BOLETIN LATINOAMERICANO Y DEL CARIBE DE PLANTAS MEDICINALES Y AROMÁTICAS
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Revision / Review

Indonesian traditional medicinal plants with potential for hepatitis treatment: A systematic review

[Plantas medicinales tradicionales indonesias con potencial para el tratamiento de la hepatitis: Una revisión sistemática]

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Section Review

Received: 10 January 2025
Accepted: 15 March 2025
Accepted corrected: 12 May 2025
Published: 30 September 2025

Citation:
Khalil M, Indriaty, Jayanthi S, Pandia ES, Sarjani TM, Ariska RN, Armanda F, Elfrida, Marjanah, Mawardi AL, Suwardi AB, Nursamsu, Atmaja THW, Mahyuny SR, Fitria D, Wahyuni A, Setyoko, Desy R, Nuraini. Indonesian traditional medicinal plants with potential for hepatitis treatment: A systematic review
Bol Latinoam Caribe Plant Med Aromat
24 (5): 688 - 704 (2025)
https://doi.org/10.37360/blacpma.25.24.5.48

Abstract: Hepatitis remains a major global health issue, especially in regions with limited treatment access. Conventional therapies are often costly and carry side effects. Indonesian traditional medicinal plants, long used for liver disorders, offer promising alternatives due to their antiviral and hepatoprotective properties. This systematic review synthesizes data from studies using *in vitro*, *in vivo*, *in silico*, and ethnobotanical approaches to assess the antihepatitis potential of these plants. Seventy-eight species from 39 families were identified, with *Phyllanthus niruri*, *Curcuma longa*, and *Artocarpus heterophyllus* showing strong activity. *In vitro* studies highlighted antiviral effects, while in vivo studies demonstrated hepatoprotective actions. Ethnobotanical data supported traditional use by local communities. These findings suggest that Indonesian medicinal plants may offer effective, affordable alternatives for hepatitis treatment. However, clinical trials are needed to confirm their efficacy and safety in humans.

Keywords: Antiviral Plants; Ethnobotany; Hepatitis Treatment; Medicinal Plant; Traditional Medicine.

Resumen: La hepatitis sigue siendo un importante problema global de salud, especialmente en regiones con acceso limitado a tratamientos. Las terapias convencionales suelen ser costosas y presentan efectos secundarios. Las plantas medicinales tradicionales indonesias, utilizadas desde hace mucho tiempo para trastornos hepáticos, ofrecen alternativas prometedoras debido a sus propiedades antivirales y hepatoprotectoras. Esta revisión sistemática sintetiza datos de estudios realizados mediante enfoques *in vitro*, *in vivo*, *in silico* y etnobotánicos para evaluar el potencial antihepatitis de estas plantas. Se identificaron setenta y ocho especies pertenecientes a 39 familias, destacando *Phyllanthus niruri*, *Curcuma longa* y *Artocarpus heterophyllus* por su fuerte actividad. Los estudios in vitro resaltaron efectos antivirales, mientras que los estudios *in vivo* demostraron acciones hepatoprotectoras. Los datos etnobotánicos respaldaron el uso tradicional por parte de las comunidades locales. Estos hallazgos sugieren que las plantas medicinales indonesias pueden ofrecer alternativas efectivas y asequibles para el tratamiento de la hepatitis. Sin embargo, se requieren ensayos clínicos para confirmar su eficacia y seguridad en humanos.

Palabras clave: Plantas antivirales; Etnobotánica; Tratamiento de hepatitis; Planta medicinal; Medicina tradicional.

INTRODUCTION

Hepatitis is a major global health concern, with viral hepatitis, particularly types B and C, being among the most severe forms. According to the World Health Organization (WHO), more than 325 million people worldwide are infected with hepatitis B and C, leading to chronic liver disease, cirrhosis, and liver cancer (Wahyuni *et al.,* 2018; Khalil & Dwitya 2023). In Indonesia, approximately 20 million people suffer from hepatitis, with the highest prevalence attributed to hepatitis B. This significant burden underscores the urgent need for effective and accessible treatment options, especially in low- and middle-income countries where access to antiviral drugs remains limited (Hartati *et al.,* 2018; Indrasetiawan *et al.,* 2019).

Current treatment for hepatitis B and C relies on antiviral therapies such as nucleos(t)ide analogs and direct-acting antivirals (DAAs). While effective, these treatments are often expensive, require long-term administration, and can be associated with adverse effects. Additionally, drug resistance remains a challenge, particularly in cases of chronic hepatitis B infection. Given these limitations, there is growing bioactive compounds such as curcumin, andrographolide, and phyllanthin, which have demonstrated antiviral and hepatoprotective properties in various experimental studies (Wahyuni *et al.,* 2013; Hartati *et al.,* 2018). Despite the wealth of ethnobotanical knowledge surrounding these plants, there has been limited systematic evaluation of their potential as hepatitis antiviral agents, especially in the context of modern scientific research (Permanasari *et al.,* 2021).

Indonesia, as one of the world's most biodiverse countries, possesses a rich heritage of traditional medicine that has been passed down through generations (Wahyuni *et al*., 2013). With its vast array of plant species, Indonesia is home to thousands of medicinal plants, many of which have been traditionally used to treat liver ailments, including hepatitis (Indrasetiawan *et al*., 2019). Indonesian traditional medicinal plants hold significant potential for addressing the hepatitis challenge. For centuries, communities across the Indonesian archipelago have relied on local flora for treating various diseases, including liver-related disorders (Wahyuni *et al*., 2018; Pelapelapon *et al*., 2023). Plants such as *Curcuma longa* (turmeric), *Andrographis paniculata* (sambiloto), and *Phyllanthus niruri* (meniran) have been widely used in traditional medicine for their purported hepatoprotective effects (Widyawaruyanti *et al*., 2020). These plants, along with many others, contain bioactive compounds such as curcumin, andrographolide, and phyllanthin, which have demonstrated antiviral and hepatoprotective properties in various experimental studies (Wahyuni *et al*., 2013; Hartati *et al*., 2018). Despite the wealth of ethnobotanical knowledge surrounding these plants, there has been limited systematic evaluation of their potential as hepatitis antiviral agents, especially in the context of modern scientific research (Permanasari *et al*., 2021).

To address this gap, this systematic review aims to comprehensively assess the available literature on Indonesian traditional medicinal plants with potential for hepatitis treatment. By synthesizing data from a wide range of studies, including *in vitro*, *in vivo*, *in silico*, and inventory studies, this review seeks to provide an in-depth understanding of the therapeutic value of these plants (Widyawaruyanti *et al.,* 2020; Permanasari *et al.,* 2021). The review will explore the mechanisms of action of key bioactive compounds, assess the efficacy of different plant species in treating various types of hepatitis, and evaluate the quality and reliability of the existing evidence (Hartati *et al*., 2018; Khalil, 2023).

Furthermore, this review will identify the plants with the most promise for further research and development as natural hepatitis treatments. It will also highlight gaps in the current literature, such as the need for more robust clinical trials, and suggest areas for future investigation. By doing so, this review not only aims to support the integration of traditional medicinal plants into modern hepatitis treatment strategies but also to promote the conservation and sustainable use of Indonesia's rich botanical resources (Wahyuni *et al*., 2013; Indrasetiawan *et al*., 2019). This systematic review of the potential of Indonesian traditional medicinal plants as antihepatitis agents seeks to bridge the gap between ethnobotanical practices and contemporary medical research. The findings will contribute to the growing body of knowledge on plant-based therapies for liver diseases and may pave the way for the development of more affordable and accessible treatments for hepatitis, particularly in resource-limited settings.

MATERIALS AND METHODS

Study design and search strategy

Materials and Methods should emphasize on the procedures and data analysis. For This systematic

review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, ensuring a transparent and standardized methodology for selecting and reviewing relevant literature (Harrisen *et al*., 2023). A comprehensive literature search was conducted across three major databases: Scopus, PubMed, and Google Scholar, to capture a broad range of studies related to the potential of Indonesian traditional medicinal plants for hepatitis treatment. The search included articles published up to December, 2024, ensuring that the most recent data were included. Boolean Operators were employed using a combination of keywords such as "Herbal medicine" OR "Medicinal plants" AND "Indonesia" AND "Hepatitis" OR "Antihepatitis" to filter relevant studies efficiently. Where necessary, advanced search techniques such as filters for study type, publication year, and language were applied to further refine the results (Harrisen *et al.*, 2023; Singh & Singh 2017). The reference lists of relevant articles were manually checked to identify any studies that might have been missed during the database search. This multi-layered approach helped ensure that all significant research relevant to the scope of this review was captured.

Study eligibility criteria

The primary inclusion criteria for this review were articles published in English up to December, 2024, ensuring that the most recent and relevant studies were captured. Articles were required to focus specifically on medicinal plants either native to Indonesia or traditionally used in Indonesian medicine, with a clear emphasis on their application for the treatment of hepatitis. The eligible studies encompassed a wide range of research approaches, including inventory studies documenting the use of medicinal plants, ethnopharmaceutical studies evaluating traditional formulations, ethnobotanical studies exploring indigenous knowledge, *in silico* analyses examining molecular interactions, *in vitro* research assessing plant extracts, and *in vivo* experiments involving animal models. This broad spectrum of study types allowed for a comprehensive understanding of both the traditional and scientific perspectives on the antihepatitis potential of these plants. On the other hand, the exclusion criteria were strictly applied to ensure the quality and relevance of the review. Conference abstracts, irrelevant content, book chapters, letters to the editor, articles with insufficient data, and studies where the full text was unavailable were excluded from the review process.

Data extraction and collection process

The process of data extraction and collection was carried out in several stages. Initially, three authors (MK, II, and SJ) independently conducted a keyword-based screening of studies retrieved from the ScienceDirect, PubMed, and Google Scholar databases. Meanwhile, the other authors (ESP, TMS, RNA, FA, EL, MJ, ALM, ABS, NS, THWA, SRM, DF, AW, SE, RD, and NU) reviewed the titles and abstracts of the identified records. Articles that did not meet the inclusion criteria were progressively excluded during the screening phase. All authors then performed a thorough full-text review of the remaining articles to verify their eligibility based on the established criteria. For each included study, relevant data such as research methodology, the medicinal plants investigated, the hepatitis treatments applied, outcomes, and key findings regarding the plants' potential as antihepatitis agents were extracted. Any disagreements encountered during the selection or data collection process were resolved through discussion among the three primary reviewers (MK, II, and SJ). In cases where consensus could not be reached, the remaining authors were consulted.

Synthesis method

The data from the included studies were synthesized using a structured and systematic approach to ensure consistency and clarity in presenting the results. First, the extracted data were categorized and organized into thematic groups to identify emerging trends in research focused on the potential of Indonesian traditional medicinal plants for hepatitis treatment. This thematic analysis allowed for the identification of patterns across studies, including recurring plant species, the specific parts of the plants utilized (e.g., leaves, roots, bark, rhizome), and the types of hepatitis targeted (e.g., hepatitis B, hepatitis C). Additionally, the methodological approaches employed in each study, such as *in vitro*, *in vivo*, *in silico*, inventory, etnopharmaceutical, or etnobotanical studies, were systematically reviewed to provide a comprehensive understanding of the research landscape. Key findings from the analysis included not only the identification of medicinal plants and the plant parts commonly used but also the specific therapeutic applications for different types of hepatitis and the experimental designs adopted by the studies. This detailed examination helped to highlight which plants showed the most promising antihepatitis effects and could potentially be further researched or

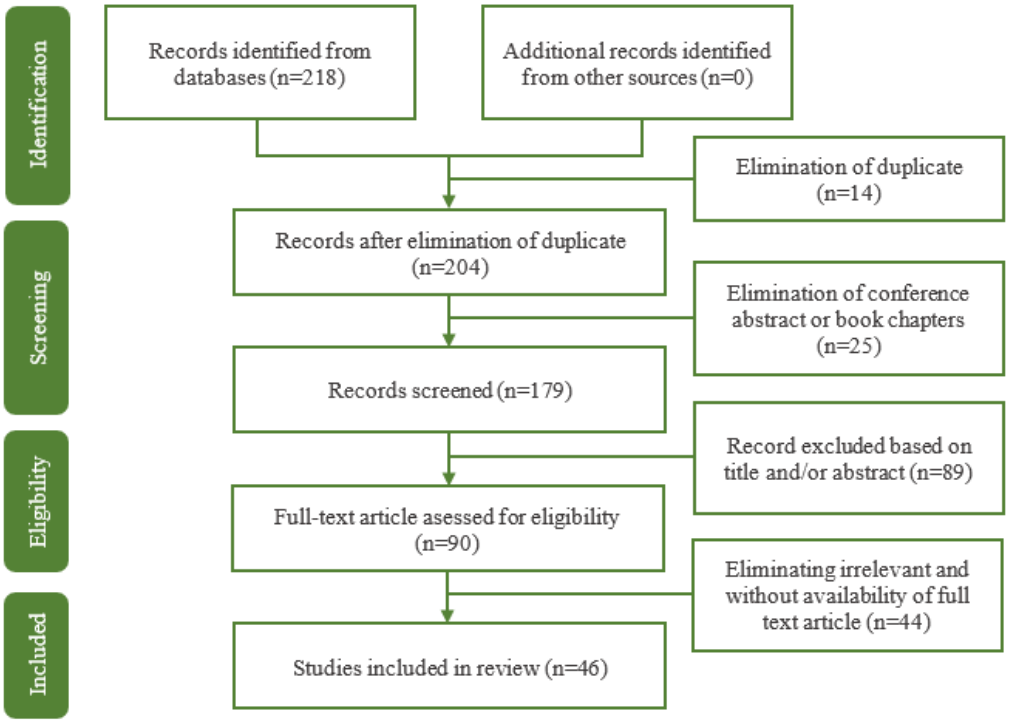
developed into viable treatments. Through this systematic synthesis, the review was able to evaluate the overall efficacy of various traditional plants and identify those with the greatest potential for future development as antihepatitis agents.

RESULTS

Study selection

From the initial search conducted across multiple databases using predefined keywords, a total of 218 records were identified. After removing duplicate entries, 204 unique records remained. A screening process was then carried out to exclude irrelevant articles based on their titles and abstracts. This initial screening narrowed the selection down to 90 articles that were deemed relevant for further evaluation. Subsequently, a thorough full-text review was conducted on these 90 articles to assess their eligibility against the established inclusion criteria. Following this detailed review, 46 articles were determined to meet the criteria and were included in the final comprehensive systematic review analysis (Figure No. 1).

Figure No. 1
Flowchart of article search strategy



Detailed information for all the included studies is provided in Table No. 1. This systematic approach ensured that only the most relevant and high-quality studies were included in the review, enhancing the reliability and depth of the analysis.

Plants identified with antihepatitis potential

Through this systematic review, a total of 78 plant species from 39 different families have been identified as having potential antihepatitis properties (Figure No. 2). These plants, traditionally used in Indonesian medicine, have demonstrated various bioactivities relevant to the treatment of hepatitis, including hepatoprotective, antiviral, anti-inflammatory, and antioxidant effects. Among the identified families, the Moraceae family contributed the most species, with seven plants showing promising antihepatitis activity. These include *Artocarpus heterophyllus*, *Artocarpus altilis*, and *Ficus fistulosa*. Several studies highlighted the significant antiviral activity of these species, particularly against Hepatitis C Virus (HCV). For example, *Artocarpus heterophyllus* exhibited strong anti-HCV activity in *in vitro* assays, with an IC_{50} value of 1.5 µg/mL, suggesting its potential to inhibit viral replication.

Table No. 1
Studies of Indonesian traditional medicinal plants as antihepatitis

Author (Year)	Plant names	Study approaches	Hepatitis Types Treated	Key Findings
Hafid *et al.* (2018)	*Toona sureni*	*In vitro*	Hepatitis C	Ethyl acetate fraction showed strong anti-HCV activity (IC_{50} 1.7 µg/mL), and gallic acid isolated from leaves had an IC_{50} value of 15.9 µg/mL.
Widyawaruyanti *et al.* (2020)	*Scoparia dulcis*	*In vitro*	Hepatitis C	Ethyl acetate and dichloromethane fractions showed significant anti-HCV activity, with IC_{50} of 12.7 µg/mL and 5.8 µg/mL.
Tanzerina *et al.* (2023)	*Hadgsonia macrocarpa*, *Fissistigma fulgens*, *Leea indica*	Inventory study	Not specified	Traditional usage of *Hadgsonia macrocarpa*, *Fissistigma fulgens*, and *Leea indica* by the Besemah tribe to treat hepatitis using plant stems and leaves.
Puspitasari *et al.* (2022)	*Luvunga scandens*, *Artocarpus sericicarpus*, *Artocarpus dadah*, *Eusideroxylon zwageri*	*In vitro*	Hepatitis C	Eleven extracts demonstrated anti-HCV activity, with IC_{50} values ranging from 0.08 to 12.01 µg/mL.
Wahyuni *et al.* (2022)	*Ruta angustifolia*	*In vitro* study	Hepatitis C	The combination of *Ruta angustifolia* extract and ribavirin increased anti-HCV activity 3.7 times compared to ribavirin alone, showing a synergistic effect.
Hafid *et al.* (2017)	*Artocarpus heterophyllus*	*In vitro* study	Hepatitis C	Dichloromethane extract exhibited strong anti-HCV activity with an IC_{50} value of 1.5 µg/mL, showing significant inhibition at the entry stage of the HCV life cycle.
Wahyuni *et al.* (2014)	*Ruta angustifolia*	*In vitro* study	Hepatitis C	Chalepin and Pseudane IX exhibited strong anti-HCV activity, with IC_{50} values of 1.7 µg/mL and 1.4 µg/mL, respectively.
Hafid *et al.* (2016)	*Ficus fistulosa*	*In vitro* study	Hepatitis C	Ethanol extract of *Ficus fistulosa* showed anti-HCV activity with IC_{50} of 20.43 µg/mL. Subfractions FFLC10 and FFLC11 exhibited the highest selectivity index.
Tumewu *et al.* (2016)	*Alectryon serratus*	*In vitro* study	Hepatitis C	*Alectryon serratus* leaves extract exhibited anti-HCV activity with IC_{50} values of 14.9 µg/mL and 9.8 µg/mL for two strains of HCV. Chlorophyll derivatives contributed to the activity.
Prasetyo *et al.* (2024)	*Acorus calamus*, *Amaranthus tricolor*, *Centella asiatica*, *Alstonia scholaris*, *Phyllanthus niruri*	Ethnobotanical study, Inventory study	Not specified	Documented traditional use of various plant species for treating hepatitis and other diseases by the Lio people.
Tahoangako *et al.* (2024)	*Andrographis paniculata*, *Chromolaena odorata*, *Curcuma longa*, *Orthosiphon*	Ethnobotanical study, Inventory study	Not specified	Documented the use of 91 plant species by traditional healers for treating various ailments, including liver conditions. Leaves were most commonly used.

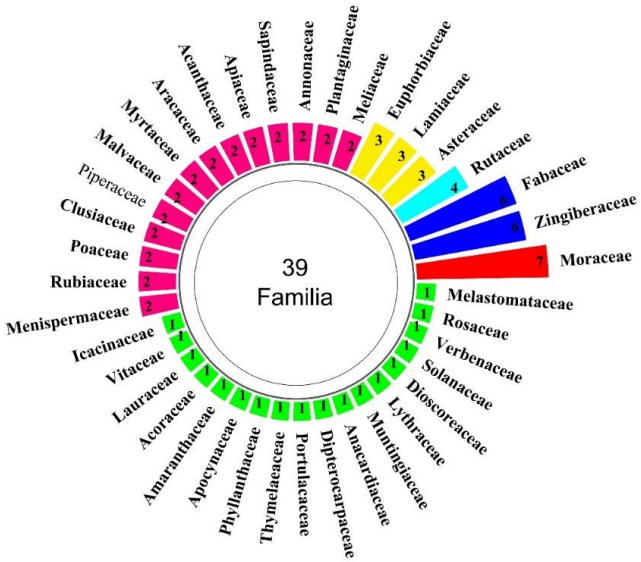
	aristatus, *Phaleria macrocarpa*			
Sari *et al.* (2024)	*Melanolepis multiglandulosa*, *Blumea balsamifera*, *Artocarpus altilis*, *Cocos nucifera*	Ethnopharmaceutical study	Not specified	Identified 14 species used for jaundice, primarily using leaves (43%). The most common preparation methods were boiling (70%) and pressing (30%).
Maulana (2024)	*Curcuma xanthorrhiza*, *Syzygium polyanthum*, *Orthosiphon stamineus*, *Andrographis paniculata*	*In vitro* study	Not specified	27 species of rare medicinal plants were identified, showing antibacterial, antioxidant, and anti-inflammatory activities.
Mallaleng & Avanti (2022)	*Kleinhovia hospita*, *Portulaca oleracea*	Ethnobotanical study	Not specified	*Kleinhovia hospita* is used to treat hepatitis, hypertension, and diabetes. It is commonly used in West Papua and Sulawesi for its anti-inflammatory and hepatoprotective properties
Wahyuni *et al.* (2024a)	*Piper betle*	*In vitro* study	Hepatitis C	Ethanol extract showed significant anti-HCV activity with an IC_{50} of 0.08 ± 0.028 µg/mL. Synergistic effects with simeprevir were observed, but not with ribavirin.
Khalil *et al.* (2023)	*Hydrocotile sibthorpioides*	*In silico* study	Hepatitis B	Molecular docking showed binding affinity ranging from -7.1 to -7.9 kcal/mol, indicating potential as an HBV replication inhibitor.
Wahyuni *et al.* (2018)	*Curcuma domestica*, *Curcuma xanthorrhiza*, *Curcuma heyneana*	*In vitro* study	Hepatitis C	*Curcuma domestica* showed the strongest anti-HCV activity with IC_{50} of 1.68 µg/ml. Curcumin was found to interact with viral proteins involved in the HCV entry and replication steps.
Aoki-Utsubo *et al.* (2023)	*Dryobalanops aromatica*	*In vitro* study	Hepatitis C	Vaticanol B exhibited potent anti-HCV activity by inhibiting viral entry and moderately suppressing replication. The compound had a selectivity index of 155.4, making it a promising antiviral agent.
Apriyanto *et al.* (2016)	*Dimocarpus longan*	*In vitro* study	Hepatitis C	*Dimocarpus longan* crude extract showed anti-HCV activity with an EC_{50} of 19.4 µg/ml. It inhibited viral entry and post-entry steps and showed synergistic effects when combined with telaprevir.
Apriyanto *et al.* (2024)	*Garcinia dulcis*	*In vitro* study	Hepatitis C	*Garcinia dulcis* leaves extract inhibited HCV replication with an IC_{50} of 17.06 µg/mL, with no cytotoxicity up to 160 µg/mL. Inhibited HCV at both co-addition and post-infection stages.
Wahyuni *et al.* (2023)	*Acacia mangium*	*In vitro* study	Hepatitis C	*Acacia mangium* extracts demonstrated strong anti-HCV activity, particularly inhibiting the post-entry step of the virus. The dichloromethane extract had the

				strongest effect, with an IC_{50} of 0.2 µg/mL, and combination with simeprevir enhanced antiviral activity.
Apriyanto *et al.* (2023)	*Garcinia lattissima*	*In vitro* study	Hepatitis C	Methanolic extract of *Garcinia lattissima* stem bark showed anti-HCV activity with EC_{50} of 4.7 µg/mL and CC_{50} of 34.2 µg/mL. It demonstrated efficacy in both co-addition and post-infection stages.
Wahyuni *et al.* (2024b)	*Sida rhombifolia*	*In vitro* study, *in vivo* study	Not specified	*Sida rhombifolia* extracts showed immunostimulant activity, with higher phagocytic index than a commercial immunostimulant. The extract had no toxic effects on hematological parameters.
Susiloningrum *et al.* (2020)	*Melicope latifolia*	*In vitro* study	Hepatitis C	The alkaloid fraction containing N-methylflindersine exhibited strong anti-HCV activity with an IC_{50} value of 6.21 µg/mL and a selectivity index (SI) of 13.31.
Wahyuni *et al.* (2021)	*Ruta angustifolia*	*In vitro* study	Hepatitis C	The 70% ethanol extract of *Ruta angustifolia* showed potential anti-HCV activity with an IC_{50} of 2.9 µg/mL. The extract contains alkaloids, flavonoids, terpenoids, and polyphenols. Rutin, a key compound, was identified as a marker for anti-HCV development.
Wahyuni *et al.* (2020)	*Phyllanthus niruri*, *Curcuma xanthorrhiza*	*In vitro* study	Hepatitis B	*Phyllanthus niruri* showed the most significant anti-HBV activity, inhibiting both viral entry and replication. *Curcuma xanthorrhiza* also showed activity but with higher toxicity. Both plants have potential for further anti-HBV drug development.
Panjaitan *et al.* (2021)	*Curcuma domestica, Mimosa pudica, Andrographis paniculata, Bambusa vulgaris, Orthosiphon aristatus, Centella asiatica*	Inventory study	Not specified	23 plant species were identified as being used for treating jaundice (a liver-related condition) by different ethnic groups in West Kalimantan. The plants have medicinal properties including hepatoprotective, antioxidant, and antibacterial effects.
Rahayu *et al.* (2021)	*Etlingera elatior*, *Bambusa vulgaris, Alpinia galanga*	Inventory study	Not specified	*Etlingera elatior* and *Bambusa vulgaris* are used to treat hepatitis. *Alpinia galanga* is also mentioned for hepatitis treatment, with preparation involving decoction.
Ivonie *et al.* (2018)	*Murraya paniculata, Lansium domesticum, Morus australis, Erythrina orientalis, Euphorbia pulcherrima, Clitoria ternatea, Mangifera indica, Muntingia calabura, Punica granatum*	*In silico* study	Hepatitis B	Several compounds identified from Indonesian medicinal plants showed strong binding to the HBV core protein. Compounds like myrtillin, sanggenol O, and yuehchukene have potential as anti-HBV agents.

Nursamsu *et al.* (2024)	*Acanthus ebracteatus*, *Nypa fruticans*, *Dioscorea hispida*, *Plectranthus purpuratus*, *Oldenlandia corymbosa*, *Uncaria gambir*, *Nicotiana tabacum*	Inventory study	Not specified	These plants were used to treat liver diseases, including hepatitis, by preparing decoctions or using other traditional methods passed down through generations.
Rujehan *et al.* (2024)	*Arcangelisia flava*, *Tinospora crispa*	Ethnobotanical study	Hepatitis A, Hepatitis B	*Arcangelisia flava* and *Tinospora crispa* were reported to be used by the Soputan Dayak tribe for the treatment of hepatitis A and B. These plants were noted for their hepatoprotective properties and are part of traditional medicinal practices.
Azis *et al.* (2020)	*Nicotiana tabacum*, *Kleinhovia hospita*, *Cymbopogon citratus*	Ethnobotanical study	Not specified	The plants *Nicotiana tabacum*, *Kleinhovia hospita*, and *Cymbopogon citratus* were reported to be used for the treatment of hepatitis.
Bhagawan *et al.* (2022)	*Phyllanthus niruri*, *Curcuma xanthorrhiza*	Ethnobotanical study, *in vitro* study	Hepatitis B	*Phyllanthus niruri* and *Curcuma xanthorrhiza* were identified as potential plants for treating liver diseases, including hepatitis B. The study also highlighted their hepatoprotective properties.
Nugroho *et al.* (2022)	*Arcangelicia flava*, *Tristaniopsis merguensis*	Ethnobotanical study	Not specified	*Arcangelicia flava* and *Tristaniopsis merguensis* are used traditionally for the treatment of hepatitis. These plants are prepared by boiling their roots or stems, and the boiled water is consumed.
Navia *et al.* (2022)	*Oldenlandia corymbosa*, *Centella asiatica*	Ethnobotanical study	Not specified	*Oldenlandia corymbosa* and *Centella asiatica* were used to treat liver conditions, including hepatitis. The plants were traditionally prepared as decoctions and used by local communities.
Elfrida *et al.* (2021)	*Elephantopus scaber*	Ethnobotanical study	Not specified	*Elephantopus scaber* was documented as a plant used in traditional medicine to treat hepatitis. The plant was prepared by boiling the root and drinking the decoction.
Tambaru *et al.* (2023)	*Plantago major Linn.*, *Lantana camara L.*, *Manihot esculenta*	Ethnobotanical study	Not specified	*Plantago major Linn.*, *Lantana camara L.*, and *Manihot esculenta* were used in traditional medicine for treating hepatitis. The plants were prepared by boiling the leaves and drinking the decoction.
Nurcahyo *et al.* (2024)	*Malus domestica*, *Morus alba*	Inventory study	Not specified	Two plants, *Malus domestica* and *Morus alba*, were noted for their use in treating hepatitis.
Mela *et al.* (2022)	*Curcuma longa*, *Cymbopogon nardus*, *Piper retrofractum*	*In vivo* study	Not specified	Several plants like *Curcuma longa* are used traditionally in the Bunaq tribe, including for hepatitis-related ailments.
Widyawaruyanti *et al.* (2020)	*Melicope latifolia*	*In vitro* study	Hepatitis C	N-methylflindersine isolated from *M. latifolia* showed strong anti-HCV activity by post-entry inhibition and reduced NS3

				protein expression
Permanasari *et al.* (2021)	*Artocarpus heterophyllus*	*In vitro* study	Hepatitis C	The dichloromethane extract of *A. heterophyllus* showed anti-HCV activity by reducing HCV NS3 protein expression and RNA replication, primarily in the post-entry stage.
Pelapelapon *et al.* (2023)	*Plantago major*	*In vivo* study	Not specified	*Plantago major* extract showed dose-dependent hepatoprotective effects by reducing SGPT, MDA, and portal inflammation in a hepatitis model induced by rifampicin-isoniazid
Ratnoglik *et al.* (2014)	*Morinda citrifolia*	*In vitro* study	Hepatitis C	Methanol extract of *Morinda citrifolia* leaves and its compounds, pheophorbide a and pyropheophorbide a, showed significant anti-HCV activity by inhibiting virus replication
Indrasetiawan *et al.* (2019)	*Cananga odorata, Cassia fistula, Melastoma malabathricum*	*In vitro* study	Hepatitis B	*Cananga odorata* extract showed high anti-HBV activity, with 72.7% reduction in HBV DNA production in Hep38.7-Tet cells. It could be a potential anti-HBV drug candidate
Wahyuni *et al.* (2013)	*Toona sureni, Melicope latifolia, Melanolepis multiglandulosa, Ficus fistulosa*	*In vitro* study	Hepatitis C	These plant extracts showed significant antiviral activities against various genotypes of the hepatitis C virus (HCV), with *Toona sureni* and *Melicope latifolia* being highly potent
Hartati *et al.* (2018)	*Archidendron pauciflorum*	*In vitro* study	Hepatitis C	The butanol fraction showed the highest anti-HCV activity with an IC_{50} of 6.3 µg/mL. Fractions 5 and 13 showed strong inhibition at post-entry and entry steps, respectively.

Figure No. 2
Number of plant species and families with potential for hepatitis treatment.



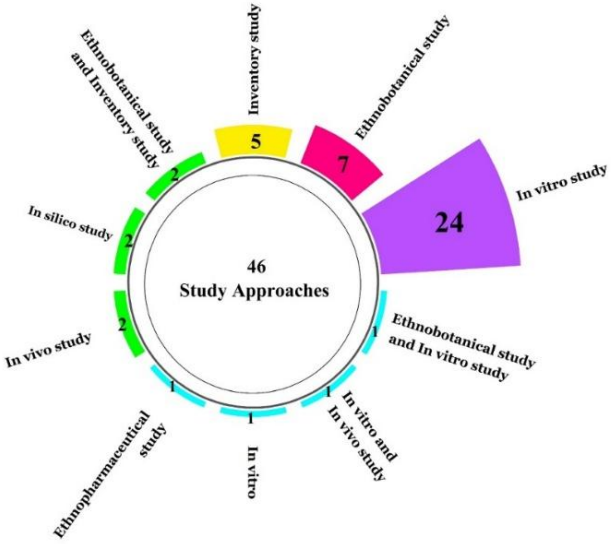
The Zingiberaceae family also plays a notable role, contributing species such as *Curcuma longa*, *Curcuma domestica*, and *Curcuma xanthorrhiza*. These plants are known for their bioactive compound, curcumin, which has shown antiviral effects against HCV. Curcumin interacts with viral proteins involved in HCV replication and entry, with studies reporting an IC_{50} of 1.68 µg/mL for *Curcuma domestica*, highlighting the therapeutic potential of these species for hepatitis treatment. Other plants identified with strong antihepatitis activity include *Toona sureni* (Meliaceae), whose ethyl acetate fraction showed potent anti-HCV activity with an IC_{50} of 1.7 µg/mL, and the isolated compound gallic acid exhibited an IC_{50} of 15.9 µg/mL. Similarly, *Scoparia dulcis* (Plantaginaceae) demonstrated significant anti-HCV activity, with ethyl acetate and dichloromethane fractions showing IC_{50} values of 12.7 µg/mL and 5.8 µg/mL, respectively. *Ficus fistulosa* (Moraceae) also exhibited strong anti-HCV activity, with an ethanol extract IC_{50} of 20.43 µg/mL.

Traditional medicinal plants used by indigenous Indonesian communities were identified for their antihepatitis potential. For instance, the Besemah tribe traditionally uses *Hadgsonia macrocarpa* and *Fissistigma fulgens* (Annonaceae) to treat hepatitis, though further scientific validation is required to assess their pharmacological efficacy. Ethnobotanical studies also revealed that *Arcangelisia flava* and *Tinospora crispa* (Menispermaceae) are used by the Dayak tribe to treat hepatitis A and B, both of which have shown hepatoprotective properties. These findings emphasize the significant potential of Indonesian traditional medicinal plants as sources of natural antihepatitis agents. However, while several species have demonstrated strong bioactivity, further research, particularly clinical trials, is needed to fully validate their therapeutic value and ensure their safety and efficacy for integration into modern hepatitis treatment protocols.

Study approaches

The studies included in this systematic review employed a range of methodological approaches to investigate the antihepatitis potential of Indonesian traditional medicinal plants (Figure No. 3). These approaches include *in vitro*, *in vivo*, *in silico*, ethnobotanical, and inventory studies, each contributing valuable insights into the biological and therapeutic properties of these plants. The variety of methods reflects the complexity of hepatitis as a disease and the diverse ways in which traditional medicinal plants may exert their therapeutic effects, whether through antiviral action, hepatoprotection, or immunomodulation. By combining these approaches, researchers were able to generate a more holistic understanding of how these plants might be utilized in the prevention and treatment of hepatitis.

Figure No. 3
Distribution of study approaches used in research.



In vitro studies were the most frequently employed method, with researchers using these controlled laboratory experiments to explore the biological activity of plant extracts on cell lines infected with Hepatitis B and C viruses (HBV and HCV). *In vitro* assays allowed for the rapid screening of multiple plant species and the identification of bioactive compounds with antiviral properties. For example, extracts from *Artocarpus heterophyllus* and *Ficus fistulosa* demonstrated significant anti-HCV activity, with low IC_{50} values indicating strong inhibition of viral replication. These studies often involved different extraction techniques, such as ethanol, dichloromethane, and ethyl acetate extractions, which enabled researchers to isolate specific compounds like curcumin and gallic acid that have shown promising antiviral and hepatoprotective activities. Furthermore, *in vitro* models provided insight into the mechanisms of action by which these compounds exert their effects, such as interfering with viral entry, replication, or protein synthesis.

In vivo studies, while less commonly employed, provided crucial insights into the efficacy and safety of these plants in whole organisms, typically using animal models. These studies are essential for understanding how plant extracts interact with complex biological systems and for assessing their potential toxicity and therapeutic effects *in vivo*. Rodent models, particularly those with chemically induced liver damage, such as carbon tetrachloride (CCl_4) or alcohol, were commonly used to simulate hepatitis-like conditions. Following induction of liver damage, plant extracts were administered to evaluate their hepatoprotective effects. For example, *Curcuma longa* and *Phyllanthus niruri* extracts significantly reduced liver enzyme levels and improved histopathological conditions in animal models, highlighting their potential for protecting the liver from hepatitis-induced damage. *In vivo* studies, therefore, offer an additional layer of evidence that supports the use of these plants for treating liver diseases, though further clinical validation is needed.

In silico studies employed computational tools to predict how bioactive compounds from medicinal plants interact with molecular targets related to hepatitis viruses. Molecular docking techniques were commonly used to simulate the binding of plant-derived compounds to key proteins involved in viral replication and infection. For instance, compounds from *Curcuma xanthorrhiza* and *Hydrocotile sibthorpioides* demonstrated strong binding affinities with viral enzymes such as HCV NS3/4A protease, suggesting their potential as inhibitors of viral replication. These *in silico* models provide a cost-effective and rapid method to screen multiple compounds before further laboratory validation. Although *in silico* studies alone are not sufficient to confirm therapeutic efficacy, they provide valuable preliminary data that guide subsequent *in vitro* and *in vivo* studies.

Ethnobotanical studies explored the traditional knowledge and practices of local communities in Indonesia concerning the use of medicinal plants for treating liver diseases, including hepatitis. These studies documented the indigenous knowledge of plant-based remedies passed down through generations, which often form the basis for scientific investigations. Plants like *Arcangelisia flava*, *Tinospora crispa*, and *Andrographis paniculata* were frequently cited in traditional medicine practices for treating liver disorders such as hepatitis A and B. Ethnobotanical research not only helps identify plants with potential therapeutic value but also emphasizes the cultural significance of these plants. However, while these studies provide crucial context, they highlight the need for rigorous scientific validation to confirm the efficacy and safety of these traditional remedies.

Inventory studies contributed to cataloging medicinal plants traditionally used for liver-related ailments across different regions of Indonesia. These studies documented species, plant parts used (e.g., leaves, roots, bark), preparation methods (e.g., decoction, infusion), and specific indications for their use in treating liver diseases. Inventory studies such as those documenting the use of *Curcuma domestica*, *Phyllanthus niruri*, and *Cymbopogon citratus* for treating jaundice and other liver conditions were critical for preserving indigenous knowledge and guiding future pharmacological research. These studies also play a key role in conservation efforts, as many of the documented species are part of Indonesia's rich biodiversity and are at risk of overharvesting.

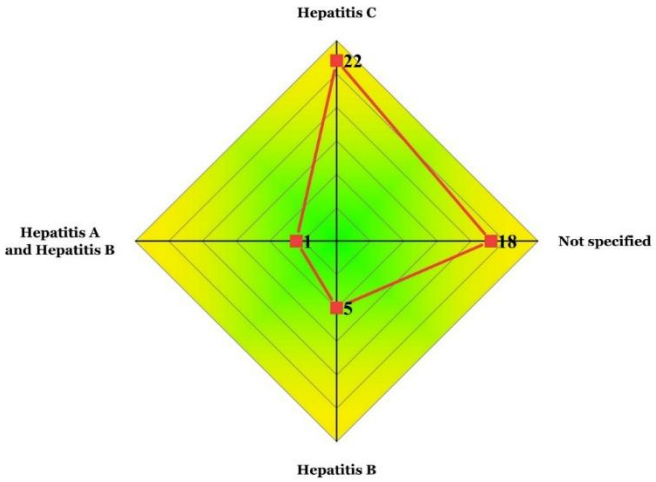
The diverse study approaches utilized in this systematic review, ranging from molecular simulations to animal experiments and field-based ethnobotanical surveys, demonstrate the multi-faceted potential of Indonesian traditional medicinal plants as antihepatitis agents. Integrating traditional knowledge with modern scientific research has enabled the identification of several plants with promising bioactivities. However, further studies, particularly clinical trials, are necessary to validate

these findings and translate them into safe, effective therapies for hepatitis patients.

Hepatitis types treated

This systematic literature review identified several studies investigating the antihepatitis potential of Indonesian traditional medicinal plants, focusing primarily on two major types of hepatitis: Hepatitis B and Hepatitis C (Figure No. 4). These two types of hepatitis are the most prevalent and severe, leading to chronic liver disease and liver cancer worldwide, particularly in regions with limited access to healthcare like Indonesia. The studies reviewed highlight the application of various plant species in treating these viral infections through different mechanisms, including antiviral, anti-inflammatory, and hepatoprotective effects.

Figure No. 4
Trends in hepatitis types studied in Indonesian traditional medicinal plants research



Hepatitis C (HCV) was the most frequently targeted hepatitis type, with many studies focusing on plants with potential to inhibit the replication of the HCV virus. *Artocarpus heterophyllus*, *Ficus fistulosa*, and *Scoparia dulcis* were among the key species demonstrating significant anti-HCV activity in *in vitro* studies. For instance, the ethyl acetate fraction of *Toona sureni* showed potent inhibition against HCV, with an IC_{50} value of 1.7 µg/mL, while the gallic acid isolated from its leaves exhibited antiviral activity with an IC_{50} of 15.9 µg/mL. Similarly, *Ruta angustifolia* combined with ribavirin enhanced the anti-HCV effects up to 3.7 times compared to ribavirin alone, indicating its potential role in combination therapy for Hepatitis C treatment.

Hepatitis B (HBV) was also a focus, though fewer studies were found compared to HCV. Traditional plants like *Phyllanthus niruri* and *Curcuma xanthorrhiza* demonstrated strong anti-HBV properties. *Phyllanthus niruri*, known for its hepatoprotective effects, showed the ability to inhibit viral replication and entry, making it a promising candidate for further exploration as an anti-HBV agent. Additionally, computational studies (*in silico*) involving *Hydrocotile sibthorpioides* revealed potential binding affinity to viral proteins involved in HBV replication, suggesting that some plants may serve as HBV replication inhibitors.

Other types of hepatitis, such as Hepatitis A, were less frequently addressed in the reviewed studies, though ethnobotanical reports documented the use of certain plants by indigenous communities for treating a variety of liver conditions. For example, the Dayak tribe traditionally uses *Arcangelisia flava* and *Tinospora crispa* to treat Hepatitis A, though further scientific validation is required to confirm their efficacy in modern medicine.

DISCUSSION

The findings of this review not only highlight the potential of Indonesian traditional medicinal plants for hepatitis treatment but also have broader implications for other countries facing similar public health challenges. Many medicinal plants traditionally used in Indonesia, such as *Phyllanthus niruri* and *Curcuma longa*, are also widely available and utilized in other tropical and subtropical regions. Their documented antiviral and hepatoprotective

properties suggest that they could serve as potential candidates for further research and clinical trials in various global settings.

A major observation from this review is the predominance of studies targeting Hepatitis C Virus (HCV), reflecting its global burden as a chronic liver disease. Several plants, including *Artocarpus heterophyllus*, *Ficus fistulosa*, and *Scoparia dulcis*, were shown to exhibit strong anti-HCV activity, with multiple *in vitro* studies demonstrating significant inhibition of viral replication (Wahyuni *et al*., 2014; Hafid *et al*., 2017). Notably, the ethyl acetate fraction of *Toona sureni* exhibited high potency against HCV, highlighting the potential of isolated compounds such as gallic acid for therapeutic use (Wahyuni e*t al*., 2013). These results align with the growing interest in plant-derived compounds for antiviral therapies, especially for diseases like hepatitis that lack affordable and accessible treatment options in many regions. The synergistic effect observed in *Ruta angustifolia* when combined with ribavirin further suggests that these plants may also play a role in enhancing existing treatment regimens for HCV, potentially improving outcomes in patients who do not respond well to standard therapies (Wahyuni *et al*., 2022).

In contrast, fewer studies addressed Hepatitis B Virus (HBV), although several traditional plants like *Phyllanthus niruri* and *Curcuma xanthorrhiza* demonstrated promising anti-HBV activity (Ratnoglik *et al.,* 2014). *Phyllanthus niruri*, in particular, has been widely studied for its hepatoprotective and antiviral properties, with some studies suggesting it can inhibit both viral entry and replication (Wahyuni *et al*., 2020). This indicates that while research on anti-HBV plants is still in its early stages, certain species show considerable potential for further exploration. Additionally, the use of computational (*in silico*) methods in studies involving *Hydrocotile sibthorpioides* and other plants suggests that molecular docking can be a valuable tool in predicting plant compounds' effectiveness against viral targets. Such predictive studies can help streamline the drug discovery process, providing valuable insights into which compounds should be prioritized for further *in vitro* and *in vivo* testing (Hartati *et al*., 2018).

Ethnobotanical studies conducted in this review also shed light on the traditional knowledge surrounding the use of medicinal plants in treating various forms of hepatitis. The Dayak tribe, for example, has long used plants such as *Arcangelisia flava* and *Tinospora crispa* for the treatment of Hepatitis A and B, which suggests that these plants possess broad-spectrum antihepatitis properties (Rujehan *et al*., 2024). However, while ethnobotanical data offer valuable insights into traditional practices, there is a pressing need for more rigorous scientific validation of these remedies. Without controlled studies, it is difficult to assess the safety, efficacy, and mechanisms of action underlying these traditional treatments (Khalil *et al*., 2023). Traditional preparation methods may influence the bioactivity of these medicinal plants. Many ethnobotanical practices involve decoctions, infusions, or fermentation, which can alter the bioavailability of active compounds. However, the variability in extraction techniques used across studies, including ethanol, methanol, and aqueous extracts, makes direct comparisons challenging. Standardizing extraction and bioassay methods will be crucial for ensuring reproducibility and consistency in future research.

The variety of study approaches utilized, ranging from *in vitro* and *in vivo* models to *in silico* analyses and ethnobotanical surveys, demonstrates the comprehensive efforts undertaken to explore the antihepatitis potential of these plants. *In vitro* studies dominated the research landscape, allowing for the rapid screening of plant extracts and identification of bioactive compounds (Wahyuni *et al*., 2013). However, *in vivo* studies remain limited, though they are crucial for understanding how these compounds behave in complex biological systems and assessing their safety and efficacy in animal models. For instance, the hepatoprotective effects of *Curcuma longa* and *Phyllanthus niruri* in rodent models suggest that these plants may not only inhibit viral replication but also protect the liver from damage, further supporting their use in treating hepatitis-related liver injuries (Permanasari *et al*., 2021).

Despite these promising findings, the review also reveals significant gaps in the literature. First, the lack of clinical trials is a major limitation in translating these preclinical findings into clinical practice. While many plant species have shown strong antiviral and hepatoprotective effects *in vitro*, their effectiveness in humans remains unproven. Future research should focus on elucidating the molecular mechanisms by which these plants exert their antiviral effects. For example, compounds such as curcumin and phyllanthin are known to inhibit viral replication and modulate immune responses, but their precise molecular targets in HBV and HCV

pathways require further investigation. Understanding these biochemical interactions could provide a stronger scientific foundation for the therapeutic use of these plants. Furthermore, the absence of standardized extraction methods and dosage forms across studies makes it difficult to compare results or establish definitive therapeutic guidelines. Future research should focus on conducting well-designed clinical trials to validate the efficacy of these plants in human populations, particularly in resource-limited settings where hepatitis remains a significant public health challenge (Wahyuni *et al*., 2023).

This systematic review underscores the potential of Indonesian traditional medicinal plants as sources of natural antihepatitis agents. While several species have demonstrated promising bioactivities, there is an urgent need for further research, especially clinical trials, to fully assess their therapeutic value (Hafid *et al*., 2017). Further interdisciplinary collaboration between ethnobotanists, pharmacologists, and clinicians to advance research in this field also needed. The development of standardized extraction protocols, detailed bioassays, and well-designed clinical trials will be critical steps in translating traditional medicinal plants into viable antiviral treatments. By leveraging Indonesia's rich biodiversity and traditional medicine heritage, there is significant potential to contribute to global efforts in combating hepatitis through natural therapeutic alternatives (Widyawaruyanti *et al*., 2020).

CONCLUSION

The systematic review concludes that Indonesian traditional medicinal plants hold significant potential as alternative treatments for Hepatitis B and C. Several key species, including *Phyllanthus niruri*, *Curcuma longa*, and *Artocarpus heterophyllus*, demonstrated promising antiviral, hepatoprotective, and anti-inflammatory properties in preclinical studies. However, while *in vitro* and *in silico* studies provide valuable insights, clinical trials are needed to validate their efficacy in human populations. The findings emphasize the importance of further research, particularly clinical trials, to confirm the therapeutic efficacy and safety of these plants. This review highlights the potential for developing affordable, accessible, plant-based therapies, especially in regions with limited access to conventional hepatitis treatments.

ACKNOWLEDGEMENT

The authors would like to thank the Institute of Research and Community Services (LPPM) of Universitas Samudra, which has funded this research under the group research scheme.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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