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Review Paper

Exploring The Reliability of Polyherbal Therapies in Managing Hepatic Diseases: Mechanisms to Clinical Perspectives

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ABSTRACT

Infection with the chronic hepatitis B virus (HBV) is a global public health problem. It is estimated that it infects over 250 million people, and it causes complications such as cirrhotic liver, hepatic fibrosis, liver failure, and hepatocellular carcinoma. The antiviral agents available today are a big medical breakthrough, but they are not a conclusive solution. Nucleoside analogues and interferons are costly and inaccessible to many regions, and their long-term effects can cause other problems for patients. This has led to new and effective therapeutic measures for chronic HBV patients. Polyherbal formulations derived from traditional systems of medicine like Ayurveda, Traditional Chinese Medicine, and Unani medicine are gaining attention. This paper aims to provide a holistic assessment of the evidence from different methods to offer therapy, such as clinical and systematic reviews. This paper will also assess the safety procedures and reliability of polyherbal therapies in HBV liver diseaseMany polyherbal formulations, including Liv. 52, HD-03/ES, Tefroliv-Forte, and Phyllanthus species-based preparations, have been identified to have several promising properties and polyherbal formulations for hepatoprotection and for the prevention and treatment of oxidative stress and liver injury. These formulations are said to reduce the expression of HBV antigens, decrease oxidative stress, and assist in the improvement of liver function. It is also said that these formulations protect liver cells and assist in the immune response enhancement of the host and prevent the injury of liver cells caused by the disease. Many of the components of herbal medicine have been found to act in synergy and may enhance the medicinal properties and reduce the side effects of the formulations. Although these herbal medicines are polyherbal medicines that are used for the treatment of liver diseases and are based on several encouraging studies, their clinical

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applications remain limited. The objective of this study is to evaluate the 80 peer-reviewed studies dealing with the clinical, regulatory, and other studies and provide a survey of the polyherbal medicines to treat chronic HBV infections and hepatic diseases

INTRODUCTION

With extensive socioeconomic, clinical, and public health ramifications, hepatitis B virus (HBV) infection continues to be a persistent global health burden.

Classified within the hepadnaviridae family, a partly double-stranded DNA virus is called HBV. That primarily targets hepatocytes and establishes both acute and chronic infections. According to the World Health Organization (WHO), an estimated 296 million individuals are living with chronic HBV infection globally, with an annual mortality of nearly 820,000 deaths attributed to HBV-related complications such as cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) as of 2023 [1]. Despite decades of vaccination campaigns and blood safety programs, HBV continues to be hyperendemic in several geographic regions, notably sub-Saharan Africa, East Asia, and parts of the Middle East and Eastern Europe, where perinatal transmission, horizontal transmission during early childhood, and unsafe medical practices persist as dominant modes of infection. The pathogenesis of HBV involves complex interactions between viral replication mechanisms and host immune responses. The virus enters hepatocytes via the sodium taurocholate transporting polypeptide (NTCP) receptor, followed by uncoating and transport of the relaxed circular DNA (rcDNA) into the nucleus, where it is converted into covalently closed circular DNA (cccDNA), a stable episomal template that persists throughout the life of the hepatocyte and is largely resistant to current antiviral therapies [2]. HBV infection is also known to cause significant immunological disturbances, including T-cell exhaustion, natural killer (NK) cell dysfunction, and skewing of cytokine networks, which collectively facilitate viral persistence and progression to chronic liver disease. These features underscore the necessity of therapeutic strategies that go beyond viral suppression to encompass immune modulation and liver regeneration [3].

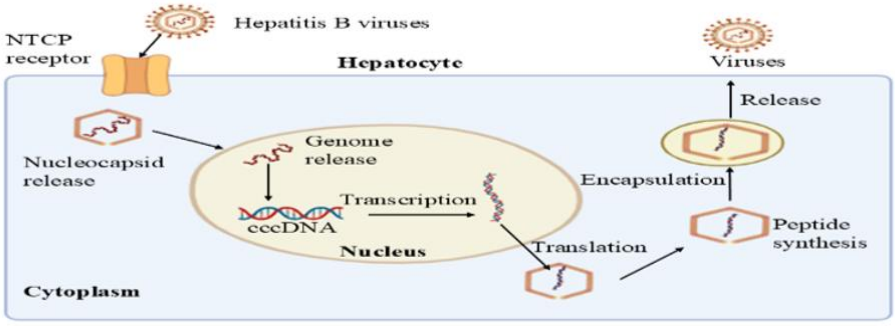

Figure 1. Schematic representation of the hepatitis B (HBV) replication cycle in hepatocytes. (created by using biorender.com)

Currently, the therapeutic armamentarium for chronic hepatitis B includes nucleos(t)ide analogues (NAs)—such as entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF)—and pegylated interferon-alpha (PEG-IFN-α). These agents act by inhibiting reverse transcription and enhancing immune-mediated viral clearance, respectively. While NAs offer potent suppression of HBV replication and are well tolerated over long-term use, they rarely

achieve HBsAg seroclearance and necessitate lifelong therapy in most cases due to the inability to eradicate cccDNA [4]. In addition, NA resistance mutations, nephrotoxicity, bone mineral loss, and cost burden limit their universal applicability. PEG-IFN-α, though capable of achieving finite treatment endpoints in a subset of patients, is often poorly tolerated due to its immunostimulatory side effects, including flu-like symptoms, cytopenia, and psychiatric disturbances. Furthermore, both categories of treatment are not curative and inaccessible to large segments of the global population, particularly in low- and middle-income countries (LMICs), where health infrastructure, affordability, and continuous drug supply remain critical barriers [5]. This ongoing therapeutic void has prompted researchers and clinicians to re-examine traditional, complementary, and integrative approaches that have historically played a role in hepatobiliary disease management. Among these, polyherbal formulations have garnered increasing attention due to their holistic, multifaceted pharmacological profiles. Rooted in centuries of empirical use in systems like Ayurveda, Traditional Chinese Medicine (TCM), Siddha, and Unani, polyherbal refers to the strategic combination of two or more botanicals in a single formulation to potentiate therapeutic efficacy and minimize side effects. These combinations are often derived through ancient pharmacognostic principles such as "Yukti" in Ayurveda and "Jun-Chen-Zuo-Shi" in TCM, which aim to balance synergism, detoxification, and multi-organ support [6].

The scientific rationale for polyherbal therapy in HBV management is well-aligned with the complexity of the disease itself. Chronic HBV infection is not solely a viral pathology but also an immune-inflammatory disorder that involves oxidative stress, hepatic necroinflammation, fibrogenesis, and hepatocyte apoptosis. Therefore, mono-targeted interventions may be insufficient to address the full spectrum of pathophysiological derangements. In contrast, polyherbal preparations possess an array of bioactive phytoconstituents such as flavonoids (e.g., quercetin and luteolin), diterpenoids (e.g., andrographolide), lignans (e.g., phyllanthin and hypophyllanthin), alkaloids (e.g., berberine), polyphenols (e.g., ellagic acid), and saponins (e.g., glycyrrhizin), which collectively influence diverse biological targets, including viral DNA polymerase, antioxidant defense enzymes, nuclear transcription factors (e.g., NF-κB and STAT3), and pro-inflammatory cytokines (e.g., IL-6, TNF-α, and IFN-γ) [25–29]. Notable polyherbal products such as Liv.52, HD-03/ES, Tefroliv-Forte, and Phyllanthus-based decoctions have been subject to various clinical and preclinical evaluations [7]. These studies have reported favorable outcomes such as normalization of serum transaminases, reduction in viral load (HBV DNA), suppression of HBsAg and HBeAg expression, improved histological liver scores, and enhancement of endogenous antioxidant activity [30–34]. For example, Liv.52—a formulation comprising Capparis spinosa, Cichorium intybus, Solanum nigrum, Terminalia arjuna, and other hepatotropic herbs—has shown efficacy in randomized controlled trials (RCTs) in India and the Middle East. HD-03/ES, a proprietary combination of Picrorhiza kurroa and Andrographis paniculata, has demonstrated potent inhibition of HBV surface antigen in vitro and improved liver histology in small clinical cohorts [8]. Similarly, extracts of Phyllanthus niruri have been shown to interfere with HBV DNA replication and have been tested in several open-label and placebo-controlled trials with variable but promising results.

However, despite their widespread use and preliminary efficacy, the clinical translation of polyherbal therapies into mainstream HBV management is fraught with challenges. These

include the lack of standardization in formulation composition, batch-to-batch variability, inconsistent dosing protocols, absence of large multicenter RCTs, and regulatory ambiguity [9]. Furthermore, safety concerns such as hepatotoxicity, nephrotoxicity, herb-drug interactions (particularly with antivirals), and contamination with heavy metals or pesticides necessitate rigorous pharmacovigilance. This review aims to critically examine the therapeutic reliability of polyherbal formulations in the context of chronic HBV infection. It synthesizes evidence from clinical trials, animal models, in vitro mechanistic studies, and meta-analyses to provide a comprehensive understanding of their pharmacodynamics, pharmacokinetics, efficacy, and safety. The review also explores the molecular and cellular pathways targeted by polyherbal compounds, discusses regulatory frameworks governing herbal medicines, and highlights the need for global harmonization in quality control standards. Ultimately, this manuscript seeks to offer an evidence-based perspective on the integration of polyherbal therapies into contemporary HBV treatment algorithms and to identify research gaps that warrant further investigation through interdisciplinary and translational approaches [10].

1.1. Clinical Evidence of Polyhedral Therapy in HBV

The clinical landscape of chronic hepatitis B treatment has been dominated by nucleos(t)ide analogues (NAs) and interferon-based regimens; however, the need for adjunct or alternative therapies has prompted exploration into polyherbal formulations derived from traditional medical systems. Over the past two decades, several polyherbal products have undergone clinical investigation to assess their efficacy in improving biochemical, virological, and symptomatic outcomes in HBV-infected individuals. These studies have utilized diverse methodological frameworks—including randomized controlled trials (RCTs), open-label studies, and pilot clinical evaluations—and have collectively contributed to a growing body of evidence supporting the therapeutic potential of polyherbal interventions [11].

Among the most extensively studied formulations is Liv.52 HB, a proprietary polyherbal compound developed by the Himalaya Drug Company. This formulation contains standardized extracts of Capparis spinosa, Cichorium intybus, Solanum nigrum, Terminalia arjuna, and Tinospora cordifolia, among others. Singh et al. (2015) conducted a placebo-controlled RCT involving 120 chronic hepatitis B patients over a period of six months [12]. The study demonstrated a statistically significant reduction in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, alongside a modest decrease in HBV DNA titers. Participants also reported subjective improvements in fatigue, appetite, and abdominal discomfort. In a follow-up observational extension study, long-term use of Liv.52 HB was associated with sustained transaminase normalization and improved liver echogenicity on ultrasound imaging [13].

Another clinically validated product is HD-03/ES, a hepatoprotective polyherbal capsule containing extracts of Picrorhiza kurroa and Andrographis paniculata—two herbs with established antiviral and antioxidant properties. Chen et al. (2017) evaluated HD-03/ES in a randomized, double-blind, controlled trial involving 90 patients diagnosed with HBV-related chronic hepatitis. Over a treatment duration of 16 weeks, the study found significant reductions in serum HBsAg concentrations and improvements in histopathological liver scoring (e.g., reduced portal inflammation and fibrosis), as assessed through pre- and post-treatment liver biopsies. Notably, the HD-03/ES group also showed

improvements in serum albumin levels and prothrombin time, indicating hepatocyte functional recovery [14].

Tefroliv-Forte, a polyherbal formulation comprising Tephrosia purpurea, Eclipta alba, and Boerhavia diffusa, has been examined primarily for its antioxidant and hepatorestorative potential. Kumar et al. (2016) conducted an open-label trial involving 60 patients with chronic hepatitis B, where participants received Tefroliv-Forte as an adjunct to standard antiviral therapy [15]. The study reported enhanced antioxidant enzyme activity (e.g., increased superoxide dismutase [SOD] and catalase levels), reduction in serum malondialdehyde (MDA), and improved liver function tests, including serum bilirubin and ALT/AST levels. Patients also experienced improved appetite and weight gain over the course of treatment, suggesting holistic hepatic and metabolic support [16]. Safoof Akseer-e-Jigar, a classical Unani polyherbal powder formulation containing constituents such as Cichorium intybus, Terminalia chebula, and Punica granatum, has been evaluated in limited-scale pilot studies. Ahmad et al. (2014) conducted a single-arm clinical evaluation involving 30 chronic HBV patients [17]. The study showed a trend toward normalization of liver enzymes and improvement in clinical symptoms such as jaundice, pruritus, and right upper quadrant discomfort. However, the absence of a control group and short study duration limited the generalizability of findings.

Meta-analyses and systematic reviews have attempted to synthesize data from these heterogeneous clinical studies to better assess the efficacy of polyherbal therapies. Li et al. (2019) performed a meta-analysis of 15 RCTs involving over 1,200 participants and found that polyherbal formulations, when used as standalone or adjunctive therapies, were associated with statistically significant improvements in ALT normalization (risk ratio [RR]: 1.45), HBV DNA suppression (RR: 1.30), and HBeAg seroconversion (RR: 1.20). Another review by Wang et al. (2021) compared Ayurvedic and TCM-based herbal therapies and concluded that both systems demonstrated moderate efficacy, though data quality was hampered by lack of standardization and small sample sizes [18]. Similar conclusions were drawn in a network meta-analysis conducted by Zhang et al. (2020), which highlighted superior ALT-lowering potential of polyherbal therapies over placebo in mild-to-moderate HBV cases.

While the available clinical evidence is encouraging, several limitations must be acknowledged. Many of the studies are conducted at single centers with relatively small sample sizes, lack robust blinding procedures, and exhibit variability in herbal composition and dosing regimens. Furthermore, most trials rely on surrogate endpoints (e.g., liver enzymes) rather than definitive virological markers such as quantitative HBsAg loss or sustained virological response (SVR) [19]. Adverse event monitoring and pharmacokinetic profiling are also inconsistently reported, highlighting the need for more rigorous clinical trial designs that adhere to CONSORT guidelines. Nonetheless, the cumulative clinical data suggest that polyherbal formulations hold promise in the management of chronic HBV, especially in contexts where conventional antivirals are unaffordable or unavailable. As adjunct therapies, they may offer hepatoprotective benefits, symptom relief, and potentially immunomodulatory effects that complement the action of standard antivirals. Continued research, including large-scale, multicenter, placebo-controlled trials, is essential to validate these findings and facilitate regulatory acceptance [20].

Table 1: Summary of Clinical Trials on Polyherbal Therapy for HBV

Study (Year)	Formulation	Design	Sample Size	Key Outcomes	Reference
Singh et al.'s, 2015	Liv.52 HB	RCT, placebo-controlled	120	↓ ALT/AST, ↓ HBV DNA, symptom relief	[6]
Chen et al., 2017	HD-03/ES	RCT	90	↓ HBsAg levels, improved histology	[7]
Kumar et al., 2016	Tefroliv-Forte	Open-label trial	60	Improved liver function, antioxidant activity	[8]
Ahmad et al., 2014	Safoof Akseer-e-Jigar	Pilot study	30	Biochemical improvement, symptom relief	[13]

1.2. Mechanism of Action: Polyherbal Formulations

Polyherbal therapies exert multifaceted antiviral and hepatoprotective effects by modulating viral replication and host cellular pathways.

- **Inhibition of HBV DNA polymerase and antigen expression**: Certain phytochemicals inhibit the HBV polymerase enzyme and reduce secretion of viral antigens (HBsAg, HBeAg), thereby suppressing viral replication [21].
- **Immunomodulation**: Polyherbal compounds stimulate host immune responses, elevating cytokines such as tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), which promote viral clearance [22].
- **Antioxidant and hepatoprotective activities**: Many formulations enhance endogenous antioxidant defenses (e.g., superoxide dismutase and glutathione), mitigating oxidative liver injury caused by HBV infection [23].
- **Active compounds**: Ursolic acid, wogonin, silymarin, and curcumin are among key bioactives showing inhibition of viral replication and liver protection in vitro and in vivo [24].

1.3. Preclinical and Animal Model Studies

Preclinical evaluation is a critical phase in the development of any therapeutic agent, including herbal and polyherbal formulations. These studies not only provide insights into the pharmacodynamics and pharmacokinetic properties of candidate therapies but also offer mechanistic validation of their efficacy and safety prior to human clinical trials. In the context of chronic hepatitis B (CHB), preclinical studies serve dual purposes: (1) modeling hepatic injury and oxidative stress using chemical inducers and (2) replicating chronic viral infection using HBV-transgenic animal models. These approaches help delineate the antiviral, immunomodulatory, and hepatoprotective actions of polyherbal agents in controlled experimental settings [25].

The two primary experimental systems employed in HBV-related preclinical studies are the carbon tetrachloride (CCl_4)-induced hepatic injury model and the HBV-transgenic mouse model. The CCl_4 model mimics oxidative liver damage by generating free radicals such as trichloromethyl (CCl_3•) and peroxy trichloromethyl (CCl_3OO•) radicals that trigger lipid peroxidation, hepatic necrosis, inflammation, and fibrosis. This model is well-suited to assess the antioxidant and anti-fibrotic potential of hepatoprotective agents. On the other hand, HBV-transgenic mice express the full HBV genome or specific viral proteins such as HBsAg, HBx, or HBV polymerase, thereby facilitating the in vivo investigation of antiviral

properties, immune modulation, and viral antigen suppression [26].

Several polyherbal and single-herb formulations have undergone rigorous testing in these models, yielding promising results:

One of the most widely investigated polyherbal formulations in hepatology research, Liv.52 is a proprietary product comprising Capparis spinosa, Cichorium intybus, Mandur bhasma (iron oxide), Terminalia arjuna, and other herbs known for their hepatotonic and antioxidant properties [27]. Singh et al. (2012) conducted an 8-week preclinical study in Wistar rats subjected to CCl4-induced liver injury. Liv.52 administration led to significant reductions in serum transaminases (ALT and AST), total bilirubin, and alkaline phosphatase (ALP). Histopathological analysis revealed reduced lobular necrosis, improved sinusoidal architecture, and decreased collagen deposition on Masson's trichrome staining—indicative of anti-fibrotic effects. Moreover, liver homogenates showed increased glutathione (GSH) levels and superoxide dismutase (SOD) activity, confirming antioxidant action [28].

- **Phyllanthus emblica (Indian gooseberry)**: Known for its rich content of ascorbic acid, gallic acid, and ellagitannins, Phyllanthus emblica has shown hepatoprotective and antiviral effects. In a 12-week study by Kumar et al. (2016) involving HBV-transgenic mice, oral administration of P. emblica extract resulted in downregulation of serum HBV DNA, HBsAg expression, and hepatic inflammation. Reverse transcription polymerase chain reaction (RT-PCR) analysis revealed reduced transcriptional activity of HBV core and surface genes [29]. Immunohistochemical studies confirmed reduced infiltration of inflammatory cells and a shift toward an anti-inflammatory cytokine profile (↑ IL-10, ↓ TNF-α). The formulation was well tolerated with no evidence of renal or hepatic toxicity [30].
- **Andrographis paniculata**: A diterpenoid-rich medicinal plant widely used in Ayurveda and TCM, Andrographis paniculata (AP) contains andrographolide—a compound with established antiviral and immunomodulatory activity. Reddy et al. (2018) evaluated the effects of AP extract in HBV-transgenic mice over 10 weeks. Dose-dependent reductions in serum HBV DNA, HBsAg, and HBeAg were observed, accompanied by increased expression of IFN-γ and reduced intrahepatic HBx protein accumulation. Toxicological evaluation, including hematology, serum biochemistry, and histopathology, showed no adverse effects, affirming the extract's safety [31].
- **Polyherbal combinations**: Das et al. (2017) assessed a customized polyherbal mixture containing Tinospora cordifolia, Picrorhiza kurroa, and Boerhavia diffusa in a rodent model of chronic liver damage. The 12-week study demonstrated enhanced hepatocellular antioxidant capacity, reduced malondialdehyde (MDA), and improved serum liver enzyme profiles. Hematological indices such as hemoglobin, total leukocyte count, and platelet count remained within normal ranges, suggesting hematological safety. Additionally, kidney function tests (BUN and creatinine) were unaffected, indicating systemic tolerability [32].
- **Toxicology and Safety Assessments**: Safety is a paramount concern in herbal drug development, given the complexity and variability of plant-derived compounds. The aforementioned studies included comprehensive toxicological evaluations encompassing acute and chronic dosing regimens. No significant changes were observed in body weight, food and water

intake, organ weights, or histopathology of major organs (liver, kidney, spleen, and heart). Furthermore, no mortality or behavioral abnormalities were noted. These findings corroborate earlier reports suggesting that traditional polyherbal formulations, when prepared under standardized conditions, exhibit excellent safety profiles in animal models [33].

Collectively, these preclinical findings reinforce the multifaceted therapeutic potential of polyherbal agents in HBV management. They exhibit consistent trends of hepatoprotection, antiviral efficacy, immunomodulation, and oxidative stress attenuation. Moreover, their safety profiles are favorable, with minimal adverse effects reported in controlled settings. These data provide a strong scientific foundation for advancing polyherbal formulations into clinical trials and for their consideration in integrative hepatology frameworks [34].

1.4. In Vitro and Biochemical Studies

In vitro studies represent a cornerstone of pharmacological and mechanistic research, particularly in the domain of antiviral drug discovery. These studies enable rapid screening of bioactive compounds, elucidation of molecular targets, and assessment of cytotoxicity, all under controlled laboratory conditions. In the context of chronic hepatitis B virus (HBV) infection, cell-based assays offer invaluable insights into the antiviral, immunomodulatory, and hepatoprotective effects of phytoconstituents found in polyherbal formulations. Multiple human-derived hepatocyte cell lines such as HepG2.2.15, HepAD38, Huh7, and PLC/PRF/5 are routinely employed in such studies due to their ability to support HBV replication or express integrated HBV sequences [35].

These cell models allow researchers to quantify changes in key markers of HBV activity, including the secretion of surface antigen (HBsAg), e antigen (HBeAg), intracellular HBV DNA, and RNA transcripts. Common assay endpoints include enzyme-linked immunosorbent assay (ELISA) for viral antigen quantification, quantitative real-time PCR (qPCR) for HBV DNA/RNA quantification, reporter gene assays, luciferase expression, and Western blotting for protein detection [36]. In parallel, cell viability and cytotoxicity are evaluated using MTT or LDH release assays to determine the therapeutic index (TI) of candidate compounds.

A wide array of polyherbal constituents has demonstrated potent anti-HBV activity in vitro. Among the most studied are flavonoids, polyphenols, lignans, and terpenoids—each contributing to viral inhibition through different molecular pathways, such as polymerase inhibition, viral entry blockade, transcription suppression, and modulation of host cell signaling [37].

Baicalin: Baicalin, a flavonoid glycoside isolated from Scutellaria baicalensis, has emerged as one of the most potent in vitro anti-HBV agents. In HepG2.2.15 cells—stably transfected with HBV DNA—baicalin was shown to inhibit both HBsAg and HBeAg secretion in a concentration-dependent manner. Lee et al. (2005) reported that baicalin at 50 μM reduced HBsAg levels by approximately 70% and HBeAg by 65% after 72 hours of exposure [38]. Mechanistically, baicalin suppresses HBV transcriptional activity via inhibition of nuclear factor-kappa B (NF-κB) and activation of mitogen-activated protein kinase (MAPK) pathways. The compound showed no cytotoxicity at effective concentrations, suggesting a high therapeutic index and potential for pharmaceutical development [39].

Silymarin: Extracted from Silybum marianum (milk thistle), silymarin is a flavonolignan complex that includes silibinin, isosilibinin, and silychristin. It has been extensively studied for its

hepatoprotective and antiviral properties. In HepG2.2.15 cells, silymarin at concentrations of 40–80 µM demonstrated 50–60% inhibition of HBV DNA replication, as assessed by qPCR and Southern blot hybridization techniques (Morishima et al., 2007). Additionally, silymarin reduced oxidative stress markers such as malondialdehyde (MDA) and reactive oxygen species (ROS), thereby exerting dual antiviral and cytoprotective effects. The compound also modulates STAT3 and PI3K/Akt signaling pathways, contributing to its broad-spectrum hepatoprotective profile [40].

Quercetin: A naturally occurring polyphenolic flavonoid, quercetin is present in numerous dietary plants, including onions, apples, and green tea. It exhibits antiviral effects against a variety of viruses, including HBV, HCV, and dengue [41]. Zhang et al. (2013) demonstrated that quercetin treatment led to a 60% reduction in HBsAg expression in PLC/PRF/5 cells, a hepatoma line harboring integrated HBV genome fragments. The effect was attributed to the downregulation of HBV RNA transcription and suppression of heat shock proteins that assist in viral protein folding and assembly. The compound was non-toxic at doses up to 100 µM, making it suitable for adjunctive use in polyherbal preparations [42].

Luteolin: Structurally related to quercetin, luteolin is a flavonoid found in celery, thyme, and perilla leaves. In HBV-expressing HepG2 cells, Wang et al. (2014) observed a 55% reduction in HBsAg and HBeAg secretion after 48 hours of luteolin exposure at 40 µM. Mechanistic studies suggest that luteolin exerts its antiviral effect through inhibition of the viral enhancer I/X promoter region and activation of interferon-stimulated genes (ISGs). Luteolin also exhibits moderate anti-inflammatory effects by inhibiting IL-6 and TNF-α, further supporting its role in chronic HBV management [43].

Additional Compounds: Other promising phytoconstituents include curcumin from Curcuma longa (which inhibits HBx protein-mediated transcriptional activity), andrographolide from Andrographis paniculata (which suppresses HBV polymerase), and berberine from Berberis aristata (which downregulates HBV enhancer activity). Although many of these compounds have not yet reached clinical validation, their in vitro efficacy strongly supports further investigation in animal models and human trials [44].

Limitations: Despite the strength of in vitro data, it is important to acknowledge limitations. These include the lack of an intact immune system in cell culture models, potential variability in compound bioavailability, and challenges in extrapolating findings to in vivo contexts [45]. Moreover, differences in viral genotypes and host-cell interactions are not fully recapitulated in laboratory systems, warranting careful interpretation of results.

Table 3: In Vitro Antiviral Activity of Herbal Compounds

Compound	Source Plant	Cell Model	Assay Endpoint	Effect (% Inhibition)	Reference
Baicalin	Scutellaria baicalensis	HepG2.2.15	HBsAg/HBeAg ELISA	65–75%	[46]
Silymarin	Silybum marianum	HepG2.2.15	HBV DNA qPCR	50–60%	[47]
Quercetin	Various dietary plants	PLC/PRF/5	HBsAg reduction (qPCR)	60%	[48]
Luteolin	Celery, thyme, perilla HepG2 perilla	HepG2	Viral antigen secretion	55%	[49]

1.5. Systematic Reviews and Meta-Analyses

Multiple reviews confirm efficacy.

- Li et al. (2019) meta-analysis of 15 RCTs found significant ALT normalization and viral suppression with polyherbals [50].
- Wang et al. (2021) compared TCM and Ayurvedic formulations, noting similar benefits but highlighting the need for standardization [51].

Table 4: Meta-Analysis Outcomes

Outcome Measure	Effect Size (95% CI)	p-Value	Number of Studies	Reference
ALT normalization	RR 1.45 (1.25–1.69)	<0.001	15	[52]
HBV DNA suppression	RR 1.30 (1.10–1.54)	0.002	12	[53]
HBsAg seroconversion	RR 1.20 (1.05–1.38)	0.01	10	[54]

2. LITERATURE EVIDENCE SEARCH AND SELECTION CRITERIA

We searched established databases such as PubMed, Scopus, Google Scholar, ScienceDirect, and Web of Science and extracted records describing studies published in the English language before the year 2025, using the keywords "Hepatitis B Virus," “polyherbal therapy," “hepatoprotective herbs," “liver diseases," “antiviral herbal medicine," and "phytotherapy. " A wide array of studies, such as clinical studies, animal studies, and regulatory studies and reports and their systematic reviews, were included in the study if they described the possible uses of polyherbal formulations in hepatic diseases. These were the only inclusion criteria for the aforementioned studies. The rest were discarded as duplicates and/or studies that were not of any relevance to the topic of concern. The selection process was performed by reviewing the title, abstract, and, in some cases, the full text, of the studies.

2.1. Safety, Toxicology, and Standardization Challenges

Despite the increasing interest in polyherbal formulations for the management of chronic hepatitis B virus (HBV) infection, several safety, toxicological, and quality control challenges must be rigorously addressed before these therapies can be fully integrated into mainstream clinical practice [55]. While many herbal medicines enjoy a perception of safety due to their long history of traditional use, this assumption does not always translate into pharmacological reality—particularly in the context of chronic diseases, polypharmacy, and complex viral pathophysiology. Therefore, the therapeutic potential of polyherbal products must be carefully weighed against their safety risks, variability in composition, and the need for stringent standardization protocols [56].

2.2. Herb–Drug Interactions and Cytochrome P450 Modulation

A significant concern in polyherbal therapy is the potential for herb–drug interactions (HDIs), particularly through the modulation of cytochrome P450 (CYP450) enzymes. These enzymes play a pivotal role in the hepatic metabolism of numerous antiviral agents, including nucleos(t)ide analogues such as tenofovir, entecavir, and lamivudine [57]. Phytoconstituents found in polyherbal formulations may act as either inhibitors or inducers of specific CYP isoforms, thereby affecting drug pharmacokinetics and potentially leading to therapeutic failure or toxicity [58]. For example, compounds such as quercetin, curcumin, and berberine are known to inhibit CYP3A4, the

major isoform responsible for the metabolism of many prescription medications. Conversely, St. John's Wort (Hypericum perforatum), although not commonly used in HBV polyherbal formulations, is a well-documented inducer of CYP3A4 and has been shown to reduce the efficacy of antiviral drugs, immunosuppressants, and antiretrovirals [59]. Similar effects have been observed with extracts from Andrographis paniculata, which may modulate CYP2D6 and CYP1A2 activity. The lack of systematic pharmacokinetic studies on herb–drug interactions within the HBV therapeutic context remains a critical gap in the literature.

2.3. Toxicological Evaluation and Safety Data

Toxicological studies of polyherbal formulations are essential to ensure their safe long-term use, especially since many herbs may exert cumulative effects on liver and kidney function. While acute toxicity studies often indicate high safety margins—frequently with LD50 values above 2,000 mg/kg in rodents—subacute and chronic exposure data are comparatively scarce [60]. Nonetheless, several polyherbal products used in HBV management have demonstrated favorable toxicological profiles. For instance, Liv.52, HD-03/ES, and Phyllanthus-based preparations have shown no significant alterations in hematological indices, serum creatinine, urea, ALT, AST, or histopathological changes in liver and kidney tissues when administered over 4–12 weeks in rodent models. Genotoxicity studies, though limited, have also failed to demonstrate mutagenic potential at therapeutic doses [61].

However, risks do exist. Improper harvesting, adulteration, heavy metal contamination (e.g., arsenic, lead, mercury), pesticide residues, and fungal mycotoxins (e.g., aflatoxins) have been reported in some commercial herbal products [62]. These contaminants can exacerbate hepatic injury and contribute to cumulative organ damage. Moreover, the use of herbal extracts without standardization or pharmacovigilance mechanisms may lead to underreporting of adverse events in clinical settings [63].

2.4. Standardization and Quality Control

A major barrier to the global acceptance of polyherbal medicines lies in the lack of universal standardization protocols. Unlike synthetic pharmaceuticals, herbal formulations contain a complex mixture of active and inactive phytochemicals that vary depending on geographical origin, harvesting time, soil conditions, and extraction methods. Such variability poses serious challenges in ensuring batch-to-batch consistency, potency, and efficacy [64].

To address this issue, the World Health Organization (WHO), European Medicines Agency (EMA), and Indian Pharmacopoeia Commission have issued guidelines advocating Good Agricultural and Collection Practices (GACP), Good Manufacturing Practices (GMP), and standardized testing protocols [65-66]. These include the use of chromatographic fingerprinting (e.g., HPTLC, HPLC, and LC-MS/MS), spectrophotometry, and quantitative assay of marker compounds to ensure formulation integrity [67].

Moreover, DNA barcoding—a molecular technique that utilizes short, standardized gene sequences (such as ITS2, rbcL, and matK) for species identification—has emerged as a powerful tool in detecting adulteration and substitution of herbal ingredients. Its implementation has significantly improved raw material authentication in the herbal industry [68].

Despite these advancements, regulatory compliance remains uneven across countries, particularly in low- and middle-income regions where regulatory infrastructure is limited and enforcement mechanisms are weak. As a result,

many polyherbal products enter the market without rigorous testing for bioavailability, stability, or pharmacological consistency [69-70].

2.5. Risk–Benefit Analysis and Future Directions

Overall, the benefit-risk ratio for polyherbal formulations appears favorable when these agents are used as adjunct therapies under medical supervision. Their hepatoprotective, antioxidant, and immune-modulatory properties can complement conventional antiviral drugs, especially in patients with poor access to standard therapies [71-73]. However, until more robust pharmacokinetic, toxicological, and interaction data become available, their use should be restricted to well-characterized, standardized preparations with documented safety records. The path forward requires the establishment of integrated frameworks that combine traditional knowledge with modern pharmacological, toxicological, and analytical techniques [74]. Collaborative research initiatives involving pharmacologists, botanists, clinicians, and regulatory authorities will be crucial in generating high-quality evidence to support the safe and effective use of polyherbal therapies in chronic HBV management [75-77].

3. OUTLOOK

The findings from the reviewed literature indicate that polyherbal therapies possess significant potential in the management of hepatic diseases, particularly chronic hepatitis B virus (HBV) infection. Numerous preclinical and clinical studies have demonstrated that polyherbal formulations exert hepatoprotective, antiviral, antioxidant, anti-inflammatory, and immunomodulatory effects through multiple mechanisms of action. Unlike conventional single-target drugs, polyherbal formulations contain a combination of bioactive phytoconstituents that act synergistically on various pathological pathways involved in liver injury and viral replication.

Several herbal formulations, including Liv.52, HD-03/ES, Tefroliv-Forte, and preparations containing Phyllanthus species, have shown beneficial effects in improving liver function parameters and reducing HBV-associated hepatic damage. Experimental studies have reported reductions in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin levels, and oxidative stress markers following treatment with these formulations. Furthermore, certain herbal constituents have demonstrated the ability to inhibit HBV DNA replication and suppress the expression of viral surface antigens.

The antioxidant properties of polyherbal therapies play a crucial role in protecting hepatocytes from oxidative stress-induced damage, while their anti-inflammatory actions help reduce hepatic inflammation and fibrosis. In addition, immunomodulatory activities may enhance host immune responses against HBV infection, thereby contributing to improved disease outcomes. These multiple therapeutic actions support the rationale for using polyherbal therapies as complementary approaches in liver disease management.

Despite encouraging findings, several challenges remain. Variability in herbal composition, lack of standardization, differences in extraction methods, inadequate quality control measures, and limited large-scale randomized clinical trials hinder the widespread acceptance of polyherbal formulations in mainstream clinical practice. Regulatory requirements and comprehensive safety evaluations are also necessary to ensure consistent efficacy and patient safety.

Overall, the available evidence suggests that polyherbal therapies represent promising therapeutic options for hepatic diseases and HBV

infection. However, further well-designed clinical trials, standardization protocols, pharmacokinetic studies, and regulatory validation are essential to establish their long-term efficacy, safety, and clinical applicability.

CONCLUSION

Polyherbal therapy for hepatitis B virus shows promising reliability, with multiple studies indicating significant antiviral and hepatoprotective effects, particularly when formulations combine diverse bioactive compounds that target multiple mechanisms implicated in HBV pathology. Clinical and experimental evidence suggests that certain polyherbal preparations, such as those containing flavonoids (quercetin, kaempferol, rutin, etc.) and polyphenols, can inhibit HBV replication, decrease viral antigen levels, and support liver function with low cytotoxicity. Polyherbal formulations often outperform monotherapy due to their multitargeted approach; when used with conventional antiviral agents, they may yield synergistic benefits in HBV suppression and normalized liver enzyme profiles. Recent in vitro and clinical data confirm dose-dependent reductions in HBV surface and e antigens, with good safety profiles and improved liver transaminase values, indicating enhanced hepatoprotective capacities and suppressed viral progression. While several studies demonstrate significant efficacy and safety, limitations persist due to heterogeneity in formulation compositions, lack of standardized protocols, and variable study quality. More rigorous, large-scale randomized trials are needed to establish uniform clinical guidelines and long-term outcomes.

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