

Bridging Public Health and Integrative Care in Hepatitis: A Review of Awareness, Nutrition, and Herbal Interventions

Marpina Likhitha¹, Chukka Jahnvi², Mutyala Kalyani³, Kondapalli Daakshayani⁴

^{1,2,3}Department of Pharmacy, CMR College of Pharmacy, Kandlakoya, Hyderabad.

⁴ Assistant Professor, Department of Pharmaceutical Analysis, CMR College of Pharmacy.

Corresponding author: likhithamarpina@gmail.com

Doi: <https://doi.org/10.5281/zenodo.22301171>

Received: 03 July 2026

Accepted: 13 July 2026

Abstract

Hepatitis is the most significant and under recognized global health concern, affecting millions of individuals worldwide by causing one million deaths annually. Hepatitis causes the chronic liver failure, cirrhosis, liver diseases and hepatocellular carcinoma. Hepatitis A, B, C, D and E viruses differ in their transmission, diagnosis, clinical features and disease progression, yet all this contributes importantly to the global health burden. Regardless of vaccinations and antiviral therapies, the disease still remains as a challenge due to lack of delayed diagnosis, low public awareness, limited access to screening and treatment. Integration with digital health technologies can enhance the disease surveillance, patient education, telemedicine and enables efficient prevention and early intervention strategies. Nutritional management plays an important role by supporting the hepatic metabolism, liver function and disease associated complications and enhances the recovery. Simultaneously, the therapeutic potential of the medicinal plants and hepatoprotective phytochemicals may enhance conventional therapy by antiviral, anti-inflammatory, antioxidant, antifibrotic and immunomodulating actions. Integrating public health endeavor with digital health, evidence based herbal interventions and nutritional care may improve prevention of hepatitis, patient management and may help in the elimination of hepatitis.

Key words: Hepatitis, Epigallocatechin-3-gallate, Silymarin, Berberine, Glycyrrhizin, Curcumin, Modern metabolomics

Introduction

Hepatitis is a group of infectious disease which is characterized by the inflammation of the liver and caused mostly by five hepatotropic viruses that is hepatitis A, B, C, D and E. (1,4) The viruses that cause hepatitis, mostly differ in genetic composition, replication strategies, transmission routes, clinical manifestations, geographic distribution and long-term outcomes rather than targeting the same organ. (1,7) Due to exposure of infected blood and body fluids, unsafe medical practices, injection drug use, sexual contact and vertical transmission from mother to child causes the

blood-borne viruses' transmission. (2,5) The HBV, HCV and HDV have the ability to possess persistent infection, that leads to chronic hepatitis, cirrhosis, progressive fibrosis, hepatocellular carcinoma and liver failure unlike HAV and HEV. These viruses range from asymptomatic and mild acute to fulminant hepatic failure and further cause chronic progressive liver disease. (3,6) Progression of this disease depends of host immune response, viral characteristic, age at infection, genetic susceptibility, underlying liver disease and environmental or metabolic cofactors. At present, the liver injury illustrates that it is caused due to immune mediated instead of ensuing direct viral cytotoxicity. (5,6)

Types of Viral Hepatitis

The five hepatic viruses possess independent biological and clinical characteristics which influence the epidemiology, management and disease progression.

Hepatitis A

HAV is an acute, self-limiting liver infection which is non-enveloped, single stranded RNA virus that belongs to Picornaviridae family. (8,12) This virus mainly transmits through fecal-oral route by contaminated food, water, or with poor sanitation. (17) The hepatocytes get infected but don't cause chronic infection and the patients recover mostly with lifelong immunity. The symptoms range from asymptomatic infection in children particularly to symptomatic disease characteristics like nausea, fatigue, fever, abdominal pain, jaundice and elevated liver enzymes in adults. (8,10)

Hepatitis B

HBV belongs to Hepadnaviridae family that composed of partially double stranded DNA, caused due to perinatal transmission, sexual contact, infected blood and body fluids and unsafe injections.(9-12) HBV causes both acute and chronic infections unlike HAV, but greatly its shows chronicity during infancy or early childhood.(9,13) Chronic HBV is considered as a global burden because it maintains covalently closed circular DNA (CccDNA) and unrelenting viral replication within the hepatocytes and leads to liver failure, liver cirrhosis and hepatocellular carcinoma.(16) The universal HBV vaccine shows decline in the disease incidence and liver cancer in many countries but millions remain undiagnosed and untreated.(17)

Hepatitis C

HCV, an enveloped, single stranded RNA virus of Flaviviridae family, caused through blood exposure by unsafe injections, transfusion of contaminated blood products particularly, and sexual and vertical transmission occurs less frequently. (15,17) Acute hepatitis C was asymptomatic yet approximately 55 to 85% of individuals are with chronic infection which is due to evade of host immune response ability. (14)

Hepatitis D

HDV, an incomplete single stranded RNA virus. To complete its lifecycle, it requires hepatitis B virus surface antigen (HBsAg). (15) The transmission of this virus is similar to HBV, the hepatitis D occurs as hepatitis B coinfection or superinfection in individuals who already infected with hepatitis B. Of all the viral hepatitis, HDV is the most chronic infection thus leading to accelerated liver fibrosis, hepatic decompensation, rapid development of cirrhosis and HCC. (17)

Hepatitis E

HEV, a single stranded RNA from Hepeviridae family, transmits through fecal-oral route by contaminated water. (8,16) The zoonotic transmission takes place by undercooked pork and other animal products in developed countries was observed increasingly. HEV cause an acute, self-limiting hepatitis that characterizes with fever, nausea, jaundice, fatigue and abdominal pain. As it do not possess any long-term consequences, thus have significant risk to pregnant women, mainly during third trimester because the infection results in fulminant hepatic failure and fetal mortality. (8,16,17)

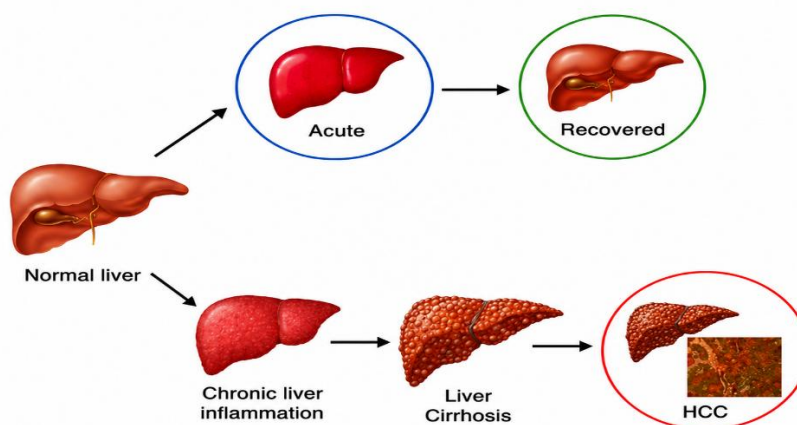


Figure 1: Disease progression of viral hepatitis

Global Epidemiology

Viral hepatitis is imparting global health burden by affecting hundreds to millions of individuals across every continent. (18,21,23) According to recent global estimation, approximately 254 million individuals are suffering from chronic hepatitis B, while around 58 million individuals have hepatitis C and results in millions of new infections annually. (18,25) Around 10-20 million individuals are infected with HDV who already living with chronic HBV infection, increasing disease severity and mortality. (24) Whereas HAV and HEV reports millions of acute infections

each year, particularly in the poor sanitation regions. (19,21) The epidemiology viral hepatitis substantiates marks geographical variation. HBV was specifically seen in Africa, Asia, and some regions of Western Pacific while the HCV prevalence was greatest in the Eastern Europe, Central Asia, North Africa and the Middle East. Hepatitis A and hepatitis E are predominantly in the low-and-middle income countries which characterized by inadequate hygiene, overcrowding, contaminated water supply and limited access to food. (20,21)

Disease burden

The viral hepatitis has become the major burden globally beyond the acute infection, conjointly viral hepatitis causing approximately around 1.3 to 1.4 million deaths annually. (22) The chronic infection was contributing majorly to the liver disease, liver cancer, disability, premature mortality worldwide. Among this, the chronic hepatitis B and hepatitis C infections accounts around 96% of the hepatitis related mortality. (22,23). Economically deprived populations are affected excessively by this disease where the healthcare resources, vaccination programs, antiviral therapies and diagnostic facilities remain unaffordable to the population. (21,23)

Public health impact

Viral hepatitis remained as major public health burden because of its high prevalence, silent progression, substantial socioeconomic and preventable complications consequences and thus leads to cause of liver disease. (25) The major challenge is that chronic HBV and HCV infections has remained to show no symptoms for decades and this resulted in failure of early diagnosis causing increased risk of complications until irreversible liver damage occurred. To eliminate this challenge, the World Health Organization (WHO) aims to remove the public health threat by 2030 to reduce the infections by 90% and hepatitis related mortality to 60%. To achieve this goal, WHO need to prevent perinatal transmission, require universal HBV vaccination safe blood transfusion and safe sanitation to the public. (1,2,3)

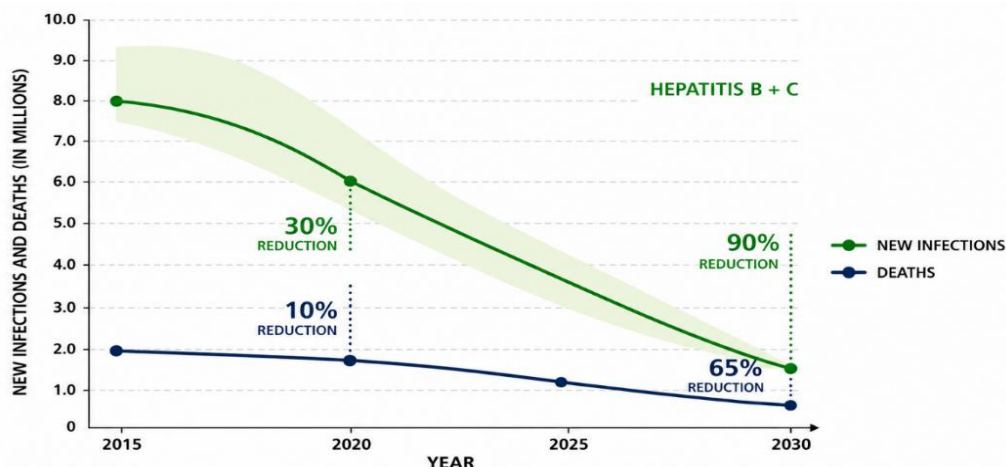


Figure 2. Global targets for viral hepatitis elimination by 2030.

The World Health Organization (WHO) aims for a 90% reduction in new infections and a 65% reduction in deaths from hepatitis B and C by 2030, compared with the 2015 baseline.

Health Awareness and Education

Digital health increases or enhances awareness of hepatitis that help public to educate regarding the causes of hepatitis, modes of transmission, risk factors, vaccination, symptoms, prevention strategies, and available treatments. (1,2) WHO aims to implement hepatitis education in primary healthcare services, schools, workplaces and other community programs to improve healthcare literacy. Educating parents, caregivers about vaccine safety and its efficacy reduce the cause of new infections.

WHO strategizes to improve treatment, lifestyle and regular monitoring of hepatitis and encourages the individuals to seek early testing and routine checkups. (23)

The major awareness program is to educate the public about different routes of hepatitis transmission as hepatitis A and E is primarily transmitted through food, water, sanitation, hygiene and whereas hepatitis B, C, D is affected by the blood fluids, unsafe injections, sexual contact hence one must understand the transmission pathways to reduce the spread of infection. (26) Healthcare acts as a pillar to prevent and control the hepatitis by routine screening and stigma reduction. (27,28)

Nutritional management and patient challenges in nutrition with hepatitis

The nutritional food for hepatitis patients to be taken are fresh fruits like apple, banana, papaya, orange & green leafy vegetables, whole grains, lean meat and fish, eggs, low-fat dairy products, pulses, legumes, nuts and seeds in moderation. The food to be avoided for hepatitis patients are likely to be alcohol, fried and oily foods, high-fat fast foods, sugary drinks, excess salt, processed and packaged foods, raw or undercooked seafood mainly in chronic (long)liver disease. (1,24)

Malnutrition is the most common and complicated disease which need to be prevention in patients with hepatitis. Due this impaired liver function, altering metabolism and decreased intake of nutrition, Protein-Energy Malnutrition (PEM) significantly increases complications. The severe malnutrition generally increases progression of liver disease, so early nutritional screening and intervention are essential for improving prognosis and survival. (23)

Macronutrients and micronutrients are responsible for the metabolism and storage of the liver. Dysfunction of liver can also lead to deficiencies of nutrients, the most important macro nutrients i e; zinc, selenium, and the vitamin A, and vitamin B12, resulting in weakened immunity, chronic inflammation, growth impairment and increased or enhanced oxidative stress. The impaired liver function may also cause excessive accumulation of iron and copper, which can damage tissues through oxidative stress and contribute to complications such as liver injury, neurological disorders, osteoporosis, and pancreatic dysfunction. Vitamin B12 levels should be carefully monitored, as adequate levels may support hepatitis C virus (HCV) clearance, whereas excessive levels may promote viral replication. (24)

Herbal interventions

Hepatocytes are damaged due to various interconnected mechanism which might be due to viral infections, excessive

alcoholic intake, metabolic disorder, toxins and autoimmune diseases. Damaged Hepatocytes leads to stress, inflammation, progressive fibrosis that leads to increased risk of liver failure. (26) Oxidative stress is one of the major factor of liver diseases as the excess reactive oxygen species damage the lipids, proteins and DNA. To counteract the liver diseases herbal interventions are emerged as a complementary therapy which contain bioactive compounds like alkaloids, flavonoids, polyphenols, antioxidants, anti-inflammatory and hepatoprotective effects. Herbal compounds inhibit stellate cell activation, promote extracellular matrix degeneration and regulate the growth factor- beta signaling. (27) Certain phytochemicals interfere with viral protein synthesis, viral replication and host responses. Despite of HBV vaccines and antiviral drugs, they suppress viral replication but rarely eliminates covalently closed DNA making it difficult to cure and long-term therapy leads to drug resistance and adverse effect therefore herbal medicines are viewed as a supportive therapy rather than replacing anti-viral drugs and acts as safer adjunctive therapy for multiple pathogenic pathways. (29)

Among the various traditional herbal system, Traditional Chinese Medicines (TCM) gained attention for the management of chronic hepatitis B. Chinese medicinal herbs are prescribed as multi herbal formulation that produce a combination effect for the anti -viral, antioxidant, hepatoprotective activity. TCM viewed liver disease involves the balance of energy, impaired circulation, toxic accumulation and weakening of vital energy. Several Chinese herbs possess biologically active compounds that have antioxidant property and hepatoprotective effects which helped the researchers to evaluate the herbal formulation for the chronic hepatitis B. (28)

The major findings are Fuzheng Jiedu Tang is a Chinese herbal formulation which reduces the viral activity of HBsAg, hepatitis B e antigen and HBV DNA. Another herbal preparations, Polyporus umbellatus, Phyllanthus amarus; polysaccharide helps in removal of HBeAg and reduces Hepatitis B DNA levels. Although findings about the herbal drugs have an effect on the anti-viral and hepatoprotective effects, the clinical evidences are limited.(29) There are numerous medicinal plants from different traditional system that has been investigated to have the ability to protect the hepatocytes, suppress viral replication.

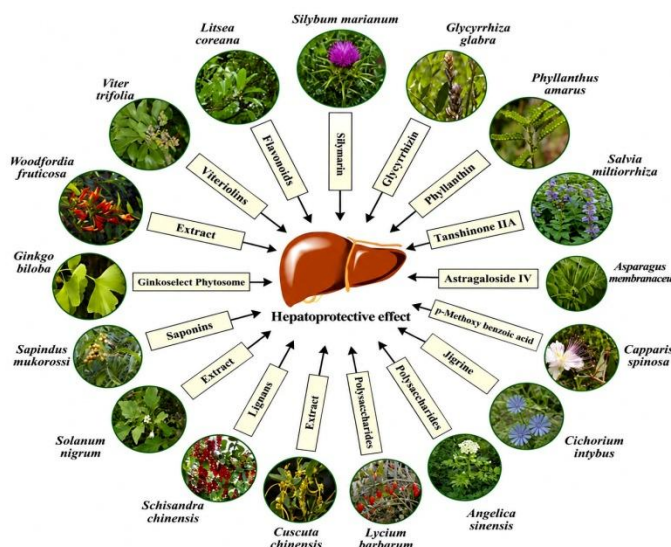


Figure 3: Medicinal plants and bioactive compound exhibiting hepatoprotective effect

Mechanism of Epigallocatechin-3-gallate (*Camellia sinensis*) against Hepatitis

The HBV infection is caused due to the attachment of virus to hepatocytes through NTCP receptor on the hepatocyte membrane. One of the compounds is Epigallocatechin-3-gallate (EGCG), present in *Camellia sinensis* (green tea), promotes the anti-viral activity by blocking the viral entry. EGCG acts on the early stage by inducing clathrin-mediated endocytosis of NTCP receptor, in which the NTCP receptors are pulled inside. (35, 36) Once the receptors are present inside the cell the receptors are transported to lysosomes and destroyed. As a result due to the fewer NTCP receptors and on the surface, HBV can't bind to the receptors and enable to enter into the liver cell and prevent the infection. (37) As per the laboratory studies EGCG reduces the more than 80% of HBV entry into the liver cells and it is more effective than HBV genotypes (A-D). EGCG works only to prevent the viral activity before it enters into the cell but it has no significant action after the viral replication or viral gene expression. Hence it does not eliminate the virus which is present inside the infected liver cells. (38)

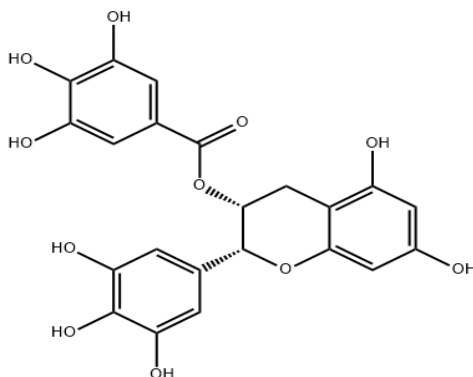


Figure 4: Epigallocatechin-3-gallate

Mechanism of silymarin (*Silybum marianum*) in Hepatitis

Silymarin is the bio active compound that is obtained from the *Silybum marianum* (milk thistle), widely used as a hepatoprotective, antioxidant and anti-fibrotic properties. Silymarin protects the liver from inducing the damage caused by the HBV and the liver to continue the normalized function. Chronic HBV infection leads to the formation of liver inflammation, this activates hepatic stellate cells and produces the excessive collagen and other extracellular proteins, scar tissue formation, eventually leads to liver fibrosis. (39-41)

Silymarin inhibits the TGF- β pathway (Transforming growth factor beta pathway) and hepatic stellate cells proliferation was suppressed. Due to reduced expression of TGF- β and phosphorylation, thereby prevents the transcription of fibrosis-related genes. It cause hepatic stellate cells inactivation and reduces collagen synthesis and maintains normal function of liver. (42)

Silymarin acts as a powerful antioxidant and inhibits lipid peroxidation by increasing endogenous antioxidant, it can directly act as a scavenger of free radicals. It increases the activity of the enzymes like superoxide dismutase, catalase, glutathione peroxidase and glutathione which neutralize reactive oxygen species and protect from oxidation. Silymarin exhibits anti-inflammatory action, it reduces the activation of nuclear factor kappa B and reduces the production and decreases chronic hepatic inflammation and minimize the continuous cycle of hepatocytes injury and repair the fibrogenesis. (43)

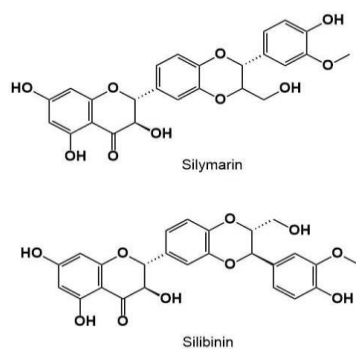
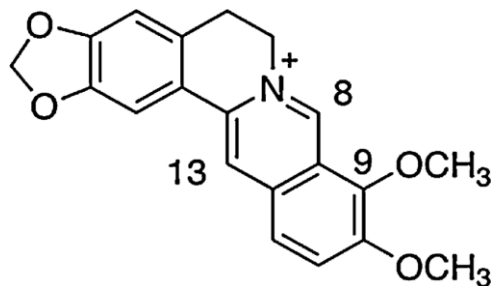


Figure 5: Structure of Silymarin

Mechanism of Berberine (*Berberis vulgaris*) against Hepatitis

Berberine is a natural isoquinoline alkaloid present in *Berberis vulgaris* and *Coptis chinensis* has a potent anti hepatitis B activity by targeting the autophagic pathway exploited by the virus for replication and reduce the synthesis, secretion of the viral protein. Autophagy stimulates the liver cell when HBV infected, these cells forms a double membrane structure called autophagosome. The virus uses this autophagosomes and facilitates the DNA replication and enhances the viral protein synthesis. (44,45)

Berberine reduces the formation of the autophagosomes, decreases the autophagic signaling this leads to the intracellular environmental loss for HBV and viral life cycle is interrupted. HBV depends on the Autophagy to replicate the genome as the pathway is inhibited viral DNA synthesis is suppressed. (46)



Berberine

Figure 6: Structure of Berberine

Mechanism of Glycyrrhizin (*Glycyrrhiza glabra*) against Hepatitis

Glycyrrhizin is the bioactive triterpenoid saponin isolated from *Glycyrrhiza glabra* (licorice). It acts against the chronic hepatitis B by various mechanisms like antiviral, anti inflammatory, hepatoprotective activities. (49) Glycyrrhizin act by disrupting viral protein processing and protects hepatocytes from immune-mediated injury. Glycyrrhizin enters the HBV infected hepatocytes and interferes with the intracellular transport of HBsAg and reduce the sialylation, this prevents the maturation and secretion of the HBsAg and decreases viral antigen and viral spread. It suppresses the inflammatory cytokines through NF-KB (Nuclear Factor Kappa B) inhibition to protect from oxidation and inflammatory damage. (50,51)

Glycyrrhizin stabilizes the outer membranes, lowers the oxidative stress and protects the liver from the necrosis and apoptosis (52-54)

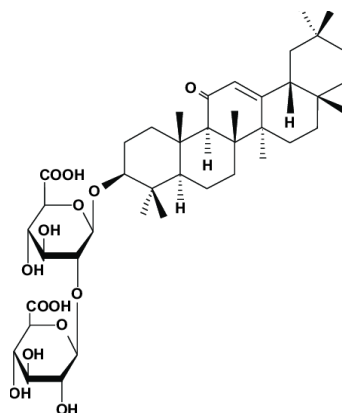


Figure 7: Structure of Glycyrrhizin

Mechanism of Curcumin (*Curcuma longa*) against Hepatitis

Curcumin which is obtained from the rhizomes of *Curcuma longa*, a polyphenolic compound possesses antiviral and antiinflammatory properties. Studies had demonstrated that curcumin has a potent anti hepatitis activity by acting against viral life cycle. (55) NTCP (Sodium Taurocholate Co-transporting Polypeptide) act as primary receptor for entry of HBV into the hepatocytes, Curcumin directly attaches to NTCP receptor present on hepatocytes membrane and inhibit activity of NTCP transporter by blocking the interaction between HBV preS1 domain (large surface protein) and receptors. This prevents hepatitis B attachment and entry of virus into hepatocytes, reduces viral internalization (decreases the cccDNA) this suppresses viral gene transcription and protein synthesis Current antiviral drugs inhibit the viral replication but does not stop new hepatocytes from infection. Whereas, curcumin can block the entry of virus and prevent HBV from infecting the healthy hepatocytes, limit the spread of the infection to the liver. (56-60)

Herbal interventions represent an approach to manage the hepatitis by targeting at multiple stages which includes viral entry, viral replication, oxidative stress, inflammation, fibrosis, disease progression. Some of the bioactive molecules like Epigallocatechin-3-gallate, silymarin, Berberine, Glycyrrhizin, Curcumin exhibit various mechanisms to suppress the viral infection, protect the liver and preserve the liver function.

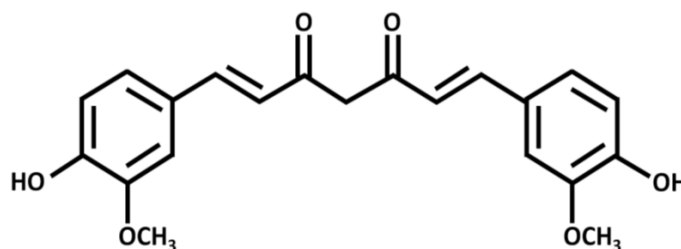


Figure 8: Structure of Curcumin

Future Prospects of herbal interventions

Herbal metabolites has promising effect as antiviral and hepatoprotective but there are several challenges that are faced during the clinical practices. To ensure the efficient therapeutic outcomes future studies should improve the standardization and quality control of the herbal extracts. (60,61) To overcome these challenges future researchers should focus on multi target phytochemicals to act simultaneously to inhibit the viral replication, reduce inflammation of liver and to prevent the fibrosis. Multiple target herbal compounds produce the greater therapeutic benefits than single phytoconstituents. (61,62)

Combination therapy is one of the most important direction in which the herbal compounds are administered along with conventional antiviral drugs, this helps to enhance the anti-viral efficacy and reduce the drug resistance, and lower the conventional drug dose. (63,64)

The discovery of novel anti-viral phytochemicals by the advanced technologies like metabolomics helps to accelerate the discovery of new compounds with potent anti- viral activity. Though the herbal drugs are studied in the small scale, there is a lack in clinical evidences. Therefore large scale clinical trials are required to determine efficacy, safety and long term therapeutic benefits. (65)

Many phytochemical exhibit the poor water solubility and less bioavailability hence the future researchers should develop nanotechnology based drugs to increase the targeted drug delivery and therapeutic effectiveness. Integrating advanced drug delivery modern metabolomics, herbal formulations and well-designed clinical trials helps to facilitate the herbal metabolites into effective therapy for hepatitis. (66,67)

Conclusion

Despite of advances in vaccination and anti-viral therapy, Hepatitis is the major global health challenge. There are different hepatitis virus that differs in transmission, pathogenesis and clinical outcomes. Considerably antiviral drugs reduce the disease progression there are several challenges like delayed diagnosis, limited healthcare access and cannot eradicate the hepatitis.

Medicinal plants and the phytochemicals help as an adjunctive therapy as they target the multiple pathogenic mechanism. These multi-target action with conventional antiviral therapy helps to reduce and prevent the disease progression.

The future hepatitis management lies in development of herbal interventions with conventional antiviral treatment. Advancement in standardization, nanotechnology- based drug delivery system and combination therapy establishes the safe and effective herbal medicines. These multidisciplinary approaches help to prevent and develop the effective antiviral drugs.

References:

1. World Health Organization. *Global hepatitis report 2024*. Geneva: World Health Organization; 2024.
2. Thomas DL. Global elimination of chronic hepatitis. *N Engl J Med*. 2019;380(21):2041–2050.
3. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. *J Hepatol*. 2019;70(1):151–171. doi:10.1016/j.jhep.2018.09.014.
4. Lemon SM, Walker CM, Alter MJ, Yi M. Hepatitis viruses. In: Knipe DM, Howley PM, editors. *Fields Virology*. 7th ed. Philadelphia: Wolters Kluwer; 2021.

5. Tang LSY, Covert E, Wilson E, Kottiril S. Chronic hepatitis B infection: A review. *JAMA*. 2018;319(17):1802–1813.
6. Manns MP, Buti M, Gane E, et al. Hepatitis C virus infection. *Nat Rev Dis Primers*. 2017;3:17006. doi:10.1038/nrdp.2017.6.
7. Rizzetto M. Hepatitis D virus: Introduction and epidemiology. *Cold Spring Harb Perspect Med*. 2015;5:a021576. doi:10.1101/cshperspect.a021576.
8. Jefferies M, Rauff B, Rashid H, Lam T, Rafiq S. From hepatitis A to E: A critical review of viral hepatitis. *World J Gastroenterol*. 2021;27(16):1691–1715. doi:10.3748/wjg.v27.i16.1691.
9. Liu J, Yuan T, Xue L, Liang H. Pathogenesis, prevention, and therapeutic advances in hepatitis B, C, and D. *Viral J*. 2025;22:274. doi:10.1186/s12985-025-02907-3.
10. Wang X, Wang N, Cheung F, Lao L, Li C, Feng Y. Chinese medicines for prevention and treatment of human hepatocellular carcinoma: Current progress on pharmacological actions and mechanisms. *J Integr Med*. 2015;13(3):142–164.
11. Mechanistic insights of clinically proven natural products in the treatment of hepatitis B focusing on clinical evidence and pathways. *Clin Tradit Med Pharmacol*. 2024. doi:10.1016/j.ctmp.2024.200183.
12. Lemon SM, Walker CM. Hepatitis A virus. In: Knipe DM, Howley PM, editors. *Fields Virology*. 7th ed. Philadelphia: Wolters Kluwer; 2021.
13. Tang LSY, Covert E, Wilson E, Kottiril S. Chronic hepatitis B infection: A review. *JAMA*. 2018;319(17):1802–1813. doi:10.1001/jama.2018.3795.
14. Manns MP, Buti M, Gane E, et al. Hepatitis C virus infection. *Nat Rev Dis Primers*. 2017;3:17006. doi:10.1038/nrdp.2017.6.
15. Rizzetto M. Hepatitis D virus: Introduction and epidemiology. *Cold Spring Harb Perspect Med*. 2015;5:a021576. doi:10.1101/cshperspect.a021576.
16. Kamar N, Dalton HR, Abravanel F, Izopet J. Hepatitis E virus infection. *Clin Microbiol Rev*. 2014;27(1):116–138. doi:10.1128/CMR.00057-13.

17. World Health Organization. *Global hepatitis report 2024*. Geneva: World Health Organization; 2024.
18. World Health Organization. Geneva: World Health Organization; 2024.
19. GBD 2021 Hepatitis B Collaborators. Global, regional, and national burden of hepatitis B, 1990–2021: Results from the Global Burden of Disease Study 2021. *Lancet Gastroenterol Hepatol*. 2024.
20. GBD 2021 Hepatitis C Collaborators. Global, regional, and national burden of hepatitis C, 1990–2021: Results from the Global Burden of Disease Study 2021. *Lancet Gastroenterol Hepatol*. 2024.
21. Jefferies M, Rauff B, Rashid H, Lam T, Rafiq S. From hepatitis A to E: A critical review of viral hepatitis. *World J Gastroenterol*. 2021;27(16):1691–1715. doi:10.3748/wjg.v27.i16.1691.
22. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. *J Hepatol*. 2019;70(1):151–171. doi:10.1016/j.jhep.2018.09.014.
23. Stockdale AJ, Kreuels B, Henrion MYR, et al. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. *J Hepatol*. 2020;73(3):523–532. doi:10.1016/j.jhep.2020.04.008.
24. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2022: A modelling study. *Lancet Gastroenterol Hepatol*. 2025.
25. Liu J, Yuan T, Xue L, Liang H. Pathogenesis, prevention, and therapeutic advances in hepatitis B, C, and D. *Virology*. 2025;22:274.doi:10.1186/s12985-025-02907-3.
26. Herbal Medicines in Chronic Liver Diseases. *Evid Based Complement Altern Med*.
27. Herbal Medicines for the Treatment of Liver Diseases. *World J Gastroenterol*.
28. Traditional Chinese Medicine for Chronic Hepatitis B. *Front Pharmacol*.
29. Li N, Feng X, An C, Liu G, Liu C. Metabolites from traditional Chinese botanical drugs with anti-hepatitis B virus activity: A review. *Front Pharmacol*. 2024;15:1331967. doi:10.3389/fphar.2024.1331967.
30. Natural Products Against Hepatitis B Virus. *Pharmacol Res. Review*.
31. Medicinal Plants Used in Viral Hepatitis. *J Ethnopharmacol*.

32. Herbal Medicines as Adjuvant Therapy in Chronic Hepatitis B. *BMC Complement Med Ther*. Systematic review and meta-analysis.
33. Hepatoprotective Activity of Medicinal Plants. *J Clin Exp Hepatol*. Review.
34. Role of Herbal Medicine in Liver Diseases. *Hepatol Int*.
35. Yang Y, Yang D, Yang Y, Wang Z, Li L, Wang M, et al. Epigallocatechin-3-gallate suppresses hepatitis B virus replication through activating the AMPK/TFEB pathway to promote autophagic degradation of viral core protein. *Chin J Nat Med*. 2026;24(3):300-312. doi:10.1016/S1875-5364(26)61105-3.
36. Huang HC, Tao MH, Hung TM, Chen JC, Lin ZJ, Huang C. (–)-Epigallocatechin-3-gallate inhibits entry of hepatitis B virus into hepatocytes. *Antiviral Res*. 2014;111:100-111. doi:10.1016/j.antiviral.2014.09.009.
37. He W, Li LX, Liao QJ, Liu CL, Chen XL. Green tea polyphenol, epigallocatechin-3-gallate, possesses the antiviral activity necessary to fight against hepatitis B virus replication in vitro. *Antiviral Res*. 2014;106:57-65. doi:10.1016/j.antiviral.2014.04.009.
38. Research Progress on the Protective Effect of Green Tea Polyphenol (–)-Epigallocatechin-3-Gallate (EGCG) on the Liver. *Int J Mol Sci*. 2025.
39. Huang CH, Wu VCC, Wang CL, Wu CL, Huang YT, Chang SH, et al. Silymarin synergizes with antiviral therapy in hepatitis B virus-related liver cirrhosis: A propensity score matching multi-institutional study. *Int J Mol Sci*. 2024;25(6):3088. doi:10.3390/ijms25063088.
40. Lin LT, Wu YT, Tsai TH. Antiviral activities of silymarin and derivatives. *Molecules*. 2019;24(8):1552. doi:10.3390/molecules24081552.
41. Mayer KE, Myers RP, Lee SS. Silymarin treatment of viral hepatitis: A systematic review. *J Viral Hepat*. 2005;12(6):559-567. doi:10.1111/j.1365-2893.2005.00636.x.
42. El-Kamary SS, Shardell MD, Abdel-Hamid M, et al. A randomized controlled trial to assess the safety and efficacy of silymarin on symptoms, signs and biomarkers of acute hepatitis. *Phytomedicine*. 2009;16(5):391-400. doi:10.1016/j.phymed.2009.02.002.

43. Ferenci P. Silymarin in the treatment of liver diseases: What is the clinical evidence? *Clin Liver Dis.* 2016;7(1):8-10. doi:10.1002/cld.522.
44. Berberine promotes K48-linked polyubiquitination of HNF4 α , leading to the inhibition of HBV replication. *Antiviral Res.* 2024. doi:10.1016/j.antiviral.2024.105927.
45. Berberine inhibits hepatitis B virus replication through regulation of the autophagic pathway. *Front Pharmacol.* 2023.
46. Deng W, Chen F, Zhao Y, Zhou M, Guo M. Anti-hepatitis B virus activities of natural products and their antiviral mechanisms. *Chin J Nat Med.* 2023;21(11):803-811. doi:10.1016/S1875-5364(23)60505-9.
47. Pan Y, Xia H, He Y, et al. The progress of molecules and strategies for the treatment of HBV infection. *Front Cell Infect Microbiol.* 2023;13:1128807. doi:10.3389/fcimb.2023.1128807.
48. Yang F, Gao R, Luo X, et al. Berberine influences multiple diseases by modifying gut microbiota. *Front Nutr.* 2023;10:1187718. doi:10.3389/fnut.2023.1187718.
49. Sato H, Goto W, Yamamura J, Kurokawa M, Kageyama S, Takahara T, et al. Therapeutic basis of glycyrrhizin on chronic hepatitis B. *Antiviral Res.* 1996;30(2-3):171-177. doi:10.1016/0166-3542(96)00942-4.
50. Takahara T, Watanabe A, Shiraki K. Effects of glycyrrhizin on hepatitis B surface antigen: A biochemical and morphological study. *J Hepatol.* 1994;21(4):601-609. doi:10.1016/S0168-8278(94)80108-8.
51. Matsumoto Y, Matsuura T, Aoyagi H, Matsuda M, Hmwe SS, Date T, et al. Antiviral activity of glycyrrhizin against hepatitis C virus in vitro. *PLoS One.* 2013;8(7):e68992. doi:10.1371/journal.pone.0068992.
52. Crance JM, L  v  que F, Biziagos E, van Cuyck-Gandr   H, Jouan A, Deloince R. Studies on mechanism of action of glycyrrhizin against hepatitis A virus replication in vitro. *Antiviral Res.* 1994;23(1):63-76. doi:10.1016/0166-3542(94)90033-7.
53. Adianti M, Aoki C, Komoto M, Deng L, Shoji I, Wahyuni TS, et al. Anti-hepatitis C virus compounds obtained from *Glycyrrhiza uralensis* and other *Glycyrrhiza* species. *Microbiol Immunol.* 2014;58(3):180-187. doi:10.1111/1348-0421.12127.
54. Ma T, Hao H, Wang S, Qiu D, Cao W, Deng W, et al. Glycyrrhizin preparations in liver diseases: A narrative review of mechanisms and therapeutic potential. *Front Pharmacol.* 2026. doi:10.3389/fphar.2026.1795174

55. Thongsri P, Pewkliang Y, Sa-ngiamsuntorn K, Borwornpinyo S, Wongkajornsilp A, Hongeng S, et al. Curcumin inhibited hepatitis B viral entry through NTCP binding. *Sci Rep.* 2021;11:19125. doi:10.1038/s41598-021-98243-x.
56. Wei ZQ, Zhang YH, Ke CZ, Chen HX, Ren P, He YL, et al. Curcumin inhibits hepatitis B virus infection by down-regulating cccDNA-bound histone acetylation. *World J Gastroenterol.* 2017;23(34):6252-6260. doi:10.3748/wjg.v23.i34.6252.
57. Rechtman MM, Har-Noy O, Bar-Yishay I, Fishman S, Adamovich Y, Shaul Y, et al. Curcumin inhibits hepatitis B virus via down-regulation of the metabolic coactivator PGC-1 α . *FEBS Lett.* 2010;584(11):2485-2490. doi:10.1016/j.febslet.2010.04.067.
58. Kim HJ, Yoo HS, Kim JC, Park CS, Choi MS, Kim M, et al. Antiviral effect of *Curcuma longa* Linn extract against hepatitis B virus replication. *J Ethnopharmacol.* 2009;124(2):189-196. doi:10.1016/j.jep.2009.04.046.
59. Anggakusuma, Colpitts CC, Schang LM, et al. Turmeric curcumin inhibits entry of all hepatitis C virus genotypes into human liver cells. *Gut.* 2014;63(7):1137-1149. doi:10.1136/gutjnl-2012-304299.
60. Ekor M. The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol.* 2014;4:177. doi:10.3389/fphar.2013.00177.
61. Zhang Y, et al. Metabolites from traditional Chinese botanical drugs with anti-hepatitis B virus activity: A review. *Front Pharmacol.* 2024. doi:10.3389/fphar.2024.1331967.
62. Deng W, Chen F, Zhao Y, et al. Anti-hepatitis B virus activities of natural products and their antiviral mechanisms. *Chin J Nat Med.* 2023;21(11):803-811. doi:10.1016/S1875-5364(23)60505-9.
63. Huang CH, et al. Silymarin synergizes with antiviral therapy in hepatitis B virus-related liver cirrhosis: A propensity score matching multi-institutional study. *Int J Mol Sci.* 2024;25(6):3088. doi:10.3390/ijms25063088.
64. Yang Y, et al. Epigallocatechin-3-gallate suppresses hepatitis B virus replication through activating the AMPK/TFEB pathway to promote autophagic degradation of viral core protein. *Chin J Nat Med.* 2026;24(3):300-312. doi:10.1016/S1875-5364(26)61105-3.
65. Mayer KE, Myers RP, Lee SS. Silymarin treatment of viral hepatitis: A systematic review. *J Viral Hepat.* 2005;12(6):559-567. doi:10.1111/j.1365-2893.2005.00636.x.

- 66.** Kumari A, et al. Medicinal plant molecules against hepatitis C virus: Current status and future prospect. *Phytother Res.*2023. doi:10.1002/ptr.7936.
- 67.** Liu Y, et al. Flavonoids in natural products for the therapy of liver diseases: Progress and future opportunities. *Front Pharmacol.* 2024. doi:10.3389/fphar.2024.1485065.