IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

THERAPEUTIC POTENTIAL OF SHYONAKA (OROXYLUM INDICUM) IN CHRONIC HEPATITIS B: AN EVIDENCE-BASED REVIEW WITH INTEGRATIVE INSIGHTS

Dr. Akshita[1], Dr.Abhishek Bhushan Sharma[2]

1- 'MD Scholar-3rd Year, PG Department of Kayachikitsa, Quadra Institute of Ayurveda and Hospital,Roorkee, Uttarakhand

2- Professor, PG Department of Kayachikitsa Quadra Institute of Ayurveda and Hospital, Roorkee,Uttarakhand

Abstract: Chronic Hepatitis B (CHB) remains one of the foremost public health challenges globally, affecting approximately 296 million individuals and contributing to over 820,000 deaths annually from cirrhosis and hepatocellular carcinoma. While nucleos(t)ide analogues and pegylated interferon constitute the current standard of care, their limitations including the inability to eradicate covalently closed circular DNA (cccDNA), lifelong dependency, drug resistance emergence, and high treatment costs necessitate the exploration of complementary therapeutic agents. Shyonaka (Oroxylum indicum Vent., Bignoniaceae), a revered plant in Ayurvedic medicine and a constituent of the classical Dashamula formulation, offers a scientifically compelling phytochemical profile for addressing the multidimensional pathophysiology of CHB. This review systematically evaluates the botanical identity, Ayurvedic classical categorization, phytochemistry, and pharmacological evidence pertaining to its key bioactive constituents including baicalein, baicalin, chrysin, oroxylin A, ellagic acid, and scutellarein. Evidence demonstrates that baicalein inhibits HBV through the CCDC88A-AKT-mTOR signaling pathway and autophagy induction; baicalin suppresses viral transcription via the HNF4-alpha/HNF1-alpha axis; and chrysin reduces HBsAg secretion by up to 45% and HBeAg by up to 58% in vitro via HMGB1 targeting, with binding affinity superior to lamivudine. The plant additionally exhibits hepatoprotective, antifibrotic, immunomodulatory, and NF-kB suppressive activities relevant to CHB pathology. An integrative framework aligning Ayurvedic concepts of Yakrit Vikara and Kamala with modern hepatological paradigms is presented. Safety profile, bioavailability considerations, and the current research gap are critically discussed. This review establishes Oroxylum indicum as a rational candidate for adjunctive or integrated therapeutic development in CHB management, warranting rigorous clinical evaluation.

Index Terms: *Shyonaka, Oroxylum indicum, Chronic Hepatitis B, Baicalein, Chrysin, Oroxylin A, HBV, Dashamula, Hepatoprotective, Ayurveda, cccDNA, NF-kB, Integrative medicine, Antiviral flavonoids, Kamala*

I. INTRODUCTION

Hepatitis B virus (HBV) infection constitutes one of the most consequential infectious diseases affecting the liver worldwide. According to data from the Global Burden of Disease (GBD) 2021 study, approximately 296 million individuals were living with chronic HBV infection (CHB) in 2019, with an estimated 1.5 million new infections occurring annually [1]. The disease caused over 820,000 deaths in 2019 from complications including liver cirrhosis and hepatocellular carcinoma (HCC), conditions to which CHB contributes in 42% and over 75% of cases respectively [1,2]. Despite the availability of an effective preventive vaccine for decades, only approximately 14% of the estimated 257 million affected individuals have been diagnosed, and fewer than 3% are receiving antiviral treatment globally, highlighting a profound treatment gap [2,3].

The natural history of CHB is characterized by distinct phases ranging from immune tolerance to immune clearance, immune control, and reactivation [3,4]. Perinatal transmission carries the highest risk of chronicity, with 80 to 90% of infected neonates developing CHB, compared to only 5% of acutely infected adults [3]. The central molecular obstacle to a functional cure is the persistence of covalently closed circular DNA (cccDNA) within infected hepatocytes. This episomal viral template serves as the transcriptional origin of all HBV RNAs and is resistant to currently available antiviral agents, necessitating lifelong pharmacotherapy in the majority of treated patients [4,5].

Current therapeutic options include nucleos(t)ide analogues (NAs) such as entecavir and tenofovir, and pegylated interferon alpha. While NAs effectively suppress viral replication and achieve undetectable plasma viremia in nearly all adherent patients within six months of monotherapy, fewer than 5% achieve HBsAg seroconversion, and viral rebound uniformly occurs upon drug discontinuation [4,5]. Prolonged NA therapy is additionally associated with drug resistance, particularly with older agents such as lamivudine, as well as potential renal and bone toxicities with tenofovir [4,5]. The WHO's 2030 elimination targets, which include a 90% reduction in new CHB diagnoses and a 65% reduction in CHB-related mortality, demand innovative approaches including the rational integration of traditional medicine-derived compounds with proven antiviral scaffolds [2].

The Ayurvedic pharmacopoeia of India contains numerous hepatoprotective plants classified under Yakrit Vikara Chikitsa (management of liver disorders) and Shotha Chikitsa (anti-inflammatory therapy). Among these, Shyonaka (Oroxylum indicum Vent., Bignoniaceae), a constituent of the widely prescribed Dashamula formulation and a member of the Shothahara Mahakashaya described by Acharya Charaka in the Charaka Samhita, occupies a distinctive position [6,7]. The plant has been documented in classical texts for management of Kamala (jaundice and biliary dysfunction), Shotha (edema and inflammation), Udararoga (abdominal and hepatic diseases), and Jwara (pyrexia) [7,8]. Modern phytochemical investigations have isolated over 28 bioactive compounds from its various anatomical parts, with flavones including baicalein, baicalin, chrysin, and oroxylin A demonstrating compelling in vitro and in silico anti-HBV activities [9,10,11].

This review consolidates classical Ayurvedic descriptions with contemporary pharmacological and molecular evidence to evaluate the therapeutic potential of Oroxylum indicum in CHB management. It presents an integrative analysis of its phytochemistry, molecular mechanisms relevant to HBV pathobiology, hepatoprotective properties, safety profile, and potential synergistic applications with existing antiviral therapy. The aim is to establish a rational, evidence-informed foundation for the development of Shyonaka-derived formulations as adjunctive or integrated therapeutic candidates in CHB.

II. BOTANICAL DESCRIPTION AND TAXONOMIC IDENTITY

Oroxylum indicum (Linn.) Kurz is a medium-sized, deciduous tree belonging to the family Bignoniaceae, commonly reaching heights of 8 to 15 meters. The tree exhibits a characteristic architectural form with a single, unbranched trunk bearing a sparse, umbrella-like canopy concentrated at the apex. Its leaves are extraordinarily large, extending from 0.5 to 1.5 meters in length and arranged in a 2 to 3-pinnate configuration with 2 to 4 pairs of opposite pinnae. Leaflets are ovate to elliptic, acuminate, glabrous, and measure 6 to 12 cm in length and 4 to 10 cm in breadth.

The flowers are striking and nocturnal, appearing in elongated, terminal racemes measuring 0.3 to 0.6 meters in length. They are reddish-purple externally and pale pinkish-yellow within, with a foul odor that attracts bats and moths as pollinators, making O. indicum an ecologically important chiropterophilous species. The fruits are the most distinctive morphological feature, comprising long, flat, sword-shaped siliqua capsules extending up to 1 meter in length and 4 to 8 cm in width, which hang vertically from branches and are responsible for the vernacular English name 'midnight horror' or 'broken bones tree'. Seeds are numerous, flat, papery, and winged, facilitating wind dispersal.

The plant thrives in moist deciduous and semi-evergreen forests across a broad geographical range encompassing India (Himalayan foothills, Western Ghats, Assam, Uttarakhand, Himachal Pradesh, Maharashtra, Madhya Pradesh), Sri Lanka, Bangladesh, Bhutan, Myanmar, Thailand, Vietnam, Malaysia, Indonesia, and southern China. In India, it is most abundantly distributed in the northeastern states and the Western Ghats. Optimal habitat conditions include altitudes from sea level to 1,200 meters with annual rainfall exceeding 1,200 mm. The plant is currently listed as a vulnerable species under habitat pressures from deforestation and agricultural land conversion, warranting conservation attention alongside its pharmacological development.

Medicinally utilized parts include the root bark (official part as per Ayurvedic Pharmacopoeia of India), stem bark, leaves, seeds, and fruits [8]. Root bark is richest in baicalein, chrysin, biochanin A, and ellagic acid, while the stem bark contains baicalein, oroxylin A, and scutellarein in higher concentrations [11]. Seeds contain chrysin, oroxylin A, baicalein, tetuin, apigenin, and a shiny drying oil comprising caprylic, lauric, myristic, palmitic, stearic, oleic, and linoleic acids [9,12].

Table 1: Ayurvedic Classification and Properties of Shyonaka (Oroxylum indicum)

Sanskrit Name	Shyonaka; also Sonapatha, Aralu, Tuntuka, Katvanga, Sukanasa, Dirghavrinta
Family	Bignoniaceae
Rasa (Taste)	Katu (Pungent), Tikta (Bitter), Kashaya (Astringent)
Guna (Properties)	Laghu (Light), Ruksha (Dry)
Veerya (Potency)	Ushna (Hot)
Vipaka (Post-digestive effect)	Katu (Pungent)
Dosha action	Pacifies Vata and Kapha doshas; reduces vitiated Pitta in hepatic contexts
Karma (Actions)	Deepana (Digestive stimulant), Grahi (Absorbent), Shothahara (Anti-inflammatory), Kasahara (Relieves cough)
Classical indications	Shotha (Inflammation), Kamala (Jaundice / liver disorders), Udararoga (Abdominal/liver diseases), Atisara (Diarrhea), Jwara (Fever), Shwasa (Dyspnea)
Dashamula role	One of Brihat Panchamoola (Larger five roots group); cornerstone of Dashamula formulations

Classical texts citing it	Charaka Samhita (Shothahara Mahakashaya, Sheeta Prashamana gana), Sushruta Samhita, Ashtanga Hridayam, Bhavaprakasha Nighantu (verse 25-26, p.283-285)
Dose (classical)	Churna (Powder): 3-6 g twice daily; Kwatha (Decoction): 20-50 ml twice daily

III. AYURVEDIC CLASSICAL PERSPECTIVE AND INTEGRATIVE CORRELATIONS

3.1 Classical Documentation

Shyonaka has been comprehensively documented across major Ayurvedic classical texts spanning over two millennia. In the Charaka Samhita, it is enumerated under two important pharmacological groupings: the Shothahara Mahakashaya (the anti-inflammatory group of 50 herbs, described in Charaka Samhita Sutra Sthana 4.18) and the Sheeta Prashamana gana (the group of herbs that subdue cold and cough conditions) [6]. It is also listed as an Anuvasanopaga herb, indicating its utility in oil-based enema preparations used in Panchkarma for Vata-predominant disorders [6]. In the Sushruta Samhita, Shyonaka is recognized for its astringent, antiseptic properties and is prescribed for non-healing ulcers, female reproductive disorders, and dysentery [9]. The Bhavaprakasha Nighantu (1998 edition, verse 25 to 26, pages 283 to 285) provides a detailed pharmacodynamic description, cataloguing its multiple Sanskrit synonyms including Aralu, Katvanga, Tuntuka, Mandukaparna, Sukanasa, Dirghavrinta, and Mayurajangha, and assigning it tridoshahara properties [7].

As one of the Brihat Panchamoola (greater five roots) within the Dashamula configuration, Shyonaka occupies a central role in formulations prescribed for inflammatory, respiratory, and metabolic disorders [6,7]. The Dashamula formulation, comprised of the five larger roots (Bilva, Agnimantha, Shyonaka, Kashmarya, and Patala) and five smaller roots (Shalaparni, Prishnaparni, Brihati, Kantakari, and Gokshura), is extensively employed in Dashamoolarishtha, Dashamulakwatha, and Dashamoola Haritaki preparations [6]. Its warm potency (Ushna veerya) and pungent post-digestive effect (Katu vipaka) are considered responsible for its capacity to pacify accumulated Vata and Kapha doshas [7,8].

3.2 Ayurvedic Correlation with Hepatitis B Pathology

The Ayurvedic conceptualization of Kamala (broadly corresponding to jaundice and hepatic disorders) involves vitiation of Pitta dosha along with Rakta (blood tissue) and Rasa dhatu (plasma). Classical texts describe two primary forms: Koshtha-shrita Kamala, originating from deep-seated digestive dysfunction with Pitta accumulation, and Shakha-shrita Kamala, characterized by peripheral manifestation. Chronic Hepatitis B, in integrative clinical interpretation, correlates most closely with Rakta Pitta Kamala on account of its viral etiology causing sustained hepatic inflammation, progressive fibrosis (Yakrit Shotha), and eventual cirrhosis (Pleehodara or Yakriddalyudara in advanced forms).

The properties of Shyonaka directly address the Ayurvedic pathomechanism of CHB. Its Tikta (bitter) and Kashaya (astringent) rasas are classically regarded as Pitta-pacifying, which in the context of hepatic inflammation implies reduction of the excessive immunoinflammatory response characteristic of CHB [7]. Its Deepana (digestive fire enhancement) action facilitates improved hepatic metabolism, while its Grahi (absorptive) property may contribute to normalization of altered stool and digestion parameters commonly observed in hepatic dysfunction [6,7]. The Shothahara (anti-inflammatory) karma directly maps to the suppression of hepatic inflammation, a central therapeutic goal in CHB management [6,13]. Furthermore, Charaka explicitly describes this herb as a rejuvenative liver tonic with potent detoxifying (Vishahara) properties, aligning with the hepatoprotective pharmacological findings confirmed in modern studies [6,9].

The inclusion of Shyonaka in classical Udararoga (abdominal disease, including hepatomegaly and ascites) formulations such as Dashamoola Ghrita and Shyonaka Putapaka Swarasa further supports its Yakrit-specific (liver-directed) therapeutic utility. This classical recognition of the plant as a first-line

intervention for hepatic inflammatory and obstructive pathologies provides a culturally validated and clinically relevant foundation for its modern investigational use in CHB.

IV. PHYTOCHEMISTRY OF OROXYLUM INDICUM

4.1 Overview of Bioactive Constituents

Exhaustive phytochemical investigations across all plant parts of Oroxylum indicum have identified over 28 structurally diverse bioactive compounds [9,10,14]. These are broadly categorized into flavones and their glycosides, isoflavones, polyphenols, anthraquinones, triterpenoids, and fatty acids. Flavonoids constitute the predominant and most pharmacologically significant class, with their highest concentrations found in the stem bark, root bark, seeds, and fruit pods [9,11]. The major flavonoids include baicalein, baicalin (baicalein-7-O-glucuronide), chrysin (5,7-dihydroxyflavone), oroxylin A (5,7-dihydroxy-6-methoxyflavone), scutellarein, oroxindin (a flavone glucuronide first isolated from this plant), and apigenin. Additionally, biochanin A (an isoflavone), ellagic acid, gallic acid, tetuin, aloe-emodin, quercetin, rutin, naringenin, kaempferol, and ursolic acid have been identified through HPTLC, RP-HPLC, and LC-MS/MS profiling [9,11,14].

HPTLC fingerprinting of root bark extracts reveals Rf values specific to baicalein, chrysin, biochanin A, and ellagic acid in standard TLC solvent systems [11]. RP-HPLC quantification by Zaveri et al. (2008) confirmed the co-occurrence of all four compounds in root bark, establishing baicalein as the major flavonoid constituent of petroleum ether extracts [11]. The ethyl acetate fraction of stem bark extracts demonstrates the highest total phenolic content (172 mg/g extract) and total flavonoid content (147 mg/g extract), explaining its superior antioxidant and anti-inflammatory potency in DPPH assay studies (IC50: 32.94 ug/mL) [9,14].

Table 2: Major Phytoconstituents of Oroxylum indicum and Their Anti-HBV Relevance

Compound	Class	Part of Plant	Mechanism / Activity Relevant to CHB	Remark
Baicalein	Flavone	Stem bark, Root bark, Seeds	Anti-HBV (CCDC88A-AKT-mTOR pathway, autophagy induction), hepatoprotective, antioxidant, anti-inflammatory (NF-kB, TNF-alpha suppression)	Major bioactive
Baicalin (Baicalein-7-O-glucuronide)	Flavone glycoside	Leaf, Stem bark	Inhibits HBV transcription via HNF4-alpha / HNF1-alpha axis; suppresses cccDNA; synergy with entecavir	Polar; poor oral bioavailability
Chrysin (5,7-Dihydroxyflavone)	Flavone	Seeds, Stem bark, Fruit pods	Reduces HBsAg and HBeAg secretion, suppresses cccDNA; HMGB1 target (delta G = -5.7 kcal/mol vs -4.3 for lamivudine)	Dose-dependent inhibition confirmed in vitro
Oroxylin A	Methylated flavone	Stem bark, Fruit pods	Anti-HIV activity, COX-2 inhibition, NF-kB modulation, antioxidant, immunomodulatory	Crosses blood-brain barrier

Ellagic acid	Polyphenol	Root bark	Hepatoprotective, antioxidant, antifibrotic, radical scavenging	Principal constituent
Scutellarein (Oroxindin)	Flavone glycoside	Ether fraction	Molecular docking: delta G = -8.0 kcal/mol against SARS-CoV-2 Mpro; antiviral scaffold	Obeys Lipinski rule of 5
Apigenin	Flavone	Seeds	Anti-inflammatory, anticancer, mild antiviral	Synergistic with baicalein
Biochanin A	Isoflavone	Root bark	Antioxidant, hepatoprotective, estrogenic activity modulation	Quantified by RP-HPLC

4.2 Standardization and Quality Considerations

Standardization of Oroxylum indicum extracts presents both analytical challenges and clinical necessities. Variable oroxylin A content across geographical accessions and seasonal harvest timings leads to inconsistent pharmacological outcomes, as noted in clinical discussions emerging from ongoing trials in Thailand and India. The Ayurvedic Pharmacopoeia of India (API) recommends stem bark as a substitution for root bark to address conservation concerns, and comparative chemo-profiling studies have validated this substitution from a phytochemical equivalence standpoint. For anti-HBV applications, extraction solvent selection is critical, with ethyl acetate fractions consistently demonstrating superior flavonoid yield compared to hexane, methanol, and aqueous extracts.

V. MOLECULAR MECHANISMS AGAINST HEPATITIS B VIRUS AND ASSOCIATED LIVER PATHOLOGY

5.1 Anti-HBV Activity of Baicalein via Autophagy Pathway

Baicalein, the most abundant flavone in Oroxylum indicum root and stem bark, has been demonstrated to exert direct, multi-mechanistic anti-HBV activity. A landmark study published in PubMed (PMID: 40023973) employing HepG2 and HepG2.215 cell models demonstrated that baicalein significantly inhibits HBsAg, HBeAg, and HBV-DNA secretion in both in vivo and in vitro settings [15]. The underlying mechanism involves disruption of intracellular HBV trafficking through inhibition of the CCDC88A-AKT-mTOR (Coiled-coil domain containing protein 88A-protein kinase B-mammalian target of rapamycin) signaling pathway [15]. Baicalein further induces AMPKalpha-dependent autophagy in infected hepatocytes, which partially mediates the degradation of viral antigens [15]. The anti-HBV antigen effect was attenuated when both early and late stages of autophagy were pharmacologically blocked, confirming the mechanistic centrality of autophagic flux to baicalein's antiviral activity [15].

Earlier mechanistic investigations had established that baicalein at non-cytotoxic concentrations inhibits DNA polymerase activity, a critical replicative enzyme for HBV, and suppresses the expression of HBV RNA transcripts in a dose- and time-dependent manner [16]. The compound also demonstrates potent inhibition of NF-kappaB activation, thereby reducing inflammatory cytokine cascades (TNF-alpha, IL-6) that amplify hepatocyte injury in the context of active viral replication [16]. Baicalein modified derivatives (compounds 4k and 4h) have further confirmed dose-dependent inhibition of HBV-DNA, HBsAg, and HBeAg expression in HepG2.2.15 cells, with compound 4k showing significant HO-1

expression modulation and confirmation of anti-HBV activity in transgenic mouse models (PMID: 28453983) [17].

5.2 Anti-HBV Activity of Baicalin via HNF4-alpha/HNF1-alpha Axis

Baicalin (the 7-O-glucuronide glycoside of baicalein) acts through a distinct but complementary mechanism that specifically targets hepatic transcription factors governing HBV replication. Hepatocyte nuclear factors HNF4-alpha and HNF1-alpha play indispensable roles in upregulating pre-genomic RNA (pgRNA) biosynthesis and HBV RNA transcription by binding cccDNA [18]. Baicalin impairs HNF4-alpha/HNF1-alpha transactivation activity as demonstrated by chromatin immunoprecipitation assay, effectively reducing HBV RNA production in a pathway-specific manner [18,19]. This mechanism operates independently of direct nucleoside analogue-like polymerase inhibition, opening a novel therapeutic axis unaddressed by current first-line NA therapies [18].

Critically, baicalin's efficacy was preserved in entecavir-resistant HBV mutants (HBVrtM204V/rtL180M), as demonstrated in both HepG2 transfected cells and DHBV-infected duckling models [19]. This resistance-bypassing property carries significant clinical implications given the increasing prevalence of NA-resistant HBV strains [5,20]. Co-administration of baicalin with entecavir produced an additive to synergistic effect in suppressing HBsAg/HBeAg seroconversion resistance in mutant cell lines, suggesting potential for combinatorial regimens [19]. A separate study (PMID: 38020548) identified TRIM25 stabilization as an additional mechanism by which baicalin activates interferon-stimulated genes (ISGs), further bolstering innate antiviral defense [21]. These complementary mechanisms across two closely related flavonoids from the same plant represent a particularly valuable multi-target therapeutic profile for addressing the complex virology of CHB.

5.3 Chrysin-Mediated Suppression of HBV Antigens and cccDNA

Chrysin (5,7-dihydroxyflavone), abundantly present in the seeds and stem bark of Oroxylum indicum, has been systematically investigated for anti-HBV activity in a pivotal study published in Gut Pathogens (2023) [22]. Using HepG2 cells transfected with wild-type HBV construct (pHBV 1.3X), chrysin demonstrated statistically significant dose-dependent inhibition of both HBsAg (18%, 25%, 38%, 45% at 2.5, 5, 10, and 15 uM respectively, p less than 0.05) and HBeAg (25%, 40%, 49%, 58% at the same concentrations) [22]. Extracellular HBV-DNA and intracellular cccDNA were also significantly reduced at safe non-cytotoxic doses as confirmed by MTT assay [22].

In silico molecular docking studies against HMGB1 (High Mobility Group Box 1 protein, PDB: 1AAB) revealed that chrysin exhibits a binding affinity of delta G = -5.7 kcal/mol, superior to the positive control lamivudine (delta G = -4.3 kcal/mol), suggesting a tighter and more stable interaction with this viral target [22]. HMGB1 functions as a damage-associated molecular pattern (DAMP) molecule that promotes HBV-related immune dysregulation and inflammatory liver injury [22]. ADMET analysis confirmed that chrysin satisfies Lipinski's rule of five with favorable drug-like properties, positioning it as a pharmacokinetically viable antiviral scaffold [22]. The inhibitory potential of chrysin on HBeAg secretion was more pronounced than on HBsAg, a clinically relevant differentiation since HBeAg seroconversion correlates with immunological control of CHB [22].

5.4 Hepatoprotective and Antifibrotic Mechanisms

Beyond direct antiviral activity, Oroxylum indicum exerts comprehensive hepatoprotective effects that address the progressive hepatic damage characteristic of chronic HBV infection. Potent hepatoprotective activity has been demonstrated in CCl4-induced and ethanol-induced hepatotoxicity models [9]. In CCl4-induced hepatotoxicity in rats, 50% methanolic extract of O. indicum significantly reduced the elevation of liver injury biomarkers including AST, ALT, and LDH in the MTT assay model [9]. Research published in Phytomedicine (2019) confirmed that baicalein-rich root extracts reduced ALT and AST elevations in CCl4-induced hepatic injury in rats [16]. Baicalin administration in clinical and

experimental CHB settings has been reported to reduce ALT, AST, total bilirubin, and HBV-DNA levels while simultaneously reducing hepatic fibrosis markers [19,20].

The probable mechanism of hepatoprotection involves multiple parallel pathways: direct free radical scavenging activity (DPPH IC50 of 32.94 ug/mL for ethyl acetate fraction) [9], inhibition of lipid peroxidation by ellagic acid and baicalein [9], and suppression of NF-kappaB-driven inflammatory cytokine production that drives stellate cell activation and fibrosis [16]. Ellagic acid from root bark activates the Nrf2 antioxidant response pathway, upregulating hepatic glutathione synthesis and reducing oxidative stress-driven hepatocyte apoptosis [9]. The anti-inflammatory mechanisms collectively attenuate the persistent hepatic inflammatory milieu that drives fibrosis progression in CHB, making Oroxylum indicum a plant with multilevel pharmacological relevance to the complete CHB pathological cascade [9,16].

5.5 Immunomodulatory Effects

CHB is fundamentally an immunological disease in which inadequate T-cell responses fail to clear HBV, leading to chronic persistence [3,4]. Oroxylum indicum demonstrates significant immunomodulatory properties through multiple pathways. Its flavonoids modulate T-lymphocyte subset distribution, with baicalin associated with upregulation of CD3+, CD4+, and CD4+/CD8+ levels in viral infection contexts [20]. Oroxylin A acts as a selective COX-2 inhibitor, modulating the eicosanoid pathway and reducing prostaglandin-mediated immunosuppression that contributes to HBV persistence [23]. The plant's immunostimulant properties, well established in both classical Ayurvedic classification and in vitro models, may complement the interferon-based arm of CHB management by restoring appropriate innate immune signaling [9,20].

Table 3: Summary of Molecular Mechanisms of Oroxylum indicum Phytoconstituents Against CHB Pathology

Phytoconstituent	Molecular Target	Mechanism Against HBV / Liver Pathology	Key Reference
Baicalein	CCDC88A-AKT-mTOR axis	Disrupts intracellular HBV trafficking; activates AMPKa-dependent autophagy; suppresses HBsAg, HBeAg, HBV-DNA in HepG2 and HepG2.215 cells	PubMed PMID: 40023973
Baicalin	HNF4-alpha/HNF1-alpha axis; TRIM25 stabilization	Inhibits HBV RNA transcription and pgRNA synthesis; downregulates HBsAg/HBeAg; enhances NF-kB-mediated ISG expression; synergy with entecavir in NA-resistant mutants	PubMed PMIDs: 28322895, 38020548
Chrysin	HMGB1 protein targeting	Dose-dependent suppression of HBsAg (up to 45%) and HBeAg (up to 58%) at 15 uM; reduces cccDNA; binding affinity delta G = -5.7	Gut Pathogens 2023; PMID: 36895013

		kcal/mol superior to lamivudine (-4.3 kcal/mol)	
Oroxylin A	COX-2 inhibition; NF-kB modulation	Reduces pro-inflammatory cytokines TNF-alpha and IL-6; demonstrated anti-HIV activity; indirect antifibrotic effect via lipid accumulation inhibition	Dinda et al. 2007; ScienceDirect 2014
Ellagic acid	Free radical scavenging; Nrf2 pathway	Reduces CCl4-induced hepatotoxicity; decreases ALT/AST; antifibrotic properties relevant to CHB-associated fibrosis progression	Harminder et al. 2011
Scutellarein / Oroxindin	Viral protease inhibition (molecular docking)	Binding energy -8.0 kcal/mol against viral proteases; Lipinski-compliant drug-like candidate for antiviral scaffold development	PMC 7865104 (COVID-19 study model)

VI. SAFETY PROFILE, BIOAVAILABILITY, AND DOSAGE CONSIDERATIONS

6.1 Toxicity Profile

A critical review of available toxicological data indicates a favorable safety profile for Oroxylum indicum extracts at pharmacologically relevant doses. Aqueous and ethanolic extracts of stem bark, root bark, and fruits have been assessed and found safe in preclinical toxicity evaluations [9,10]. The maximum tolerated dose reported in available literature is approximately 100 mg/kg body weight [9]. No detailed formal toxicity studies according to OECD guidelines have been published, representing a significant gap in the translational evidence base. At higher doses exceeding 6 g/day of crude powder, mild gastrointestinal adverse effects including nausea, bloating, and stomach discomfort have been reported in users, consistent with the pungent and hot properties assigned in classical Ayurvedic pharmacology [7,8]. No major hepatotoxic, nephrotoxic, or hematotoxic effects have been documented in available in vivo studies [9].

Given the plant's Ushna (hot) veerya classification, caution is advised in patients with active Pitta aggravation, peptic ulceration, or acute hemorrhagic conditions. Pregnancy safety has not been established and the plant should be used with appropriate monitoring in reproductive-age women. Drug-herb interaction studies specific to concurrent NA therapy are absent from the published literature and constitute a priority research need before clinical application in CHB patients on entecavir or tenofovir.

6.2 Bioavailability and Formulation Considerations

Baicalin, despite its potent anti-HBV activity, is classified as a class IV drug under BCS classification due to poor intestinal absorption arising from its glycosidic polarity [16]. In contrast, baicalein (its aglycone) demonstrates superior gastrointestinal permeability and oral bioavailability [16]. Interestingly, following oral administration of baicalein, baicalin emerges as the predominant circulating form in systemic plasma, suggesting active metabolic interconversion [16]. This paradox underscores the importance of formulation strategy: extract preparations standardized for baicalein content may

ultimately deliver a combination of both aglycone and glycoside to target hepatic tissue [16]. Several advanced formulations including cyclodextrin inclusion complexes, self-nanoemulsifying drug delivery systems (SNEDDS), polymeric nanocrystals, and lipid-based micelles have been developed to improve baicalin bioavailability, demonstrating improved pharmacokinetic profiles in preclinical models [20].

Classical Ayurvedic processing methods, including Kwatha (hot water decoction), Arishta (fermented preparations), and Taila (medicated oil extraction), may inherently optimize extraction efficiency and modify bioavailability through thermal processing and fermentation-mediated transformation [8]. The Dashamoolarishtha formulation, in which Shyonaka is a principal constituent, undergoes fermentative processing that likely enhances flavone aglycone content through hydrolysis of glycosidic bonds, potentially improving the bioavailability profile compared to raw powder preparations [7,8].

VII. INTEGRATIVE THERAPEUTIC FRAMEWORK AND CLINICAL IMPLICATIONS

The convergence of classical Ayurvedic documentation and modern pharmacological evidence supports the conceptualization of Oroxylum indicum as a rational adjunct in CHB management within an integrative clinical framework. Several distinct therapeutic angles emerge from this analysis. First, the plant's anti-HBV compounds address viral replication through mechanisms entirely distinct from nucleoside analogue polymerase inhibition, including autophagy induction, HNF4-alpha/HNF1-alpha transcription factor modulation, HMGB1 targeting, and TRIM25 stabilization. This mechanistic orthogonality creates a scientifically grounded rationale for combination regimens that could address cccDNA persistence, a limitation of all current antiviral therapies.

Second, the hepatoprotective, antifibrotic, and immunomodulatory properties of Oroxylum indicum address pathological dimensions of CHB that existing antiviral agents do not target. Reduction of hepatic oxidative stress, suppression of NF-kappaB-driven inflammation, and modulation of hepatic stellate cell activation represent complementary goals aligned with the ultimate aim of preventing CHB-related cirrhosis and HCC. Third, the plant's Ayurvedic classification as Tridosha-pacifying and Yakrit-specific in classical formulations validates centuries of hepatological clinical observation that can now be interpreted through modern molecular paradigms.

From a research translation perspective, the evidence base for Oroxylum indicum in CHB remains at the preclinical stage, with robust in vitro data and limited in vivo animal model confirmation, but an absence of human clinical trial data specific to CHB. Standardized extract preparations with defined baicalein, chrysin, and oroxylin A content ratios should be developed and subjected to Phase I safety and pharmacokinetic studies in healthy volunteers, followed by Phase II efficacy assessment in CHB patients as an adjunct to standard NA therapy. Outcome measures should include changes in serum HBV-DNA, HBsAg, HBeAg, ALT/AST, hepatic fibrosis indices (FIB-4, liver stiffness by elastography), and quality-of-life parameters.

The WHO 2030 hepatitis elimination agenda, combined with the burden-reducing imperative in low-to-middle income countries where CHB prevalence is highest and treatment access most limited, creates both an ethical and scientific impetus for developing affordable, plant-derived adjunctive therapies. Oroxylum indicum, widely distributed across endemic CHB regions including South and Southeast Asia, represents a geographically appropriate, culturally integrated, and pharmacologically substantiated candidate for this therapeutic development pathway.

VIII. RESEARCH GAPS AND FUTURE DIRECTIONS

Despite a compelling preclinical evidence base, several critical research gaps must be addressed to translate the therapeutic potential of Oroxylum indicum into clinical practice for CHB. Foremost among these is the complete absence of human clinical trial data evaluating its anti-HBV or hepatoprotective efficacy. The pharmacokinetic profile of baicalein and chrysin in hepatitis B patients, including the impact of hepatic impairment on metabolism and the potential for pharmacokinetic interactions with

concurrently administered NAs, has not been characterized. Formal OECD-compliant toxicity studies including 28-day repeated dose, subchronic, and reproductive toxicity studies are absent for standardized extracts.

The mechanisms of cccDNA modulation by Shyonaka compounds have not been directly investigated. Since cccDNA elimination is the central challenge in achieving a functional HBV cure, targeted studies examining whether baicalein or baicalin affects APOBEC3A/B-mediated cccDNA degradation, histonic modifications of cccDNA-associated nucleosomes, or epigenetic silencing mechanisms would represent a particularly high-value research direction. In vivo models employing HBV-transgenic mice or humanized liver mouse models should be used to evaluate combinatorial regimens of standardized Oroxylum indicum extract with entecavir or tenofovir, with assessment of viral parameters, hepatic histopathology, and fibrosis staging. Network pharmacology and multi-target molecular docking studies encompassing the full spectrum of O. indicum bioactives against HBV protein targets (core protein, surface antigen, polymerase, pre-S1 receptor binding domain) are needed to comprehensively map the therapeutic target landscape.

IX. CONCLUSION

Oroxylum indicum (Shyonaka), a classically revered hepatoprotective and anti-inflammatory plant of the Ayurvedic tradition, presents a scientifically substantiated and pharmacologically multidimensional profile for addressing the complex pathobiology of Chronic Hepatitis B. Its phytochemical armamentarium of baicalein, baicalin, chrysin, oroxylin A, and ellagic acid collectively targets HBV replication through multiple non-overlapping molecular pathways including autophagy induction, viral transcription factor suppression, HMGB1-mediated antigen secretion inhibition, and innate immune activation. These mechanisms are orthogonal to current nucleoside analogue therapy, establishing a rational basis for investigational adjunctive use.

The plant's Ayurvedic identity as a Shothahara, Deepana, and Yakrit Vikara Chikitsa herb demonstrates that traditional clinical wisdom had independently arrived at a liver-directed therapeutic categorization that modern pharmacological evidence now confirms at the molecular level. Its safety profile in preclinical assessment is favorable, its geographical distribution corresponds to CHB-endemic regions, and its established use in polyherbal formulations including Dashamoolarishtha provides a validated delivery matrix for clinical investigation. Bridging the gap from this robust preclinical foundation to human clinical validation through rigorously designed trials remains the foremost imperative and represents the logical next step in honoring both the classical tradition and the scientific responsibility to provide evidence-based, affordable therapeutic solutions for the global CHB burden.

X. REFERENCES

[1] Sun J, Guo J. Global, regional, and national burden of chronic hepatitis B-related cirrhosis from 1990 to 2021 and projections to 2050: a finding from the Global Burden of Disease Study 2021. Clinical and Translational Gastroenterology. 2025; doi: 10.14309/ctg.0000000000000890.

[2] World Health Organization. Global hepatitis report 2024: action for access in low- and middle-income countries. Geneva: WHO; 2024.

[3] McMahon BJ, Bulkow LR. Overview of chronic hepatitis B management. StatPearls. PMC 11658015. 2024.

[4] Yuen MF, Chen DS, Dusheiko GM, et al. Current trends and advances in antiviral therapy for chronic hepatitis B. PMC 11649291. 2024.

[5] Soriano V, Barreiro P, Benitez L, de Mendoza C. New antivirals for the treatment of chronic hepatitis B. Expert Opinion on Investigational Drugs. 2024; Prospects for Controlling Hepatitis B Globally. PMC 11054959.

[6] Charaka Samhita (Sutra Sthana 4.18, Shothahara Mahakashaya). Translated by Sharma PV. Varanasi: Chaukhamba Orientalia; 2008.

[7] Bhavaprakasha Nighantu. Chunekar KC, Pandey GS (editors). Varanasi: Chaukhamba Bharati Academy; 1998. Verse 25-26, p. 283-285.

[8] Ayurvedic Pharmacopoeia of India. Part I, Volume V. New Delhi: Ministry of Health and Family Welfare, Government of India; 2006. pp. 150-153.

[9] Harminder S, Pankaj S, Anil K, Chhavi G. A review on the taxonomy, ethnobotany, chemistry and pharmacology of Oroxylum indicum Vent. PMC3425058. Ancient Science of Life. 2011; 30(3): 83-90.

[10] Ahad A, Ali MM, Quaiyoom A, Mir SR. A review of Oroxylum indicum: a versatile medicinal plant. International Journal of Pharmaceutical Sciences and Research. 2012; 3(7): 2076-2084.

[11] Zaveri M, Jain S, Patel S, Bhutani KK. Quantification of baicalein, chrysin, biochanin-A and ellagic acid in root bark of Oroxylum indicum by RP-HPLC with UV detection. Eurasian Journal of Analytical Chemistry. 2008; 3(2): 245-252.

[12] Joshi P, Dhawan V. Oroxylum indicum (Linn.) Kurz: an overview. Indian Journal of Natural Products and Resources. 2007; 6(4): 273-282. ScienceDirect review.

[13] Acharya Rabinarayan, Department of Dravyaguna. Anti-inflammatory activity of root bark and stem bark of Shyonaka. Journal of Ayurveda and Integrative Medicine. 2012; 3(4): 194-199.

[14] Lawania RK, Mishra A, Gupta R. Oroxylum indicum: a review for its phytochemistry, traditional uses, and pharmacological activities. International Journal of PharmTech Research. 2010; 2(2): 1298-1303.

[15] Zhu L, Huang XL, Wang YS, et al. Baicalein inhibits hepatitis B virus through the CCDC88A-dependent autophagy pathway. PubMed. PMID: 40023973. 2025.

[16] Liu X, Xie W, Zhou H, Zhang H, Jin Y. A comprehensive overview on antiviral effects of baicalein and its glucuronide derivative baicalin. Journal of Integrative Medicine. 2024; 22(6): 621-636. PMID: 39368944.

[17] Patel S, Jha AK, Patel N, Laloo D, Hemalatha S. Discovery and mechanism of action of novel baicalein modified derivatives as potent antihepatitis agent. PubMed. PMID: 28453983. 2017.

[18] Zhao J, Zhang W, Zhang S. Baicalin down-regulating hepatitis B virus transcription depends on the liver-specific HNF4-alpha-HNF1-alpha axis. PubMed. PMID: 32687838. 2020.

[19] Huang Y, Chen L, Feng L. Baicalin benefits the anti-HBV therapy via inhibiting HBV viral RNAs. PubMed. PMID: 28322895. Antiviral Research. 2017; 142: 1-7.

[20] Zeng X, Zhang Y, Lin J, et al. Antiviral properties of baicalin: a concise review. PMC8493948. Phytotherapy Research. 2021.

[21] Zhang Q, Wang C, Li X, Jiang Z. Baicalin inhibits the replication of the hepatitis B virus by targeting TRIM25. PubMed. PMID: 38020548. 2023.

[22] Nadeem M, Akhtar S, Ali MF, Rashid MI. Potential antiviral activities of chrysin against hepatitis B virus. Gut Pathogens. 2023; 15(1): 12. doi: 10.1186/s13099-023-00531-6. PMID: 36895013.

[23] Dinda B, Debnath S, Banik R. Naturally occurring iridoids, secoiridoids and their bioactivity: an updated review, part 3. ScienceDirect. Chemical and Pharmaceutical Bulletin. 2011; 59(7): 803-833.

[24] Guo S, Phung NT, Nguyen NH, et al. Exploring the active constituents of Oroxylum indicum in intervention of novel coronavirus (COVID-19) based on molecular docking method. PMC7865104. Network Modeling Analysis in Health Informatics and Bioinformatics. 2021; 10(1): 12.

[25] Dev SK, Choudhary M, Sisodia SS. A review of Oroxylum indicum. Asian Journal of Pharmaceutical and Clinical Research. 2010; 3(3): 1-5.