation and induce apoptosis of HCC through inhibiting the SIVA/mTOR signaling pathway (176)
18.	*Tephrosia purpurea (L.) Pers* *Fabaceae* Wild indigo	All parts, root	*Bitter, Astringent , Pungent Light, Pungent, Hot*	Tephrosin, pongaglabol, semiglabrin	***Leaves and root extracts***- exhibited anticancer activity in HepG2 cells through induced cell shrinkage, DNA condensation and fragmentation, mitochondrial membrane depolarization and upregulated caspase-3 expression (177) , Cirrhotic and nodular

			Pacify Vata and Kapha		changes induced by CCL4 -effectively prevented by stabilizing cell membranes (178).
19.	*Tinospora cordifolia (Willd.) Miers Menispermaceae* Guduchi	Stem	*Bitter, Pungent, SweetHeavy, Unctuous Sweet, Hot Pacify all three dosha*	11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, cordifolioside A, magnoflorine, tinocordiside and syringing	***Epoxy clerodane Diterpenoid (ECD)*** - preventive and curative DEN induced animals increased the level of antioxidants and detoxification enzymes, and decreased serum transaminase level and hepatic marker enzymes to near normal, reduced tumor incidence and reversed damaged hepatocytes to normal (179). ***Kupffer cell functions using carbon clearance test***- significant improvement in kupffer cell function and a trend towards normalization, Protective effects on thiobarbituric acid reactive substances (tbars) levels and increase the level of gsh, ascorbic acid, protein, and the activities of anti-oxidant enzymes (180,181)
20.	Zingiber officinale Roscoe *Zingiberaceae* Dry ginger	Rhizomes	*Pungent, Light, Dry, Sweet, Hot Pacify Vat Kapha*	Gingerols, gingerols,gingerols, Shogaol, Paradol, gingerdione	***Protective effect*** - against several toxic agents, like bromobenzene and cisplatin (182), the chemo preventive effect of ginger against cancer (183) ***Extract***- decreased the level of growth factors and α-fetoprotein (liver tumor marker) (184), inhibit the proliferation of cells in HepG-2 cell line (IC50, 900 μg/ml) (185). ***6-shogaol***- anticancer effects against hepatoma cell line through the activation of ROS-mediated caspase-dependent apoptosis in a multidrug resistance (186). ***Extract***- Higher expression levels of nfκb and tnf-α reduced significantly in rat act both as an anti-inflammatory and anti-cancer agent for inactivating nfκb through the suppression of tnf-α pro-inflammatory pathway (187).

Toxic plants-

Along with medicinal plants toxic plants like *Arka, Dhatur, Bhalltaka* are used in various types of cancer as *rasayan*. These toxic plants are used after the *shodhan samskar* [various purification methods]. *Shodhana* is being used with a broader perspective as it means a process of not only purification but also involves the detoxification and enhancing the efficacy of the drugs. It converts poison or toxins of the plant/ part of the plant in safe, effective and life saving medicine.

Table 3: Most potential toxic plant dugs for Liver disorders in ASU system

Sr no.	Botanical name	Parts used	*ASU attributes*	Phytochemical constituents	Proposed mechanism of action
1.	*Abrus precatorius Fabaceae Crabs eye*	Seeds, Root	Bitter, astringent Light, Dry, pungent Hot potency pacify both Kapha and Vata	Root- abrasine, abrol, precol and pre-casine, Seeds -abrin. essential amino acids like alanine, serine, choline, valine, methyl ester	AGG inhibits the growth and progression of HepG2 cells by inducing caspase-mediated cell death [164], reduced the NDEA-induced elevated levels of various hepatic markers (188)
2.	*Calotropis Gigantea (Linn). R. Brown Asclepiadaceae (Periplocaceae) Madar*	Latex Root	Pungent, bitter lightness, dryness, pungent hot, potency balances Vata, Kapha	Laurane, Saccharose, B-amyrin; a&B calotropeols; holarrhetine, Cyanidin-3-rhamnoglucoside; Taraxsterol isovalerate; Giganteol; Calotroposide;Calactin, Calotoxin; Calotropins DI &DII, Gigantin	Complete protection against hepatocarcinogenesis due to its differentiable targets and non-interference with regular pathway of apoptosis (189, 190), Methanolic root extract induces apoptosis in HepG2 cells by altering bax/bcl-2 expression (191), Methanol extract (ME) of root bark and chloroform soluble fraction (CF) possesses significant antitumor activity on the growth of Ehrlich ascites carcinoma (EAC) and life span of EAC bearing in Swiss albino mice(192).
3.	*Cannabis sativa Linn. Cannabaceae Marijuana*	Leaves	Bitter, light, Sharp, spreads to all parts of the body swiftly, pungent, Hot, Balances Vata, Kapha	Cannabinol, Tetrahydro-cannabiol, Cannabidiol, Cannabichromene, I-dehydro-tetrahydrocannabinol, eugenol, sequiterpenenes, cannabinodis	Protective on liver cancer induced by dimethylnitrosamine in mice(193) Cannabinoid- inhibit tumor growth and ascites in an orthotopic model of HCC xenograft (194)
4.	*Nerium indicum (N. odorum Soland). Apocyanaceae* Indian Oleander	Roor, Root bark	Pungent, bitter lightness, dryness, hot, pungent Balances Kapha, Vata	Karabin, Neriodorein, Neriodorin, B-Sitosterol, Neriodin, Neriodorin, Nerium D, Nerioum E (Anhydrooleandrin), B- D Digitaloside, Nerioside, obandrin, Digitoxigenin, oleandroside, rutin, plumericin	CCl_4 mediated hepatotoxic model-ameliorated the damaged liver of rats by decreasing the levels of glutamic oxaloacetic transaminase, glutamic-pyruvic transaminase, alkaline phosphatase, bilirubin, and malondialdehyde (196), gradually increase of antitumor activity on Ehrlich ascites carcinoma cells line (197), liver cancer cell line (HEPG2) using 10 concentrations- the inhibition of tumor cell line (198), cytotoxic effects of dichloromethane extracts of the leaves and flowers on HepG-2: human hepatocellular

					carcinoma (Pasteur, C124) and K562- high cytotoxic effects (199).
5.	*Strychnos nuxvomica Loganiaceae* Nux Vomica	Root	Pungent, bitter Light to digest, pungent, hot in potency Balances Vata and Kapha, increases Pitta	Brucine, Strychnine and vomicine; Kajine & Novacine (N Methyl Pseudobrucine); strychnine & isostrychine; Cuchiloside loganic acid	***Root extracts*** on human multiple myeloma cell line - RPMI 8226- Anti-proliferative and cytotoxic effects (200). ***Brucine- alkaloid***- suppressing HCC cell migration in vitro and lung metastasis in vivo , inhibition of the MCF-7 cell line significant inhibition of HepG2 cell proliferation, apoptotic programmed cell death including cell shrinkage, nucleus condensation formation of the apoptotic body, and membrane blebbing (201,202,203, 204) *Indole-alkolid*- ameroliating the galactosamine-mediated reduction of hepatocytes viability as well as bile volume and contents in vitro and in vivo models of liver injury (205)
6.	*Semecarpus anacardium L.f.* *Anacardiaceae* Marking nut	Fruit	*Pungent, Astringent, Sweet Light, Pungent, Hot, Pacify Kapha, Vata*	Bhilavanol A,bhilavanol B,semecarpuflavanone, semecarpetin, anacarduflavanon.	Antioxidant and protective effect, both liver enzymes and HCC marker along with neoplastic changes in liver decreased in *Semecarpus anacardium* nut milk extract treated group (206, 207) ***Methanolic extract*** (MESA)- increase the endogenous antioxidant defence mechanism in NDEA induced hepatocarcinogenesis (208), Nut extract- potential anticarcinogenic activity against aflatoxin B1-induced experimental hepatocellular carcinoma (HC) (209)

These plants having anti-oxidative potential and cause for 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. Studies have shown that traditional medicines could delay 1) tumour progression, 2) increase survival and life quality, and 3) improve the quality of life due to synergistically efficient chemotherapy/ radiotherapy option.

DISCUSSION

Liver diseases if left uncured can lead to cirrhosis and ultimately to HCC. Globally large population is using ASU potential plants and formulations for various types of liver disorders, But it is not as mainstream of medicine. Treatment approaches in ISM have been reported as life style modification, management of underlying diseases and topical or systemic drug administration as well as various procedures. There is an urgent need to investigate the integrative therapeutic solutions for cirrhosis of liver and heapatocellular carcinoma.

Pharmacodynamic of ISM

Pharmacodynamic of ISM are based on the concepts of six tastes (*Rasa, Cuvai*), biophysical attributes (*Guna, Kuam*), potency (*Vriyam*), post-digestive transformation (*Vipak, Pirivu*) and specific pharmacological action (*Prabhav, Makimai*). Adjuvant, vehicle, and dietary regimen also play a role in Pharmacodynamic. Many drugs are prescribed for various ailments based on the clinical manifestation, body constitution and age. The same drug / formulation, by merely changing the vehicle, can possibly change the signalling pathways of medicine and probably target different receptors resulting in different therapeutic effects. Unani medicine recognizes the four *'mizaj, the temperament'* as the main chrematistic - heat, coldness, moisture or dryness - of a substance for its effectiveness on the bodily functions.

According to ISM, the disease process inevitably leads to conjugation of *dosha* and *dushya*, to conquer a disease separation of *dosha* and *dushya* is the main aim of the treatment. During the disease process metabolism of affected tissues is disturbed, it produces toxin- waste material is accumulated in the body. This accumulated waste is responsible for continuation of disease process.

The general approach of the various pharmacological activities of various drugs is to increase the appetizer& digestion power, elimination of the waste toxins, reduce the inflammation, as scraping agent, d*rastic*, separation or disunion of adhered dosha & eradication or uproot the separated dosha out of the body. Rejuvenation therapy [*Rasayan*] helps in maintenance & promotion of health.

ISM formulations have played irreplaceable role in traditional system of medicine. Single plants, poly herbal, herbomineral formulations are common clinical practices. These formulations are widely used in India/ Asian country for its proven antioxidant, anti-inflammatory and hepatoprotective effect.

Mechanism of action

The hepatoprotective herbal drugs act through various mechanisms to protect against various deleterious effects summarized in figure. By involving through one or more mechanisms, they act on the hepatocytes/liver directly or indirectly and help in proper functioning. The mechanisms include an increase in antioxidant level/decrease in oxidants (ROS formation), inhibition of cytochrome P450s, increase and decrease level of Liver enzymes, reduced peroxidation / Lipid peroxidation (MDA), and increase in level of glutathione or reducing equivalents.

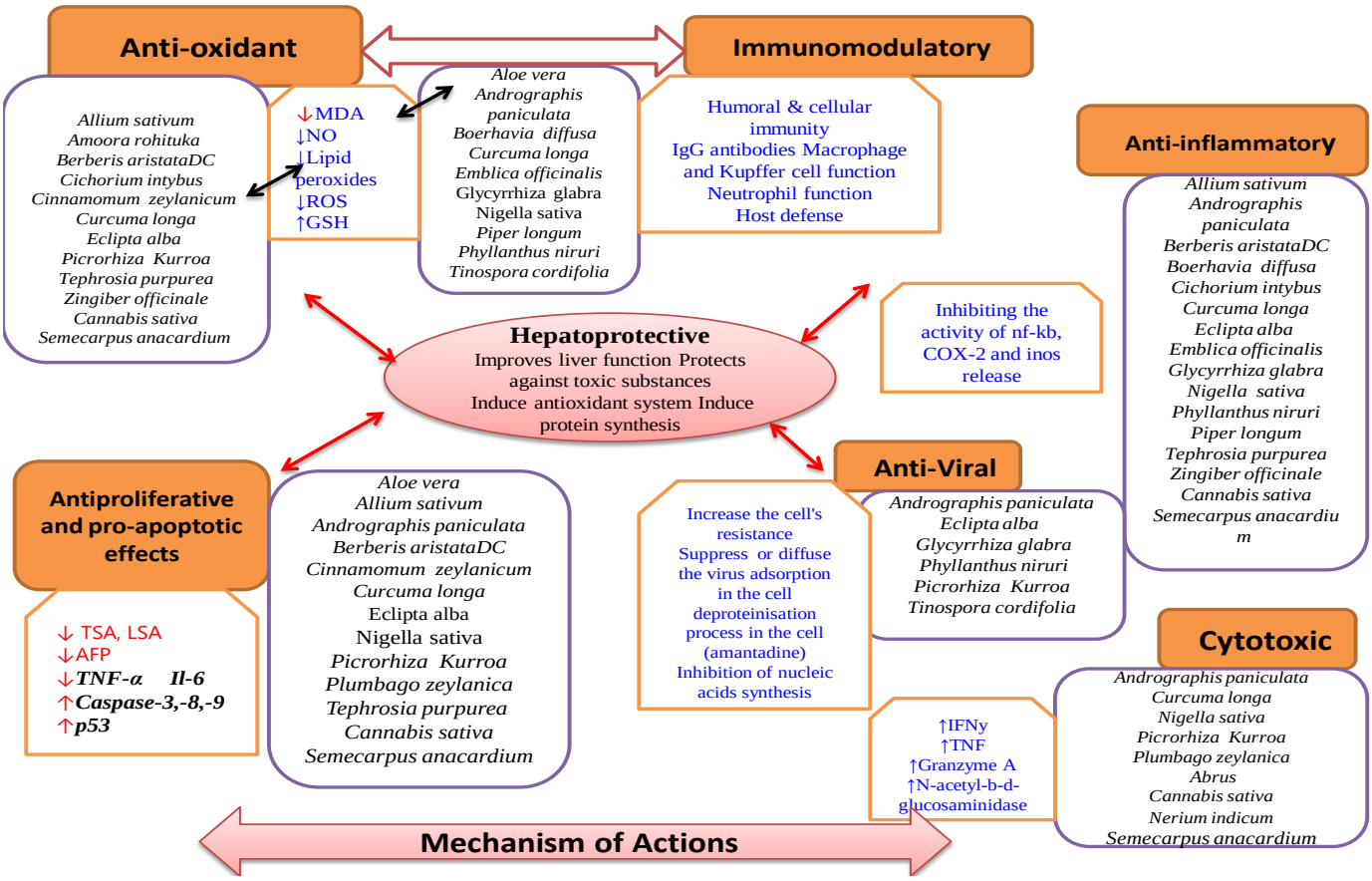


Figure 5. Mechanism of actions

A number of herbal plants show promising effects against in vitro/vivo or in clinical trials. In this review, we have systematically presented published information on experimental, clinical and mechanism of action on cirrhosis and HCC in experimental models. Also some of the plants have shown minor toxicity. All the recent research studies are proven the evidence for novel lead drug design and rational use of ASU for its therapeutic and toxic mechanisms.

LIMITATIONS AND FURTHER SCOPE

Some limitations are yet to be solved.

- Standardization of herbal medicines has been a challenge.
- Another concern is about the variation of in experimental and clinical models/study. Several clinical trials were carried out with a focus on the use of plant drugs and formulations against HCC.
- Prospective, randomized multicentre clinical trial as per good clinical practices is lacking to support their efficacy.
- Study of the Pharmacokinetics / Pharmacodynamic, impact of compatibility of products for the toxicity and its mechanism is yet not studied.
- Safety assessments concerned with formulations are highly needed in today' era.

Liver diseases has an interesting philosophical background with a long history, but it received increasing uncertainty due to the lack of evidence based efficiency as shown by high quality trials. There is also need to establish network for records& documentation of liver patients, especially liver tumors and to develop strategy

for use of potential plants and formulations as preventive therapy to avoid HCC progression and decrease its global incidence.

Key issues of presently available classical ASU 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.

Bringing scientific validation and improvement of the current quality standard of ASU plants and its related products will be useful to bring new insight of bioactive lead compound for new drug design.

CONCLUSION

ASU medicinal plants and formulations act through various mechanisms and maintain the functionality of important organ. Although different herbal drugs are available in the market, their precise mechanism of action is not well understood. More in-depth studies are required to know about various pathways and molecules involved in their action.

Considering community practice settings, patient expectations, compliance and cost effectiveness, standardization and quality production of herbal products may allow us to develop low cost therapies with reduced risk over pharmaceuticals.

Learning from the past, examining the present and advancing to the future, there is an urgent need for additional, carefully conducted, high-quality intensive integrative research to evaluate its efficacy and to develop integrative approach to meet new challenges for Cirrhosis of Liver and Heapatocellular carcinoma. ASU medicines could represent a promising tool to postpone the need of liver transplantations, increase the Quality life of patients and reduce the complications.

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