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Physiopathology of Liver cirrhosis: A Growing Public Health Concern in Sub-Saharan Africa

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A B S T R A C T

This study aims to comprehensively review the literature pertaining to the management of liver diseases, especially cirrhosis in sub-Saharan Africa. Specifically, it involves a meticulous synthesis and analysis of data concerning the physiopathology of liver cirrhosis, an assessment of the clinical manifestations associated with the condition, and an exploration of the presence and efficacy of therapeutic approaches utilizing conventional medicinal plants. The present study investigation included studies published between 2017 and 2022, focusing on the physiopathology of liver cirrhosis, primarily attributed to HBV and HCV etiologies. Additionally, we examine clinical manifestations and investigate the therapeutic potential of plant-derived remedies for liver cirrhosis. Inclusion criteria encompassed clinical studies, clinical trial protocols, and evaluation studies, while studies concurrently involving cirrhosis, HIV, and Covid-19, as well as reviews, correspondences, books, and case reports were excluded. A total of twenty-one articles were selected for this review. Physiopathology of liver cirrhosis: the collective evidence underscores the role of chronic hepatitis B virus (HBV) infection as a risk factor for liver cirrhosis. Age distribution within the cirrhotic population ranged from 18 to 71 years, with a predominance of male patients (ranging from 58.89% to 91%). Disease progression revealed distinct phases encompassing fibrosis, compensated cirrhosis, and decompensated cirrhosis culminating in the definitive establishment of liver cirrhosis. Ultimately, liver cirrhosis was associated to mortality due to hepatocellular carcinoma (HCC). Clinical manifestations of liver cirrhosis: analytical parameters encompassed serum, plasma, liver, total blood, and spleen evaluations. Serological tests involved liver biochemical markers (ALT, AST, TBIL, ALB, AFP, Bilirubin, PT, GGT), Antigens and/or Antibodies (HBsAg, HBeAg, Anti-HBs, anti-HBe), blood cell and lymphoid cell assessments (blood count, PLT), T lymphocytes, NK-Cells, Neutrophils, Leukocytes, Erythrocytes), HBV DNA, cytokines (IFN, IL, TNF, TGF), and creatinine levels. The patient demographics encompassed those with Hepatitis B-induced cirrhosis, patients with chronic HBV infection, those with concurrent HBV infection and liver fibrosis/cirrhosis, co-positive HBsAg/Anti-HBs individuals, single-positive HBsAg patients, individuals with prolonged positive HBsAg status, patients with compensated HBV-associated cirrhosis, individuals with hepatotoxicity, and patients with chronic liver disease. Existence and utility of a therapeutic management based on traditional drugs: several studies highlight the presence of treatment modalities utilizing traditional recipes. Notable among these are "erzhu jiedu," Echinacea-based formulations, and Curcumin-based regimens. This study compiled a comprehensive dataset comprising liver cirrhosis, encompassing its physiopathology, clinical manifestations, and the feasibility of therapeutic interventions grounded in traditional medicine. These findings provide importants insights for future research endeavors, potentially endorsing the adoption of traditional medicinal recipes while concurrently assessing the biological parameters elucidated in this study.

Introduction

Hepatic diseases comprises inflammations of the liver, which can originate from viral, drug-induced, toxic, or autoimmune sources. Notably, viral hepatitis, a significant subset of hepatic diseases, presents a global public health challenge, impacting millions of individuals annually (Elouard, 2002; WHO, 2013). Among these, viral hepatitis B and C stand out as the leading to the liver damage with the potential progression to cirrhosis or liver cancer in Sub-Saharan Africa and South-East Asia (WHO, 2013).

According to a 2014 report by the World Health Organization (WHO), viral hepatitis accounts for 1.4 million deaths each year, comparable to 1.6 million deaths from HIV/AIDS, 1.3 million from tuberculosis, and 600,000 from malaria. This report also highlights that approximately 2 billion people have been infected with the hepatitis B virus (Organisation mondiale de la Santé, 2014). HBV and HCV strains of hepatitis notably contribute to substantial mortality and morbidity.

In West Africa, hepatitis B is endemic, with a prevalence of 8%, the highest worldwide (Santé, 2012). Additionally, approximately 2% of the region's population carries chronic hepatitis C (Santé, 2012). Burkina Faso serves as an example, exhibiting a high prevalence of HBV (12-14.5%) and lower prevalence of HCV (1-2.8%) (Tao *et al.*, 2014). Chronic hepatitis significantly escalates the risk of cirrhosis and primary liver cancer, which claim 900 and 1300 lives annually in the country, respectively (WHO, 2002).

While therapeutic interventions exist for chronic hepatitis B and C, limited access to diagnosis and treatment in the african region poses a significant obstacle. Moreover, the high cost of drugs exacerbates the issue. For instance, in Burkina Faso, treating hepatitis C costs between US $10,000 to $20,000 (l'Afrique, 2014) excluding ancillary expenses like ultrasound and hospitalization. Additionally, these drugs often induce toxic side effects such as diarrhea, nausea, vomiting, dizziness, weakness, and rashes, which hinder patient adherence.

In Burkina Faso (2013), the cost of treating hepatitis B with interferon alpha-2α is US $302.87 per person per week, totaling US $14,537.92 per year. Tenofovir treatment amounts to US $841.32 per person per month, or US $10,095.78 per year (Somda *et al.*, 2013). These expenses are beyond the reach of individuals in developing countries with a daily income of US $0.76 or less (INSD, 2020). This limitation in modern therapeutic options fuels a significant interest in exploring the bioactive compounds found in traditionally used plants for liver diseases (Mukazayire *et al.*, 2011). Moreover, these challenges often lead patients to seek assistance from traditional health practitioners.

Currently, over 80% of the west african population turns to traditional medicine when ill (Zhang and WHO, 2002; 2005). Additionally, there's an increasing interest in studying medicinal plants employed in treating liver diseases across various regions worldwide in recent decades (Muthu *et al.*, 2006). Burkina Faso, for example, has identified 2000 medicinal plant species by 2004, with some specifically used for hepatitis treatment (Meda, 2010). This highlights the necessity of providing scientific rationale for the utilization of medicinal plants, particularly in the context of hepatobiliary disorders.

The physiopathology of hepatitis contributes to the generation of free radicals that induce oxidative stress. Antioxidants play a pivotal role in not only replacing damaged liver tissues but also protecting the liver from free radical-induced effects (Dougnon *et al.*, 2009).

Considering the cost of treatment, the existence of traditional options, and the frequently delayed or insufficient diagnosis of liver cirrhosis, this study aims to comprehensively review the available literature on liver cirrhosis management over a five-year span (2017-2022). More specifically, the study entails (1) collecting and analyzing data concerning the physiopathology of liver cirrhosis, (2) assessing

the range of clinical manifestations associated with liver cirrhosis, and (3) highlighting the existence and effectiveness of therapeutic strategies grounded in traditional medicine.

Materials and Methods

A systematic review was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Meda, 2010).

Study Eligibility Criteria

The study considered research published between 2017 and 2022, specifically addressing the physiopathology of liver cirrhosis attributed mainly to HBV and HCV, as well as clinical manifestations of liver cirrhosis and the effectiveness of plant-based management.

Inclusion criteria comprised articles reporting Clinical Studies, Clinical Trial Protocols, and Evaluation Studies. However, studies encompassing cirrhosis, HIV, Covid-19, reviews, correspondence, books, and case reports were excluded.

Information Sources and Search Strategy

The review included searches across PubMed, Google Scholar, and Science Direct databases. The search was limited to studies published from January 1, 2017, to May 6, 2022. Keywords used for the search included: ((Pathogenesis AND liver cirrhosis AND HBV) OR (cirrhosis HBV liver OR clinical OR therapeutic -HCV -Covid -HDV -review) OR (Pathogenesis (Ti) and liver cirrhosis (Ti))).

Study Selection and Data Extraction

From each selected study, the following data were extracted: author and publication date, country, study type, clinical trial status, clinical manifestations, in vivo and in vitro tests, phytomedicine and therapeutic interventions, HBV, liver cirrhosis, and aspects related to biochemistry, pharmacology, toxicology, immunology, and microbiology.

Results and Discussion

Article Selection Procedure

The search yielded a total of 20,038 articles, distributed as 1,383 from PubMed, 16,800 from Google Scholar, and 1,855 from Science Direct, based on the provided keywords in the Materials and Methods section. Following application of exclusion and inclusion criteria, and removal of duplicates, a set of 132 articles were retained. Subsequently, through further refinement according to the specified methodology, 35 articles were shortlisted. Among these, 7 were from PubMed, 14 from Google Scholar, and 14 from Science Direct.

After eliminating duplicates and excluding articles not pertinent to hematological, biochemical, and serological investigations, the final selection for the review comprised 21 articles (Fig. 1).

Data Extraction

The data extraction process encompassed articles focusing on the physiopathology of liver cirrhosis, clinical manifestations of the condition, and insights regarding the existence and efficacy of therapeutic management utilizing traditional drugs.

Physiopathology of liver cirrhosis

Data collection involved Causes of the disease, Average age of patients, Gender distribution (Male/Female), Time taken for induction, Stages leading to cirrhosis, and the progression of liver cirrhosis.

Results

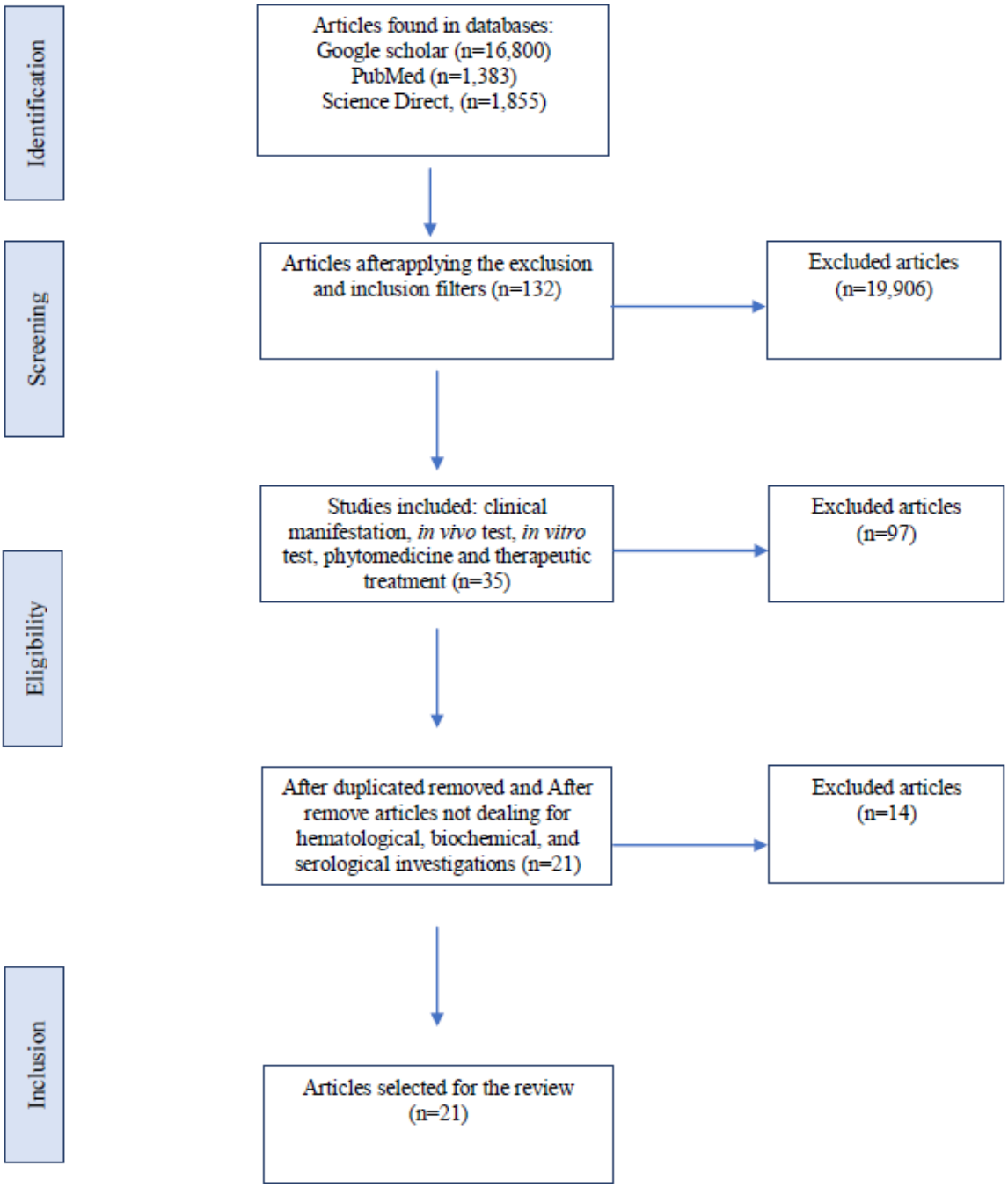
All 21 articles concurred that liver cirrhosis primarily arises from chronic HBV infection. The age of cirrhosis patients ranged from 18 to 71 years. Predominantly, men were affected (Min: 58.89%, Max: 91%) in 17 out of 21 studies. Regarding the duration for HBV-induced cirrhosis, 5 studies indicated a minimum induction period of 6 months, while 16 studies yielded non-definitive results. Pre-

clinical stages indicated that fibrosis, compensated and decompensated cirrhosis typically precede the final establishment of liver cirrhosis. Furthermore, 8 studies linked liver cirrhosis to Hepatocellular Carcinoma (HCC), 2 studies associated it with mortality, and 11 studies yielded non-definitive outcomes.

Clinical manifestations of liver cirrhosis

Data collection encompassed the Type of samples utilized, Serological tests / Clinical signs (serving as standard reference), and the Type of population.

Fig.1 Article selection procedure



Results

Among the 21 studies, Serum samples were utilized in 12 studies for analysis, while Plasma was used in 3 studies. Liver samples were employed in 10 studies, Total blood in 9 studies, and Spleen in 2 studies, with 2 studies yielding inconclusive results. Concerning serological tests, of the 21 studies, 15 addressed liver biochemical markers (ALT, AST, TBIL, ALB, AFP, Bilirubin, PT, GGT), 14 discussed Antigens and/or Antibodies (HBsAg, HBeAg, Anti-HBs, anti-HBe), 10 covered blood and lymphoid cell assessments (blood count, PLT, T lymphocyte, NK-Cell, Neutrophils, leucocytes, erythrocytes), 10 studied HBV DNA, 4 explored cytokines (IFN, IL, TNF, TGF), 1 examined BMI, 1 assessed LSM and abdominal ultrasonography, 1 studied Fibroscan, and 1 investigated creatinine. Regarding the type of population, 12 studies focused on Hepatitis B cirrhosis patients, 3 on Patients with chronic HBV infection, 1 on patients with chronic HBV infection linked to liver fibrosis/cirrhosis, 1 on HBsAg/Anti-HBs co-positive and HBsAg single-positive patients, 1 on patients with liver cirrhosis and positive HBsAg for over 6 months, 1 on patients with compensated HBV-induced cirrhosis, 1 on patients with hepatotoxicity, and 1 on patients with chronic liver disease.

Existence and utility of a therapeutic management based on traditional drugs

Data collection centered on identifying the nature of drugs used for therapeutic management.

Results

Among the studies, 3 indicated the presence of treatment recipes. These recipes were identified as erzhu jiedu, Echinacea, and Curcumin.

For a concise overview of the selected articles, refer to Table 1 (Supplemental Digital Content) in the provided supplementary materials.

Physiopathology of liver cirrhosis

Causes of disease, time of induction

It is essential to recognize that not all HBV infections lead to cirrhosis. Cirrhosis emerges as the end stage of various chronic liver diseases that progress gradually over many years or decades (Smith *et al.,* 2019). The transition of viral hepatitis to a chronic state occurs when hepatotropic viruses like Hepatitis C and B persist along with liver inflammation and symptoms beyond six months (Guyot *et al.,* 2006). Chronicity in HBV is marked by the persistence of HBsAg for more than 6 months after acute infection onset (Paccoud *et al.,* 2019). The natural history of chronic hepatitis B encompasses phases of "chronic infection" and "chronic hepatitis" (Paccoud *et al.,* 2019). The progression to cirrhosis from HBV infection typically spans 10 to 20 years (Smith *et al.,* 2019). Therefore, our findings align with existing knowledge, demonstrating the potential for chronic HBV infection to lead to cirrhosis, with induction times ranging from several months to years (Wiegand and Berg, 2013).

Stages below the disease

Our results highlight that fibrosis, compensated cirrhosis, and decompensated cirrhosis are intermediate phases preceding the establishment of definitive liver cirrhosis. These stages correlate with the dynamic progression of liver fibrosis and the distinct phases in the natural history of chronic hepatitis B (Smith *et al.,* 2019). Chronic HBV infection is a dynamic process; whose natural history schematically passes through five sequentially phases. The latest classifications allow the fundamental distinction in the natural history of chronic hepatitis B between phases of “chronic infection” and “chronic hepatitis” phases (Paccoud *et al.,* 2019). These observations underscore that cirrhosis is an advanced form of fibrosis (Saile and Ramadori, 2007).

Average age and gender of patients

Our study indicates that cirrhosis affects a wide age range, with patients as young as 18 and as old as 71. Male gender was consistently more impacted by liver cirrhosis, which is consistent with global trends where HBV cirrhosis predominantly affects males

(Chu and Liaw, 2006). Cirrhotic patients median age was 54 years range 44–67 years and 67% were male (female 33%) (D'Amico *et al.,* 2006). Cirrhotic patients median age was 54 (range: 15–90 years), and male gender was predominant (59.1%) (Idilman *et al.,* 2021). Factors associated with an increased risk of progression to cirrhosis include increased age, medical comorbidities, particularly patients coinfected with HIV and HCV, and male sex (Smith *et al.,* 2019).

Evolution of liver cirrhosis

The evolution of cirrhosis can lead to hepatocellular carcinoma (HCC) and eventual death. This aligns with existing knowledge that cirrhosis patients are at risk of various complications, including HCC, decompensation, and mortality (Smith *et al.,* 2019). The progression to HCC is a significant concern and is often preceded by cirrhosis. Approximately, 1/3 to 1/4 of people chronically infected with HBV are expected to develop progressive liver disease, including cirrhosis and hepatocellular carcinoma (HCC) with 4.4% of mortality for HBV Cirrhosis (Chu and Liaw, 2006).

Once the stage of cirrhosis has been reached, the risk of progression to HCC is estimated at between 2 and 5% per year (Paccoud *et al.,* 2019). Liver cirrhosis is responsible for a significant morbidity and mortality. The poor prognosis of cirrhosis is aggravated by the frequent occurrence of HCC (Saile and Ramadori, 2007). Most cases of HCC arise in a cirrhotic liver (Parola and Pinzani, 2019).

Clinical manifestations of liver cirrhosis

Type of samples

Serum is the primary sample used for analysis, followed by liver, whole blood, plasma, and spleen. These samples serve as crucial indicators for monitoring chronic HBV-induced cirrhosis. Liver biopsy remains the reference standard in diagnosing cirrhosis (Smith *et al.,* 2019).

Liver was used for lipid peroxidation products and antioxidant enzyme activity detection and also used for morphology and histopathological observation (Zhu *et al.,* 2020). Today ultrasensitive assays for serum HBV DNA and hepatitis B surface antigen (HBsAg) levels are available (Chang and Liaw, 2014).

HBV may persist after development of liver cirrhosis as reflected in the presence of serum hepatitis B e antigen (HBeAg) or HBV DNA (Chu and Liaw, 2006). Serum was collected from blood and the serum levels of ALT, AST, ALB and TNF-α, IL-6 and IL-8 were detected (Zhu *et al.,* 2020). Spleen size increase is a variable related to portal hypertension in the compensated cirrhosis (Smith *et al.,* 2019; D'Amico *et al.,* 2006).

Serological tests / Clinical signs (standard reference)

The comprehensive array of parameters used for serological tests and clinical signs provides valuable insights into liver cirrhosis progression. Among the 21 studies, 15 treat about liver biochemical markers (ALT; AST, TBIL; ALB; AFP; Bilirubin, PT, GGT), 14 treat about Antigen and/or Antibody (HBsAg, HBeAg, Anti-HBs, anti-HBe,), 10 treat about blood cell and lymphoid cell (blood count, PLT), T lymphocyte, NK-Cell, Neutrophils, leucocytes, erythrocytes), 10 treat about DNA (HBV), 04 treat about cytokines (IFN, IL, TNF, and TGF), 01 treat about BMI, 01 treat about LSM and abdominal ultrasonography, 01 treat about Fibroscan and 01 treat about creatinine.

All these parameters make it possible to discern the state of the liver in relation to cirrhosis. The variations may be a sign of an improvement or a worsening of the patient's condition. The following results from other studies show the usefulness of monitoring these different parameters. The indication for antiviral treatment depends on three simple parameters: the viral load, the value of transaminases, and the severity of liver damage (Paccoud *et al.,* 2019).

Table.1 Summary table of the twenty-one selected articles

Author, Year, Country	Physiopathology of liver cirrhosis					Clinical manifestations of liver cirrhosis			Existence and utility of a therapeutic management based on traditional drugs
	Causes of the disease	Average age of patient	Gender of patient (Male/ Female)	Time of induction and Stages below the disease	Evolution of liver cirrhosis	Type of samples	Serological tests / Clinical signs (standard reference)	Type of population	Nature of drugs
ASIA									
Yan, Y. and Z.J, 2018[15]China	Chronic HBV infection	ND	114 (82%)/25 (18%)	ND; liver fibrosis	To HCC	ND	HBeAg; IFN	patients with chronic HBV infection associated with liver fibrosis/cirrhosis	ND
LIU, J.-l., *et al*., 2018 [16]China	Chronic HBV infection	Patients with HBsAg/Anti-HBs co-positive: 46.8±9.4; patients with HBsAg single-positive: 47.8±10.2	patients with HBsAg/Anti-HBs co-positive: 70/11; patients with HBsAg single-positive: 152/15	no less than 6 months	ND	Serum HBsAg/Anti-HBs co-existence and Serum single HBsAg	ALT; TBIL; ALB; PT prolongation; HBeAg; HBV DNA;	patients with HBsAg/Anti-HBs co-positive and patients with HBsAg single-positive	ND
Yuan-yuan, K., *et al*., 2020 [17]China	Chronic HBV infection	51 (44-59)	71.3/28.7 (%)	More than half a year; compensated and decompensated cirrhosis	ND	Serum	ALT; TBIL; ALB; Platelets; HBeAg;	liver cirrhosis patientswith positive HBsAg for more than 6 months	ND
Tseng, T.C *et al*., 2018 [18]Chine Taiwan	Chronic HBV infection	28-39: 1,076 (51.86) 40-49 : 579 (27.90) 50-59 : 302 (14.55) ≧ 60 : 118	1222 (58.89%)/853 (41.11%)	More than six month; fibrosis	ND	Serum	ALT; TBIL; ALB; Platelets; FIB-4 index; HBeAg; HBV DNA; HBsAg	patients with chronic HBV infection	ND

		(5.69)							
Wang, J.H., *et al*.,2019 [19]Chine Taiwan	Chronic HBV infection	Meanage: 52.6 years	273/98	ND	To HCC	Serum HBV s-antigen; liver and spleen images,	AST, ALT, t-Bil, AFP,PLT, HBV e-Ag and BMI	Patients with HBV-related cirrhosis	ND
Wang, L., *et al*., 2021[20]	Chronic HBV infection	47.1 (40.0, 55.0)	695 (74.2%)/242 (25.8%)/	ND	6 months laterTo decompensated cirrhosis ; HCC, death	Serum, blood, liver	blood count, liver biochemistries, HBV DNA, AFP, LSM,and abdominal ultrasonography. HBV DNA, HBsAg, HBeAg, and anti-HBeAg	Patients with compensated HBV-induced cirrhosis	ND
Jeon, M.Y., *et al*., 2017[21]	Chronic HBV infection	51.5 (46.0–58.0)	355 (65.7%)/185 (34.3%)	ND	HCC	Serum, blood, liver	serum ALT, HBeAgstatus, and HBV DNA level	patients with chronic hepatitis B	ND
Li K, *et al*. chine 2017[22]	Chronic HBV infection	50.6 ± 9.1	229 (77.4%)/ 67 (22.6%)	ND	HCC	Serum, blood, liver	AST, ALT, ALB,t-Bil, AFP, PLT, HBV Viral load , Th17 cell and Treg cell levels in serum	Patients with liver cirrhosis due to HBV infection	ND
Conglin, Z., *et al*.,2020[23] Chine	Chronic HBV infection	Complication group : 49.85±7.24 Non-complication group : 50.47±6.83	Complication group: 33 (68.75%)/5 (31.25%) Non-complication group : 25 (65.79%) / 13 (34.21%)	ND	ND	Serum, blood, liver, pleen	AST, ALT, TBIL, Fibroscan;	Patients with liver cirrhosis due to HBV infection	ND
Chen, T.Y., *et al*., 2021[24]	Chronic HBV infection	55.17±7.89	22 (61.1%) / 14 (38.9%)	ND	ND	Liver biopsy	ALT, AST, TBIL, AFP; GGT, Alb, HBV-DNAlevel; T lymphocyte subgroup indexes [CD3+, CD4+, CD8+,CD4+/CD8+]	patients suffering from hepatitis B cirrhosiswith hyperalphafetoproteinemia	erzhu jiedu recipe

Jiang, X.Y., *et al*.,2021[25]	Chronic HBV infection	**Observation group:** 74 (77.08)/ 22 (22.92) **Control group:** 119 (92.24) / 10 (7.76)	**Observation group:** 59.50 (48-67) **Control group:**48 (41-58)	ND	HCC	Blood, serum	ALT, AST, TBIL, AFP; HBV-DNAlevel; HBsAg; HBeAg; PLT	Hepatitis B cirrhosis patients	ND
Barathan, M., *et al*. 2021 [26]Malaisia	Chronic HBV infection	ND	ND	liver cirrhosis patients with positive HBsAg for more than 6 months	ND	Plasma; liver	Cytokines; TNF-α and IL-6 levels; HBsAg	Hepatitis B cirrhosis patients	ND
Xu, W., *et al*.,2021[27] China	Chronic HBV infection	ND	ND	ND	ND	ND	ALT, AST, enzymes and total bilirubin, HBV DNA; HBsAg, HBeAg;	Hepatitis B cirrhosis patients	Echinacea
Khan, H., H. Ullah, and S.M. Nabavi,2019[28] Pakistan	Chronic liver toxicity	ND	ND	ND	ND	Liver, plasma, serum	ALT, AST;	Patients with hépatotoxicty	curcumin
Al-Qahtani, A.A., *et al*., 2020[29]Arabie Saoudite	Chronic HBV infection	54.48 ± 9.84	28 (73.68%) / 10 (26.32%)	ND	HCC	Liver, plasma, serum	anti-HBcA; HBsAg; anti-HBsAg; anti-HBeAg; ALT; AST	Hepatitis B cirrhosis patients	ND
Wungu, C.D.K., *et al*., 2019 [30]Indonesia	Chronic HBV infection	Median age 49 male and 54 female; theyoungest patient was 30 years old and the oldest patientwas 71 years old.	patients with liver cirrhosis 24 (80%)/6 (20%)	liver cirrhosis patientswith positive HBsAg for more than 6 months	ND	blood samples	TNF-α	liver cirrhosis patientswith positive HBsAg for more than 6 months	ND

EUROPA									
Rennert, C., *et al.* 2021[31] Allemagne	Chronic HBV infection	61 (45- 78)	20/13	ND	HCC	Liver	NK-Cell	patients with liver cirrhosis ; patients with chronic HBV infection	ND
Estevez, J., *et al.*, 2017[32]	Chronic HBV infection	47.3±12.6	76 (63.3%)/44 (36.7)	ND	HCC	Blood, serum, plasma	Cytokines,	patients with chronic liver disease	ND
AMÉRICA									
Wooddell, C.I., *et al.* 2017[33]	Chronic HBV infection	ND	ND	ND	ND	Blood samples	HBeAg; HBsAg; HBV DNA;	CHB patient	ND
AFRICA									
Duah, A., *et al* 2021[34] Ghana	Chronic HBV infection	46(20–78)	124 (66.7%) / 62 (33.3%)	ND	Death	blood sample	Neutrophils; Proteins, leucocytes, erythrocytes, pus cell ; HBsAg ; albumin; AFP;	Patientswith liver cirrhosis	ND
Desalegn, H., *et al.*, 2018[35] Ethiopia	Chronic HBV infection	18–25: 64 (19.5) 26–35: 122 (37.2) 36–45: 83 (25.3) > 45: 59 (18.0)	260 (79.3) / 68 (20.7)	ND	ND	Blood	HBsAg; complete blood count, bilirubin,ALT, AST, creatinine; HBV DNA viral load	Patients with Liver fibrosis	ND

Legend

ALB : Albumin; AFP : alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: body mass index; CD: cluster of differenciation; CHB: Chronic Hepatitis B; DNA: deoxyribonucleic acid; FIB-4: Fibrosis-4; GGT: Gammaglutamyl transpeptidase; HBcA: Hepatitis B Core Antibody; HBeAg: Hepatitis B e-antigen; HBsAg: hepatitis B virus surface antigen; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; IFN: interferon; IL-6: Interleukin-6; LSM: liver stiffness measurement; ND: not defined; NK-Cell: Natural Killer-Cell; PLT: platelet count; PT: prothrombin time; TBIL: Total bilirubin; Th17: T helper 7; TNF-α : Tumor Necrosis Factor-α; Treg cell: Regulatory/suppressor T cells.

Basic laboratory tests, including complete blood count, ALT, AST, albumin, alkaline phosphatase, gamma-glutamyl transferase (GGT), total bilirubin, and PT/INR, should be ordered (Smith *et al.*, 2019). Cirrhosis is characterized by HBV DNA > $2x10^3$ IU/ml with ALT > 5x ULN upper limit of normal (Chang and Liaw, 2014).

HBsAg is the main marker of active infection; it reflects, to some degree, the presence of intrahepatic HBV DNA, the transcription of covalently closed circular DNA, the transcriptional model of the virus (cccDNA) and the host immune response (Paccoud *et al.*, 2019). TH1 responses, mainly through interferon-γ (IFN-γ) released by TH1 lymphocytes, NK or NK-T cells are usually antifibrotic through different mechanisms. In particular, NK cells can operate as cells able to specifically kill senescent hepatic stellate cells (HSC) and, through their release of IFNγ, reinforced by IL-15, to induce cell cycle arrest and apoptosis in HSC. However, CD4+ T lymphocytes, by interacting with either NK cells and activated HSC, can suppress NK cells favoring HSC survival (Parola and Pinzani, 2019).

Type of population

More than half of the articles (12) had as target population, patients with cirrhosis due to chronic HBV infection. The data collected could in this case make it possible to directly monitor the evolution of cirrhosis. Three (03) studies used patients with chronic HBV infection and 01 used patients with chronic HBV infection associated with liver fibrosis/cirrhosis. These two choices could make it possible to follow the onset of cirrhosis from chronic HBV infection and also to show the relationship between chronic HBV infection and fibrosis/cirrhosis. The others studies used HBsAg/Anti-HBs co-positive and patients with HBsAg single-positive, patients with liver cirrhosis with positive HBsAg for more than 6 months, patients with compensated HBV induced cirrhosis, patients with hepatotoxicity and patients with chronic liver disease. These choices focus on the antigens and antibodies involved in cirrhosis, a chronic liver disease whether viral or toxic in nature. These could be references for tracking these parameters.

Existence and utility of a therapeutic management based on traditional drugs

The primary goals of liver disease management are to prevent cirrhosis complications, liver decompensation, and death (Smith *et al.*, 2019). It is of great medical value to find new drugs that can effectively inhibit liver cirrhosis. Ixeris denticulate is a dry whole plant used as a traditional Chinese medicine, which was widely used in the treatment of hepatitis and liver cirrhosis.

The result showed that Ixeris denticulate (water extract) could be a potent hepatoprotective agent in clinical therapy in the future (Zhu *et al.*, 2020). Our results showed that herbal recipes exist for the therapeutic management of liver cirrhosis. Three recipes have been listed, namely the recipe based on erzhu jiedu, Echinacea and Curcumin. The results showed that erzhu jiedu recipe can significantly inhibit the levels of AFP and AFP-L3 in patients with hepatitis B cirrhosis and hyperalphafetoproteinemia and have good security.

Echinacea exhibited excellent activities in resisting a variety of hepatopathy induced by different causes in preclinical experiments and clinical trials by regulating cell proliferation and apoptosis, antioxidant defense mechanism… Hepatoprotective effects of curcumin have been reported using different hepatotoxic models including acetaminophen, alcohol, lindane, CCl4, diethylnitrosamine and heavy metals induced hepatotoxicity.

The study focused on understanding the physiopathology and clinical manifestations of cirrhosis and evaluating the potential of traditional medicines for therapeutic management. The findings revealed that chronic hepatitis B can lead to cirrhosis, affecting individuals as young as 18 years old, with men being more affected than women.

Various sample types, including serum, liver, plasma, whole blood, and spleen, were used for analysis of clinical markers. Importantly, the study identified potential herbal treatments like erzhu jiedu, Echinacea, and Curcumin for cirrhosis management. These findings have implications for early diagnosis and intervention, and they suggest promising avenues for future research in traditional medicine-based treatments for cirrhosis.

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