Consequences of Alcohol induced Hepatic injury and it's Management through Hepatoprotective Unani Formulations

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Abstract: As a major contributor to cirrhosis, liver cancer, and both acute and chronic liver failure, alcoholic liver disease (ALD) has a substantial rate of morbidity and fatality. In many European countries, alcohol consumption is down marginally, while in other countries, it is increasing, and it is still high in many other countries. Though it is still not fully understood, the pathophysiology of ALD is mostly related to the direct toxic effects of alcohol and acetaldehyde, its primary intermediary.

Systematic scans of the complete human genome have recently revealed new putative mechanisms, which lead to new theories about pathways that were previously unknown. The latter may aid in the creation of prognostic risk scores by identifying host genetic risk factors for severe liver damage. A liver biopsy is rarely necessary for the diagnosis of ALD, which can be made with a panel of well-evaluated diagnostics. ALD is challenging to treat, with abstinence serving as the main therapeutic objective. After cirrhosis is identified, treatment for ALD is much the same as for other causes of severe liver disease. For carefully chosen individuals with cirrhosis and alcoholic hepatitis, liver transplantation is a good alternative because the prognosis is similar to other aetiologies and relapse rates are low. The distribution of donor livers for ALD patients is still restricted in many nations. In general, there aren't many treatment options for severe ALD.

Keywords: Hepatitis, alcoholic, Corticosteroid therapy, Carcinoma, hepatocellular, Liver transplantation, Malnutrition,

INTRODUCTION: About 3.8% of all fatalities globally and 4.6% of disability-adjusted life years are caused by alcohol usage. This problem is particularly relevant in Europe[1], where alcohol use accounts for 6.5% of all fatalities. One Furthermore, risky drinking, particularly when combined with alcohol dependence, is thought to be the cause of one in seven deaths among men and one in thirteen deaths among women between the ages of 15 and 64, according to current estimates. [2]. In Europe, alcoholic liver disease (ALD) is the main cause of mortality in adults related to alcohol-, and alcohol use disorders (AUD) are the most frequent cause of liver cirrhosis. [3]. The mortality rate from liver cirrhosis has declined in most Western European countries during the past 30 years, whereas it has increased in certain Eastern European countries, the United Kingdom, Ireland, and Finland.[4]- Significantly, the all-cause death rate for middle-aged white non-Hispanic men and women increased significantly in the United States between 1999 and 2013, primarily as a result of an increase in cirrhosis, chronic liver disease, drug and alcohol poisoning.[5]. For many patients, but not all of them, the alcohol use disorder —a very common behavioural disorder characterized by tolerance to the psychotropic effects of alcohol consumption, obsession with alcohol, and repeated drinking despite its negative consequences—is a strong predictor of alcohol-related organ damage. Binge drinking and long-term alcohol use also contribute to a variety of physical and mental maladies and injuries,

as well as many diseases that are mostly or exclusively brought on by alcohol, such as alcohol-induced pancreatitis. [6], the deadly alcoholism condition.[7] additionally, a number of illnesses and injuries are caused by alcohol. Oropharyngeal, oesophageal, liver, colon, rectum, and female breast cancers are some of the most serious illnesses that are impacted by alcohol consumption; Neuropsychiatric conditions (depressive illnesses, epilepsy); [8] cardiovascular diseases; [9].

PREVALENCE OF HEPATIC DISORDER IN INDIA: The prevalence of hepatic disorder in India is 4.6% of disability-adjusted life years and 3.8% of all fatalities worldwide are attributed to alcohol use. [11] This issue appears to be more prevalent in Europe, where alcohol use accounts for 6.5% of all fatalities, [1]

According to recent estimates, one in seven fatalities in males and one in thirteen deaths in women between the ages of 15 and 64 are caused by dangerous drinking, especially when it is linked to alcohol dependence. [2]

The majority of Western European nations had a decrease in liver cirrhosis mortality over the previous 30 years, but numerous Eastern European nations, as well as the UK, Ireland, and Finland,[3] saw an increase.[4] White middle-aged men and women, non-Hispanic in the United States increased dramatically between 1999 and 2013, primarily due to rising incidence of cirrhosis, chronic liver disease, and drug and alcohol poisoning. [5]

Second only to tobacco-related morbidity (11.7%), alcohol-related morbidity accounts for 10.3% of disability adjusted life years (DALY) in wealthy countries, according to the World Health Organization. In this group, liver cirrhosis accounts for 70–80% of the directly reported alcohol-related mortality. 80,600 deaths in 2010 were attributable to alcohol-related liver cancer (14,800 deaths in women and 65,900 deaths in men), and 493,300 deaths were attributable to alcoholic liver cirrhosis (47.9% of all liver cirrhosis deaths), or 0.9% of all deaths overall (0.7% of all deaths in women and 1.2% of all deaths in men). A dozen [3] Studies have shown that the prevalence of alcohol in the elderly population ranged from 17.1% to 21.83%; rates for males and women were 16.3% to 19.30% and 0.8% to 2.53%, respectively. [12, 13] Alcohol use has long been a major global social and health concern. Worldwide, the use of alcohol is increasing, [14]

The prevalence of alcohol use disorder (AUD), which is more prevalent in low- and middle-income countries, is higher among younger Southeast Asian generations, those aged 15 to 19. During the week ending March 2020, alcohol consumption increased by 54% compared to the previous year, a phenomenon that has been connected to the COVID-19 epidemic. It would probably be very similar in Asia and India. [15] [16],

ALCOHOLIC LIVER DISEASE HAS THREE HISTOLOGIC PHASES.[17, 18]

MORPHOLOGIC FEATURES: In alcoholic liver disease three types of morphologic lesions are described— fatty liver, alcohol induced hepatitis, and alcoholic cirrhosis.

1. ALCOHOLIC STEATOSIS (FATTY LIVER). On a gross level, the liver is yellow, swollen, firm, and oily, with a smooth, glossy capsule. Initially micro vesicular fat droplets in the hepatocyte cytoplasm are observed followed by the more prevalent and noticeable macro vesicular big fat droplets that push the nucleus to the side under a microscope. Hepatocytes that contain fat may burst and consolidate, leading to the development of fat cysts. Rarely, lipogranulomas that are composed of a cluster of macrophages, lymphocytes, and a few multinucleate large cells can be discovered.

2. ALCOHOLIC HEPATITIS. In most cases, alcoholic hepatitis occurs promptly after a period of severe drinking. It is most likely that alcoholic cirrhosis develops as a result of repeated bouts of alcoholic hepatitis after pre-existing fatty liver. According to histology, alcoholic hepatitis has the following characteristics.

i) Hepatocellular necrosis: Single or small clusters of hepatocytes, especially in the centrilobular area (zone 3), undergo ballooning degeneration and necrosis.

ii) Mallory bodies or alcoholic hyaline: These intracytoplasmic inclusions, known as eosinophilia, are found at perinuclear locations in enlarged and swollen hepatocytes. They are collections of prekeratin, or cytoskeletal intermediate filaments. Connective tissue stains such as Masson's trichrome and chromophobe aniline blue, as well as immune-peroxidase techniques, are the most effective ways to visualize them. Although they are not specific for alcohol-induced hepatitis, mallory bodies are strongly indicative of it [18],[19].Mallory bodies are also seen in a few other illnesses, including focal nodular hyperplasia, hepatocellular carcinoma, Wilson's disease, cholestasis syndromes, primary biliary cirrhosis, Indian childhood cirrhosis, and intestinal bypass surgery.

iii) Inflammatory response: An inflammatory infiltration, primarily composed of polymorphs and a few isolated mononuclear cells, is linked to the regions of Mallory bodies and hepatocellular necrosis. The inflammatory infiltration is more pervasive and may affect the entire lobule in cases of more severe necrosis.

iv) Fibrosis: The majority of alcoholic hepatitis cases are characterized by pericellular and perivenular fibrosis, which gives the condition known as chicken wire or web-like look. Creeping collagenosis is another name for this condition.

3. ALCOHOLIC CIRRHOSIS. About 60–70% of all cirrhosis cases are alcoholic cirrhosis, making it the most prevalent kind of lesion. This kind of cirrhosis has been referred to by a number of names, including diffuse cirrhosis, hobnail cirrhosis, Laennec's cirrhosis, portal cirrhosis, and micro nodular cirrhosis. On a gross level, alcoholic cirrhosis typically starts as micro nodular cirrhosis, which is characterized by nodules smaller than 3 mm in diameter and a big, fatty liver that weighs more than 2 kg. Finally, after several years,

The liver resembles post-necrotic cirrhosis, shrinks to less than 1 kg in weight, becomes non-fatty, and develops macro nodular cirrhosis (nodules larger than 3 mm in diameter). Forming regenerating nodules with hepatocyte masses that are disorganized. Early in the disease, there is a significant fatty alteration in the hepatic parenchyma inside the nodules. But the amount of fat in hepatocytes decreases when the fibrous septa thicken. Consequently, the quantity of fat and fibrous scarring in the nodules are inversely correlated.[19, 20, 21, 22]

ETHANOL METABOLISM. Alcohol contains seven calories per gram. However, alcohol must be oxidized, primarily in the liver, because it cannot be stored in the body. Therefore, these empty calories only provide energy and have no nutritional value. Following consumption and absorption from the small intestine, ethanol travels through the liver, where two enzymes—acetaldehyde dehydrogenase (ALDH) in the hepatocytes' mitochondria and alcohol dehydrogenase (ADH) in the cytosol—oxidize approximately 90% of it to acetate. The body oxidizes the remaining 10% of ethanol in other places.

Step one: In the liver, ethanol is catabolized to acetaldehyde via three major and two minor pathways:
i) By alcohol dehydrogenase's (ADH) primary rate-limiting pathway in the cytosol.
ii) Through microsomal P-450 oxidases (also known as the microsomal ethanol oxidizing system, or MEOS), which only partially metabolize ethanol in the smooth endoplasmic reticulum.
iii) H_2O_2 and other minor catalase-mediated pathways in the peroxisomes.
The hazardous chemical acetaldehyde can lead to cell necrosis and damage to membranes. Concurrently, Nicotinamide adenine dinucleotide (NAD), a coenzyme that accepts hydrogen, is reduced to NADH. [19]

Step two: Takes place in the mitochondria, where Aldehyde Dehydrogenase functions as a co-enzyme to convert acetaldehyde to acetate. After exiting the liver, the majority of the acetate is either oxidized to carbon dioxide and water or transformed into other molecules, such as fatty acids, by the citric acid cycle. The fundamental biochemical change that takes place during ethanol metabolism is the simultaneous reduction of the same cofactor, NAD, to NADH, which raises the NADH: NAAD redox ratio. The ratio of its oxidized and reduced metabolites, known as the lactate-pyruvate ratio and the β-hydroxyl butyrate-acetoacetate ratio, provides a close estimate of the NADH: NAAD ratio.[19, 22].

RISK FACTORS FOR ALCOHOLIC LIVER DISEASE:

Not everyone who abuses alcohol experiences liver injury. About 10–15% of alcoholics who undergo autopsy have cirrhosis. Although the exact cause of certain people's susceptibility to alcoholic cirrhosis is unknown, numerous risk factors have been identified. These are following:

Pattern of Drinking: Chronic alcoholism has been linked to alcoholic cirrhosis in the majority of epidemiologic research. The information that is now available indicates that heavy and long-term alcohol use always results in fatty liver in over 90% of chronic alcoholics, alcoholic hepatitis in 10%–20% of cases, and alcoholic cirrhosis in more than 10% of cases. It is widely acknowledged that consuming 60–80 grams of ethanol per day in any kind of alcoholic beverage for a minimum of ten years is likely to cause alcoholic cirrhosis.

Liver harm is not correlated with the type of alcoholic beverage consumed, but rather with the amount of ethanol consumed and how long it lasts. Although the amount of ethanol in alcoholic beverages is indicated on the container label, it is typically between 4 and 6% in beer, 10 to 12% in wine, and 40 to 50% in brandy, whiskey, and scotch. Long-term intermittent drinking is less damaging because it gives the liver time to heal. [23]

2. Gender: Women who consume significantly less alcohol (20–40 g/day) are more likely to acquire severe alcoholic liver disease. Although the cause of this gender disparity in illness progression is unknown, it is most likely related to oestrogen's effects. [24, 25, 26]

3. Malnutrition: The development of cirrhosis is thought to be influenced by absolute or relative protein and vitamin deficiency. It is not starvation per se that causes alcoholic liver disease, but rather persistent alcohol consumption along with poor nutrition. Alcohol seems to replace other nutrients with calories, causing malnutrition and vitamin deficiencies in alcoholics. Malnutrition in alcoholics is also influenced by pancreatitis and chronic gastritis. Improvements in alcoholic cirrhosis cases following treatment with protein-rich diets provide clinical and morphologic evidence for the synergistic effect of malnutrition in chronic alcoholism.

4. Infections: Patients with cirrhosis frequently experience recurrent bacterial infections, which can hasten the progression of the illness. Non-alcoholic patients with a history of viral infections may develop lesions resembling those of alcoholic cirrhosis.

5. Genetic factors: Genetics controls the pace of ethanol metabolism. It is mostly associated with different ethanol elimination rates brought on by genetic variations in the two primary enzyme systems, alcohol dehydrogenase (ADH) and MEOS (microsomal P-450 oxidases). Although no one genotype has been found yet, several HLA histocompatibility types have been linked to various populations' vulnerability to alcoholic liver injury.[15, 27]

6. Hepatitis C infection: Concurrent HCV infection is a significant risk factor for the development of alcoholic liver disease. A persistent alcoholic who has an HCV infection develops alcoholic liver disease at a considerably lower rate (20–50 g/day), the disease progresses earlier is more severe, has a higher chance of developing cirrhosis and hepatocellular carcinoma, and has a lower overall survival rate.[19, 22]

PATHOGENESIS:

It is still unknown what the precise pathophysiology of alcoholic liver disease is and why some chronic drinkers experience the whole range of liver abnormalities while others do not. However, the outdated theory of liver damage brought on by starvation has been abandoned as a result of increased knowledge and comprehension of ethanol metabolism. Rather, it is now understood that ethanol and its metabolites cause liver damage in a vulnerable chronic alcoholic with the risk characteristics listed above. In summary, the cellular and biological pathophysiology brought on by long-term alcohol use that results in alcoholic steatosis (fatty liver) morphologic abnormalities,

1. Direct hepatotoxicity by ethanol. There is documentation that routinely consumption of ethanol for 8–10 days may directly harm the liver and result in fatty changes. Ethanol directly damages hepatocyte membranes, mitochondria, and microtubules.

2. Hepatotoxicity by ethanol metabolites. The primary metabolites of ethanol is acetaldehyde, responsible for the majority of its hepatotoxic effects. Chronic alcoholics have higher blood acetaldehyde levels. Two adducts are produced by acetaldehyde, which causes hepatotoxicity.

i) Production of highly hazardous protein-aldehyde adducts that can damage membranes and cytoskeletons and result in hepatocellular necrosis.
ii) The creation of malon-di-aldehyde-acetaldehyde (MAA) adducts, which stimulate the autoimmune response and generate autoantibodies. Because of the hepatocytes' peroxisome proliferator-activated receptor (PPAR)-γ, these adducts also contribute to hepatic fibrogenesis.

3. Oxidative stress. When cytochrome P450 oxidases (MEOS) oxidize ethanol, free radicals are produced, which damages proteins and membranes oxidatively.

4. Immunological mechanism. In alcoholic liver disease, cell-mediated immunity is compromised.[19, 22]

PATHOPHYSIOLOGY OF ALCOHOLIC LIVER DISEASE:

It takes around 20 minutes for blood alcohol levels to reach their peak, though stomach contents may cause this. The liver uses one of two mechanisms to metabolize it virtually exclusively. Alcohol dehydrogenase converts around 80% of alcohol to acetaldehyde, which is subsequently converted to acetate by aldehyde dehydrogenase.
Nicotinamide adenine dinucleotide (NAD) is changed into NADH via this mechanism, which also modifies the cell's redox potential. By primarily using the inducible cytochrome p450 2E1, the microsomal ethanol-oxidizing system (MEOS) metabolizes up to 20% of alcohol and produces acetaldehyde and oxygen free radicals. Low dosages of paracetamol can cause hepatotoxicity in chronic drinkers because the CYP2E1 enzyme also metabolizes acetaminophen.[60]

Both pathways' acetaldehyde is hazardous and changes the structure of proteins in cells. Oxidative stress is caused by this, which also alters mitochondrial function and produces reactive oxygen species. By disrupting the beta-oxidation of fatty acids and up regulating sterol regulatory element-binding protein 1 (SREBP1C), the changed ratio of reduced/oxidized NAD stimulates the production of fatty acids. When hepatocytes are damaged, damage-associated molecular patterns (DAMPs) such necrotic debris or mitochondrial DNA cause immune cells to become activated.[61]
Additionally, alcohol causes dysbiosis and increased gut permeability. It also delivers pathogen-associated molecular patterns (PAMPs) like bacterial DNA and lipopolysaccharide through the portal vein, which activate immune cells and cause the release of interleukin (IL)-1, IL-2, and IL-8 as well as tumour necrosis factor alpha (TNF-α). Each of these cytokines has been linked to the pathophysiology of liver fibrosis. The most prevalent sign is hepatic steatosis, or alcohol-related fatty liver, which is a buildup of triglycerides within hepatocytes.
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PATHOLOGICAL FEATURES OF ALCOHOL-RELATED LIVER DISEASE

Immunologic attack on hepatocytes: Some cases of alcohol-related liver cell damage persist even after stopping alcohol use, which is explained by immunologic processes. Although the most popular theory for its formation is the aggregation of intermediate filaments of the prekeratin type as a result of alcohol-induced cytoskeleton disarray, immunological mechanisms may also account for the genesis of Mallory's alcoholic hyaline.

Inflammation: Consuming ethanol over an extended period of time harms intestinal cells in addition to hepatocytes. Endotoxins produced by damaged intestinal cells release pro-inflammatory cytokines,

primarily TGF-β, IL-1, IL-6, and tumour necrosis factor-α. Endotoxinaemia and these cytokines cause hepatocyte necrosis and apoptosis, which starts an inflammatory response in the liver injured by alcohol.[62]

Fibrogenesis: Main event facilitating hepatic fibrogenesis is activation of stellate cells by various stimuli:

i) By damaged hepatocytes,
ii) By malon-di-aldehyde-acetaldehyde adducts,
iii) By activated Kupffer cells, and
iv) Direct stimulation by acetaldehyde.

All forms of collagen are increased and there is the increased transformation of fat-storing lto cells into myofibroblasts and fibrocytes.

Increased redox ratio: Lactic acidosis is caused by a substantial increase in the hepatocytes' NADH:NAAD redox ratio, which raises the redox ratio of lactate to pyruvate. Numerous metabolic outcomes, including alcoholic fatty liver (ALD), collagen production, gout, poor gluconeogenesis, and altered metabolism of steroid, have been linked to this altered redox potential.

Retention of water and proteins by liver cell: Alcohol inhibits the liver's ability to secrete newly synthesized proteins, which causes the hepatocytes to retain them. Hepatocytes swell as a result of water being retained in the cell proportionate to the protein, which causes hepatomegaly in alcoholics.

Hypoxia: Alcohol consumption over time raises the liver's oxygen requirements, creating a hypoxic state that leads to hepatocellular necrosis in the centrilobular zone (zone 3). Zone 3 also exhibits more pronounced redox alterations.
Increased liver fat: The liver's capacity to store fat increases with chronic alcoholism. This can be due to increased lipid synthesis by the liver itself, excess mobilization from adipose tissue, or external (dietary) sources. This could explain the hepatocytes' lipid buildup.[63]

PHYSICAL EXAMINATION:

One of the main symptoms of alcoholic hepatitis, which is clinically described as a condition of liver failure with fever and severe hepatomegaly often present, is jaundice. It usually manifests between the ages of 40 and 50 and is associated with severe alcohol use. It is common for patients to report consuming at least 30 to 50 grams of alcohol daily, but above 100 grams is the norm. After weeks of abstinence, a patient may be admitted. Jaundice that develops quickly is the hallmark sign. Other symptoms include fever, proximal muscle atrophy, and ascites (SAAG greater than 1.1). Patients may have encephalopathy if they have severe alcoholic hepatitis. The liver is typically sore and enlarged.

Common physical examination findings: Include jaundice, hepatomegaly, splenomegaly, spider telangiectasia's, Dupuytren contractures, testicular atrophy, decreased libido, enlarged parotid and lacrimal glands, white nails, Muecke lines, asterixis, and portal hypertension symptoms like caput-medusa (distended and engorged superficial abdominal veins), ascites, pedal oedema, and encephalopathy. [29]

Abdominal paracentesis should be performed in all patients with newly identified ascites.

EVALUATION SHOULD INCLUDE: [29.]

CBC: One performs a full blood count (CBC) to rule out infection. Furthermore, cirrhosis-related side effects such thrombocytopenia, anaemia, and a leukemic reaction in alcoholic hepatitis are noted.
LFT: A much higher level of aspartate aminotransferase (AST) than alanine aminotransferase (ALT) is indicative of alcoholic liver damage. There is hypertriglyceridemia, hyperbilirubinemia, and hypo albuminuria. Furthermore, there is usually an increase in gamma-glutamyl Tran's peptidase, or GGTP.

INR: (to evaluate liver synthetic function) and prothrombin time (PT): Higher values signify more serious illness. When searching for liver tumours and biliary blockage, abdominal imaging, or abdominal ultrasonography, can be helpful.

BMP: A basic metabolic profile (BMP) should be conducted to assess for renal failure and electrolyte abnormalities (low potassium, magnesium, and phosphorus levels).
It is necessary to calculate the serum-ascites albumin gradient, or SAAG, of Ascitic fluid in order to identify the source of any ascites. Testing for chronic liver illness, including viral hepatitis.
Endoscopy: In cirrhosis patients to check for oesophageal varices caused by portal hypertension.

Biopsy: For cases where the diagnosis is unclear, a liver biopsy can provide a definitive answer. Prognosis, staging, therapy monitoring, and severity assessment are its most common uses.[30]

MANAGEMENT:

The single most crucial therapy and prognosis factor is quitting alcohol. The best suggestion is to abstain for the rest of your life. Regardless of the stage of liver disease, this improves overall health and life expectancy. Once cirrhosis is present, abstinence can even stop its progression, hepatic decompensation, and death. Alongside the liver illness, it's critical to recognize and predict Wernicke's encephalopathy and alcohol withdrawal in the initial presentation of ALD. In cases of severe alcoholic hepatitis, survival is correlated with calorie intake, indicating the need of nutrition. Patients who are incapable of meeting their needs may require enteral feeding using a fine-bore nasogastric tube. There has been much discussion on whether medication therapy is the best course of action for treating severe alcoholic hepatitis (Maddrey's discriminative score > 32).
Patients with a clinical diagnosis of severe alcoholic hepatitis participated in the major, multicentre, double-blind, randomized STOPAH research. This demonstrated that pentoxifylline, a mild anti-TNF drug, had no effect on survival. Prednisolone showed a marginal decrease in 28-day mortality, but no benefit at three months or a year. Increased incidence of gastrointestinal haemorrhage and sepsis were linked to prednisolone. Although early tests did not reveal any advantages, N-acetyl cysteine (NAC) may also reduce oxidative stress. Intravenous NAC may be beneficial for people receiving prednisolone, according to one investigation. The medications should be discontinued if, seven days after beginning glucocorticoids, the bilirubin level has not decreased.

In both Europe and the US, ALD is a common reason for liver transplantation. With survival rates comparable to other indications and no chance of disease recurrence provided the patient stays abstinent, transplantation for ALD has a satisfactory outcome. Finding patients who pose an intolerable risk of resuming hazardous alcohol use is the difficult part. Before being evaluated for transplantation, several programs demand a patient to abstain from alcohol for six months. A patient is considered for transplantation.

Although duration of abstinence is only one factor in predicting risk of relapse and the length required is debatable, a period of abstinence will allow recovery of liver function sufficient to avoid transplantation in some, as well as identify those at highest risk of early recidivism. Transplantation for alcohol period of abstinence will allow liver function to recover sufficiently to prevent transplantation in some people and identify individuals at the highest risk of early recidivism, even if the length of time needed is controversial and only one factor in predicting likelihood of relapse. Although transplantation for alcoholic hepatitis has been reported in carefully chosen patients with satisfactory short-term results, it is rarely carried out because of worries about the longer-term danger of recidivismlic hepatitis has been described in highly selected individuals with acceptable short-term outcomes but it is seldom performed due to concerns about longer-term risk of recidivism.[19]

DETAILED DESCRIPTION OF UNANI FORMULATIONS: Patients can be offered Unani pharmacopeia formulations that have been clinically established to be safe and efficient in treating Amraz-kabid (hepatic disorders). A few compounds that have been clinically proved are listed below.

Therapeutic Interventions:

Internal medications	**Dose**
Dawa ul Kurkum	5 gm/day twice daily
Majoon Dabeedul ward	5gm twice daily
Sharbat-e-Deenar	25 ml twice daily
Arq-e-Mako	60ml twice daily
Arq-e-Kasni	60ml twice daily

DAWA-UL-KURKUM: Is a semi solid medicinal compound preparation in the form of Majoon. Chief Ingredient if this medicine is Kurkum/Kesar (Crocus sativa). It is also called Dawa-ul-Zafran. It is first prepared by Jalinoos and is the best drug among all drugs which are used for liver diseases. Temperament of this formulation described as Haar 2^0 & Motadil or Ratab1^0
Jurjani asserts that Dawa ul Kurkum reduces the symptoms of anaemia and ascites, which are brought on by inflammation of the liver and spleen. Stomach discomfort, anorexia, and ascites.
In cases of ethanol-induced liver injury, this polyherbal preparation, Dawa-ul Kurkum, offers hepatoprotective advantages. [31, 32]

This medication is the preferred treatment for Sue Mizaj Barid Kabid wa Tihaal (liver and spleen); it relieves renal colic, has a carminative effect, releases obstruction, and eliminates stubborn phlegmatic materials through urine. Dawa ul Kurkum, when used for Waram-e-Kabid Barid (chronic hepatitis) and Waram-e-Sulb (liver cirrhosis) has been shown by Ibn Sina & Razi to be more effective and advantageous. As part of its hepatoprotective properties against the liver damage caused by paracetamol, Dawa-Ul-Kurkum and its hydroalcoholic extract modify immunological systems. [31,32,33,34]

The preservation or restoration of the oxidant-antioxidant homeostatic balance may mediate the protective effects. Due to its ability to treat dystemperament and the fact that many of its constituents have palatable (Mushtahi) qualities.

Dawa-ul-Kurkum enhances hunger [31,32,33,34] by increasing the stomach's production of heat (Taskhin), and by including several substances with anti-emetic and digestive qualities, Dawa-ul-Kurkum lessens nausea. Increased Burudat (coldness) and the buildup of Ghaleez Balgham (viscous phlegm) in the stomach and liver may be the cause of conversion to the Su-e-Mizaj Kabid Barid. Dawa ul Kurkum lessens this ailment by fixing Mizaj and getting rid of Balgham. [32, 33].
There are multiple other Unani formulation also available to correct Su-e-Mizaj Kabid Barid e.g. Qurṣ-e-Afsanteen, Dawa-ul-Turanjabeen, Majoon Dabeed-ul Ward, Sharbat-e-Deenar, Dawa-ul-Kurkum, Iṭrīfal Saghir, Jawarish Bisbasa, and so on are just a few examples. A polyherbal formulation called Dawa-ul-Kurkum has an advantage over all of these medications in the treatment of liver problems because of its composition.Its ingredient have Musakkin, Mufatteh-e-Sudad, Kasir-e-Riyah, Muhallil-e-Warm-e-Kabid wa Tihaal, and Muqawwi-e-Jigar, Meda wa Am'a properties [31,32,33,34]

MAJOON-E-DABEED-UL-WARD: Has been recommended to treat a variety of conditions, including psoriasis, eczema, vertigo, liver problems, and prostate inflammation. In the healthcare systems of many nations, traditional medicine plays a significant role. Approximately 80% of people worldwide use herbal medication to cure illnesses, according to WHO data. [35] *Majoon-e-Dabeed-ul-ward* (MD) is a polyherbal formulation which is prepared with mixing of useful parts of 21 medicinal plants[34]

Ibn-e-Sina: Described Majoon Dabeed ul Ward as a treatment for jaundice and hepatitis[35, 36]

Al-Razi: Described the formulation as a Hepatoprotective agent, preventing liver damage [34].

Hakim Ajmal Khan: Described *Majoon Dabeed ul Ward* as a treatment for liver disorders, promoting liver function.[34, 35.]

SHARBAT-E-DEENAR: Sharbat-e-Deenar (SD) is a Unani Herbal formulation which are prepared mixing of eight medicinal plants, and standardized according to the National Formulary of Unani Medicine (NFUM). Some medicinal plants of this formulation such as Cichorium intybu, Rheum emodi, and Rosa damascene, have been reported to have antioxidant and hepatoprotective activity. Therefore, a study was carried out by Arvind Kumar Shakya, and Sangeeta Shukla, the present study was aimed to evaluate the hepatoprotective effects of SD against acetaminophen-induced hepatotoxicity in rats,

ARQ-E-MAKO: Is used in the treatment of hepatitis, gastritis, diarrhoea and other inflammation of viscera [37,38,39,40,41,42,43,] act as Dafe Humma (antipyretic), Musbarrid (refrigerant), Mudir-e-Baul (diuretic), Kasir Riyah (carminative), Mulattif (demulcent), Mulaiyyin (laxative), Munaffis (expectorant), Musaffi-e-Dam (blood purifier), Musakkin Alam (analgesic), and Mohallil-e-warm (anti-inflammatory) Warm Meda (Gastritis), Yarqan (Jaundice), Suda (Headache), Warm Rahim (Metritis), Warm Jigar (Hepatitis), and Warm-e-Ahsha (Inflammation of Viscera). Istisqa Lahmi, Anasarca [43]

Mako leaves are good for you. Mako decoction aids in the onset of rashes in cases of chickenpox where the rashes appear gradually.[43]

Root of Mako with Jaggery induces sleep, gargle of decoction of Mako is beneficial in Tonsillitis[42].

ARQ-E-KASNI: Is hepatoactive in a number of illnesses, such as Yaraqan (jaundice), Sudda Jigar (liver obstructive disorder), and Humma (fever) brought on by Safra (bile). Chakida Kasni is beneficial for Warm-i-Jigar (hepatitis), Warm-i-Rehm (metritis) and Warm-i-Tihal (splenic inflammation); the leaves are Musakkin-i-hararat (coolant of heat) and Musakkin-i Tishnagi (relieves thrust) [44] is hepatoactive in a number of illnesses, such as Yaraqan (jaundice), Sudda Jigar (liver obstructive disorder), and Humma (fever) brought on by Safra (bile). Chakida Kasni is beneficial for Warm-i-Jigar (hepatitis), Warm-i-Rehm (metritis), and Warm-i-Tihal (splenic inflammation); the leaves are Musakkin-i-hararat (coolant of heat) and Musakkin-i Tishnagi (relieves thrust) [44].

REVIEW OF LITERATURE:

Study-1: Sharbat-e-Deenar and Majoon Dabeedul ward:

In Vivo as well as in vitro Study of Sharbat-e-Deenar and Majoon Dabeedul ward:

In order to assess the impact of SD and MD on oxidative stress indicators, Arvind Kumar Shakya et al. conducted a study that demonstrated the protective effect of SD and MD against CCl4-subchronic toxicity. When compared to the control group, the antioxidant enzymes Super oxide dismutase (SOD), catalase, GR, and GPx showed considerably lower activity in the animals treated with CCl4. Animals treated with CCl4 showed a considerable increase in antioxidant enzyme activity (54–62%) after receiving MD for 5 days, followed by SD. Herbal formulation therapy restored AH enzymatic activity comparable to that of silymarin, the positive control. This recovery may result from cells' improved membrane integrity following SD and MD treatment.[48]
Researchers also looked at endogenous antioxidant enzymes called oxidative stress indicators, such as SOD, CAT, GPx, and GR, and non-enzymatic antioxidants like GSH, which help to neutralize free radicals and reduce cellular oxidative stress.[49]

Reducing these enzyme levels raises the risk of lipid peroxidative damage and free radical-induced oxidative stress, which compromises membrane integrity and ultimately impairs hepatocyte function. In contrast to the normal control animals, they discovered in their tests that the injection of CCl4 results in a decrease in the levels of all these hepatic antioxidant enzymes.[50, 51.]They also assessed DNA damage using single-cell gel electrophoresis. Known as the COMET test, this test analyses comet tail length to assess the extent of DNA damage.[52, 53]
Data demonstrated that DNA damage was caused by oxidative stress mediated by CCl4. Additionally, they found that therapy with SD and MD decreased DNA damage. These findings show that herbal formulations

may shield DNA from oxidative damage brought on by exposure to subchronic CCl4. Compared to those treated with SD, a greater decrease in DNA damage was seen in groups treated with MD. These groups' observations were similar to those of the silymarin-treated groups.

The cytotoxic effects of SD, MD, and the positive control silymarin were examined at concentrations of 25, 50, and 100 µg/mL for cytotoxicity in HepG2 cell lines and were shown to be non-toxic to the cells. This was the in vitro hepatoprotective effect of MD in CCl4-treated HepG2 cell lines. The cell culture was exposed to CCl4 and then treated with MD extract at varying doses of 25, 50, and 100 µg/ml. In culture conditions, HepG2 cell line proliferation was enhanced by MD-treated cells in a concentration-dependent manner.

MD showed a strong, dose-dependent defence against the decrease of cell viability caused by CCl4. According to the data, the highest cell viability was 90% at 100 µg/mL, followed by 78% at 50 µg/mL and 77% at 25 µg/mL. These results were comparable to those of the positive control silymarin. Impact of MD on the development of the cell cycle in rat hepatocytes treated with CCl4.

Flow cytometric analysis was utilized to ascertain the DNA content profile in the cell cycle-S phase of cultivated hepatocyte cells. The impact of MD on the S phase of the cell cycle in CCl4-treated cells was noted. The percentage of cells in the cell cycle (S phase, DNA content) significantly decreased in CCl4-treated culture hepatocytes, while the administration of SD and MD at 100 µg/mL boosted cell density in a manner comparable to silymarin.

Study-2: Dawa-ul-Kurkum:

A study performed by Mohd Reshi et.at, on Hepatoprotective Effects of Dawa-Ul-Kurkum, in Experimental Model of Ethanol Induced Liver Damage in Rats.

The results showed a substantial decrease in the rise in serum SGOT, SGPT, ALP, total bilirubin, and direct bilirubin levels when Dawa-Ul-Kurkum and 50% hydro-alcoholic extract were mixed with ethanol. Additionally, oxidative stress parameters in liver homogenates showed that hydroalcoholic extracts and Unani polyherbal preparations provided protection against elevated reactive oxygen and nitrogen species levels in response to ethanol, as demonstrated by significantly higher GSH levels and lower MDA and NOx levels.

The Dawa-ul-Kurkum effects on the oxidative stress scale were identical to those of the HA extract. Although some peri-biliary fibrosis was also observed, the majority of the hepatic tissue appeared normal in both Dawa-Ul-Kurkum and HA extract, confirming the polyherbal formulation's ability to protect against ethanol-induced liver damage. However, both the HA extract and Dawa-Ul-Kurkum showed a protective effect. These results demonstrated the efficacy of Dawa-Ul-Kurkum and it’s HA formulation as hepatoprotective medications that prevent liver necrosis.[54]

Study-3: Mako:

Immuno-stimulant activity: Mako's immune-stimulating properties were investigated by Hanifa (2011) as a viable substitute for fish illness prevention. According to the study's findings, the group treated with ethanol and methanol extract had a lower death rate than the group treated with water extract and chloroform toluene. It was determined that plant extracts might be utilized to treat infectious disorders brought on by microorganisms and had a lot of potential as immune stimulants against microorganisms (Hanifa, 2011).[55]

Anti-HCV study: In their 2011 study, Javed et al. found that SO (SN) seed extracts in methanol and chloroform inhibited HCV by 37% and over 50%, respectively, at non-toxic concentrations. The study's findings showed that GAPDH stayed constant but the expression or function of HCV NS3 protease was reduced in a dose-dependent manner by chloroform extract of Solanum extracts. According to these findings, SO extract may contain antiviral compounds that can combat HCV, and treating chronic HCV would be more effective if SN extract and interferon were combined (Javed, 2011).[56]

Anti -inflammatory study: To assess the phytochemical and pharmacological efficacy of SO's ethanolic extract in experimental animal models, Ravi et al. (2009) conducted a study. The study's findings demonstrated that the ethanolic extract of SO had a dose-dependent, significant anti-inflammatory effect (P

< 0.05). Therefore, it was determined that the berries' flavonoids may be the active ingredient causing their anti-inflammatory properties.[57]

Using experimental animal models, Arunachalam et al. examined the anti-inflammatory properties of a methanolic extract of entire Solanum nigrum L. plants. The hind paw oedema was lessened by the methanolic extract. 375 mg/kg b.w. of Solanum nigrum methanolic extract has demonstrated strong anti-inflammatory properties. 2009's Arunachalam.[58].The antioxidant activity of the methanolic extract of SO plant berries was investigated by Jainu & Devi (2004) using a tissue biochemical antioxidant profile. The study's findings demonstrated that the berry extract have substantial antioxidant property.

Study-4: Kasni:

In order to demonstrate the antioxidant activity and hepatoprotective efficacy of Cichorium intybus (Kasni) seed extract against carbon tetrachloride-induced liver damage in rats, Shakil Ahmad et al. Studies reveal that the aqueous-methanol seed extract of C. intybus possesses strong hepatoprotective and antioxidant properties. Given that flavonoids and polyphenol chemicals are known to have hepatoprotective and antioxidant qualities, this could be the result of their existence.

Glutathione peroxidase (22.1 mg GSH consumed/min/mg protein), superoxide dismutase (14.2 units/min/mg protein), glutathione (18.1 µmole of GSH/mg protein), and catalase (48.90 µmole of H2O2 consumed/min/mg protein) were all at their highest levels in the rats given the extract (500 mg/kg dose), according to the results for biochemical markers.
The treated groups showed a substantial ($p < 0.01$) rise in serum biochemical markers, such as direct bilirubin, alkaline phosphate (ALKP), serum glutamate oxaloacetate transaminase (SGOT), and serum glutamate pyruvate transaminase (SGPT). Different doses of C. intybus seed extract administered orally prevented hepatic cells from being impaired in a substantial way ($p < 0.01$). Compared to the standard (silymarin) and control groups, the extract-treated rats' haematological parameters and biochemical indicators were also normal.[59]

DRUG COMPOSITION DETAILS:

COMPOSITION OF DAWA UL KURKUM [32, 33]

S. No.	Name of the drug	Scientific name	Part used	Quantity
1.	*Sumbul-ut-tib*	Nord Stachys jatamansi DC. Syn. Valeriana jatamansi	Dried Rhizomes	1 Part
2.	*Murmakki*	*Commiphora myrrha (Nees) Engl. Nord Stachys jatamansi DC. Syn. Valeriana jatamansi*	Gum resin	1 Part
3.	*Saleekha*	*Cinnamomum cassia Blume*	Bark	1 Part
4.	*Qust*	*Saussurea lappa C.B. Clarke*	Dried roots	1 Part
5.	*Shagofa Izkher*	*Cymbopogon jwarancusa Schult Syn. Andropogon*	*Flower*	1 Part
6.	*Darchini*	*Cinnamomum zeylanicum Blume*	Bark	1 Part
7.	*Zafran*	*Crocus sativus Linn.*	Style and stigma	1 Part
8.	*Sharaab Musallas*	-	-	Q.S
9.	*Asal or Qand Safaid*	-	-	Q.S

Dose: 5 gm /twice daily.

Actions: Muhallil-e-waram (Anti inflamatory), Muqawwi (supports the Quwwate Taba'ia) Hazim (Digestive),
Method of administration: To be taken 5-7 gm twice a day orally with water

COMPOSITION OF MAJOON DABEEDUL WARD: [36]

Majoon Dabeedul ward (MD) is a polyherbal formulation which is prepared with mixing of useful parts of medicinal plants

Name of the drug	Scientific name	Part used	Quantity
Sumbul-ut-Teeb	Nardostachys	Whole plant	10gm
Mastagi	Pistacia lentiscus	Resin	10gm
Zafran	Crocus sativus	Flower (stigma)	10gm
Tabasheer	Bambusa bambos	Resin	10gm
Darchini	Cinnamomum zeylanicum	Stem bark	10gm
Izkhar	Cymbopogon jwarancusa	Whole plant	10gm
Asaroon	Asarum europaeum	Root	10gm
Qust Shireen	Saussurea hypoleuca	Root	10gm
Gul-e-Ghafis	Gentiana olivieri	Root	10gm
Tukm-e-kasoos	Cuscuta reflexa	Seed	10gm
Majeeth	Rubia cordifolia	Root	10 gm
Luk Maghsool	Coccus lacca	Secretion by leaves insect	10gm
Tukm-e-Kasni	Cichorium intybus	Seed	10gm
Tukm-e-Karafs	Apium graveolens	Seed	10gm
Zarawan Taweel	Aristolochia donga	Root	10gm
Habb-e-Balsan	Commiphora opobalsamum	Fruit	10gm
Ood-e-Hindi	Aquilaria agalocha	Stem	10gm
Qaranful	Syzygium aromaticum	Dried buds	10gm
Heel-e-Khurd	Elettaria cardamomum	Dried fruit	10gm

DOSE: 5-7 gm twice daily

Actions: Muhallil-e-waram (Anti inflamatory), Muqawwi (supports the Quwwate Taba'ia) Hazim (Digestive),

Method of administration: To be taken 5-7 gm. twice a day orally with water

COMPOSITION OF SHARBAT-E- DEENAR:

Useful in hepatitis, enlargement of liver, dropsy and pleurisy. Removes constipation and increases urination,

Each dose of 25 ml contains: Aqueous extract from.

Name of the drug	Scientific name	Part used	Quantity
(Gul-e-Nilofar)	Nymphaea lotus	Flower	0.86 g
(Berg-e-Gaozaban)	Borago officinalis	Leaves	0.86 g
(Rewand Chini	Rheum emodi	Bark	1.15 g
Tukhm-e-Kasni)	Cichorium intybus	Seeds	1.58 g
(Gul-e-Surkh)	Rosa damascena	Flower	1.58 g
(Tukhm-e-Kasoos)	Cuscuta reflexa	Seeds	2.54 g
(Bekh-e-Kasni)	Cichorium intybus	Root	3.17 g
Sugar			23,07 g

DOSE: 25 ml twice daily

Actions: Mohallil (Anti-inflammatory) Mulayyin (Laxative)Mudir (Diuretic) Mufatteh Sudad (De-obstruent)

Therapeutic uses: Hepatitis, Metritis, Obstructive Jaundice, Ascites, Pleurisy, Constipation

Method of administration: To be taken 25 ml twice a day orally with water

Composition of Arqe Mako: each 10 ml contain

Name of the drug	Scientific name	Part used	Quantity
Mako Khushk	Solanum nigrum	Dis. of dried fruit	0.476 g
Water	-	-	9.523 ml
Preservative	Sodium Benzoit (IP)	-	-

Dose: 60 ml twice daily

Actions: Mohallil (Anti-inflammatory), detoxifier, mudir

Murattib (normalizes Sui Mizaj), Musakkin, Muqawwi.

Therapeutic uses: Hepatitis, Jaundice, Excessive thirst

Method of administration: To be taken 60 ml twice daily orally with water

(NFUM, part-1, P.217)

Composition of Arqe Kasni each 10 ml contain

Name of the drug	Scientific name	Part used	Quantity
Kasni	Cichorium intybus	Dis. Of Seeds	0.476 g
Water	-	-	9.523 ml
Preservative	Sodium Benzoit (IP)	-	-

DOSE: 60 ml twice daily

Actions: Mohallil, Mufatteh Sudad, Dafe Yarqan, Muqawwi Kabid

Therapeutic uses: Hepatitis, Jaundice, Excessive thirst

Method of administration: To be taken 60 ml twice daily orally with water

DIETARY GUIDELINES:

Diet has an important role in the management of liver issues. A balanced diet is recommended since Su-e-Mizaj Barid is caused by both starvation and overeating.
The liver is one of the most important organs in the body. Because the liver has an impact on a person's overall health, it is imperative to maintain and care for it. Traditional therapy is insufficient to treat the liver problem. The Quwwat (faculties) of the liver and brain are also affected by alcohol consumption and any type of hepatic injury, which ultimately reduces their capacity to function. In order to optimize nitrogen balance, perhaps improve liver function, and lessen the accumulation of hepatic fat, a range of nutrient-dense diets should be recommended, especially those high in protein calories.

Recommended diet: For example, mūng dāl khichdi, pigeon pea, sabudana kheer, aab-e-nokhod, palak (spinach), pudina (mint), and barley water (Maul shaeer), as well as porridge, lentils, and rice (Zūd hazm wa latīf aghziya).

Restricted diet: Khamr (Sharab), aghziya muwallid-e-safra, such as cheese and buttermilk, Muwallid-e-sawda aghziya, such as red flesh, For example, milk, eggs, and other such as sīr (garlic) and unsul (onion) in aghziya harra Aggziya musakhkhina, such as spices and foods that are hard to digest (Aggziya saqila), [46,47]

Conclusion:

ALD has three histologic phases: alcoholic steatosis, hepatitis, and alcoholic cirrhosis. Ethanol metabolism plays a crucial role in the development of ALD in two ways: first, ethanol is catabolized to acetaldehyde in the liver's cytosol, and then, with ALDH acting as a co-enzyme, acetaldehyde is converted to acetate in the mitochondria. The prevalence of hepatic disorders in India is approximately 4.6% of DALY, and over the past 30 years, the mortality rate has decreased in European countries.

Women are more susceptible, and malnourished people are more likely to develop ALD. Infections and hepatitis C also play a significant role, and finally, genetic factors play a major role in altering the rate of ethanol elimination, such as in MEOS and ADH. Alcohol has short-term effects on neurotransmitter activity, cognitive function, and the lining of the digestive tract. Over time, alcohol consumption may have more detrimental effects on the body. The most severe liver symptoms include cirrhosis, steatosis, and inflammation.

Reactive oxygen species, which are damaging to proteins, lipids, and DNA, are created when alcohol breaks down. ROS interact with body components to produce damage and the creation of adducts. Adducts were found in the livers of chronic alcohol users. Southeast Asian youths between the ages of 15 and 19 are more likely to suffer from alcohol use disorder (AUD), which is more common in low- and middle-income nations.

Numerous research have examined the hepatoprotective properties of various Unani formulations, including Dawa-ul-Kurkum,Majoon Dabeed-ul-Ward ,Sharbat-e-Deenar, Arq-e-Mako, Arq-e-Kasni as a treatment for hepatitis and jaundice because of its hepatoprotective qualities against the liver damage produced by paracetamol, Dawa-ul-Kurkum, and its hydroalcoholic extract that alters immune systems. [35, 36] the formulation is a hepatoprotective drug that prevents liver damage, according to Zakaria Razi [34]. According to Hakim Ajmal Khan, Majoon Dabeed-ul-Ward promotes liver function and treats liver ailments. Additionally, an aqueous solution of Mako and Kasni has a hepatoprotective action against disorders of the alcoholic liver.

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