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Activity and potential of *Phyllantus niruri* L. and *Phyllantus urinaria* L. as Hepatitis B virus inhibitors: A narrative review of the SANRA protocol

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ABSTRACT: *Terna* plants are used by Indonesians as raw materials for herbal and traditional medicine, including *Phyllantus niruri* L. and *Phyllantus urinaria* L. Therefore, this study aimed to explore, analyze and compile the activities and potential of *Phyllantus niruri* L. and *Phyllantus urinaria* L. as agents of hepatitis B virus (HBV) inhibitors using a narrative review approach. It was conducted based on the *Scale for the Assessment of Narrative Review Articles* (SANRA) by establishing inclusion and exclusion criteria. The study selected and reviewed 15 out of 38 articles. The Phyllantus genus is a group of seasonal herbs containing bioactive compounds and activity as HBV Inhibitors. In this study, 23 compounds were identified in the two species, including Nirtetralin, Phyllanthin, Niranthin, Hinokinin, Ellagic acid, Ethanol, Phyllanthosterol, Ethyl brevifolincarboxylate, Tenofovir, Quercetin, Quercitrin, Astragalin, Repanducinic acid, Corilagin, Gallic acid, Aloe-emodin-8-O-β-D-glucopyranoside, Catechin, D-glucopyranoside, Ethyl gallate, Protocatequatic acid, Chebulanin, Albibrissinoside B, and (-)-Epicatechin. Meanwhile, the activity in inhibiting cells infected with HBV was reported *in vitro, in vivo, ex vivo*, and *in silico*. The mechanism of bioactive compounds as HBV inhibitors focuses on suppression, blocking, and inhibiting the synthesis, secretion, and expression of HBsAg, HBcAg, and HbeAg in test media. The results showed that *Meniran* red and green bioactive compounds have the potential to be developed as raw materials as herbal medicine with promising prospects as commercial drug candidates.

KEYWORDS: Anti hepatitis B Virus; *meniran*; medicinal plants; therapeutic agents; traditional medicine

1. INTRODUCTION

Over the past decade, there has been an increase in the incidence of hepatitis B virus (HBV) transmission, particularly among pregnant women according to epidemiological data [1]. The perinatal period poses a risk for mother-to-baby transmission of the virus, emphasizing the importance of maternal screening and appropriate medical interventions to prevent transmission [2]. The Ministry of Health of Indonesia report for 2021 stated that the prevalence of pregnant women undergoing the hepatitis B surface antigen rapid diagnostic test (RDT-HBsAg) with reactive status reached 47,550 people at 1.61%. Pregnant women were positively infected with HBV in the highest provinces, namely, East Java, Central Java, West Java, East Nusa Tenggara, and South Sulawesi, with 8,071, 5,942, 5,819, 3,148, and 2,685 cases, respectively [3]. Given the high incidence of hepatitis B infection, strategic efforts are needed, especially to carry out prevention and control, as well as to identify and develop drug candidates that are safe and effective in suppressing the development of the virus using medicinal plants [4–6].

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In Indonesia, the use of plants as raw materials for herbal and traditional medicine has been a culture for generations [7]. This is based on public beliefs regarding the therapeutic effects provided and certain ethnic cultures that claim the functions and benefits of an herbal product [8,9]. With the rapid pace of technological advancements, the utilization of plant components as raw materials for herbal remedies has gained increasing recognition and undergone continuous development [10]. Furthermore, many bioactive compounds derived from plants have been isolated and used as candidates for commercial drugs [11]. In addition to being rich in secondary metabolites, medicinal plants are easy to obtain and are harmless when used in the right doses, even in the long term [12,13].

One of the medicinal plants that are widely used and researched today is *Phyllantus niruri* L. and *Phyllantus urinaria L.*, obtained from the genus *Phyllanthus*, a family of flowering plants (Phyllanthaceae) [14,15]. Compounds and their derivatives have been widely studied through *in vitro*, *in vivo*, and *in silico* approaches [16]. Previous studies have shown that compounds found in the roots, stems, leaves, and flowers of these two species effectively inhibit the life cycle of the hepatitis virus. Therefore, their antiviral effects can be developed in the future [5,17–19]. Arbab et al. [20] identified and evaluated the antiviral activity of 60 plant species, concluding that the compounds contained in *P. niruri* L. and *P. urinaria* L. were active as HBV inhibitor agents [21]. Meanwhile, pure compounds from the *Meniran* plant were reported to inhibit the replication and expression of HBV in cells used as test models [4,22–26] and were hepatoprotective [27–30]. The inhibition process has been shown to occur in viral replication, mutation, and capsid formation [17,31]. This study aimed to review information about the differences between *Phyllantus niruri* L. and *Phyllantus urinaria* L., identify bioactive compounds reported as HBV inhibitory agents, and elucidate the mechanisms underlying the occurrence of anti-HBV effects.

2. RESULTS

2.1 Profile of *Phyllantus niruri* L. and *Phyllantus urinaria* L.

Phyllantus niruri L. and *Phyllantus urinaria* L. (Figure 1) are herbaceous plants commonly found in tropical and subtropical regions [32]. This plant is known as *Meniran,* support child, *sampa-sampalukan*, and gale of the wind in Indonesia, Malaysia, Tagalog, and English [12]. Based on data from the Integrated Taxonomic Information System, the genus Phyllanthus consists of 833 species that are widespread in Asia, America, China, and the Indian Ocean and are used as raw materials for traditional medicine and cosmetics [23,33]. The community has widely used *Meniran* in Indonesia, and this plant is not cultivated but grows wild in shrubs or areas with fertile, humid, and dry soil [34].

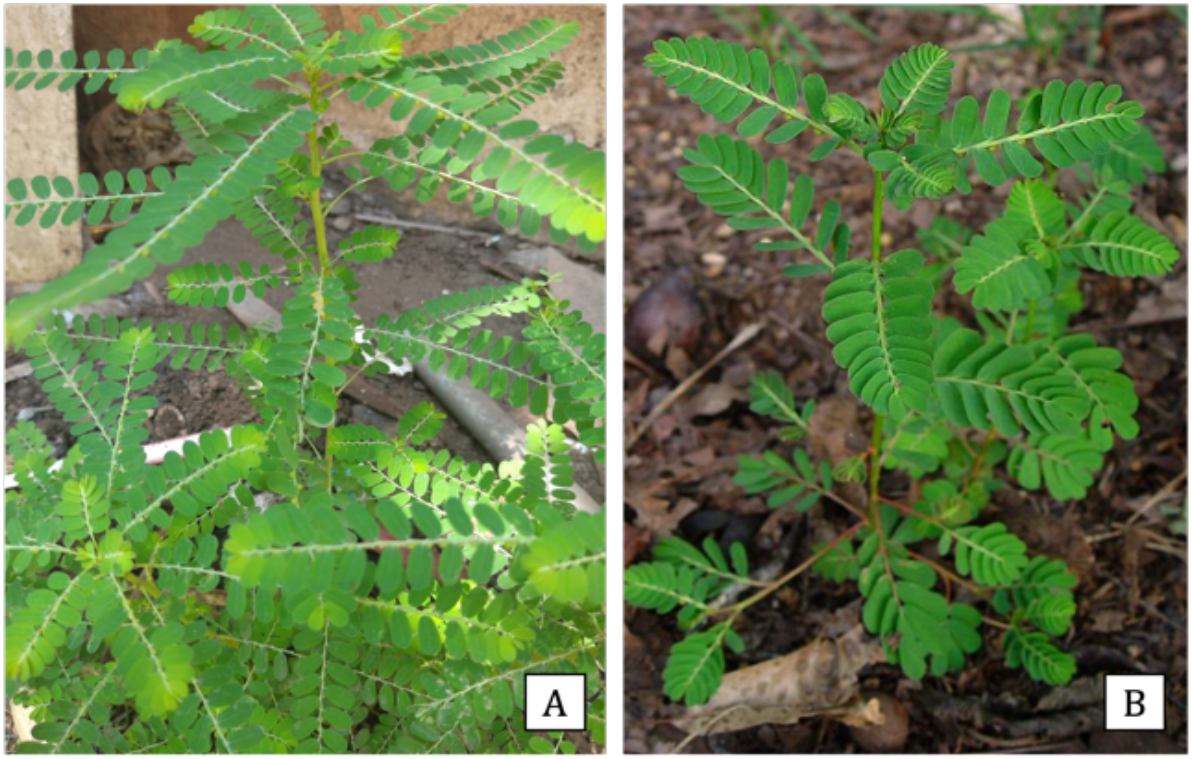


Figure 1. Plant morphology *Phyllantus niruri* L. and *Phyllantus urinaria* L. Description: *Phyllantus niruri* L. all stems and stem branches are green (A) while *Phyllantus urinaria* L. stem base and stem branches are purplish-red (B).

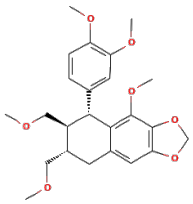
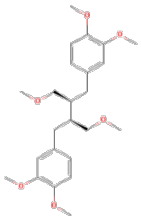
Meniran plants are morphologically divided into green (*Phyllantus niruri* L.) and red (*Phyllantus urinaria* L.). These two plants have differences in macroscopic structure [35,36]. The green *Meniran* plant (*P. niruri* L.) grows upright at approximately 38 cm with green stems and can be found in grassy areas. Some characteristics include a single leaf, oval, blunt tip, and rotundatus base with pinnate veins (penninervis). The leaf surface is smooth (laevis) with a length of 8-11 mm and a width of 2-4 mm. In addition, the stems are wet and round (teres) with a straight growth direction, and monopodial branches grow up to 24 cm high. The roots of this plant are tapered and branched with a slightly yellowish-white color [37–39].

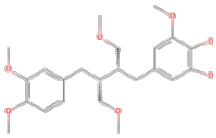
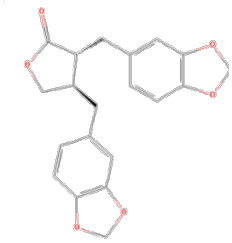
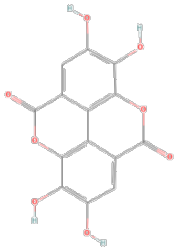
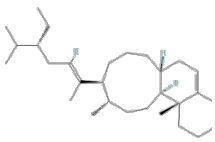
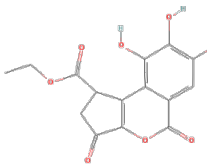
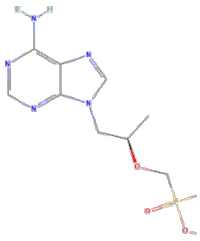
Morphologically, *Phyllantus urinaria* L. is an annual herbaceous plant and grows upright, reaching 19.5 – 21.7 cm. The base is slightly woody with a characteristic red stalk commonly found in damp areas and grows in shrubs. The characteristics include single leaf morphology, oval in shape, apex obtusus, base rotundatus (rounded), and a smooth surface, as well as 6-9 mm in length and 1-3 mm in width. The leaves are smaller than those of *P. niruri* and light green. This plant has round stems that are wet and slippery. The erectus growing area has sympodial branches 5-7.5 cm high and is purplish-red in color. The roots are wet, tap-shaped, and branched with a pale yellowish-white color. Meanwhile, the flowers and fruits are under the leaves and start growing from May to December. Flowers are round, found in each leaf axil, and facing downward or toward the roots [12,34,40].

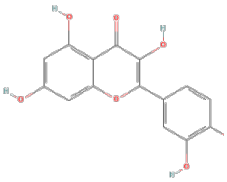
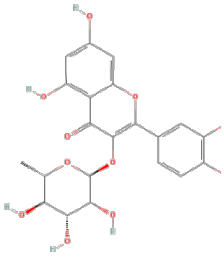
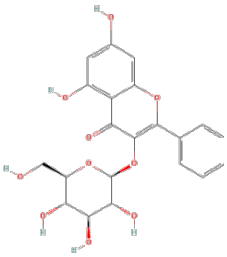
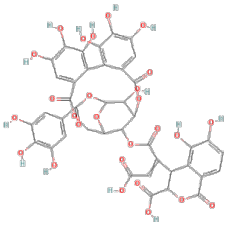
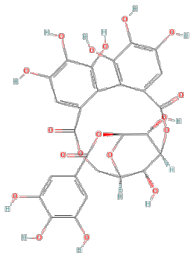
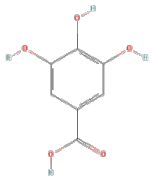
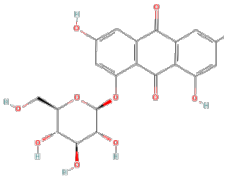
2.2. Compounds *Phyllantus niruri* L. and *Phyllantus urinaria* L. documented as anti-HBV

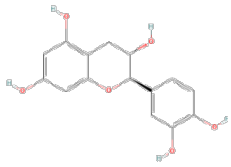
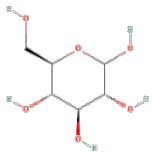
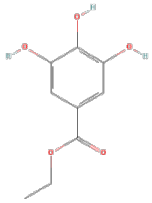
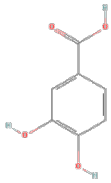
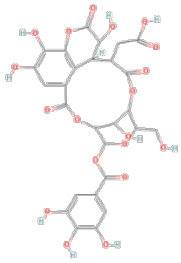
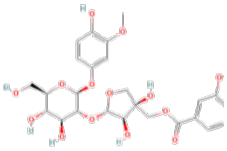
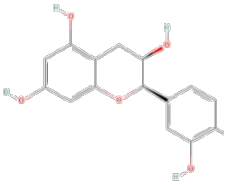
Phyllantus niruri L. and *Phyllantus urinaria* L. are known and used by the community as traditional medicines and raw materials for herbal products due to their health benefits [5,15,41]. Furthermore, the components of the roots, stems, leaves, and fruits of these two species are shown to contain compounds with the potential to be used in medicine [15,16,42]. Handayani and Nurfadillah [34] reported that *Phyllanthus niruri* L. contains tannins (catechole), saponins, and carbohydrates, while *Phyllanthus urinaria* L. contains tannins (catechole) and saponins. In addition, Geethangili and Ding [12] explained the phytochemical compounds found in parts of the *Phyllantus urinaria* L. plant, namely, lignans, tannins, flavonoids, phenolics, terpenoids, and other secondary metabolites. Sabdoningrum et al. [32] stated the results of phytochemical screening of the *Phyllantus niruri* L. nanoparticle extract and obtained the contents of flavonoids, tannins, saponins, terpenoids, and alkaloids. Similarly, Nisar et al. [16] explained the dominance of the compounds in Phyllanthus species, namely, tannins, terpenes, alkaloids, glycosidic, saponins, flavonoids, gallic acid, and ellagic acid. *Phyllantus niruri* L. and *Phyllantus urinaria* L. contain bioactive compounds identified and clinically tested for use as commercial traditional drug candidates (herbal medicine, standardized herbal medicine and phytopharmaceuticals) [43]. Inhibitory agents of HBV are presented in Table 1, while the structure and molecular formula are adopted from PubChem [44].

Table 1. Compounds of *Phyllanthus niruri* L. and *Phyllanthus urinaria* L. as anti-HBV agents

Compound	Chemical Structure	Group	IUPAC	Molecular Formula	Ref.
Neutralin		Lignan	(7*R*,8*R*,9*S*)-9-(3,4-dimethoxyphenyl)-4-methoxy-7,8-bis(methoxymethyl)-6,7,8,9-tetrahydrobenzo[g][1,3]benzodioxole	$C_{24}H_{30}O_7$	[45–47]
Phyllanthin		Lignan	4-[(2*S*,3*S*)-3-[(3,4-dimethoxyphenyl)methyl]-4-methoxy-2-(methoxymethyl)butyl]-1,2-dimethoxybenzene	$C_{24}H_{34}O_6$	[48]

Niranthin		Lignan	6-[(2*R*,3*R*)-3-[(3,4-dimethoxyphenyl)methyl]-4-methoxy-2-(methoxymethyl)butyl]-4-methoxy-1,3-benzodioxole	$C_{24}H_{32}O_7$	[46,49]
Hinokinin		Lignan	(3*R*,4*R*)-3,4-bis(1,3-benzodioxol-5-ylmethyl)oxolan-2-one	$C_{20}H_{18}O_6$	[49]
Ellagic acid		Flavonoid	6,7,13,14-tetrahydroxy-2,9-dioxatetracyclo[6.6.2.0^{4,16}.0^{11,15}]hexadeca-1(15),4,6,8(16),11,13-hexaene-3,10-dione	$C_{14}H_6O_8$	[30,50]
Ethanol		Alcohol	ethanol	C_2H_6O or CH_3CH_2OH	[50]
Phyllanthosterol		Flavonoid	(1*S*,2*R*,5*R*,10*R*,14*S*,15*S*)-14-[(*E*,5*R*)-5-ethyl-6-methylhept-2-en-2-yl]-2,15-dimethyltricyclo[8.7.0.0^{2,7}]heptadec-7-en-5-ol	$C_{29}H_{50}O$	[18]
Ethyl brevifolin carboxylate		Coumarin	ethyl 7,8,9-trihydroxy-3,5-dioxo-1,2-dihydrocyclopenta[c]isochromene-1-carboxylate	$C_{15}H_{12}O_8$	[51]
Tenofovir		Analog Nukleosida	[(2*R*)-1-(6-aminopurin-9-yl)propan-2-yl]oxymethylphosphonic acid	$C_9H_{14}N_5O_4P$	[51]

Quercetin		Flavonoid	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one	$C_{15}H_{10}O_7$	[51]
Quercitrin		Flavonoid	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxychromen-4-one	$C_{21}H_{20}O_{11}$	[51]
Astragalin		Flavonoid	5,7-dihydroxy-2-(4-hydroxyphenyl)-3-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one	$C_{21}H_{20}O_{11}$	[51]
Repandusinic acid		Tannin	4-[1-carboxy-3-[[6,7,8,11,12,13,22-heptahydroxy-3,16-dioxo-21-(3,4,5-trihydroxybenzoyl)oxy-2,17,20-trioxatetracyclo[17.3.1.$0^{4,9}$.$0^{10,15}$]tricosa-4,6,8,10,12,14-hexaen-23-yl]oxy]-3-oxoprop-1-en-2-yl]-5,6,7-trihydroxy-1-oxo-3,4-dihydroisochromene-3-carboxylic acid	$C_{41}H_{30}O_{28}$	[31]
Corilagin		Tannin	[(1*S*,19*R*,21*S*,22*R*,23*R*)-6,7,8,11,12,13,22,23-octahydroxy-3,16-dioxo-2,17,20-trioxatetracyclo[17.3.1.$0^{4,9}$.$0^{10,15}$]tricosa-4,6,8,10,12,14-hexaen-21-yl] 3,4,5-trihydroxybenzoate	$C_{27}H_{22}O_{18}$	[52]
Gallic acid		Coumarin	3,4,5-trihydroxybenzoic acid	$C_7H_6O_5$ or $C_6H_2(OH)_3COOH$	[52]
Aloe -emodin-8-O-β-D-glucopyranoside		Phenol	1,6-dihydroxy-3-methyl-8-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyanthracene-9,10-dione	$C_{21}H_{20}O_{10}$	[53]

Catechin		Flavonoid	(2*R*,3*S*)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2*H*-chromene-3,5,7-triol	$C_{15}H_{14}O_6$	[53]
D-glucopyranoside		Glucose	(3*R*,4*S*,5*S*,6*R*)-6-(hydroxymethyl)oxane-2,3,4,5-tetrol	$C_6H_{12}O_6$	[53]
Ethyl gallate		Phenol	ethyl 3,4,5-trihydroxybenzoate	$C_9H_{10}O_5$	[53]
Protocatehuic Acid		Phenol	3,4-dihydroxybenzoic acid	$C_7H_6O_4$	[53]
Chebulanin		Phenol	2-[13,17,18,21-tetrahydroxy-7-(hydroxymethyl)-2,10,14-trioxo-5-(3,4,5-trihydroxybenzoyl)oxy-3,6,9,15-tetraoxatetracyclo[10.7.1.1^{14,8}.0^{16,20}]henicosa-1(19),16(20),17-trien-11-yl]acetic acid	$C_{27}H_{24}O_{19}$	[53]
Albibrissinoside B		Phenol	[(3*S*,4*R*,5*S*)-5-[(2*S*,3*R*,4*S*,5*S*,6*R*)-4,5-dihydroxy-2-(4-hydroxy-3-methoxyphenoxy)-6-(hydroxymethyl)oxan-3-yl]oxy-3,4-dihydroxyoxolan-3-yl]methyl 4-hydroxy-3,5-dimethoxybenzoate	$C_{27}H_{34}O_{16}$	[53]
(-)-Epicatechin		Flavonoid	(2*R*,3*R*)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2*H*-chromene-3,5,7-triol	$C_{15}H_{14}O_6$	[54]

2.3 Efficacy of *Phyllantus niruri* L. as an inhibitor of HBV

The literature search in the database yielded 21 articles, of which 9 met the criteria for inclusion. The main considerations were the discussion of the variables studied and the completeness of their content. All 9

selected articles focused on the inhibitory activity of compounds in *P. niruri* L. against HBV. The different parts of the plant were used as drug candidates and then tested as extracts on virus colonies, infected cells, or through computational methods. *In vitro* testing was mainly carried out using HepG2 cells 2.2.15, while *in vivo* and *ex vivo* analyses were performed on ducks infected with HBV (DHBV). In contrast, *in silico* testing uses viral material or parts such as DNA, capsid, and amino acids. The inhibition mechanisms included the secretion and expression of HBsAg, HBcAg, and HBeAg. The efficacy of *P. niruri* L. as an inhibitor of HBV is summarized in Table 2.

Table 2. Summary of the efficacy of *P. niruri* L. as an inhibitor of HBV

Part/Compound/preparation	Method	Test medium	Mechanism	Results	Ref.
Lignans (Nirtetralin, A, B)/Extracts	*In vitro*	HepG cells 2.2.15	Nirtetralin and nirtetralin B effectively suppress HBsAg and HBeAg secretion in HepG 2.2.15 cells by reducing HBV concentrations and inhibiting hepatitis B virus replication.	Nirtetralin, nirtetralin A, and B effectively suppress HBV antigen secretion dose-dependently. IC50 for HBsAg 9.5 mM (nontetralin A), 16.7 mM (nirtetralin B) and 97.2 mM (nontetralin), IC_{50} for HBeAg of 17.4 mM (nontetralin A), 69.3 mM (nontetralin B) and 232.0 mM (nontetralin). The presence of the 4-methoxy-6-(3-methoxypropyl) benzo[d]1,] dioxol fragment is the key to anti-HBV activity in the *P. niruri* L. lignans.	[45]
Leaves and stems/Extracts	*In vitro*	HepG2-NTCP and Hep38.7- tet cells	*P. niruri* compounds inhibit HBV entry and replication steps. Phyllanthin compounds are thought to interact with the incoming receptors of the hepatitis virus and show hepatoprotective activity.	*P. niruri* extract produced anti-HBV activity by inhibiting HBV entry into HepG2-NTCP and HBV DNA levels in HepAD38.2 cells. Administration of *P. niruri* Extract resulted in a strong reduction of HBs production in HepG2-NTCP cells. The resulting inhibition of *P. niruri* was IC_{50} 170.5 g/ml and CC value >400 g/mL and inhibited postentry steps (extracellular HBV DNA) without showing cytotoxicity.	[45]
Niranthin/Extract	*In vitro* and *in vivo*	HepG2.2.15 cells and ducks infected with hepatitis B virus (DHBV).	Niranthin compounds inhibit DHBV DNA replication, HBV antigen expression, and HBsAg and HbeAg secretion. Niranthin causes intracellular retention of HBV DNA by inhibiting HBV polymerase activity.	*P. niruri* extract significantly reduced HBsAg and HBeAg secretion in HepG2.2.15 cells after treatment with niranthin for 144 hours. IC_{50} values for HBsAg were 15.6 M, and IC_{50} values for HBeAg were 25.1 M. In DHBV-infected ducks, niranthin significantly reduced serum DHBV DNA, HBsAg, HBeAg, ALT, and AST. Niranthin in *P. niruri* extract is effective as an anti-hepatitis B (HBV).	[48]

All parts/extract	*In vitro*	HBV MS-G2 cells	Niranthin compounds inhibit HBsAg secretion, while Hinokinin inhibits HBeAg secretion in HBV MS-G2.	The compounds niranthin (1), nirtetralin (3), hinokinin (5), and geraniin (13) effectively suppress the production of HBsAg and HbeAg with an effective concentration of 50% (EC_{50}) at the suppression of HBsAg 33.6 µm, 36.9 µm, 36 .7 µm, and> 50 µm, respectively. The niranthin compound showed higher activity than α-interferon (EC_{50} = 960.8 units/mL) and osesthole (EC_{50} = 59.1µm).	[46]
All parts/extract	*In vitro*	HepG2/C3A cells	The ethanol fraction of P. niruri extract reduces HBeAg production in HepG2/C3A and SK-HEP-1 cells	*P. niruri* extract showed anti-HBV activity on HepG2/C3A cells. The isolated active compound showed a half-maximum inhibitory concentration (IC_{50}) of 120 g/mL. Ellagic acid does not affect HBV DNA replication and reproduction. However, the ethanol fraction of *P. niruri* extract inhibited the growth of HepG2/C3A and SK-HEP-1 cells with HBV.	[49]
Nirtetralin B/ Extract	*In vitro* and *in vivo*	HepG2 2.2.15 cells and ducks infected with hepatitis B virus (DHBV).	Nirtetralin B reduces serum HBV DNA levels and HBsAg and HbeAg secretion, which further inhibits DHBV DNA replication and rebound	Nirtetralin B isolated from *P. niruri* effectively suppressed HBV antigen secretion dose-dependently. The IC_{50} value for HBsAg was 17.4 M, and the IC_{50} value for HBeAg was 63.9 M. In DHBV-infected ducks, nirtetralin B (oral and doses of 25, 50, and 100 mg/kg/day) significantly reduced serum DHBV DNA, HBsAg, HBeAg, ALT, and AST, as well as nirtetralin B have an effect hepatoprotective.	[50]
Phyllanthosterol Molecule/Virtual extract	*In silico*	The amino acid capsid of the hepatitis B virus	Phyllanthosterol compounds in P. niruri inhibit the development of wild-type and mutant hepatitis B virus (HBV) and interact with alkyl hydrophobic binding residues.	The binding energy of phyllantosterol was found to be 6.7 and 7.4 kcal/mol in the molecular docking and mutant studies. The ARG98 residue is associated with hydrogen bonding interactions and the mutant protein. However, the wild-type structure has no hydrogen bonds with the binding residues. TRP102 and PHE103, in addition to certain common residues such as LEU100, LEU101, and HIS104, were found to be involved in hydrophobic	[55]

				interactions in wild-type and mutant proteins.	
Secondary Metabolites/Virtual Extracts	*In silico*	Hepatitis B virus DNA polymerase (HBV-DP)	There is a strong and active interaction between the ligands (Ethyl brevifolincarboxylate, Tenofovir, Quercetin, and Quercitrin) from P. niruri and HBV-DP hence it is a potential inhibitor for HBV-DP	35 phytochemical compounds of *Phyllanthus niruri* yielded 582 conformers and 60 ligands. Brevifolincarboxylic ethyl (binding energy-195,409 kcal/mol) and astragalin (binding energy-195,431 kcal/mol). Quercitrin has the lowest binding energy (–283.757 kcal/mol). The compound interacts with hydrogen bonds. Lys32, Asn36, Val84, and Asp205 in the HBV-DP pocket. Furthermore, the quercetin compound with binding energy (-263.645) interacts with the hydrogen bonds of Lys32, Asn36, and Arg41 in the HBV-DP pocket. All of the phytocompounds except brevifolincarboxylate ethyl showed hepatotoxicity. The strongest interaction occurred between the active HBV-DP residue and ethyl brevifolincarboxylate	[18]
Secondary Metabolites/ Virtual Extracts	*In silico*	Crystal structure of the VHB core protein	Repanducinic acid compound inhibitions viral replication by inhibiting capsid formation formed by HBV core protein dimers.	Repanducinic and amino acid residues have the highest scores. The phenolic group of repanducinic acid interacts with the B chain of Thr 33, Trp 102, and Phe 23. The C chain forms hydrogen bonds with the amino acids Thr 128, Val 124, and Glu 117. The O2 atom of the carbonyl group interacts to form a hydrogen bond Leu 140 Tyr 118 and Ser 141 of the VHB core protein B chain.	[51]

2.4 Efficacy of *Phyllantus urinaria* L. as an inhibitor of HBV

The literature search in the database yielded 17 articles, of which six were suitable for this review based on their relevance to the variables and the completeness of their contents. These six articles all focused on the anti-HBV properties of compounds found in *Phyllantus urinaria* L. The study found that the roots, stems, and leaves of *P. urinaria* L. were the most commonly used parts of the plant and were tested in the form of extracts on viral colonies or cells infected with HBV. The test medium was found to consist of plasmid pHBV1.1, HepG2 cells 2.2.15, SMMC-7721, and Huh 7 cells, which are human hepatomas commonly used in drug metabolism and hepatotoxicity studies. The mechanisms explored as HBV inhibitors centered on the secretion and expression of HBsAg, HBcAg, and HBeAg. A summary of the efficacy of *Phyllantus urinaria* L. as an anti-HBV agent is presented in Table 3.

Table 3. Summary of the efficacy of *P. urinaria L.* as an inhibitor of HBV

Part/Compound/preparation	Method	Test medium	Mechanism	Results	Ref.
All parts/extracts	*In vitro*	Plasmids pHBV1.1	*Phyllanthus urinaria* L. extract reduced HBsAg levels in the supernatant, suppressed intracellular HBcAg expression, and inhibited HBV DNA levels at concentrations of 0.8 and 0.2 g/L.	The supernatant HBsAg concentration increased compared to normal cells (p<0.05), HBsAg levels decreased in the supernatant after extract application at concentrations of 0.8 and 0.2 g/L (p<0.05), reduced levels of HBV rc DNA, ds DNA, ss DNA (p<0.01) and strong inhibition of HBcAg expression (p<0.01).	[22]
Flavonoids (ellagic acid)/Extracts	*In vitro*	Sel HepG2 2.2.15	*P. urinaria* L. ellagic acid (flavonoid) blocks HBeAg secretion in HBV-infected HepG2 2.2.15 cells. Ellagic acid reduces HBeAg by destabilizing HBeAg, increasing HBeAg proteolysis, and modifying HBeAg.	The amount of extracellular HBeAg decreased, while intra and extracellular HBsAg with intracellular HBeAg remained constant. Value CC_{50} 936 µg/mL, IC_{50} = 0,07 µg/mL and LD_{50} of 5 µg/kg	[30]
Corilagin and gallic acid/Extract	*In vitro*	Sel HepG2	P. urinaria extract inhibited HBV DNA synthesis and HBsAg and HBcAg secretion by inducing the expression of mRNA interferon-beta (IFN-ÿ), COX-2 (cyclooxygenase-2), IL-6 (interleukin-6)	Expression of intracellular HBV DNA in HepG2 cells decreased after being given the extract, and HBsAg and HBcAg secretion decreased depending on the dose. There was an increase in the expression of TLR-3, RIG-I, TRAF-6, MyD88, COX-2, IL-6, and IFN-ÿ in HepG2 cells, P. urinari extract triggered an inflammatory response, thereby inhibiting HBV replication. The mean CC_{50} yield was 757.0±56.5 g/mL, and EC_{50} and EC_{90} were 78.6 ± 1.3 and 154.8±11.8 g/mL, respectively. The EC_{50} of the extract with HBsAg and HBcAg secretion were 252.5±27.0 and 185.9 ± 30.1 µg/mL, respectively.	[52]
Phenolic/extract	*In vitro*	Sel HepG2.2.15	The compounds emodin-8-O-ÿ- D-glucopyranoside, catechin, 3-O-methylgalic acid, ethyl gallate, and protocatechuic acid inhibit the secretion of HBsAg and HBeAg on HepG2.2.15 cells.	Approximately 16 isolates of phenolic compounds in *P. urinaria* extract were identified. All isolates showed significant antioxidant activity. Isolates 4 (chebulanin) and 5 (albibrissinoside B) had oxygen radical absorbance capacities of 5.12 and 8.13 U/mol and strong inhibitory activity with IC_{50} values of 5.50 and 5.55 µM, respectively. The compounds emodin-8-O-ÿ-D-glucopyranoside, catechin, 3-O-methylgalic acid, ethyl gallate,	[53]

				and protocatechuic acid were the most active and significantly inhibited HBsAg and HbeAg secretion.	
Whole section/Extract	*In vitro, in vivo, ex vivo*	HepG2 cells, SMMC-7721, Huh 7	*P. urinaria* extract induced autophagic degradation of Cav-1 (Caveolin-1), activated the Akt/GSK3β-mediated proteasome degradation of -catenin through activation of ubiquitination, and resulted in suppression of the metastasis-promoting effect of Cav-1 in HBV-associated HCC.	*In vitro* test results of P. urinaria extract inhibited HepG2, SMMC-7721, and HuH-7 cells, significantly reducing the colony size and number of HCC, HepG2, SMMC-7721, and HuH-7 cells. Suppress cell proliferation of HBV-associated HCC, including HepG2-HBx and HepG2-URG11 dose-dependent and inhibited the formation of clones of HepG2-HBx and HepG2-URG11 cells. *In vivo* and *ex vivo* tests showed that P. urinaria inhibited tumor growth and HBV-related HCC metastasis in mouse liver cancer xenograft models and zebrafish xenotransplantation.	[56]
Whole section/extract	*İn Vitro and İn Vivo*	HepG2-HBx cells and mice infected with HBx	*P. urinaria* extract reduces HBx expression, as well as inactivates the expression of Sonic hedgehog (SHH) mRNA and protein, patched transmembrane receptor (PTCH-1), smoothened (SMO), homologous transcription factor oncogene-1 (GLI-1), and homologous transcription factor oncogene-2 (GLI-2). In brief, the extract inhibited the expression of SHH, PTCH-1, GLI-1, HBx RNA and proteins.	Compound *P. urinaria* has anti-HBV-related HCC capability by disabling the pathway axis HBx-Hedgehogs. HepG2-HBx cells, overexpressing HBx, were treated with CP (70 g/ml and 35 g/ml, respectively) for 48 h, and mice receiving HepG2-HBx cells were given P. urinaria extract (625 mg/kg and 300 mg/kg, respectively) for 17 days to evaluate the effect of the extract on HCC – HBV. HBx can accelerate HepG2 cell proliferation, clone formation, and migration *in vitro* and can strengthen mouse tumor growth. Therefore, *P. urinaria* extracts significantly reduced HepG2-HBx cell proliferation, clone formation, and migration *in vitro* and inhibited tumor growth in mice, depending on the dose.	[57]

3. DISCUSSION

Hepatitis B virus infection is a disease prone to increased morbidity and mortality, especially in pregnant women. The virus leads to liver fibrosis and cirrhosis caused by viral infections, contamination of toxic substances, or autoimmune diseases [2,3]. This disease can be prevented by using vaccines. However, many people are still trying to obtain other alternatives by utilizing plant parts as herbal and traditional medicines [23,58,59]. The prevailing public conviction regarding the potency of the components present in medicinal plants and their associated properties has prompted a significant number of investigations to explore the advantages and viability of plant compounds as commercially viable pharmaceutical agents [5,60]. Recent studies have shown that *Phyllantus niruri* L. and *Phyllantus urinaria* L. can be used as HBV inhibitory agents [31,52]. Furthermore, the secondary metabolites in both *Meniran* species have active and significant antiviral and hepatoprotective benefits in their anti-inflammatory, antioxidant, and anticancer properties

[29,48]. Natural compounds in the form of lignans, coumarins, ethanol, flavonoids, tannins, glucose, and phenols are found in all parts of *Meniran* [16,19,30,32,38,39,61].

Lignan compounds in meniran, such as *niretralin A* and *B, phyllanthin, niranthin, and hinokinin,* are reported to have an inhibitory effect on cells infected with HBV. This is similar to the finding of Wei et al. [45], where nitetralin A and B effectively suppressed HBsAg and HBeAg secretion in HepG2.2.15 cells by lowering HBV concentrations and inhibiting HBV replication. Furthermore, the *in vitro* test conducted by Huang et al. [49] found that niranthin had a very strong inhibitory effect on HBsAg secretion, and hinokinin inhibited HBeAg in HBV MS-G2 cells. Liu et al. [46] reconfirmed this finding using two test models, where the same results were obtained in the *in vitro* and *in vivo* tests. The effects of the potential and significant niranthin compound as an anti-HBV significantly reduced serum DHBV DNA, HBsAg, HBeAg, ALT, and AST. Therefore, the lignan class compounds obtained from *Meniran* have anti-HBV biological activity, including hepatoprotective effects.

Other natural compounds of the coumarin group reported to have potential as HBV inhibitors, including ethyl brevifolincarboxylate and gallic acid, as well as a nucleoside analog in the form of tenofovir, work by inhibiting viral DNA synthesis as well as HBsAg and HBcAg secretion. These compounds induce the expression of interferon-beta (IFN-ÿ), COX-2 (cyclooxygenase-2), and IL-6 (interleukin-6) mRNA [19,51,52]. Furthermore, the isolation of flavonoid compounds, including ellagic acid, phyllanthosterol, quercetin, quercitrin, astragalin, catechin, and (-)-epicatechin in *Meniran,* has been shown to have inhibitory effects on HBeAg. The HepG2 cell line 2.2.15 is employed as a test medium through the process of destabilization, which results in the amplification of the degradation of proteins into polypeptides and the modification of the activity and properties of HBeAg. Therefore, HBV is impaired in its normal functioning, making it a valuable and productive candidate as a viral blocking agent [18,30,50,51,53,61].

Firdayani et al. [31] explained that the repanducinat acid contained in *Meniran* could inhibit viral replication during the formation of the protein shell. Furthermore, Jung et al. [52] stated that pure corylaginous compounds significantly inhibit HBV DNA synthesis with HBsAg and HBcAg secretion. Corilagin, in contact with HBV, can induce IFN-ÿ, COX-2, and IL-6 mRNA expression. Phenol group compounds, including aloe-emodin-8-O-β-D-glucopyranoside, ethyl gallate, protocatequatic acid, chebulanin, and albibrissinoside B, can be developed as HBV inhibitory agents. This is because tannin class compounds were reported to be active and strong in inhibiting HBsAg and HBeAg secretion in HepG2.2.15 cells and showing other activities as hepatocellular carcinoma inhibitory agents [19,47,53].

The potential for the isolation of natural and bioactive compounds from the species *Phyllantus niruri* L. and *Phyllantus urinaria* L. is very promising, especially in their development as candidates for commercial and modern drug development [5]. Furthermore, the identification of bioactive molecules and specific targets related to the HBV receptor should be studied further. The pharmacological properties of the *Meniran* species have shown promising potential for the development of standardized herbal medicines and phytopharmaceuticals, particularly in Indonesia. Several studies have identified the pharmacological activity of *Phyllantus niruri* L. and *Phyllantus urinaria* L., which further require clinical trials and official registration regarding the use of 23 *Meniran* bioactive compounds as HBV inhibitory agents.

4. STUDY LIMITATIONS

The limitations of this study are the lack of articles obtained related to the topic of study, and the application of strict criteria allows articles that have similar topics not identified by search engines. Accurate data on the inhibition mechanism of *P. niruri* L. and *P. urinaria* L. from sources used as references cannot clearly describe the processes and results. This is because differences in test samples and targets are the main considerations; hence, further investigation is needed.

5. CONCLUSION

Phyllantus niruri L. and *Phyllantus urinaria* L. are a group of seasonal herbs that contain bioactive compounds and activity as HBV inhibitors. These plants contain 23 compounds, namely, niretralin, phyllanthin, niranthin, helinokinin, ellagic acid, ethanol, phyllanthosterol, ethyl brevifolincarboxylate, tenofovir, quercetin, quercitrin, astragalin, repanducinic acid, corilagin, gallic acid, aloe-emodin-8-O-β-D-glucopyranoside, catechin, D-glucopyranoside, ethyl gallate, protocatequatic acid, chebulanin, albibrissinoside B, and (-)-epicatechin. The activity in inhibiting cells infected with the hepatitis B virus was reported through *in vitro*, *in vivo*, *ex vivo*, and *in silico* analyses. Furthermore, the mechanism of bioactive compounds such as HBV inhibitors focuses on suppressing, blocking, and inhibiting the synthesis, secretion, and expression of HBsAg, HBcAg, and HbeAg in the indicators of anti-HBV. The bioactive compounds *Phyllantus niruri* L. and *Phyllantus urinaria* L. can be developed as raw materials for herbal medicine and have

promising prospects as commercial drugs. Hopefully, this review will provide the latest information and stimulate further study related to the activity and potential of *P. niruri* L. and *P. urinaria* L. as inhibitors of HBV. Future studies are needed regarding the pharmacological effects, toxicity, and mechanism of HBV inhibition using molecular or genomic scales.

6. MATERIALS AND METHODS

The study is guided by the Scale for the Assessment of Narrative Review Articles (SANRA) [62]. Eligibility is determined independently by reviewing the title and abstract that fulfils the requirements based on the following criteria: (1) the study discusses the activity and efficacy of *Phyllantus niruri* L. and *Phyllantus urinaria* L. as HBV inhibitors, (2) testing was carried out on animals, HBV virus culture and computational tests *in vivo*, *in vitro* and *in silico*, (3) original study articles, (4) open access and in English, (5) years of publication between 2000 and 2022 and (6) entry into a reputable journal, such as Scopus or Web of Science. The journal's reputation was considered to check its credibility. To be included in this review, articles should address HBV/HBsAg/HBeAg inhibition after administration of *P. niruri* L. and *P. urinaria* L. plant parts, mechanisms of inhibition, phytochemical screening, IC_{50} testing, and toxicity at CC_{50}, LD_{50} or EC_{50} and EC_{90}. At this stage, articles that do not comply with the eligibility criteria, present duplication, and are not relevant were omitted.

Articles were collected using the PubMed (MesH), SciFinder, ScienceDirect, MedLine, Web of Science, ProQuest, and Embase databases with the keyword '*Phyllantus niruri* L.' OR '*P. niruri*', '*Phyllantus urinaria* L.' OR '*P. urinaria*', 'anti-hepatitis B' AND 'HBV,' 'antivirals,' 'HBV inhibitors, 'HBsAg,' 'HbeAg,' 'HBcAg,' and 'medicinal plants.' Furthermore, all potential articles were included and screened in two stages of eligibility. In the first assessment stage, screening was carried out by selecting titles and abstracts. The second stage was filtered based on the results and discussion under the study topic, and a comprehensive and independent analysis was performed [63]. Data extraction was carried out by collecting the names of the authors and the year of publication, the identified compounds of *P. niruri* L. and *P. urinaria* L., data on HBV inhibition, preparations used, plant parts, dosage amounts, and test results. Toxicity, bibliographic data, outcome features, and follow-up results were extracted independently. Subsequently, these data were reconciled to obtain information on the activity and potency of *P. niruri* L. and *P. urinaria* L. as HBV inhibitory agents and their underlying mechanisms. All data were presented in summary tables, graphs, and narratives.

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