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A SYSTEMATIC REVIEW OF UNANI FORMULATIONS FOR POTENTIAL IN TREATMENT OF HEPATOCELLULAR CARCINOMA

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ABSTRACT: Background: Hepatocellular carcinoma (HCC) represents the third most common cause of death in the world. It is resistant to most chemotherapeutics and associated with a poor prognosis. Unani system of medicine offers effective treatment for various chronic liver diseases. These treatments have shown reversal of inflammation and fibrosis in various clinical conditions. In the present study, we have reviewed Unani formulations to identify plant drugs that are valuable for the development of novel and effective drugs in management of HCC. **Method:** PubMed and Google Scholar were searched using mesh terms 'hepatocellular carcinoma'; 'liver diseases' 'name of individual Unani formulation and plant drug'. The outcome of interest included formulations used for liver diseases; phytochemical and pharmacological information of individual plant drugs. The additional information sources were the National Formulary of Unani Medicine and Unani Pharmacopoeia of India (Formulation). The outcome of interest was the composition and applications of formulations prescribed for liver diseases. **Result:** Total of 710 unique formulations were searched, out of which 59 formulations having hepato-protective, hepatotonic, deobstruents, and astringent activity was selected for the present study. They were reviewed for individual ingredients. About 16 plant drugs among these were repeated in more than 7 formulations, each having a specific role in treatment options. They were further searched using PubMed and Google Scholar for phytochemical content and pharmacological activity and were found to have a high potential for use in HCC. **Conclusion:** The exhaustive review of 59 Unani formulations used for the treatment of liver dysfunctions identified about 16 traditionally proven plant drugs for exploration in the treatment of HCC.

INTRODUCTION: The liver is a glandular organ of digestive system. It has a complex role in metabolism of the body. More than 100 vital functions are known to have an association with the liver. Some of its important functions are regulation of metabolic pathways, storage of glycogen, secretion of hormones, synthesis of protein, detoxification, digestion, and decomposition of RBC [1]. Progressive destruction and regeneration of liver parenchyma are commonly observed pathological processes that lead to various chronic liver diseases. Viral hepatitis, alcoholic or non-alcoholic fatty liver disease, autoimmune hepatitis, cirrhosis, and hepatocellular carcinoma are a few of the commonly observed chronic liver diseases [2].

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Excessive alcohol consumption, virus infection, obesity, diabetes, and drug-induced liver damage are the main causative factors. About 3.9 to 6.9 deaths per 100,000 populations are caused due to chronic liver diseases in various regions of the world [3].

Progression of chronic liver diseases to hepatocellular carcinoma is not uncommon in India. Approximately 22,000 new cases of primary liver cancer are reported annually in the country. The incidence of secondary liver cancer is about twenty times higher than primary cancer. HCC is very complex and unique when compared with other cancer types. It is mostly associated with chronic liver diseases such as hepatitis or cirrhosis from any cause. They influence each other as cirrhosis is a precursor for most HCC, and growing HCC deteriorates liver function. Moreover, HCC has resistance to a large array of toxins and most chemotherapeutics. Several clinical trials have attempted to overcome the resistance with high doses of chemotherapeutic agents. Such attempts have, however, failed to produce any meaningful survival advantage for patients with HCC. Another characteristic feature of HCC is the natural tendency of HCC cells to invade the portal vein and grow in its lumen, which can get carried away by the bloodstream resulting in distant metastasis. These adversities of HCC impose significant restrictions on treatment options. Treatment such as surgical resection, ablation, chemoembolization is useful only to selected patients.

Protein kinase inhibitors like sorafenib enhance survival for only a short period. Overall very low (4%) survival rate of HCC underlines the limitations in treatment options and marks it as a cause of major health burden. At present, liver transplantation remains the only curative option for patients with cirrhosis and end-stage liver diseases [4].

The Unani system of medicine is one of the oldest traditional medicinal systems which has been offering treatments for chronic liver diseases and cirrhosis for centuries. A large number of single and compound drug formulations are documented to have benefits over chronic liver conditions. These formulations are mostly used for antifibrotic and liver regenerative effects [5].

The pioneer of the Unani system of medicine the great Roman physician Galen 129– 217 (A. D.) described the liver as a counterpart of the sun which is a source of energy for other planets [6]. The Unani system of the medicine referred to the liver as an organ responsible for the production of humor (*Akhlat)* which are named as sanguine (*Dam)*, phlegm *(Balgum)*, yellow bile (*Safra)* and black bile *(Sauda)*. The liver is also identified as an organ that produces four vital powers (*Quwa)*, namely the power of absorption *(Quwat-e-jaziba*), power of digestion *(Quwat-e-ghaziya*), power of retention (*Quwat-e-masikah*), and power of excretion (*Quwat- e-dafiya*). It is also known to be an organ responsible for the production of innate heat *(hararat-e-gariziya)* [7]. An appropriate balance of these forces and humor are necessary for maintaining a healthy metabolic state of the liver.

The imbalance in any of these may lead to pathological changes via alteration in the temperament of humor. The options for treatment of chronic liver diseases are based on measures for correction of altered temperaments, evacuation of morbid matter, and empowerment of liver.

The reviews on therapeutic principles of liver diseases in the Unani system of medicine have earlier been published by Shabnam Ansari (2015) [8] Aisha Siddique (2017) [9] and Mohammad Siddiqui (2015) [10]. Shabnam Ansari *et al.* have summarized various pathological conditions of the liver as Su-*e-Mizaj* [Abnormal / Pathological temperament of the Liver], *Zauf-e Jigar* [Dullness of Liver, hepatosisor Hypocholeretic), *Sudda-e-Jigar* (Hepatic obstruction), *Dard-e-Jigar* (Hepatalgia), *Warm-e-Jigar* (Hepatitis), *Zarba-e-Jigar* (Trauma), *Dabila-e-Jigar* (Hepatic Abscess), *Segar-e-jigar* (Cirrhosis of Liver), *Su-ul-Qinaya* (Anaemia) and *Istiska* (Ascites)". The review has described diagnosis and treatment options offered in the Unani system of medicine and pointed out the drugs which are useful in the treatment of all kinds of liver ailments. They included Kasani (*Cichorium intybus*), karafs (*Apium graveolens*), Ghafis (*Gentiana olivierii*), Izkhar (*Cymbopogon jwarancusa*), Kishneez (*Coriandrum sativum*), Kasoos (*Cuscuta reflexa*), Mundi (*Sphaeranphus indicus*), Turmus (*Lupinus albus*) having properties of astringent, diuresis and deobstruents [8].

Ayesha Siddiqui *et al.*, have described various temperaments of the liver as an indicator of a normal or pathological state. The normal temperament (*Mizaj*) of liver is hot (*Haar)* and moist (*Ratab)*. Due to excessive consumption of alcohol, erratic dietary habits, excess fatty foods its temperament (*Mizaj)* gets altered to cold *(Barid)* and dry (*Yabis)* which is not acceptable to the liver. This leads to pathological changes allowing the accumulation of morbid matter *(Akhlat-e-Galiza*) in the liver [9]. Mohammed Akhtar Siddiqui *et al.*, (2015) presented various case studies demonstrating a significant decrease in fibrosis and improvement in liver functions due to systematic treatment in patients with decompensated liver cirrhosis [10]. These findings emphasized the potential of Unani medicines in the treatment of chronic liver diseases.

The therapeutic benefits offered by the well-defined Unani system of medicine have however not been explored for the development of drugs in the management of advanced-stage liver diseases such as HCC. In the present review paper, we have attempted to survey the potential of Unani drugs for search of novel drug leads against HCC. All the formulations prescribed in the National Formulary of Unani Medicine (NFUM) and the Unani Pharmacopeia of India (UPI) for the treatment of chronic liver disease were considered and categorized according to their specific therapeutic indications. They were then compared for individual composition, phyto-chemical content, and pharmacological activity. The information thus obtained was useful in identifying plant drugs that are used in a maximum number of formulations and are most valuable in reverting inflammation and fibrotic conditions of advanced-stage liver diseases. The study is intended to provide helpful insights for the development of therapeutic or preventive strategies against HCC.

The Unani formulations used in the treatment of various liver dysfunctions were reviewed from authentic publications of the Central Council for Research in Unani Medicine (CCRUM), Ministry of AYUSH, Government of India. The present study also describes the concept of the liver, its physiology and pathological conditions as given in the Unani system of medicine. This information is derived from classical Unani text Al Qanoon fit-Tibb (Hakim Kantoori's Urdu translation), Moalejaat-e-buqratiya, and Firdaus-ul-Hikmat. Published papers on the concept of the liver in Unani medicine searched from PubMed, and Google Scholar was also reviewed for this description. About four papers were identified that fulfilled the criteria.

The Unani formulations used in the treatment of various liver disorders were reviewed from CCRUM publications namely; National Formulary for Unani Medicine (NFUM) Volume I, II, III, IV, VI [11-15] and Unani Pharmacopoeia of India (UPI) Volume II: Part I and Part II [16-17]. The eligibility criteria used was to select the formulations that are prescribed for hepatic disorders and having hepatoprotective, hepatotonic, deobstruents, and astringent activity. Formulations used in disorders unrelated to the liver were excluded. Non-traditional, commercially developed formulations that are not part of classical texts are also excluded.

A total of 1091 formulations are described in NFUM and UPI referred volumes out of these 381 were duplicate. So a total of 710 formulations were screened. About 59 formulations fulfilling inclusion and exclusion criteria were selected for the present study. They were grouped based on their mode of action and compared for their composition. The plant drugs which are used in more than seven formulations were identified and reviewed for phytochemical content and pharmacological effect. The published review and research articles on these plants were searched from PubMed and Google Scholar using the terms phytochemical constituents and pharmacological activity. No restriction on years of publication was applied for these searches. A total of 40 relevant articles were identified in this literature search. The reference lists of the retrieved articles were hand-searched to identify additional relevant articles. After a review of the titles, 10 of these records were found to be duplicated and were excluded. The abstracts of the remaining 30 records were reviewed, and a further eight were excluded. The remaining 22 records underwent a full-text review for assessment of eligibility. A total of 21 [18-38] articles met the eligibility criteria and were included in the systematic review.

The National Formulary of Unani Medicines and Unani Pharmacopoeia of India provides detailed

information on symptoms, diagnosis, and treatment options of various diseases, including all chronic liver diseases. About 12 diseased conditions of the liver are defined in these texts. They are given in **Table 1** and compared with the counterpart described in the modern system of medicine.

TABLE 1: LIST OF PATHOLOGICAL LIVER CONDITIONS DESCRIBED IN UNANI TEXTS AND ITS COUNTERPART IN MODERN MEDICINE

S. no.	Unani term	Modern term
1	*Su-ul-Qinaya*	Anemia
2	*Yarqan*	Jaundice
3	*Istiska*	Ascites
4	*Warm-e-Jigar/ kabid*	Hepatitis
5	*Dard-e-Jigar / Waj-ul-kabid*	Hepatalgia
6	*Tasaddud-e-kabid*	Hepatic obstruction
7	*Su-e- Mizaj*	Abnormal/ Pathological temperament of the Liver
8	*Zauf-e Jigar/Zof-e-kabid*	The dullness of Liver, Hepatosis, or Hypocholeretic/weakness of the liver
9	*Zarba-e-Jigar*	Trauma
10	*Dabila-e-Jigar*	Hepatic Abscess
11	*Segar-e-jigar*	Cirrhosis of Liver
12	*Salabat-e-Tehal&Salabat-e-kabid*	induration of spleen/ Liver

Trauma, inflammation, hepatic obstruction, fibrosis, and regeneration are important features determining the severity of hepatic damage in various chronic liver diseases. Specific treatment regimens are suggested depending on the extent of liver damage**.** The diagnostic features and the treatment options for each of these conditions are detailed in classical Unani texts. A total of about 59 compound formulations were described. The composition, method of preparation, mode of action, therapeutic indications, and doses of each formulation were described in detail. The list of these formulations and pathological conditions for which they are used are presented in **Table 2**.

TABLE 2: CLASSICAL UNANI FORMULATIONS PRESCRIBED IN NFUM AND UPI FOR TREATMENT OF VARIOUS CHRONIC LIVER DISEASES

S. no.	Unani Formulations	Muqawwi-e-jiger	Waram-e-kabid/ Jigar (hepatitis)	Tasaddud-e-kabid (hepatic obstruction)	Zof-e-kabid (weakness of liver)	Yarqan (jaundice)	Waj-ul-kabid (hepatalgia)	Su-ul-qiniya (anaemia)	Salabat-e-Tehal/ kabid (induration of spleen/ Liver)
1	Araq-e-afsanteen		√	√					
2	Araq-e-biranjasif		√						
3	Araq-e-kasni		√			√			
4	Dawa-ul-kurkum		√						
5	Dawa-ul-luk		√						√
6	Habb-e-barhami		√		√				
7	Habb-e-Kabar		√						
8	Habb-e-kabidnaushadari		√						
9	Habb-e-mazaryun		√		√				
10	Majoon-e-Rewand		√				√		
11	Majoon-e-gul		√						
12	Jawarish-e- amla sada		√						
13	Qurs-e- sumbul-ut-teeb		√				√		
14	Qurs-e-firanjmushk		√		√	√			
15	Qurs-e-ghafis		√			√			√
16	Qurs-e-hummaz		√						
17	Qurs-e-sumbul		√						
18	Sharbat-e-deenar		√			√			
19	Tehali		√						√
20	Zimad-e-Iklilulmalik (local		√						

	application)									
21	Majoon-e-Dabidul ward	√	√					√		
22	Qurs-e-zarishk	√	√					√		
23	Jawarish-e-Tamar hindi	√								
24	Majoon-e-jalinooslului	√			√					
25	Qurs-e-ambarbaris	√		√	√					
26	Qurs-e-ambarbaris qawi	√		√	√					
27	Qurs-e-istisqa	√								
28	Qurs-e-kabdi	√			√					
29	Qurs-e-luk	√								
30	Sharbat-e-faulad	√								
31	Sikanjabeen-buzoorimotadil	√		√						
32	Sikanjabeenlemuni	√			√					
33	Sufoof-e-maleh	√					√			
34	Yashbi	√			√					
35	Zimad-e-feesaghorus(local application)				√					
36	Araq-e-mako				√					
37	Fawakeheen				√					
38	Gulqand-e-Gulab				√					
39	Jawarish-e-utraj				√					
40	Jawarish-e-jalinoos				√					
41	Jawarish-e-aamlaambary				√					
42	Jawarish-e-aamlaluluvi				√					
43	Jawarish-e-Darchiniqawi				√					
44	Jawarish-e-fawakeh				√					
45	Jawarish-e-narmushk				√					
46	Jawarish-e-anarain				√					
47	Kushta-e-faulad				√			√		
48	Kushta-e-khabsulhadeed				√					
49	Majoon-e- Buqrat				√					
50	Majoon-e-khabs-ul-hadeed				√			√		
51	Majoon-e-sangdanamurgh				√					
52	Murabba-e-aamla				√					
53	Sabadaritoos				√		√		√	
54	Sharbaat-e-bazoorimotadil			√						
55	Qurs-e-ward			√						
56	Zimad-e-qutoon (local application)								√	
57	Majoon-e-Juntiyana								√	
58	Qurs-e-gul					√				
59	Habb-e-Ghafis					√	√			

The specific pathological condition for which the formulation is recommended has been indicated by a tick.

The above table provides information on 59 formulations used in various stages of liver diseases. The table shows that some formulations are specific to only particular disease whereas other covers broad range of liver diseases. This specificity of formulations is due to the unique

properties of individual plant drugs. Grossly the formulations could be arranged into six groups based on their mode of action. A large number of formulations are heptatonic *(Muqawwi –e-kabid*) and therefore used in the dullness of the liver*(Zof-e-kabid)*. Some formulations such as *Arq-e-kasani, Habb-e-ghafis, Dawa-ul-luk, Qurs-e-ambarbaris* have the deobstructive (*Muffat-e-sudad)* activity and hence find their use in conditions of hepatic obstruction. The formulations such as *Dawa-ul-kurkum, Dawa-ul-luk, Majoon-e-dabidul ward, Sharbat-e-dinar,* and *Qurs-e-kabidi* have Diuretic *(Muddir-e-baul)* activity and are useful in the treatment of ascites. Due to the anti-inflammatory *(Muhalil-e-warm)* property of *Arq-e-afsanteen, Ark-e-kasani, Habb-e-kabid naushadri, Jawarish-e-amla sada, Qurs-e-ghafis,* they are used in hepatitis. The formulations *Dawa-ul-kurkum, Dawa-ul-luk,* and *Qurs-e-afsanteen* possess hot temperament hence used in the altered cold temperament of the liver which is responsible for the dullness of liver (*Zof-e-kabid),* ascites (*Istisqa),* and anaemia (*Su-ul-Qinaya*). Lastly, more complex formulations like *Dawa-ul-kurkum, Dawa-ul-luk, Habb-e-ghafis, Majoon-e-dabidul ward, Sharbat-e-dinar, Jawarish-e-tamar hindi,* and *Shikanjabeen bazoori motadil* possess multiple properties of diuresis, deobstruction, and astringent and hence are strongly advised for multiple disease conditions.

Comparison of Formulations for Individual Composition: The formulations enlisted in table 2 were searched for individual components. It was observed that a total of 121 plant drugs, 18 minerals, and 6 animal-derived drugs had been used in the preparation of 59 formulations compiled in **Table 2**. The literature review for research studies undertaken on each of these plants was carried out using various search options. Most of them possessed hepatoprotective potential and were rich in flavonoids, saponins, and tannins. Few plants out of these were extensively investigated and had multiple medicinal properties. Incidentally, these plants were also a constituent of various formulations. Such plants were identified and grouped. **Table 3** presents the plants which are part of multiple formulations for application in various diseased conditions of the liver.

TABLE 3: LIST OF MEDICINAL PLANTS USED IN MULTIPLE FORMULATIONS

S. no.	Unani name	Botanical name	Common name	Parts used	Temperament	No. of times Used in Formulations
1	*Sumbul-ut-teeb*	*Nardostachys jatamanasi*	Spikenard	Rhizomes	Hot Dry	21
2	*Warq-e-gul-e-surkh*	*Rosa damascena*	Rose	Flowers	Cold Dry	21
3	*Rewand chini*	*Rheum emodi*	Indian Rhubarb	Roots and rhizomes	Hot Dry	18
4	*Mastagi*	*Pistacia lentiscus*	Mastic	Resin	Hot Dry	16
5	*Tukhm-e-Kasni*	*Cichorium Intybus*	Chicory	Seeds	Cold Dry	16
6	*Filfil siyah*	*Piper nigrum*	Black pepper	Fruits	Hot Dry	15
7	*Zanjabeel*	*Zingiber officinale*	Dry Ginger	Rhizomes	Hot Dry	13
8	*Zafran*	*Crocus sativus*	Saffron	Stamens	Hot Dry	13
9	*Tukhm-e-karafs*	*Apium graveolens*	Celery	Seeds	HotDry	12
10	*Darchini*	*Cinnamomum zeylanicum*	Cinnamon	Bark	Hot Dry	11
11	*Anisoon*	*Pimpinella anisum*	Aniseeds	Seeds	HotDry	9
12	*Qust*	*Saussurea lappa*	costus or kuth	Rhizomes	Hot Dry	9
13	*Shagufa-e-Izkhar*	*Cymbopogon jwarancusa*	Jwarancusa	Flowers	Hot Dry	8
14	*Anarshireen*	*Punica granatum*	Pomegranate	Seeds, Bark	Cold Moist	8
15	*Zarishk*	*Berberis aristata*	Indian barberry	Stem, root	Hot Dry	7
16	*Tukhm-e-Kasoos*	*Cuscuta reflexa*	Dodder	Whole plant	Hot Dry	4

Table 3 presents a list of plants that are used in multiple Unani formulations for the treatment of chronic liver diseases. The common name, part of the plant used, its temperament and the number of times it is used in formulations are detailed.

Table 3 points out that sixteen medicinal plant drugs out of 121 are used in multiple Unani formulations. Repeated use in elevation of liver dysfunctions underlines the importance of their

medicinal value. Information of chemical composition and biological effect of these plants would be of help in exploring their use in a more complex and severe condition such as HCC. **Table 4** summarised the information of phytochemical content and pharmacological effects of these sixteen selected plants as obtained through Google and PubMed searches. It will be worthwhile determining their active ingredient and mechanism of action for exploring their use in the management of HCC.

TABLE 4: PHYTOCHEMICAL CONTENT AND BIOLOGICAL EFFECT OF PLANTS LISTED IN TABLE 3

S. no.	Plant Drugs	Part Used	Phytochemical Composition	Biological Effect and Mechanism
1	Sumbul-ut-teeb *Nardostachys jatamanasi*[18]	Rhizomes	Sesquiterpenoids, terpenic coumarins, lignans, jatamansone or valeranone, alpha-patcho-ulense, angelicin, β-sitosterol, calarene, elemol, jatamansin, jatamansinol, n-hexaco-sanyl, n-hexacosane, oroselol, patchouli alcohol, valeranal, nardostachnol, seychellene, seychelane, nardostachone, volatile oil, resin, sugar, starch, ketone, jatamansic acid, jatamansonesemicarbazone, lupelol, malliene, calarenol, terpenic, coumarin-jatamansin, propionate, cyclohexanal ester, hepatacosanylpentanoate, diethaniod bicyclic-ketone-nardostachone, actidine, Nardal.	Used in Ayurvedic and Unani Systems of medicine for the treatment of liver and CNS disorders. It is used as a stimulant, tonic, antispasmodic, laxative, bronchodilator, vasodilator, and tranquilizer. Investigated properties: Antifungal, hepatoprotective, anticonvulsant, neuroprotective, antiparkinson's, antidepressant, tranquilizing, antioxidant, antidiabetic, antihysteric, hypotensive, antispasmodic, anti-inflammatory, cardiotonic, antimicrobial, vasodilator, antiepileptic.
2	Warq-e-gul-e-surkh *Rosa damascena*[19]	Flowers	Tannin, flavonoids, glycosides, carboxylic acid, ascorbic acid, a long polyunsaturated fatty acid having formula $C_{37}H_{64}O_2$ is an active constituent, cyanidin-3-O-β-glucoside, quercetin, gentiobioside, maurones, rugaurone, maritimein, tetrahydroxyaurone, siamaurone, damaurone.	Used in Unani system of medicines for pain management, digestive problems, menstrual bleeding, and strengthening of the heart. Anti-inflammatory agent in managing and treating various inflammatory conditions. Properties: Significant analgesic, anti-inflammatory, cardiotonic, anti-HIV, antibacterial, antioxidant,antitussive, hypnotic, antidiabetic, relaxant, analgesic, laxative, wound healing, skin tonic, gastrointestinal diseases, menstrual bleeding, pregnancy-related disorders, mental disorder, depression, anxiety. Beneficial for liver dysfunction and have liver tonic properties. Induced neurite outgrowth activity and inhibited Aβ induced atrophy and cell death. -Isolation of long -Protects Aβ (25-35) induced atrophy and displayed strong neurite outgrowth activity.
3	Rewand chini *Rheum emodi*[20]	Roots and rhizomes	Anthraquinones, emodin, chrysophanol, aloe-emodin, rhein, physcion, charysophanol, piceatannol, resveratrol, oxanthrone esters.	Anticancer properties against breast cancer, liver cancer, lung squamous cell carcinoma, gastric cancer, colon cancer, prostate cancer, melanoma, leukemia and lymphoma cell lines. It shows these activities by arresting cell cycle, regulation of Bid, BiK, BoK, Fas, P21, BcL xl, BCL-2 proteins, activation of caspase, loss of mitochondrial potential, and release of cytochrome. It also has antioxidant, anti inflammatory, antimicrobial, antifungal, antiplatelet, antidiabetic, antiulcer, hepatoprotective, immune booster, nephroprotective activities.
4	Mastagi	Resin	Beta pinene, Alpha pinene, catechin,	Anticancer, hepatoprotective,

	Pistacia lentiscus[21]		verbenone, thymol, limonene, terpene, carvacrol, gallic acid, myreene, linalool, Alpha tocopherol.	antiatherogenic, antimicrobial, antioxidant, anti-tumor antiarthritic, antigout, hypotensive, antifungals.
5	Tukhm-e-Kasni *Cichorium intybus*[22]	Fruits, Seeds	Sesquiterpene lactones (Lectucin, Lactucopicrin, 8-desoxy lactucin, guianolid glycosides, including chicoroisides B and C sonchuside C), caffeic acid derivatives (chicoric acid, chlorogenic acid, isochlorogenic acid, dicaffeoyl tartaric acid), inulin, sugars, proteins, hydroxycoumarins, flavonoids, alkaloids, steroids, terpenoids, oils, volatile compounds, Coumarin, and vitamins.	Hepatoprotective, gastroprotective hypolipidaemic, anticancer, anti-inflammatory, wound healing. Significant histological damage (steatosis, inflammation, fibrosis) to the cells and tissues are reverted via downregulation of SRVEP_1c and PPAR α genes that follow steatosis induction. Inhibition of PGE2, TNFα dependent induction of COX -2 induction and activation of Nf- kappa B in human colon carcinoma cell line.
6	Filfil siyah *Piper nigrum*[23]	Fruits	Alkaloids, lignans, terpenes, piperine, propanedioicacid, dimethyl ester, bicycloheptane, 3-Carene, Cyclohexene ethylpyrrolidine, L-α-Terpineol, lavandulyl acetate, Pyrrolizin-ethyl(ester), Eugenol, alfa. Copaene, epiglobulol, Caryophyllene, α- langene, β-copaeneisocalamendiol.	CNS depressant, antipyretic, analgesic,anti-inflammatory, antioxidant, hepatoprotective, anti-tumor, anti-helicobacter pylori, anti-candida, anti-aging, anti-hyperlipidemia, Anti-termitic, anti-osteoporosis, antiulcer, antiatherosclerotic, anti-HIV.
7	Zanjabeel *Zingiber officinale*[24]	Rhizomes	Gingerols, shogaol, paradol, gingerdione, zerumbone.	Reduced the elevated expression of tumor necrosis factor –Alfa (TNF-α) and NF-kB by extract ginger in liver cancer of rat. Hepatoprotective, cytotoxic, nephroprotective, larvicidal, anti-bacterial, anti-diarrhea, antidiabetic, antioxidant, anthelmintic, anti-fungal, anti-inflammatory, analgesic
8	Zafran *Crocus sativus*[25]	Stamens	Crocin, crocetin, afranal picrocrocin.	Crocin enhances apoptosis by raising the Bax/Bcl-2 ratio in gastric cancer. Inhibit nuclear factor-kappa b activation, increase cleavage of caspase-3 as well as DNA damage. Antihypertensive, anticonvulsant, antitussive, antigenotoxic, anxiolytic, aphrodisiac, antioxidant, antidepressant antinociceptive, relaxant, anticancer for skin cancer, cervical cancer, leukemia, breast cancer, colorectal cancer, liver cancer, pancreatic cancer.
9	Tukhm-e-karafs *Apiumgraveolens*[26]	Seeds	Carbohydrates, flavonoid, alkaloids, steroids, glycosides, phenols, furocoumarins, celerin, furocoumarins, limonene (60%), β-pinene, camphene, cymene, limonene, αthuyene, α-pinene, β-phellendrene, p-cymene, γterpinene, phthalide sabineneterpinolene, myristic, linoleic, petroselinic, palmitoleic, palmitic, oleic, myristoleic, stearic acid, santalol, β-eudesmol, α-eudesmol, sedanenolide.	An antioxidant inhibitory effect on hepatocarcinogenesis, anti-inflammatory, cytotoxic, antimicrobial, hypolipidaemic.
10	Darchini *Cinnamomum zeylanicum*[27]	Bark	Proanthocyanidin compound, procyanidin B2.	Anti-allergenic, anti-inflammatory, antipyretic, antibacterial, antifungal, anesthetic, antioxidant [27]. CE and specific characterized CE components, typeA procyanidin trimer and tetrameric procyanidins, effectively

				inhibitedVEGFR2 kinase activity as well as VEGF signaling in endothelial Cells [28]
11	Anisoon *Pimpinella anisum* [29]	Seeds	Anethol, Alkaloids, flavonoids, saponins, tannins, terpenoids, phenolic compounds, cardiac glycosides.	Diuretic, laxative, expectorant, anti-spasmodic, antioxidative, anti-diabetic.[29] Anethol can suppress NF-kB activation through the inhibition of IkBα degradation [30]
12	Qust *Saussurea lappa* [31]	Rhizomes	Resins,alkaloids, steroids, flavonoids, costunolide, antamarine,1saussureamines, chrysophanol.	Antioxidant, anti-inflammatory, anticancer, antitumor, hepatoprotective, hypnotic, analgesic, antiaging, immunomodulatory[31]. TNFα-induced cell migration and invasion were inhibited by eithercostunolide. suppressed TNFα-induced NF-κB translocation to the nucleus and transcriptional activity. Besides, costunolide specifically inhibited IKKphosphorylation and IκBαdegradation [32]
13	Shagufa-e-Izkhar *Cymbopogon jwarancusa* [33]	Flowers	Citronellal, piperitone, geraniol, pentatriacontane, 6- pentatriacontanone, elemal.	Antioxidant, anti-allergic, antimicrobial, antiparasitic, analgesic, and antipyretic.
14	Anar *Punica granatum* [34]	Seeds, Bark	Tannins, saponins, Quinone, terpenoids, steroids, phenols, flavonoids, alkaloids, glycosides, anthocyanin, betacyanin.	Antiviral, antioxidant, estrogen depletement, anticancer, anti-inflammatory. Suppress NF-kB activation [30]
15	Zarishk *Berberis aristata*[35]	Stem, root	Berberine, oxyberberine, berbamine, aromoline, palmatine, oxycanthine, taxilamine, alkaloids, reducing sugar, Coumarin, saponins, flavonoids, steroids, glycosides, tannin, polyphenol, terpenoids.	Hypoglycaemic, antibacterial, anti-fungal, hepatoprotective, anti-cancer, anti-diarrhoeal, anti-inflammatory, anti-microbial, anti-pyretic, anti-oxidant, antimalarial, immunomodulatory [35]. TNF-α induced cell invasion is prevented by berberine treatment in a human breast cancer cell. Berberine prevent MMP- 9 induced degradation of ECM including type IV collagen, leading to inhibition of AP-1 DNA binding activity [36]
16	Tukhm-e-Kasoos *Cuscuta reflexa* [37]	Whole plant	Alkaloids, flavonoids, terpenoids, fixed oil, phytosterols, saponins, fats, carbohydrates, protein, glycoside. Cuscutalin (1%) and cuscutin (0.02%). quercetin, amarbelin, amino acids, scoparone, melanettin, hyperoside, aromadendrin, taxifolin, astragalin	Anti-inflammatory, anticancer, antimicrobial, antifungal, hypotensive, hypoglycaemic [37]. It blocked NF-kB binding to its motifs and induced apoptosis in Hep3B cells. It upregulated pro-apoptotic factors BAX and p53 and down-regulated anti-apoptotic factor Bcl-2 [38]

Table 4 Phytochemical content and biological effects of plants used in various Unani formulations for the treatment of chronic liver diseases.

In addition to the plants listed in **Table 3**, few others (not mentioned in **Table 3**) are also a part of multiple formulations. They are namely; *Citrus aurantifolia, Pimpinella anisum, Trachyspermum ammi, Foeniculum vulgare, Myristica fragrans, Piper nigrum, Rosa damascene, Amomum subulatum, Elettaria cardamomum, Portulaca oleracea, Mentha arvensis, Aloe barbadensis, Citrus medica,* and *Zingiber officinale.* Most of these are herbs or spices used in the diet. They are rich in essential oils and are known for preventing oxidative damage and suppress inflammation. They are also known to possess a spectrum of biological activity. They are used for antioxidant and anti-inflammatory effects in addition to flavoring agents in complex formulations.

The other plants referred to in **Table 4** such as *Saussurea lappa, Rheum emodi, Cinnamomum zeylanicum, Berberis aristata, Nardostachy jatamanasi, Crocus sativum, Piper nigrum, Cuscuta reflexa, Pistacia lentiscus, Cichorium intybus, Apium graveolens, Pimpinella anisum,* are rich in polyphenols, lignin, flavonoids and possess

a broad spectrum of biological activities. They have demonstrated inhibition of cell proliferation and induction of caspase-3 dependent apoptosis of cancer cell lines *via* vital signaling pathways. Few of them induced apoptosis by inhibiting topoisomerase I or II, which are nuclear enzymes that control DNA supercoiling during DNA replication and transcription. The study suggests that these 16 plants are likely to have high anti-tumour potential to combat the cancer cells of liver. Extensive studies for these plants should provide insight into pharmaceutical efficacy for the prevention and therapy of HCC.

CONCLUSION: The present study attempted to review the formulations described in the National Formulary of Unani Medicine and Unani Pharmacopoeia of India for the treatment of liver diseases. A total of fifty-nine formulations were described. They were grouped into six groups based on their biological action and medicinal value. The comparison of these formulations for composition identified that they were prepared using 121 plant drugs, 18 minerals, and 6 animal-derived products. About sixteen plant drugs out of these had a profound biological effect and were used in multiple formulations for treatments of mild to severe conditions of the liver. The review points out that these sixteen plants having potential bioactive compounds, pharmacological effects and clinical application should be explored for the development of newer effective drugs in the treatment of hepatocellular carcinoma.

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