Review Article
Natural Products: Review for Their Effects of Anti-HBV

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1. Introduction

Viral hepatitis B, referred to as hepatitis B, is a disease caused by the infection of hepatitis B virus (HBV, Figure 1). The infection of HBV can cause liver failure, acute or chronic hepatitis, cirrhosis, and even hepatocellular carcinoma (HCC). About 2 billion people worldwide are infected with HBV, of which 400 million are long-term carriers [1, 2]. According to research reports by the World Health Organization (WHO), about 600,000 people die of HBV infection or liver diseases related to HBV infection every year [3, 4]. China has the largest population of HBV-infected people worldwide and is confronting this large disease burden with efficient antiviral drugs.

At present, there are mainly two kinds of drugs used in the clinic, namely, interferons (INFs) with antiviral and immunoregulatory functions and nucleoside analogues that can inhibit the reverse transcription of HBV [5, 6]. In recent years, although these drugs have a certain therapeutic effect on HBV infection in the clinic, there are serious side effects and drug resistance [7, 8]. Thus, there are more and more researchers focus on natural product [9–11]. Some researches report a variety of natural medicines with novel structure and anti-HBV activity, including some candidate drugs with good anti-HBV effects. However, these reports were mainly involved in isolation and identification of compounds with anti-HBV activity; the mechanisms and targets of compounds were less. The mechanism of clinical medicines (nucleoside analogues and interferon) on anti-HBV is basically clear, but the emergence of drug-resistant HBV mutants weakens the clinical effects. Thus, the development of safe and effective anti-HBV drugs with novel mechanism is the top priority in the current research [7, 12]. In this manuscript, in order to help researchers understand HBV and develop the anti-HBV drugs, all kinds of natural products (Table 1) with anti-HBV effects and the infection process of HBV (Figure 1) [13–17] were summarized. The types of natural products with anti-HBV activity include phenylpropanoids, flavonoids, alkaloids, terpenes, glycosides, and others (such as lactones and organic acids).
29.60 μStreblus asper Lour core material, had significant anti-HBV activity by inhibiting the secretion of HBsAg and HBeAg with IC50 of 10.34 μM and 3.67 μM, respectively. For inhibiting the secretion of HBeAg, IC50 was 8.83 μM and 14.67 μM, respectively, without cytotoxicity. Honokiol (7) and (7′ R, 8′ S, 7′ R, 8′ S)-erythron-Streblus lignanol G (8), isolated from methanol extract of roots of S. asper, have strong anti-HBV activity by inhibiting the secretion of HBsAg and HBeAg. In addition, compounds 7and 8 could significantly inhibit the replication of HBV-DNA, with IC50 values of 9.02 and 8.67 μM, respectively [22, 23]. Coumarin lignan (9) isolated from the stem of Kadsura heteroclita could inhibit the production of HBsAg and HBeAg with concentration of 25 μg/mL. The inhibition of compound 9 (57% and 48%) was even better than that of positive control, lamivudine (10% and 46%) [24]. Niranthin (10), isolated from Phyllanthus niruri, could inhibit the secretion of HBsAg and HBeAg in dose-dependent, with IC50 values of 16.5 μM and 25.1 μM. The inhibition rates of 10 on HBsAg and HBeAg were 90.4% and 83.1% with 55.5 μM while the inhibition rates of lamivudine were 55.6% and 44.5% with 43.6 μM. The anti-HBV effect of compound 10 was better than that of lamivudine. The inhibition rates of compound 10 on DHBV-DNA, HBsAg, and HBeAg were higher than that of lamivudine, and the recovery rate was smaller after drug withdrawal, indicating that compound 10 had a good prospect in the development of new anti-HBV drugs.

2. The Natural Products of Anti-HBV

2.1. Phenylpropanoids. Phenylpropanoids have a wide range of biological activities, including antitumor, antivirus, liver protection, and antioxidation. For example, a variety of lignans in fruits of Schisandra chinensis have liver protective effects and can reduce serum alanine aminotransferase level. Schisandrae esteril A and its analogues have been used in the treatment of chronic hepatitis in China [18].

6-Hydroxy-7-methoxyl-coumarin (1), isolated from the Streblus asper Lour core material, had significant anti-HBV effect on HepG 2.2.15 cells [19]. And the mechanism of compound 1 on anti-HBV effect may be related to its inhibition on secretion of hepatitis B virus surface antigen (HBsAg) and hepatitis B virus e antigen (HBeAg), and the IC50 were 29.60 μM (selective index, SI = 6.76) and 46.41 μM (SI = 4.31), respectively. Esculetin (2) from Microsorium fortunei (Moore) Ching, could not only inhibit the expression of the HBV antigens and HBV-DNA but also inhibit the expression of hepatitis B virus X(HBx) protein in a dose-dependent manner [20]. Chen et al. [21] isolated a series of phenylpropanoids from the core material, bark and root of S. asper, all of which had significant anti-HBV activity. Among them, Magnatriol B (3) showed moderate anti-HBV activity by inhibiting the secretion of HBsAg and HBeAg with low cytotoxicity. Honokiol (4) showed significant anti-HBV activity and strong inhibition on HBsAg and HBeAg with IC50 of 3.14 μM (SI = 21.47) and 4.74 μM (SI = 14.22), respectively. The inhibition effect of honokiol on HBsAg and HBeAg was stronger than that of positive control, lamivudine. Isomagnolol (5) and isocarpine (6) from the bark and roots of S. asper showed significant anti-HBV activity by HepG 2.2.15 cell assay and significantly inhibited HBsAg secretion with IC50 of 10.34 μM and 3.67 μM, respectively. For inhibiting the secretion of HBeAg, IC50 was 8.83 μM and 14.67 μM, respectively, without cytotoxicity. Honokiol (7) and (7′ R, 8′ S, 7′ R, 8′ S)-erythron-Streblus lignanol G (8), isolated from methanol extract of roots of S. asper, have strong anti-HBV activity by inhibiting the secretion of HBsAg and HBeAg. In addition, compounds 7and 8 could significantly inhibit the replication of HBV-DNA, with IC50 values of 9.02 and 8.67 μM, respectively [22, 23]. Coumarin lignan (9) isolated from the stem of Kadsura heteroclita could inhibit the production of HBsAg and HBeAg with concentration of 25 μg/mL. The inhibition of compound 9 (57% and 48%) was even better than that of positive control, lamivudine (10% and 46%) [24]. Niranthin (10), isolated from Phyllanthus niruri, could inhibit the secretion of HBsAg and HBeAg in dose-dependent, with IC50 values of 16.5 μM and 25.1 μM. The inhibition rates of 10 on HBsAg and HBeAg were 90.4% and 83.1% with 55.5 μM while the inhibition rates of lamivudine were 55.6% and 44.5% with 43.6 μM. The anti-HBV effect of compound 10 was better than that of lamivudine. The inhibition rates of compound 10 on DHBV-DNA, HBsAg, and HBeAg were higher than that of lamivudine, and the recovery rate was smaller after drug withdrawal, indicating that compound 10 had a good prospect in the development of new anti-HBV drugs.
Table 1: The compounds with anti-HBV effects from natural products.

| No. | Compound | Target | Source | Ref |
|-----|----------|--------|--------|-----|
| 1   | 6-Hydroxyl-7-methoxyl-coumarin | HBsAg and HBeAg | *S. asper* | [19] |
| 2   | Esculetin | HBsAg, HBeAg, and HBV-DNA | *M. fortunei* | [20] |
| 3   | Magnatriol B | HBsAg and HBeAg | *S. asper* | [21] |
| 4   | Honokiol | HBsAg and HBeAg | *S. asper* | [21] |
| 5   | Isomagnolol | HBsAg | *S. asper* | [22, 23] |
| 6   | isocarpine | HBsAg | *S. asper* | [22, 23] |
| 7   | Honokiol | HBsAg | *S. asper* | [22, 23] |
| 8   | (7′ R, 8′ S, 7′ R, 8′ S)-(7,8)-erythron-Streblus lignanol G | HBsAg, HBeAg, and HBV-DNA | *S. asper* | [22, 23] |
| 9   | Coumarin lignan | HBsAg and HBeAg | *K. heteroclita* | [24] |
| 10  | Niranthin | HBsAg and HBeAg | *P. niruri* | [25] |
| 11  | (+)-Dehydrod-iconiferyl alcohol | HBsAg | *S. patens* | [26] |
| 12  | Dehydrozingerone | HBsAg | *S. patens* | [26] |
| 13  | (+)-Cycloolivil-4′-O-β-D-glucopyranoside | HBsAg, HBeAg, and HBV-DNA | *S. chirayita* | [27] |
| 14  | Syringaresinol 4-O-β-D-glucopyranoside | HBsAg | *S. chirayita* | [27] |
| 15  | Luteolin | HBsAg and HBeAg | *S. macroserperma* | [29] |
| 16  | Isovitexin | HBsAg, HBeAg, and HBV-DNA | *S. mussotii* | [30] |
| 17  | LPRP-Et-97543 | Core, S, and preS promoters | *L. muscari* | [31] |
| 18  | Quercetin | HBeAg | | [32] |
| 19  | Glabaarachalcone | HBV-DNA | *P. pinnata* | [33] |
| 20  | Isopongachromene | HBV-DNA | *P. pinnata* | [33] |
| 21  | Isooriention | HBsAg, HBeAg, and HBV-DNA | *S. mussotii* | [34] |
| 22  | Epimedium Hyde II | HBsAg, HBeAg, and HBV-DNA | | [35] |
| 23  | Norbellidifolin | HBV-DNA | *S. mussotii* | [36] |
| 24  | 1,5,8-Trihydroxy-3-methoxyxanthone | HBsAg and HBeAg | *S. mussotii* | [36] |
| 25  | 2-C-β-D-glucopyranosyl-1,3,7-trihydroxyxanthone | HBsAg and HBeAg | *S. mussotii* | [36] |
| 26  | Norswertianolin | HBV-DNA | *S. mussotii* | [36] |
| 27  | Norswertianin-1-O-β-D-glucoside | HBV-DNA | *S. mussotii* | [36] |
| 28  | 1,7-Dihydroxy-3,8-dimethoxynanthone | HBV-DNA | *S. mussotii* | [36] |
| 29  | 7-O-[β-D-xlypyranosyl-(1→2)-β-D-xlypyranosyl]-1,8-dihydroxy-3-methoxyxanthone | HBV-DNA | *S. mussotii* | [36] |
| 30  | Mangiferin | HBV-DNA | *S. mussotii* | [36] |
| 31  | Methyl6,8-dihydroxy-3-methyl-9-oxo-9H-xanthene-1-carboxylate | HBsAg | *Penicillium sp.* | [37] |
| 32  | 1,8-Dihydroxy-3,5-dimethoxynanthone | HBsAg, HBeAg, and HBV-DNA | *S. yunnanensis* | [30] |
| 33  | Norswertianolin | HBV-DNA | *S. yunnanensis* | [30] |
| 34  | Neolancerin | HBsAg, HBeAg, and HBV-DNA | *S. yunnanensis* | [30] |
| 35  | 1,5,8-Trihydroxy-3-methoxyxanthone | HBeAg and HBV-DNA | *S. delavayi* | [38] |
| 36  | (−)-2′ R-1-hydroxyisorhodoptilometrin | HBsAg and HBeAg | *Penicillium sp.* | [37] |
| 37  | Asterric acid | HBsAg | *Penicillium sp.* | [37] |
| 38  | Questinol | HBsAg | *Penicillium sp.* | [37] |
| 39  | Endocrocin | HBsAg | *Penicillium sp.* | [37] |
| No. | Compound                                      | Target                   | Source                  | Ref  |
|-----|----------------------------------------------|--------------------------|-------------------------|------|
| 40  | (+)-2′S-isorhodoptilometrin                  | HBsAg                    | Penicillium sp.         | [37] |
| 41  | Sulochrin                                    | HBsAg                    | Penicillium sp.         | [37] |
| 42  | Monochlorsulochrin                           | HBsAg and HBeAg          | Penicillium sp.         | [37] |
| 43  | Dihydrogeodin                                | HBsAg                    | Penicillium sp.         | [37] |
| 44  | 1,3-Dihydroxy-2-hydroxymethyl-9,10-anthaquinone | HBeAg and HBsAg        | P. connata              | [40] |
| 45  | Rubiadin                                     | HBeAg, HBsAg, HBx, and HBV-DNA | P. connata              | [40] |
| 46  | Anthraquinone bile acid conjugates           | HBeAg and HBsAg          | P. connata              | [40] |
| 47  | Aloin B                                      | HBV-DNA polymerase       | Aloe vera               | [41] |
| 48  | Aloe-emodin                                  | HBsAg, HBeAg             | Aloe vera               | [41] |
| 49  | Hypericin                                    | HBsAg, HBeAg, HBV-DNA, and pgRNA | A. tataricus            | [42] |
| 50  | Ursolic acid                                 | HBsAg and HBeAg          | S. asper                | [19] |
| 51  | MH                                           | HBsAg and HBeAg          | V. tenaifolia           | [44] |
| 52  | Sweryunnangenin A                            | HBsAg and HBeAg          | S. yunnanensis          | [26] |
| 53  | 3-Epitaraxerol                               | HBsAg and HBeAg          | S. yunnanensis          | [26] |
| 54  | Oleanolic acid                               | HBsAg and HBeAg          | S. yunnanensis          | [26] |
| 55  | Erythrocentaurin                             | HBsAg, HBeAg, and HBV-DNA | S. yunnanensis          | [26] |
| 56  | Astataricusones B                            | HBeAg, HBV-DNA, and HBsAg | A. tataricus            | [45] |
| 57  | Epishionol                                   | HBsAg, HBeAg, HBV-DNA    | A. tataricus            | [45] |
| 58  | Astershionones C                             | HBsAg, HBeAg, and HBV-DNA | A. tataricus            | [46] |
| 59  | 4″-Hydroxyγ-3″-methoxyalbiflorin             | HBsAg, HBeAg, and HBV-DNA | P. sinjiangensis        | [47] |
| 60  | 6′-O-p-hydroxybenzoyl-4″-Hydroxyalbiflorin   | HBsAg, HBeAg, and HBV-DNA | P. sinjiangensis        | [47] |
| 61  | Albiflorin                                   | HBsAg, HBeAg, and HBV-DNA | P. sinjiangensis        | [47] |
| 62  | Oxypaeoniflorin                              | HBsAg, HBeAg, and HBV-DNA | P. sinjiangensis        | [47] |
| 63  | Paeoniflorin                                 | HBsAg, HBeAg, and HBV-DNA | P. sinjiangensis        | [47] |
| 64  | Paeonins B                                   | HBsAg, HBeAg, and HBV-DNA | P. sinjiangensis        | [47] |
| 65  | Benzoylpaeoniflorin                          | HBsAg, HBeAg, and HBV-DNA | P. sinjiangensis        | [47] |
| 66  | Perovskatone A                               | HBsAg                    | P. atriplicifolia       | [48] |
| 67  | Demethylsalvicanol                           | HBsAg                    | P. atriplicifolia       | [48] |
| 68  | Chrysanolid B                                | HBsAg and HBeAg          | D. indicum              | [49] |
| 69  | Chrysanolid C                                | HBsAg and HBeAg          | D. indicum              | [49] |
| 70  | Chrysanolid A                                | HBsAg and HBeAg          | D. indicum              | [49] |
| 71  | Pimelotide A                                 | HBsAg                    | P. elongata foliage     | [50] |
| 72  | Wikstroelide W                               | HBV-DNA                  | W. chamaedaphne         | [51] |
| 73  | Genkwaneine P                                | HBV-DNA                  | W. chamaedaphne         | [51] |
| 74  | laurefolioside A                             | HBV-DNA                  | W. chamaedaphne         | [51] |
| 75  | 2-Epi-laurefolioside A                       | HBV-DNA                  | W. chamaedaphne         | [51] |
| 76  | Laurifolioside B                             | HBV-DNA                  | W. chamaedaphne         | [51] |
| No. | Compound                                                                 | Target                | Source               | Ref   |
|-----|-------------------------------------------------------------------------|-----------------------|----------------------|-------|
| 77  | 2-Epi-laurifolioside B                                                 | HBV-DNA              | W. chamaedaphne      | [51]  |
| 78  | Laurifolioside                                                         | HBV-DNA              | W. chamaedaphne      | [51]  |
| 79  | 2-epi-laurifolioside                                                   | HBV-DNA              | W. chamaedaphne      | [51]  |
| 80  | Oleanolic acid 3-O-β-D-glucuronopyranoside                            | HBV-DNA              | A. philoxeroides     | [52]  |
| 81  | 4,5-Dihydroblumenol                                                   | HBV-DNA              | A. philoxeroides     | [52]  |
| 82  | Swercincitosides A                                                    | HBV-DNA and HBsAg    | S. cincta            | [53]  |
| 83  | Swercincitoside B                                                     | HBV-DNA              | S. cincta            | [53]  |
| 84  | 9-Epi swertiamarin                                                    | HBV-DNA and HBsAg    | S. cincta            | [53]  |
| 85  | 2′-O-m-hydroxybenzoyl swertiamarin                                    | HBV-DNA              | S. cincta            | [53]  |
| 86  | 4″-O-actyl swertianoside E                                            | HBV-DNA and HBsAg    | S. cincta            | [53]  |
| 87  | Swertiaside                                                            | HBV-DNA and HBsAg    | S. cincta            | [53]  |
| 88  | Swertianoside C                                                       | HBV-DNA and HBsAg    | S. cincta            | [53]  |
| 89  | Decentapicrin B                                                       | HBV-DNA              | S. cincta            | [53]  |
| 90  | ET derivatives 1e                                                     | HBV-DNA              | Synthesis            | [54]  |
| 91  | ET derivatives 1f                                                     | HBV-DNA              | Synthesis            | [54]  |
| 92  | Swertiakoside A                                                       | HBV-DNA and HBsAg    | S. delavayi          | [38]  |
| 93  | 2′-O-acetylswertiamarin                                               | HBV-DNA              | S. delavayi          | [38]  |
| 94  | Asiaticoside                                                           | HBsAg, HBeAg, and HBV-DNA | H. sibthorpioides | [55]  |
| 95  | Diosgenin                                                              | HBsAg and HBeAg      |                      | [56]  |
| 96  | 7-Eudesm-4(15)-ene-1β,6α-diol                                         | HBV-DNA              | A. capillaris        | [57]  |
| 97  | Pumilaside A                                                           | HBeAg, HBsAg, and HBV-DNA | A. capillaris | [57]  |
| 98  | Erythro-1-[1-oxo-9(3,4-methylenedioxyphenyl)-8,9-dihydroxy-2E-nonenyl]-piperidine | HBsAg and HBeAg | P. longum            | [59]  |
| 99  | Threo-1-[1-oxo-9(3,4-methylenedioxyphenyl)-8,9-dihydroxy-2E-nonenyl]-piperidine | HBsAg and HBeAg | P. longum            | [59]  |
| 100 | Piperine                                                               | HBsAg and HBeAg      | P. longum            | [59]  |
| 101 | Guineesine                                                            | HBsAg and HBeAg      | P. longum            | [59]  |
| 102 | (2E,4E)-N-isobutyleicosa-2,4-dienamide                                | HBsAg and HBeAg      | P. longum            | [59]  |
| 103 | 3β,4α-dihydroxy-1-(3-phenylpropanoyl)-piperidine-2-one                | HBsAg and HBeAg      | P. longum            | [60]  |
| 104 | DHCH                                                                  | HBsAg, HBeAg, cccDNA, and DNA | C. saxicola | [61]  |
| 105 | 8S-deca-9-en-4,6-diyne-1,8-diol                                       | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [63]  |
| 106 | (S)-deca-4,6,8-triyne-1,3-diol                                        | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [63]  |
| 107 | (S)-3-hydroxyundeca-5,7,9-triynoic acid                               | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [63]  |
| 108 | 3S-Hydroxyundeca-5,9-triynoic acid 3-O-β-D-glucopyranoside            | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [63]  |
| 109 | Atractylodin                                                           | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [63]  |
| 110 | Dendroarboreol B                                                      | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [63]  |
| 111 | Dehydrofalcarinol                                                     | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [63]  |
| 112 | Dehydrofalcardinol                                                   | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [63]  |
| No. | Compound | Target | Source | Ref |
|-----|----------|--------|--------|-----|
| 113 | (E)-deca-2-en-4,10-diol | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [63] |
| 114 | (Z)-deca-2-en-4,10-diol | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [63] |
| 115 | 8-Diol 1-O-β-D-glucopyranoside | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [63] |
| 116 | 3S,8S-dihydroxydec-9-ene-4,6-diyne-1-O-β-D-glucopyranoside | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [63] |
| 117 | 5-Benzylthiophencarboxylic acid | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [63] |
| 118 | 2-Methyl-6-phenyl-4H-pyran-4-one | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [63] |
| 119 | 3S,8S-dihydroxydec-9-en-4,6-yne 1-O-(6′-O-cafeoyl)-β-D-glucopyranoside | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [64] |
| 120 | 3S,8S-dihydroxydec-9-en-4,6-yne 1-O-(2′-O-cafeoyl)-β-D-glucopyranoside | HBsAg, HBeAg, and HBV-DNA | A. capillaris | [64] |
| 121 | m-Hydroxybenzoic acid | HBsAg, HBeAg, and HBV-DNA | S. mussotii | [34] |
| 122 | p-Hydroxybenzoic acid | HBsAg, HBeAg, and HBV-DNA | S. mussotii | [34] |
| 123 | 4-Hydroxy benzenmethanol | HBsAg, HBeAg, and HBV-DNA | S. mussotii | [34] |
| 124 | 3,4-Dihydroxybenzonic acid | HBsAg, HBeAg, and HBV-DNA | S. mussotii | [34] |
| 125 | Ethyl 3,4-dihydroxybenzoate | HBsAg, HBeAg, and HBV-DNA | S. mussotii | [34] |
| 126 | Ethyl 2,5-dihydroxybenzoate | HBsAg, HBeAg, and HBV-DNA | S. mussotii | [34] |
| 127 | 3,3′,5-Trihydroxybiphenyl | HBsAg | S. chirayita | [27] |
| 128 | Taraffinisoside A | HBsAg and HBeAg | T. affinis | [65] |
| 129 | Descaffeoyl crenatoside | HBsAg and HBeAg | T. affinis | [65] |
| 130 | 3,4-Dihydroxyphenylethanol-8-O-[β-D-apiofuranosyl (1→3)]-β-D-glucopyranoside | HBsAg and HBeAg | T. affinis | [65] |
| 131 | p-Hydroxy acetophenone (PHAP) | HBsAg | A. morrisonensis | [66] |
| 132 | p-HAP derivative 2f | HBV-DNA | A. capillaris | [67] |
| 133 | Matijin-Su | HBV-DNA | D. repens | [68] |
| 134 | N-[N-(3,4-dimethoxy-benzoyl)-L-phenylalanyl]-O-propionyl-L-phenylalaninol | HBV-DNA | Synthesis | [71] |
| 135 | N-[N-(3,4-dimethoxy-benzoyl)-L-phenylalanyl]-4-ethoxy-L-phenylalaninol | HBV-DNA | Synthesis | [71] |
| 136 | N-[N-(3,4-Dimethoxy-benzoyl)-L-phenylalanyl]-4-ethoxycarbonylmethyl-L-tyrosinol | HBV-DNA | Synthesis | [71] |
| 137 | N-[N-(4-chlorobenzoyl)-O-methyl-L-tyrosyl]-L-Phenylalaninol | HBV-DNA | Synthesis | [72] |
| 138 | N-[N-(4-chlorobenzoyl)-O-propyl-L-tyrosyl]-L-Phenylalaninol | HBV-DNA | Synthesis | [72] |
| 139 | N-[N-(4-chlorobenzoyl)-O-isopropyl-L-tyrosyl]-L-Phenylalaninol | HBV-DNA | Synthesis | [72] |
| 140 | N-[N-(3-trifluoromethylbenzoyl)-L-tyrosyl]-L-Phenylalaninol | HBV-DNA | Synthesis | [73] |
| 141 | N-[N-(3-trifluoromethylbenzoyl)-L-phenylalanyl]-O-propionyl-L-tyrosine methyl ester | HBV-DNA | Synthesis | [73] |
in vivo [25]. (+)-Dehydrodiconiferyl alcohol (11) and dehydrozingerone (12) showed moderate inhibitory activities on the secretion of HBsAg with IC$_{50}$ value of 1.94 mM (SI 1.06) and 0.50 mM (SI 2.88) [26]. (+)-Cycloolivil-4′-O-β-D-glucopyranoside (13) and syringaresinol 4″-O-β-D-glucopyranoside (14) showed inhibitory activity on HBsAg secretion with IC$_{50}$ values of 0.31 ± 0.045 and 0.149 ± 0.033 mM. In particular, compound 13 exhibited inhibition not only on the secretions of HBsAg and HBeAg with IC$_{50}$ values of 0.31 ± 0.045 mM (SI = 4.29) and 0.77 ± 0.076 mM (SI = 1.75), respectively, but also on HBV DNA replication with an IC$_{50}$ value of 0.29 ± 0.034 mM (SI = 4.66) [27]. The chemical structures of compounds 1-14 showed in Figure 2.

2.2. Flavonoids. Flavonoids have a wide range of biological activities, including anti-inflammatory, anticancer, and antibacterial. It has a prominent role in protecting liver; for example, silymarin shows significant effect on protecting liver and has successfully developed into a protect liver medicine [28]. Recently, flavonoids have been reported with good anti-HBV effect. Luteolin (15), isolated from Swertia macroserpina C. B. Clark, could significantly inhibit the secretion of HBsAg and HBeAg with IC$_{50}$ values of 0.02 mM on HepG 2.2.15 cells in vitro [29]. Isovitexin (16) isolated from S. yunnanensis had good anti-HBV activity, which could not only inhibit the secretion of HBsAg and HBeAg, with IC$_{50}$ values of 0.04 mM, <0.03 mM, and 0.23 mM, but also significantly inhibit the replication of HBV-DNA, with the IC$_{50}$ values of 0.09 mM, <0.01 mM, and 0.05 mM [30]. Huang et al. [31] isolated LPRP-Et-97543 (17) from Liriopemuscari (Decne.) L.H.Bailey, which had significant anti-HBV activity and could significantly reduce the activity of Core, S, and

| No. | Compound | Target | Source | Ref |
|-----|----------|--------|--------|-----|
| 142 | N-[N-(3-trifluoromethylbenzoyl)-L-phenylalanyl]-O-ethyl-L-tyrosine | HBV-DNA | Synthesis | [73] |
| 143 | Compound 8n | HBV-DNA | Synthesis | [74] |
| 144 | Compound 8o | HBV-DNA | Synthesis | [74] |
| 145 | Compound 9 a | HBV-DNA | Synthesis | [75] |
| 146 | Compound 9 b | HBV-DNA | Synthesis | [75] |
| 147 | Compound 9 c | HBV-DNA | Synthesis | [75] |
| 148 | Cyclic (glycine-L-proline) | HBsAg, HBeAg, and HBV-DNA | | [76] |
| 149 | Cyclic (4-hydroxy proline-phenylalanine) | HBsAg, HBeAg, and HBV-DNA | | [76] |
| 150 | Cyclic (L-2-hydroxy proline-phenylalanine) | HBsAg, HBeAg, and HBV-DNA | | [76] |
| 151 | N-acetyl phenylalanine | HBsAg and HBeAg | P. crinitum | [77] |
| 152 | Two dimers of oxantrone | HBsAg, HBeAg, and HBV-DNA | S. punicea | [78] |
| 153 | Iridoid lactone | HBsAg, HBeAg, and HBV-DNA | S. punicea | [78] |
| 154 | Anis lactone B | HBeAg | I. henryi | [79] |
| 155 | NC-8 | HBsAg and HBeAg | Synthesis | [80] |
| 156 | IN-4 | HBV-DNA | Synthesis | [81] |
| 157 | Scoparamide A | HBsAg, HBeAg, and HBV-DNA | A. scoparia | [64] |
| 158 | Cichoric acid | DHBV-DNA | C. intybus | [82] |
| 159 | Rosmarinic acid | e-Pol binding | | [83] |
| 160 | 3-Caffeoylquinicacid | HBsAg, HBeAg, and HBV-DNA | L. japonica | [84] |
| 161 | Cryptochlorogenic acid | HBV-DNA | L. japonica | [84] |
| 162 | Neochlorogenic acid | HBV-DNA | L. japonica | [84] |
| 163 | 3,5-Dicafeoylquinic acid | HBsAg, HBeAg, and HBV-DNA | L. japonica | [84] |
| 164 | 4,5-Dicafeoylquinic acid | HBsAg, HBeAg, and HBV-DNA | L. japonica | [84] |
| 165 | 3,4-Dicafeoylquinic acid | HBsAg, HBeAg, and HBV-DNA | L. japonica | [84] |
preS promoters. Moreover, the mechanism may be that it inhibited the replication of viral DNA by regulating viral proteins. In recent years, molecular docking technology was used to screen the active ingredients against HBV, a 3D structure of HBV polymerase (Pol/RT) was modeled and docked with the active compounds, and quercetin (18) was proved that could enhance its anti-HBV activity up to 10% [32]. In addition, some researchers found that glabaarachalcone (19) and isopongachromene (20), isolated from P. pinnata, could bound with HBV-DNA polymerase protein target [33]. Isoorientin (21), isolated from S. mussotii, displayed significant anti-HBV activities against the secretions of HBsAg and HBeAg with IC_{50} value of 0.79 and 1.12 mM, as well as HBV-DNA replication with IC_{50} value of 0.02 mM [34]. Epi-medium Hyde II (22), a potential Chinese herbal active ingredient against HBV, could inhibit the replication of HBV-DNA and the expression of HBsAg and HBeAg in the serum of HBV-replicated C57BL/6 mice [35]. The chemical structures of compounds 15~22 showed in Figure 3.

2.3. Xanthones. Norbellidifolin (23), 1,5,8-trihydroxy-3-methoxyxanthone (24), 2-C-β-D-glucopyranosyl-1,3,7-trihydroxyxanthone (25), norswertianolin (26), norswertianin-1-O-β-D-glucoside (27), 1,7-dihydroxy-3,8-
dimethoxyxanthone (28), 7-O-[β-D-xylopyranosyl-(1 → 2)-β-D-xylopyranosyl]-1,8-dihydroxy-3-methoxyxanthone (29), and mangiferin (30) showed remarkable inhibition on HBV-DNA replication with IC₅₀ values from 0.01 mM to 0.13 mM. Compounds 23-25 with three or more hydroxy groups showed significant inhibitory activity with IC₅₀ values of 0.77, >0.98, and 0.21 mM for HBsAg, and <0.62, 0.35, and 0.04 mM for HBeAg, respectively. It was deduced that hydroxy groups in the xanthone structure were essential for maintaining the inhibitory effects on the secretion of HBsAg and HBeAg. Glycosidation of hydroxy groups led to activity decreasing against HBsAg and HBeAg by comparing the activity of compounds 24, 26, and 27. It was concluded that two or more hydroxy groups were essential for inhibiting HBV-DNA replication, and methylation of hydroxy groups decreased or abolished anti-HBV activity. In addition, the position of the hydroxy groups of the isolated xanthones did not significantly affect the inhibition on HBV-DNA replication. The preliminary structure-activity relationships were deduced as (1) the anti-HBV activity of xanthones depends on the structure and substitution pattern of the hydroxy groups; (2) the hydroxy groups play very important roles in the anti-HBV activity; (3) the anti-HBV activity will be decreased after methylation orglycosidation [36]. Methyl6,8-dihydroxy-3-methyl-9-oxo-9H-xanthene-1-carboxylate (31), isolated from mangrove-derived aciduric fungus Penicillium sp., inhibited HBsAg secretion more effectively than that of the positive control, 3TC, in a dose-dependent manner [37]. 1,8-Dihydroxy-3,5-dimethoxyxanthone (32), norswertianolin (33), and neolancerin (34), isolated from S. yunnanensis, had good anti-HBV effect. Among of them, compound 34 could not only inhibit the secretion of HBsAg and HBeAg, with IC₅₀ values of 0.21, 0.10, and 1.51, but also significantly inhibit the replication of HBV-DNA, with the IC₅₀ values of 0.09 mM, <0.01 mM, and 0.05 mM. However, compounds 32 and 33 only showed inhibitory effect on HBV-DNA replication, which may be caused by methylation or glycoylation of the hydroxy group of the compounds [30]. 1,5,8-Trihydroxy-3-methoxyxanthone (35) exhibited significant inhibitory activity on HBV-DNA replication with IC₅₀ values of 0.09 and 0.05 m mol L⁻¹ (SI of 10.89) and showed potent activity against the secretion of HBeAg with IC₅₀ values of 0.35 (SI of ≥2.80) [38]. The chemical structures of compounds 23–35 are shown in Figure 4.

2.4. Anthroquinones. Anthroquinones, often found in the metabolites of lichens and fungi of higher plants and lower plants, have the functions of hemostasis, antisepsis, purgation, and diuretic. In recent years, the anti-HBV activity of anthroquinones was reported [39].

(-)–2’ R-1-hydroxyisorhodoptilometrin (36), asterric acid (37), questinol (38), endo crocin (39), (+)-2’ S-isorhodoptilometrin (40), sulochrin (41), monochlorsulochrin (42), and dihydrogeodin (43) were isolated from mangrove-derived aciduric fungus Penicillium sp. and inhibited HBsAg secretion more effectively than that of the positive control, 3TC, in a dose-dependent manner. Compared with 13%
inhibition by 3TC, compounds 36 and 42 at 20 μM inhibited HBeAg secretion by 17 and 35%, respectively. Compound 36 showed much stronger antipanin B virus activity than that of the positive control, lamivudine, strongly inhibiting the secretion on HBsAg and HBeAg of HepG 2.2.15 cells. These results showed that extremophiles are a valuable resource of bioactive compounds, and that pH regulation is an effective strategy to induce metabolite production in aciduric fungi [37]. Peng et al. [40] found that 1,3-dihydroxy-2-hydroxy-methyl-9,10-anthraquinone (44), Rubiadin (45), and Anthraquinone bile acid conjugates (46) have significant anti-HBV effects on HepG2.2.15 cells. The IC50 values of them were 12.41, 8.03, 17.05, and 8.13 g/mL, respectively. When the drug concentrations were 8 g/mL, the inhibitory rates of HBsAg were 61.42%, 43.79%, and 69.30%, respectively. Particularly, compound 45 could not only significantly decrease HBeAg and HBsAg secretion level and inhibit HBV-DNA replication, due to its aldehyde group of 89.91 and 97.61 μM. A triterpenoid, named MH (51), was isolated from the Vicia tenuifolia Roth, which had significant inhibitory effect on the secretion of HBsAg and HBeAg in a dose-dependent manner [44]. Sweriyunnagenin A (52), 3-epitaraxerol (53), oleanolic acid (54), and erythrocentaurin (55), isolated from S. yunnanensis, could inhibit the secretion of HBsAg with IC50 values of 0.28, 0.70, and 1.26 mM, respectively. They also had good inhibitory effects on the secretion of HBeAg, with the IC50 values of 0.29, 1.41, and 0.94 mM, respectively. Especially, compound 55 could effectively inhibit the replication of HBV-DNA, due to its aldehyde group [26]. Zhou et al. [45] isolated a series of heptane terpenoids from the roots and rhizomes of Aster tataricus L.f. Among them, astataricusones B and andepishionol (56-57) could inhibit the secretion of HBeAg, with IC50 value of 18.6 and 40.5 μM, and the replication HBV-DNA, with IC50 value of 2.7 and 30.7 μM. In addition, compound 56 had inhibitory effect on the secretion of HBsAg with IC50 value of 23.5 μM. Zhou et al. [46] carried out further research on A. tataricus, and 6 new shionane-type triterpenes were isolated.

2.5. Terpenoids. Terpenes are a kind of compounds with isoprene as the basic structural unit. Terpenes have extensive biological activities, mainly including anti-inflammatory and antiviral effects [43].

Li et al. [19] isolated ursolic acid (50) from S. asper core material. Compound 50 had strong anti-HBV activity by inhibiting the production of HBsAg and HBeAg, with IC50 of 89.91 and 97.61 μM. A triterpenoid, named MH (51), was isolated from the Vicia tenuifolia Roth, which had significant inhibitory effect on the secretion of HBsAg and HBeAg in a dose-dependent manner [44]. Sweriyunnagenin A (52), 3-epitaraxerol (53), oleanolic acid (54), and erythrocentaurin (55), isolated from S. yunnanensis, could inhibit the secretion of HBsAg with IC50 values of 0.28, 0.70, and 1.26 mM, respectively. They also had good inhibitory effects on the secretion of HBeAg, with the IC50 values of 0.29, 1.41, and 0.94 mM, respectively. Especially, compound 55 could effectively inhibit the secretion of HBsAg and HBeAg, as well as the replication of HBV-DNA, due to its aldehyde group [26]. Zhou et al. [45] isolated a series of heptane terpenoids from the roots and rhizomes of Aster tataricus L.f. Among them, astataricusones B and andepishionol (56-57) could inhibit the secretion of HBeAg, with IC50 value of 18.6 and 40.5 μM, and the replication HBV-DNA, with IC50 value of 2.7 and 30.7 μM. In addition, compound 56 had inhibitory effect on the secretion of HBsAg with IC50 value of 23.5 μM. Zhou et al. [46] carried out further research on A. tataricus, and 6 new shionane-type triterpenes were isolated.

Figure 4: Chemical structures of representative anti-HBV xanthenes 23-35.
Among them, astershionones C (58) had good anti-HBV activity by inhibiting the secretion of HBsAg and HBeAg and the replication of HBV-DNA with IC\textsubscript{50} values of 23.0, 23.1, and 22.4 \(\mu\)M, respectively. Bi et al. [47] found that 7 monoterpenes (4″-hydroxy-3″-methoxyalbiflorin (59), 6′-O-p-hydroxybenzoyl-4″-Hydroxyalbiflorin (60), albiflorin (61), oxypaeoniflorin (62), peoniflorin (63), peonins B (64), and benzoylpaeoniflorin (65)) of the Paeonia siniangensis K. Y. Pan had anti-HBV activity and could inhibit the secretion of HBsAg and HBeAg as well as the replication of HBV-DNA. Among them, compound 59 had the highest anti-HBV activity, which was even better than that of positive drug, 3TC. Perovskatone A and demethylsalvicanol (66-67), isolated from Perovskia atriplicifolia, had anti-HBV activity. It was for the first report on the anti-HBV effect of P. atriplicifolia [48]. Chrysanolide B-C and A (68-70) were isolated from Dendranthema indicum, and compound 70 had unknown trimer carbon skeleton. Compounds 68-70 had good anti-HBV activity on HepG 2.2.15 cell, and their anti-HBV activity was positively correlated with the degree of polymerization [49]. In the anti-HBV test, Pimelotides A (71) showed significant inhibition on the secretion of HBsAg, with an IC\textsubscript{50} value of 0.016 g/mL and TI up to 355.63. However, the anti-HBV mechanism of compound 71 should be carried out for the further study [50]. Genkwanine P (73) and laurifolioside A (74), isolated from Wikstroemia cha-maedaphne Meisn, exhibited potential antihepatitis B virus activities with IC\textsubscript{50} values of 46.5 and 88.3 mg/mL, respectively. Wikstroelide W (72), 2-epi-laurifolioside A (75), laurifolioside B (76), 2-epi-laurifolioside B (77), laurifolioside (78), and 2-epi-laurifolioside (79) showed certain inhibitory effects on HBV-DNA replication with the inhibition ratios ranging from 2.0% to 33.0% at the concentrations ranging from 0.39 to 6.25 mg/mL [51]. It is reported that the extracts of Alternantheraphiloxeroides (Mart.) Griseb have antiviral properties in vitro. And oleanolic acid 3-O-\(\beta\)-D-glucurono-pyranoside (80) and 4,5-dihydroblumenol (81), isolated from the extracts, showed significant inhibition against HepG2.2.15 cells transfected with cloned HBV-DNA; their inhibitive ratios were 85.38% and 87.37% at 50 \(\mu\)g/mL, respectively [52]. Nine compounds 82-89 isolated from S. cincta, namely, swericinctosides A (82), swericinctoside B (83), 9-epi swertiamarin (84), 2′-O-\(\beta\)-D-glucurono-pyranoside (85), 4″-O-actyl swertianoside E (86), swertiaside (87), swertianoside C (88), and decentapicrin B (89), possessed inhibitory activity on HBV-DNA replication with IC\textsubscript{50} values from 0.05 to 1.83 mM. Compounds 82, 84, and 86-88 showed moderate activity against HBsAg with IC\textsubscript{50} values in the range of 0.24–2.46 mM, and compounds 82, 84, 87, and 88 could inhibit HBV-DNA replication with.

**Figure 5:** Chemical structures of representative anti-HBV anthroquinones 36-49.
IC\textsubscript{50} values of 0.30–0.62 mM. Compound 87 exhibited the most promising activity against HBV-DNA replication with an IC\textsubscript{50} value of 0.05 mM (SI = 29.1), as well as moderate activity against the HBsAg secretion (IC\textsubscript{50} = 0.79 mM) [53]. Geng et al. [54] found that the anti-HBV activity of erythronematoxin C (ET) derivatives was significantly improved. In particular, ET derivatives 1e and 1f (90, 91) showed the highest activity of inhibiting the replication of HBV-DNA, with IC\textsubscript{50} values of 0.026 mM (SI > 70.8) and 0.045 mM (SI > 36.0), respectively. Swertianoside A (92) and 2′-O-acetylsweetianoside (93) exhibited significant inhibitory activity on HBV-DNA replication with IC\textsubscript{50} values from 0.05 to 1.46 mmol·L\textsuperscript{-1} [38]. Huang et al. [55] isolated asiaticoside (94) from Hydrocotyle sibthorpioides Lam and found that asiaticoside could effectively inhibit the secretion of HBsAg and HBeAg. In addition, asiaticoside could significantly reduce the transcription and replication of HBV-DNA by inhibiting the core, s1, s2, and x gene promoter activity. Liu et al. [56] found diosgein (95) could effectively inhibit the secretion of HBsAg and HBeAg, with the inhibition rate reaching 40% and 50%. 7-Eudesm-4(15)-ene-1β,6a-diol (96) and Pumilaside A (97), isolated from Artemisia capillaris, exhibited promising activity against HBV-DNA replication with IC\textsubscript{50} values of 19.70 and 12.01 μM, with SI values of 105.5 and 139.2. In addition, compound 97 could also suppress the secretions of HBsAg and HBeAg with the IC\textsubscript{50} values of 15.02 μM (SI = 111.3) and 9.00 μM (SI = 185.9) [57]. The chemical structures of compounds 50–97 showed in Figure 6.

2.6. Alkaloids. Alkaloids, a kind of natural nitrogen heterocyclic, have complex ring structure, most of which have physiological activity [58]. Jiang et al. [59] found that the ethanol extract of Piper longum L. fruit had good anti-HBV effect, and erythro-1-[1-oxo-9(3,4-methylenedioxyphenyl)-8,9-dihydroxy-2E-nonenyl]-pipericidine (98), threo-1-[1-oxo-9(3,4-methylenedioxyphenyl)-8,9-dihydroxy-2E-nonenyl]-pipericidine (99), piporine (100), guineesine (101), and (2E,4E)-N-isobutylenecosa-2,4-dienamide (102) had significant inhibitory effect on the secretion of HBsAg and HBeAg on HepG2 2.2.15 cells. 3β,4α-dihydroxy-1-(3-phenylpropanoyl)-pipericidine-2-one (103), isolated from P. longum ethanol extract, had significant anti-HBV activity and could inhibit the secretion of HBsAg and HBeAg, with IC\textsubscript{50} of 1.80 and 0.21 mM, respectively. The selectivity of compound 103 on HBeAg inhibition was up to 16.4, which was better than that of positive drug, 3TC, and has a good development prospect [60]. Zeng et al. [61] obtained a quaternary ammonium alkaloid DHCH (104) from Corydalis saxicola Bunting, which could significantly inhibit the secretion of HBsAg and HBeAg on HepG2 2.2.15 cells, with TI of 7.32 and 6.77, respectively. Further study showed that compound 104 could further reduce the levels of cccDNA and DNA in dose and time dependence manner, with IC\textsubscript{50} values of 15.08, 7.62, and 8.25 μM, respectively. The chemical structures of compounds 98–104 are shown in Figure 7.

2.7. Enediyynes. A. capillaris (Yin-Chen) is a famous traditional Chinese medicine (TCM) for treating acute and chronic hepatitis in China [62]. Geng et al. [63] isolated 14 compounds, 8S-deca-9-en-4,6-diene-1,8-diol (105), (S)-deca-4,6,8-triyne-1,3-diol (106), (S)-3-hydroxyundeca-5,7,9-triynoic acid (107), 3S-Hydroxyundeca-5,9-triynoic acid 3′-O-β-D-glucopyranoside (108), Atractylodin (109), Dendoarboroele B (110), Dehydrofalconrin (111), Dehydrofalcariindiol (112), (E)-deca-2-en-4,10-diol (113), (Z)-deca-2-en-4,10-diol (114), 8-diol 1′-O-β-D-glucopyranoside (115), 3S,8S-dihydroxydec-9-ene-4,6-diyne 1′-O-β-D-glucopyranoside (116), 5-benzylthiophenecarboxylic acid (117), and 2-methyl-6-phenyl-4H-pyran-4-one (118), from A. capillaris. All the compounds were assayed for their anti-HBV activity, and the structure-activity relationships were summarized based on the biological effects. In particular, compound 108 could significantly inhibit the secretions of HBsAg, HBeAg, and HBV-DNA replication with IC\textsubscript{50} values of 197.2 (SI > 5.1), 48.7 (SI > 20.5), and 9.8 (SI > 102) μM. Hydroxyl and glycosyl groups are preferable for maintaining activity. In subsequent studies, Geng et al. [64] found that 3S,8S-dihydroxydec-9-en-4,6-yn-1-O′(6′-O-caffeoyl)-β-D-glucopyranoside and 3S,8S-dihydroxydec-9-en-4,6-yn-1-O′-(2′-O-caffeoyl)-β-D-glucopyranoside (119–120) had the activity against the secretions of HBsAg and HBeAg and HBV DNA replication. Especially, compounds 119 and 120 inhibited HBV-DNA replication with IC\textsubscript{50} values of 0.077 ± 0.04 and 0.0127 ± 0.05 mM, with SI values of 23.6 and 17.1, respectively. Compounds 119 and 120 as a pair of isomers showed similar inhibition on HBsAg secretion with IC\textsubscript{50} values of 0.797 ± 0.23 mM (SI = 2.1) and 0.887 ± 0.20 mM (SI = 2.3), but no activity against HBeAg secretion. Compound 119 displayed the highest inhibitory activity on HBVDNA replication with an IC\textsubscript{50} value of 0.077 ± 0.04 mM (SI = 23.6), and compound 120 showed slightly decreased activity with an IC\textsubscript{50} value of 0.127 ± 0.05 mM (SI = 17.1). The above analyses suggested that the caffeoyl group played an important role in maintaining the anti-HBV activity but the substitution position may not be crucial. The chemical structures of compounds 105–120 are shown in Figure 8.

2.8. Aromatics. Six phenols, m-hydroxybenzoic acid (121), p-hydroxybenzoic acid (122), m-hydroxy benzenemethanol (123), 3,4-dihydroxybenzoic acid (124), ethyl 3,4-dihydroxybenzate (125), and ethyl 2,5-dihydroxybenzoate (126), exhibited anti-HBV activities by inhibiting HBsAg and HBeAg secretion with IC\textsubscript{50} values from 0.23 to 5.18 mM, and HBV-DNA replication with IC\textsubscript{50} values from 0.06 to 2.62 mM. Compounds 121-123, with one hydroxyl and one carboxyl, showed anti-HBV activity with IC\textsubscript{50} values of 3.76, 5.18, and 4.55 mM for inhibitory HBsAg secretion and 2.36, 2.54, and 2.62 mM for inhibitory HBV-DNA replication, respectively. Compounds 124-126 with two hydroxyls and one carboxyl displayed remarkable inhibition on HBV-DNA replication with IC\textsubscript{50} values of <0.06, 0.22, and 0.29 mM. Furthermore, compounds 125 and 126 showed significant inhibitory effect on the secretion of HBsAg (IC\textsubscript{50} = 0.14 and 0.23 mM) and HBeAg (IC\textsubscript{50} = 5.03 and 3.74 mM) [34].
Figure 6: Continued.
Figure 6: Continued.
3,3′,5-Trihydroxybiphenyl (127), isolated from *S. chirayita*, showed activity against HBeAg secretion with IC₅₀ values of 0.77 ± 0.076 and 5.92 ± 1.02 mM [27]. Taraffinoside A (128), descaffeoyl crenatoside (129), and 3,4-dihydroxyphenylethanol-8-O-β-D-apiofuranosyl (1→3)]-β-D-glucopyranoside (130) isolated from *Tarphochlamys affinis* (Griff.) could inhibit the secretion of HBsAg and HBeAg [65]. Huang et al. [66] isolated 3-hydroxy acetophenone
Figure 7: Chemical structures of representative anti-HBV alkaloids 98-104.

Figure 8: Chemical structures of representative anti-HBV enediynes 105-120.
(PHAP) (131) from *A. morrisonensis*, which could significantly inhibit the replication of HBV. The mechanism may be that PHAP was involved in regulating the expression of surface protein genes and blocks the release of virus particles by interfering with the signaling pathway of endoplasmic reticulum. Zhao et al. [67] found that PHAP and derivatives have good anti-HBV activity, and structural modification on p-HAP and its glycoside led to a series of derivatives; among them, p-HAP derivative 2f (132) had the strongest effect on inhibiting the replication of HBV-DNA (IC₅₀ = 5.8 μM, SI = 160.3). The primary structure-activity relationships suggested that the conjugated derivatives of p-HAP glycoside and substituted cinnamic acids obviously enhanced the activity against HBV-DNA replication. The chemical structures of compounds 121–132 are shown in Figure 9.

2.9. Phenylalanine Dipeptides. Yang et al. [68] isolated and modified the phenylalanine dipeptide Matijin-Su (133) with anti-HBV activity from *Dichondra repens* Forst, and four derivatives were screened with anti-HBV activity in vitro. Yang et al. [69] found that compound 101 could inhibit the replication of HBV-DNA, with IC₅₀ value of 1.33 μM, and inhibit the replication of various mutant HBV strains. Xu et al. [70] synthesized a series of MTS derivatives with anti-HBV activity by the design of the Matijin-Su (MTS). One of the preferred MTS derivatives (Y101) was conducted in the clinical preclinical study and received the clinical approval of the CFDA.

Kuang et al. [71] used the compound MTS as lead compound; a novel MTS derivative was designed and synthesized by introducing the structure unit of veratrol acid; N-[N-(3,4-dimethoxy-benzoyl)-L-phenylalanyl]-O-propionyl-L-phenylalaninol (134), N-[N-(3,4-dimethoxy-benzoyl)-L-phenylalaninyl]-4-ethoxy-L-phenylalaninol (135), and N-[N-(3,4-Dimethoxy-benzoyl)-L-phenylalaninyl]-4-ethoxycarbonylmethyl-L-tyrosinol (136) were tested the anti-HBV activity in vitro. All the compounds have the significant anti-HBV activity. Subsequently, a series of MTS derivatives were designed and synthesized with compound MTS as the lead compound, by introducing fluorine or chlorine substitution, and the obtained MTS derivatives were tested for anti-HBV activity in vitro. N-[N-(4-chlorobenzoyl)-O-methyl-L-tyrosyl]-L-Phenylalaninol (137), N-[N-(4-chlorobenzoyl)-O-propyl-L-tyrosyl]-L-Phenylalaninol (138), and N-[N-(4-chlorobenzoyl)-O-isopropyl-L-tyrosyl]-L-Phenylalaninol (139) showed good anti-HBV activity, with IC₅₀ of 12.61, 10.53, and 6.46 mol/L,
showed strong anti-HBV activity, and their IC$_{50}$ reached 1.43 and 1.41 mol·L$^{-1}$, respectively [72]. Cui et al. [73] synthesized 20 MTS derivatives containing trifluoromethyl substitution and tested the anti-HBV activity of the synthesized target compound in HepG 2.2.15 cells in vitro. Among them, N-[N-3-trifluoromethylbenzoyl]-L-tyrosyl-L-phenylalanine methyl ester (141) and N-[N-(3-trifluoromethylbenzoyl)-L-phenylalanyl]-O-propionyl-L-tyrosine methyl ester (144), and N-[N-(3-trifluoromethylbenzoyl)]-L-phenylalanyl]-O-ethyl-L-tyrosine (145) showed strong anti-HBV activity, and their IC$_{50}$ reached 11.74, 8.73, and 11.41 mol·L$^{-1}$, respectively [72]. Cui et al. [73] synthesized 20 MTS derivatives containing trifluoromethyl substitution and tested the anti-HBV activity of the synthesized target compound in HepG 2.2.15 cells in vitro. Among them, N-[N-3-trifluoromethylbenzoyl]-L-tyrosyl-L-phenylalanine methyl ester (141) and N-[N-(3-trifluoromethylbenzoyl)-L-phenylalanyl]-O-propionyl-L-tyrosine methyl ester (144), and N-[N-(3-trifluoromethylbenzoyl)]-L-phenylalanyl]-O-ethyl-L-tyrosine (145) showed strong anti-HBV activity, and their IC$_{50}$ reached 11.74, 8.73, and 11.41 mol·L$^{-1}$.

Jang et al. [74] synthesized twenty novel $n$-methyl derivatives of MTS, among which compounds 8n (143) and 8o (144) showed certain anti-HBV activity, with IC$_{50}$ of 52.5 mol·L$^{-1}$ and 49.2 mol·L$^{-1}$, respectively. Compounds 9a-c (145-147) were triantennary cluster galactosides of MTS with potential for hepatic targeting. The anti-HBV activities of those were evaluated in HepG 2.2.15 cells. And all those compounds had inhibitory effect on HBV-DNA replication in HepG2 2.2.15 cells in a dose-response manner [75]. Huang et al. [76] evaluated the 20 species of marine natural small molecule compounds by HepG 2.2.15 cell lines; three kinds of compounds cyclic (glycine-L-proline) (148), cyclic (4-hydroxy proline-phenylalanine) (149), and cyclic (L2-hydroxy proline-phenylalanine) (150) had anti-HBV activity on the inhibition of HBsAg, HBeAg, and HBV-DNA, with the treatment of index greater than 2. N-acetyl phenylalanine (151) had certain inhibitory effects on HBsAg and HBeAg with the IC$_{50}$ values of 55.5, 69.5 µg/mL, respectively [77]. The chemical structures of compounds 133-151 are shown in Figure 10.

![Figure 10: Chemical structures of representative anti-HBV phenylalanine dipeptides 133-151.](image)

The mechanism might be that IN-4 suppressed the expression and blocking the TLR2/NF-$\kappa$B signaling pathways of host cell. It is for the first report of isosteviol analogues against HBV [80]. Huang et al. [81] got a series of new derivatives, including the IN-4 (156) with high anti-HBV activity. The mechanism might be that IN-4 suppressed the expression of HBV gene and the replication of HBV-DNA by interfering with the NF-$\kappa$B signaling pathways of host cell.

2.10. Others

2.10.1. Lactones. Two dimers of oxanthrone andiridoid lactone (152, 153) were isolated from S. punicea, which could inhibit the secretion of HBsAg with IC$_{50}$ value of 0.25 and 0.29 mM, and the secretion of HBeAg with IC$_{50}$ value of 0.86 and 0.31 mM. In addition, compounds 152-153 also could inhibit the replication of HBV-DNA, with the IC$_{50}$ values of 0.18 and 0.19 mM, respectively [78]. Anis lactone B (154), a kind of nor sesquiterpene lactone with unique structure from the fruit of Illicium henryi, had high anti-HBV activity and could inhibit the secretion of HBeAg on HepG 2.2.15 cell with IC$_{50}$0.079 ± 0.035 mM in vitro [79].

2.10.2. Isosteviol. The analogue of isosteviol, NC-8 (155), had anti-HBV activity by inhibiting the secretion of HBsAg and HBeAg, with the IC$_{50}$ value of 7.89 g/mL, which was better than that of the positive control (lamivudine). The mechanism of NC-8 was interfering with HBV replication and gene expression and blocking the TLR2/NF-κB signaling pathway of host cells. It is for the first report of isosteviol analogues against HBV [80]. Huang et al. [81] got a series of new derivatives, including the IN-4 (156) with high anti-HBV activity. The mechanism might be that IN-4 suppressed the expression of HBV gene and the replication of HBV-DNA by interfering with the NF-κB signaling pathways of host cell.

2.10.3. Organic Acids. Scoparamide A (157) could inhibit not only the secretions of HBsAg and HBeAg with IC$_{50}$ values of 0.617 ± 0.25 mM (SI = 2.1) and 0.887 ± 0.25 mM (SI = 1.4), respectively [72, 73]. Cui et al. [73] synthesized 20 MTS derivatives containing trifluoromethyl substitution and tested the anti-HBV activity of the synthesized target compound in HepG 2.2.15 cells in vitro. Among them, N-[N-(3-trifluoromethylbenzoyl)-L-tyrosyl]-L-phenylalanine methyl ester (141), N-[N-(3-trifluoromethylbenzoyl)-L-phenylalanyl]-O-propionyl-L-tyrosine methyl ester (144), and N-[N-(3-trifluoromethylbenzoyl)]-L-phenylalanyl]-O-ethyl-L-tyrosine (145) showed strong anti-HBV activity, and their IC$_{50}$ reached 11.74, 8.73, and 11.41 mol·L$^{-1}$.

Jang et al. [74] synthesized twenty novel $n$-methyl derivatives of MTS, among which compounds 8n (143) and 8o (144) showed certain anti-HBV activity, with IC$_{50}$ of 52.5 mol·L$^{-1}$ and 49.2 mol·L$^{-1}$, respectively. Compounds 9a-c (145-147) were triantennary cluster galactosides of MTS with potential for hepatic targeting. The anti-HBV activities of those were evaluated in HepG 2.2.15 cells. And all those compounds had inhibitory effect on HBV-DNA replication in HepG2 2.2.15 cells in a dose-response manner [75]. Huang et al. [76] evaluated the 20 species of marine natural small molecule compounds by HepG 2.2.15 cell lines; three kinds of compounds cyclic (glycine-L-proline) (148), cyclic (4-hydroxy proline-phenylalanine) (149), and cyclic (L2-hydroxy proline-phenylalanine) (150) had anti-HBV activity on the inhibition of HBsAg, HBeAg, and HBV-DNA, with the treatment of index greater than 2. N-acetyl phenylalanine (151) had certain inhibitory effects on HBsAg and HBeAg with the IC$_{50}$ values of 55.5, 69.5 µg/mL, respectively [77]. The chemical structures of compounds 133-151 are shown in Figure 10.
respectively, but also HBV-DNA replication with an IC\textsubscript{50} value of 0.477 ± 0.14 mM (SI = 2.7) [64]. Zhang et al. [82] isolated cichoric acid (158) from the leaves of Chicory intybus L and found that it had significant anti-HBV activity. Rosmarinic acid (159) inhibits HBV replication in HBV-infected cells by specifically targeting ε-Pol binding. In addition, they analyzed an additional 25 rosmarinic acid derivatives and found that the “two phenolic hydroxyl groups at both ends” and the “caffeic acid-like structure” of rosmarinic acid are critical for the inhibition of ε-Pol binding [83]. It is well known that phenolic acids have better antiviral activity. The studies showed that 3-caffeoylquinic acid (160) [84]
could inhibit the secretion of HBsAg, HBeAg, and the replication of HBV-DNA on Hep G 2.2.15 cells at the concentration of 100 μg/mL. In order to reveal the anti-HBV activity and structure-activity relationships of the analogues of chlorogenic acid, 9 chlorogenic acid analogues were evaluated on HepG 2.2.15 cell lines in vitro and found that chlorogenic acid, cryptochlorogenic acid (161), neochlorogenic acid (162), 3,5-dicaffeoylquinic acid (163), 4,5-dicaffeoylquinic acid (164), and 3,4-dicaffeoylquinic acid (165) possessed potent activity against HBV-DNA replication with IC_{50} values in the range of 5.5±0.9-13.7±1.3 μM. Di-cafeoyl analogues (163-165) also exhibited activity against the secretions of HBsAg and HBcAg. The number of caffeoyl moiety may contribute to the inhibitory activity against HBsAg and HBcAg secretions, while the position of caffeoyl units play little role on anti-HBV-DNA activities. In addition, carboxyl group is closely associated to the antiviral activity [85]. The chemical structures of compounds 152-165 are shown in Figure 11.

2.10.4. Polysaccharides. Natural polysaccharide is mainly referred to widely exists in the nature of cellulose and its derivatives, chitin, and other natural polymer materials. Polysaccharides have a wide range of biological activities, such as enhanced immunity, antiviral, and anti-inflammatory [86, 87].

In recent years, clinical researches of natural polysaccharides on anti-HBV have increased gradually; they have been proved to have significant anti-HBV effect [88]. Lentian polysaccharide has a prominent effect on antiviral and immune regulation and is also used as an auxiliary drug for cancer and HBV [89, 90]. Zhao et al. [91] obtain two polysaccharide fractions (LEP-1 and LEP-2) from Lentinus edodes (Berk.) sing. The results of LEPs possess potent anti-HBV activity in vitro. In addition, the polysaccharides from Hedyotis caudatifolia Merr.et Metcal (50, 100, and 200 mg/L) significantly inhibited the secretion and expression of HBV-DNA on HepG 2.2.15 cells and effectively inhibited the secretion of HBsAg and HBeAg. Its mechanism may be related to the activation of JAK/STAT signaling pathway and the promotion of antiviral protein expression [92]. Zhan et al. [93] found that snail polysaccharides have a certain inhibitory effect on the replication of HBV-DNA \((P < 0.01)\), which indicated that the maximum inhibition rate of HBsAg and HBeAg in HepG 2.2.15 cells is 42.8% and 52.1%, respectively, slightly below the positive control group \((P < 0.05)\), and the inhibition effect of snail polysaccharide on HBeAg was better than that of HBsAg. The results of real-time fluorescence quantitative PCR test showed that snail polysaccharide had a certain inhibitory effect on the replication of HBV-DNA \((P < 0.01)\). The anti-HBV effect of polypropylene polysaccharide may be related to the regulation of the body’s immune function, breaking the body’s immune tolerance or low state [94]. Angelica sinensis polysaccharide [95] could promote DC mature of HBV transgenic mice, raise its coordinated stimulus molecules on the surface, enhance its promoting lymphocyte proliferation and secretion, strengthen its antigen oral ability, induce cellular immune response, reduce serum concentrations of HBsAg, and play a role in antiviral immunity. Liu et al. [96] extracted Chinese whelk polysaccharide by water extraction and transfected human hepatocellular carcinoma cells with HBV-DNA cloning as an experimental model. The results showed that PCC significantly inhibited HBV-DNA in HepG 2.2.15 cells at 0.1 mg·mL^{-1} and 1 mg·mL^{-1}. Xia et al. [97] investigated the effect of polysaccharides of Sipunculus nudus Linnaeus on anti-HBV; the results showed that polysaccharide with different dose groups were different degree of inhibition of HBV-DNA replication \((P < 0.05)\), and the effects of high, middle dose group were similar to acyclovir.

3. Conclusion and Perspectives

At present, a variety of natural products with novel structure and high anti-HBV activity were isolated from natural resources. Among them, we found that terpenoids with antihepatitis B activity are the most (Figure 6 and Table 1), and the activity is more significant. However, the research content were disorderly and mainly focus on the simple isolation and identification of anti-HBV activity ingredients; the in-depth studies of anti-HBV mechanisms and targets are relatively rare. Moreover, most of the studies are limited to cell level, lack of animal model experiments, and no in-depth research of ingredients with significant anthepatitis B activity. Therefore, there are three suggestions for product research and development:

3.1. Search for New Natural Product Resources. The research on natural products against hepatitis B mainly focuses on the field of traditional Chinese medicine on land. The research on traditional Chinese medicine against hepatitis b has been very matured. However, it is still difficult to develop active natural products against HBV. In addition, there are few researches on marine natural products, microbial fermentation products, plant polysaccharides, and other aspects. In recent years, studies have found that marine natural products have good biological activity due to their special growth environment. Huang et al. [76] screened significant anti-HBV active ingredients from small marine molecules. Microbial fermentation products are a novel source of natural products. In recent years, many novel compounds are derived from microbial fermentation products. It is an interesting way to study the anti-HBV activity of microbial fermentation products. Plant polysaccharides have a wide range of biological activities, and studies [88–95] have shown that the chemical components of polysaccharides have a good anti-HBV activity. It is of great significance to search for anti-HBV active ingredients from novel natural products.

3.2. Novel Method for Screening. The traditional screening of anti-HBV activity involves the separation and identification of chemical components in traditional Chinese medicinal materials and then the screening of their activity, which often takes time and effort and is difficult to obtain accurate screening results. In recent years, researchers used computer-aided drug design (molecular simulation docking) to screen out suitable compounds from the database and then carried out screening in vitro. This method has strong purpose and high
accuracy. A series of derivatives with good anti-HBV activity were obtained by modifying the structure of known compounds with anti-HBV activity, and the derivatives with the best activity were screened out through activity test. This method also provides a new idea for discovering anti-HBV compounds with better activity [71–75].

3.3. Synergy Effect. Single-chemical components of natural products are no longer effective against HBV, and drug resistance will appear. For example, artemisinin is combined with other components to fight malaria. In anti-HBV studies, treatment methods of combination drugs are also widely used [98].

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

Authors’ Contributions

All authors contributed to the manuscript. W.K. and Z.L. conceived this subject. X.L. and C.M. searched, collected, and analyzed the relevant literature, as well as prepared the first draft. W.K. and X.L. critically read and revised the paper. All authors read and approved the final manuscript.

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