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Hepatitis B Treatment in Light of Natural Sources

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Abstract

Hepatitis B virus causes acute and chronic inflammation of liver which may leads to hepatocellular carcinoma, cirrhosis and death. Chronic hepatitis B is usually accompanied by the presence of detectable hepatitis B surface antigen (HBsAg) in the blood for greater than 6 months. The presence of hepatitis B envelope antigen (HBeAg) is related to higher rates of viral replication leading to more infection.

Objective: Currently vaccination for prevention of hepatitis B is present and its treatment includes pegylated interferon α, lamivudine, telbivudine and entecavir (nucleoside analogues) and adefovir (nucleotide analogues). This treatment is partially effective and has significant dose dependent side effects and resistance after long term use. Hence, there is a need to develop new more safe and potent agents against hepatitis B from medicinal plants.

This review illustrates the description of medicinal plants, family, their active ingredients, parts and extracts used to treat hepatitis B by their mechanisms. The pharmaceutical companies are striving to discover appropriate alternative and natural inhibitors of targeting different steps of HBV life cycle, because single plant contains an invaluable number of active ingredients which could help in the manufacture of pharmaceutical grade proteins and has wide spectrum of antiviral activity. However, information of antiviral activity of plants is still inadequate.

Keywords: Hepatitis B virus; Medicinal plants; HBs Ag; Hepatoprotective activity; Antiviral activity; Pharmaceutical grade proteins; Chronic hepatitis B; Liver cancer; Cirrhosis; Vaccination; Pegylated interferon α; Telbivudine; Lamivudine; Adefovir; Terpenoids; Lignans; Phenolic compounds; Polyphenols; Tannins

Abbreviations: HBsAg: Hepatitis B Surface Antigen; NLS: Nuclear Localization Signaling; NPC: Nuclear Pore Complex; BN: *Boehmeria nivea*; HBV: Hepatitis B Virus

Introduction

Hepatitis B, a devastating ailment is distressing over 2 billion population all over the world. Amongst those more than 360 million people suffering from chronic hepatitis B Lavanchy [1]. Every year, the death rate is 0.5-1.2 million people owing to chronic hepatitis, cirrhosis as well as liver cancer according to WHO. In Pakistan, over 15 million peoples have been infected with hepatitis B because of ignorance of vaccination with carrier rate of 3-5% (Ott, 2012). HBV is transmitted via blood transfusion, use of unhygienic tools for shaving, unsterilized instruments during surgery as well as use of contaminated syringes [2].

Hepatitis is spread via sexual means owing to several sexual partners as well as via diseased mother to children Enemuor et al. [3]. Patients undergoing dialysis for more than two years are at greater risk for hepatitis Wasley et al. [4]. HBV having eight genotypes such as A to H are predominant in numerous areas globally. Genotype A is prevalent globally; B along with C exists in Asia; D in South Europe; E in Africa as well as F and G in USA. Currently, in Central America genotype H has been invented. White patients with genotype A exhibit greater reduction of HBeAg as well as HBV DNA and unceasing removal of HBeAg seroconversion as compare to patients with genotype D. Patients having genotype B in Asia, exhibit HBeAg seroconversion in early age are at greater risk of developing hepatitis and demonstrate superior response to interferon as compare to patients of genotype C. Patients having genotype B are different from those with genotype C in developing hepatocellular carcinoma Saleem & Sumi et al. [4,5].

Vaccination against hepatitis B is available but infection remains prominent in many countries such as India, eastern Asia and Pakistan Chu et al. [7]. Currently several therapeutic agents for instance pegylated interferon α, telbivudine, lamivudine,

adefovir (nucleotide analogues) as well as entecavir (nucleoside analogues) have been used however owing to their adverse effects and resistance, medicinal plants have been used to cure hepatitis B Papatheodoridis et al. [8]. Phyto medicines derived from plants are used throughout the world particularly in developed countries such as in Europe and United States.

Pharmaceutical industries are more interested in phytomedicines due to their importance and demand worldwide. The active ingredients (e.g. terpenoids, lignans, phenolic compounds, polyphenols and tannins etc.) obtained from plants are proved to be effective against HBV Huang & Aftab et al. [9,10]. Therefore, this review focuses on traditional plants used for treatment of HBV. Numerous medicinal plants having active ingredients along with classes for instance terpenoids, alkaloids, lignans, flavonoids as well as polyphenols, have specific mechanism of actions on HBV life cycle are demonstrated in Table 1.

Table 1: Plants with their classes & active ingredients used in treatment of Hepatitis B.

Sr No	Class with Active Ingredients	Plant Name & Part Used	Local Name	Family	Effects	References
1	Terpenoids: Astataricusone B Astataricusone B and Epishionol	*Aster tataricus* (Roots and rhizomes)	Tartarian aster	Asteraceae	HBsAg secretion HBeAg secretion HBV DNA replication	Zhou et al. [25]
2	Betulinic acid	*Pulsatilla chinensis*	Bunge	Ranunculaceae	HBV DNA replication	Yao et al. [26]
3	Pumilaside A	*Artemisia capillaris*	Redstem wormwood	Asteraceae	HBsAg and HBeAg secretion HBV DNA replication	Zhao et al. [27]
4	Artesunate	*Artemisia annua*	Sweet wormwood	Asteraceae	HBsAg secretion HBV DNA replication	Xu et al. [28]
5	Asiaticoside	*Hydrocotyle sibthorpioides*	Lawn marshpenny wort	Araliaceae	HBsAg and HBeAg secretion HBV DNA replication	Huang et al. [29]
6	Dehydroandrographolide and andrographolide	*Andrographis paniculata*	Green chirayta, King of bitters	Acanthaceae	HBV DNA replication	Chen et al. [30]
7	Alisol A	*Alisma orientalis* (Rhizomes)	Asian water plantain	Alismataceae	HBsAg and HBeAg secretion	Zhang et al. [31]
8	Perovskatone A and demethylsalvicanol	*Perovskia atriplicifolia*	Russian sage	Lamiaceae	HBsAg and HBeAg secretion	Jiang et al. [32]
9	SweriyunnangeninA and 3-epitaraxerol	*Swertia yunnanensis*	Felworts	Gentianaceae	HBsAg and HBeAg secretion	Cao et al. [33]
10	Caudatin 3-O- (3, 4, 5-trimethoxy) cinnamoylcaudatin	*Cynanchum auriculatum*	Leather eater	Apocynaceae	HBsAg secretion HBV DNA replication Interfers HBV enhancers and promoters	Wang et al. [34]
11	Alisol A 24-acetate, 25 anhydro alisol A, 13β,17 β-epoxy alisol A, alisol B 23-acetate, alisol F and alisol F 24-acetate	*Alisma orientalis (Rhizomes)*	Asian water plantain	Alismataceae	HBsAg and HBeAg secretion	Zhang et al. [35]
12	Glycyrrhizin and glycyrrhetinic acid (GA)	*Glycyrrhizae glabra* (Root)	Licorice	Fabaceae	HBsAg and HBeAg secretion HBV DNA replication	Wang et al. [36]
13	Phyllaemblicins G6-G8 and phyllaemblicin	*Phyllanthus emblica*	Amla	Phyllanthaceae	HBsAg and HBeAg secretion	Lv et al. [37]
14	Methyl helicterate	*Helicteres angustifolia*	Shan zhi ma (Chinese plant)	Malvaceae	HBsAg and HBeAg secretion HBV DNA replication	Huang et al. [38]
15	Phyllanthacidoid acid methyl ester and phyllanthacidoids A, B, C, D, F, G, H, I and M	*Phyllanthus acidus*	Malay gooseberry, star berry	Phyllanthaceae	HBsAg and HBeAg secretion	Lv et al. [39]
16	Ursolic acid	*Streblus asper* (Heartwood)	Sandpaper tree	Moraceae	HBsAg and HBeAg secretion	Li et al. [40]

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Sr no	Class with Active Ingredients	Plant Name & Part Used	Local Name	Family	Effects	References
17	LIGNANS Schisanwilsonin D, schisantherin C, deoxyschizandrin and (+) -gomisin K3	*Schisandra wilsoniana (Fruits)*	Chinese plant	Schisandraceae	HBsAg and HBeAg secretion	Ma et al. [41]
18	Helioxanthin (HE-145)	*Taiwania cryptomerioides* (Heartwood)	Chinese plant	Cupressaceae	HBV DNA replication	Tseng et al. [42]
19	(7'R,8'S,7″R,8″S)-erythro-strebluslignanol G, magnolol, isomagnolol and isolariciresinol	*Streblus asper* (Root)	Sandpaper tree	Moraceae	HBsAg and HBeAg secretion	Li et al. [43]
	(7'R,8'S,7″R,8″S)-erythro-strebluslignanol G and magnolol				HBV DNA replication	
20	(+)-(7′S, 7″S, 8′R, 8″R)-4, 4′, 4″-trihydroxy-3, 5′, 3″ trimethoxy-7-oxo-8-ene [8-3′, 7′-O-9″, 8′-8″, 9′-O-7″] lignoid,(1S)-4-hydroxy-3-[2-(4 hydroxy-3 methoxy phenyl)-1 hydroxymethyl-2-oxo-ethyl] -5-methoxy benzaldehyde and herpetetrone	*Herpetospermum caudigerm* (Seeds)	Chinese plant	Cucurbitaceae	HBsAg and HBeAg secretion	Yu et al. [44]
21	(+)-Cycloolivil-4′-O-β-D glucopyranoside	*Swertia chirayita*	Chirayata	Gentianaceae	HBsAg and HBeAg secretion HBV DNA replication	Zhou [45];
22	9-β-xylopyranosyl-isolariciresinol and honokiol	*Streblus asper* (stem bark)	Sandpaper tree	Moraceae	HBsAg and HBeAg secretion	Chen et al. [47]
23	Niranthin and nirtetralin B	*Phyllanthus niruri L.*	Stone breaker	Phyllanthaceae	HBsAg and HBeAg secretion	Liu et al. [48]
24	Phenolic Acids: 3,4-O-dicaffeoylquinic acid, 4,5-O dicaffeoylquinic acid, 3,5-O-dicaffeoylquinic acid, 3,5-Odicaffeoyl-mucoquinic acid, 5 O-caffeoylquinic acid, 3-O-caffeoylquinicacid and 5-O-(E)-p-coumaroylquinic acid	*Lactuca indica L.* (aerial parts)	Indian lettuce	Compositae	Reduced HBV DNA level	Kim et al. [49]
25	3,4-O-dicaffeoylquinic acid and 3,5-O dicaffeoylquinic acid	*Laggera alata*	Winged stem laggera, Lumra	Asteraceae	HBsAg and HBeAg secretion Decreased HBV cccDNA content	Wu et al. [50]; Hao et al. [51]
26	Polyphenols: Neolancerin	*Swertia yunnanensis*	Felworts	Gentianaceae	HBsAg and HBeAg secretion	Cao et al. [33]
	Norswertianolin, 1,8-dihydroxy-3,5 dimethoxy xanthone and neolancerin				HBV DNA replication	
27	M-hydroxybenzoic acid, phydroxybenzoic acid, m hydroxybenzenmethanol, 3,4-dihydroxybenzoic acid, ethyl 3,4 dihydroxy benzoate and ethyl 2,5 dihydroxybenzoate)	*Swertia mussotii*	Felworts	Gentianaceae	HBsAg and HBeAg secretion HBV DNA replication	Cao et al. [52]
28	LPRP-Et-97543	*Liriope platyphylla* (Roots)	Lilyturf, border grass	Asparagaceae	HBV DNA replication	Huang et al. [53]

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Sr no	Class with Active Ingredients	Plant Name & Part Used	Local name	Family	Effects	References
29	Ellagic acid	*Phyllanthus urinaria*	Chamber bitter, stone breaker	Phyllanthaceae	HBeAg secretion	Shin et al. [54]
30	Mulberrofuran G	*Morus alba*	White mulberry	Moraceae	HBV DNA replication	Geng et al. [55]
31	Curcumin	*Curcuma longa*	Turmeric, haldi	Zingiberaceae	HBeAg secretion Inhibits HBV gene expression and DNA replication	Qi et al. [56]; Rechtman et al. [57]
32	Magnatriol B	*Streblus asper*	Sand paper tree	Moraceae	HBsAg and HBeAg secretion	Chen et al. [58]
33	Protocatechuic aldehyde (PA)	*Salvia miltiorrhiza*	Red sage, chinese sage	Lamiaceae	HBsAg and HBeAg secretion HBV DNA replication	Zhou et al. [59]
34	Flavonoids: Ellagic acid	*Phyllanthus niruri*	Stone breaker	Phyllanthaceae	HBeAg secretion	Shin et al. [54]; Kang et al. [60]
35	Wogonin	*Scutellaria baicalensis*	Baikal skullcap	Lamiaceae	HBsAg and HBeAg secretion HBV DNA replication	Cui et al. [24]; Huang et al. [61]
36	Lactones: 6-hydroxyl-7-methoxyl-coumarin	*Streblus asper* (Heartwood)	Sandpaper tree	Moraceae	HBsAg and HBeAg secretion	Li et al. [62]
37	Costunolide and dehydrocostus	*Saussurea lappa* (Root)	Kust, kuth	Asteraceae	HBsAg and HBeAg secretion	Chen et al. [58]
38	Herpetosperin B	*Herpetospermum caudigerum* (Seeds)	Beej karela	Cucurbitaceae	HBsAg secretion	Xu et al. [63]
39	Artemisinin	*Artemisia annua*	Sweet wormwood	Asteraceae	HBsAg secretion HBV DNA replication	Romero et al. [64]
40	Erythrocentaurin (ET)	*Swertia yunnanensis*	Felworts	Gentianaceae	HBsAg and HBeAg secretion HBV DNA replication	Cao et al. [33]; Geng et al. [65]
41	Swerilactones E and F Swerilactones H-K	*Swertia mileensis*	Felworts	Gentianaceae	HBsAg and HBeAg secretion HBV DNA replication	Geng et al. [66]
42	Clausenidin and nordentatin	*Clausena excavata*	Pink lime-berry	Rutaceae	HBsAg secretion	Su et al. [67]
43	Swerilactones C and D	*Swertia mileensis*	Felworts	Gentianaceae	HBsAg and HBeAg secretion	Geng et al. [68]
44	Glycosides: Astragaloside IV	*Radix astragali*	Milk vetch root	Leguminosae	HBsAg and HBeAg secretion	Ren et al. [69]
45	Saikosaponin C	*Bupleuri radix*	Chaiku saiko	Umbelliferae	HBsAg secretion HBV DNA replication	Chiang et al. [70]
46	Alkaloids: Oxymatrine	*Sophora flavescens*	Ku Shen	Fabaceae	HBsAg and HBeAg secretion HBV DNA replication	Du et al. [71]; Cui et al. [33]
Sr no	**Class with Active Ingredients**	**Plant Name & Part Used**	**Local Name**	**Family**	**Effects**	**References**
47	N, N-dimethyltryptamine N12 oxide	*Evodia fargesii Dode*	_____	Rutaceae	HBV DNA replication	Qu et al. [72]
48	Oxymatrine	*Sophora japonica*	Japanese pagoda (Chinese tree)	Fabaceae	HBV DNA replication Decrease resistance	Chen et al. [33]

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49	Dihydrochelerythrine	*Corydalis saxicola Bunting*	Crested lark	Papaveraceae	HBsAg and HBeAg secretion	Wu et al. [73]
50	Cepharanthine hydrochloride (CH)	*Stephania cepharantha Hayata.*	(Chinese plant)	Menispermaceae	HBeAg secretion HBV DNA replication	Zhou et al. [74]
51	Dehydrocavidine, dehydroapocavidine and dehydroisoapocavidine	*Corydalis saxicola Bunting*	(Chinese plant)	Papaveraceae	HBsAg and HBeAg secretion	Li et al. [75]
52	Dauricumidine	*Hypser panitida*	_____	Menispermaceae	HBsAg secretion	Cheng et al. [76]
53	Flavonoids: Epigallocatechin-3-gallate (EGCG)	*Camellia sinensis*	Green tea	Theaceae	HBV entry HBsAg and HBeAg secretion HBV DNA replication and has more effect than lamivudine	Huang et al. [53]
54	Isoorientiion	*Swertia mussotii*	Felworts	Gentianaceae	HBsAg and HBeAg secretion HBV DNA replication	Cao et al. [52]
55	Wogonin	*Scutellaria radix*	Skullcaps	Lamiaceae	HBsAg and HBeAg secretion HBV DNA replication	Guo et al. [77]
56	Luteolin and isovitexin	*Swertia yunnanensis*	Felworts	Gentianaceae	HBsAg and HBeAg secretion HBV DNA replication	Cao et al. [78]
57	Robustaflavone	*Rhus succedanea*	Wax tree	Anacardiaceae	HBV DNA replication	Zembower et al. [79]
58	Others: Chrysophanol 8-O-β –D glucoside, emodin, rhein and sennoside A	*Rheum palmatum*	Chinese rhubarb, turkish rhubarb	Polygonaceae	HBV DNA replication HBsAg secretion	Li et al. [80], Sun et al. [81]
59	6-O-Caffeoyl-p –hydroxyacetophenone-4-O-β-D glucopyranoside	*Artemisia capillaries*	Chinese moxa weed	Asteraceae	HBV DNA replication	Zhao et al. [82]
60	7-Dehydroxyl-zinniol	*Alternaria solani*	Early blight of tomato	Pleosporaceae	Moderate activity against HBV	Ali et al. [83]
61	β -Thujaplicinol	*Chamaecyparis obtusal* (Heartwood)	Western red cedar trees	Cupressaceae	HBV DNA replication	Hu et al. [84]
62	P-Hydroxyacetophenone (p -HAP)	*Artemisia morrisonensis*	(Chinese plant)	Asteraceae	HBV DNA replication HBsAg secretion	Zhao et al. [85]
63	Resveratrol and polydatin	*Polygonum cuspidatum*	Knot weed, smart weed	Polygonaceae	HBeAg secretion HBV DNA replication	Zhang et al. [86]
64	Luteolin-7-O-β-D glucopyranoside and luteolin	*Glossogyne tenuifolia*	(Chinese plant)	Asteraceae	HBsAg secretion	Wu et al. [87]

Pathogenesis of Hepatitis B Virus (HBV)

HBV, a moderately double stranded (ds) DNA virus has family of hepadnaviridae. This virus contains nucleocapsid having DNA genome of 3.2 kb and DNA polymerase. Assembled hepatitis B core antigen form nucleocapsid which is protected by lipid envelope comprising of hepatitis B envelope antigen (HBeAg) as well as hepatitis B surface antigen (HBsAg) Baumert et al. [11]. HBV replication begins when virus enters host cell and releases its DNA into nucleus. First step is attachment of virus having pre S1 receptors at its surface and heparin sulfate proteoglycans on liver cells. Then virus penetrates hepatocytes via endocytosis or fusion which depends on host factors involving the endosome synthesis. Nucleocapsid of virus, having partially double stranded relaxed circular (rcDNA), is secreted into cytoplasm prior to reaching to nucleus of hepatocytes. Capsid brings its rcDNA to nucleus by nuclear pore complex (NPC) which is due to association between nuclear localization signaling (NLS) in C-terminal of capsid protein and nuclear import receptors (importin-α and β).

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After that rcDNA is converted into covalently closed circle DNA (cccDNA) via viral DNA polymerase. ccc DNA is used as template for synthesizing of pregenomic RNA which at that time undergo assembly of viral DNA as well as mRNA results in encoding entirely new viral proteins. During the reverse transcription of pregenomic RNA into complementary DNA, the pregenomic RNA is tainted. Initially HBV surface proteins are formed along with polymerized in rough endoplasmic reticulum. The proteins are transferred into ER and pre golgi sections and growing of nucleocapsid is started. Consequently, whole virus is liberated from host cell for stating new life cycle Lu & Block [12].

Hepatitis B Virus and Medicinal Plants

Boehmeria nivea (BN) is traditionally used for curing hepatitis B. For screening of activity of ethanolic extract of leaves of BN against hepatitis B virus in vivo, viremia HBV mice models which were generated by subcutaneous inoculation of hepatoma G tumor cell lines (HepG2 2.2.15) for period of 13 days, were used. A result exhibited that BN extract given orally and intraperitoneally effectively inhibited the formation of HBV DNA and HBsAg. However intraperitoneal administration suppressed serum HBV DNA levels more than oral Chang et al. [13]. In earlier investigations, ethanolic extract of the roots of BN could diminish the supernatant hepatitis B virus (HBV) DNA in HBV producing HepG2 2.2.15 cells.

Also, ethyl acetate and chloroform fractions of BN leaves inhibited HBeAg and HBsAg secretion in cells of HepG 2.2.15 without any observed cytotoxic effects. Phyllanthus amarus suppressed hepatitis B virus polymerase activity, decreased episomal hepatitis B virus DNA content and suppressed releasing of virus into cells of HepG 2 2.2.15. As a consequence, it inhibited HBV replication. G26 hepatitis B virus transgenic mice did not produce serum HBsAg but neither HBcAg nor virion particles were used to study transcriptional control mechanisms. The hepatic HBsAg mRNA levels were decreased, indicating transcriptional or post-transcriptional down-regulation of the transgene Saleem & Lee et al. [14,15]. Alternanthera philoxeroides have valuable constituents such as flavones, triterpenoid, anthraquinones, saponins, phytosterols, and organic acids. Numerous oleanolic acid analogues from it have potential against HBV. Two new 6-C-boivinopyranosyl flavones along with three known analogues separated from plant, suppressed HBsAg secretion in HepG 2.2.15 cells.

Oenanthe javanica has traditional use in management of hepatitis in China. Therefore in vitro method i.e. culture of Hep G 2.2.15 cells along with *in vivo* for instance duck hepatitis B virus (DHBV) infection model were used to investigate anti-HBV activity. Results exhibited that phenolic compounds from ethanolic extract of fruit of this plant significantly blocked HBV replication, HBsAg and HBeAg secretion in Hep G2.2.15 cells line and suppressed DHBV replication in ducks in a dose dependent manner. The concentration of HBsAg and HBeAg in cell culture medium was measured via use of enzyme immune assay after being treated with extract for 9 days. DHBV DNA in duck serum was analyzed by dot blot hybridization assay Huang et al. [16].

Methanolic extracts of leaves of *Enicostemma axillare* and seeds of *Terminalia bellerica*, blocked HBV DNA polymerase while methanolic extract of leaves of Hybanthus enneaspermus blocked HBs Ag binding in plasma of patients in vitro using ELISA kits Anbalagan et al. [17]. Alcoholic extract of leaves of *Acanthus ilicifolius* decreased transaminase levels such as ALT and AST in duck hepatitis B virus serum but did not significantly suppress hepatitis B virus DNA in ducks. Thus, extract had hepatoprotective effect against HBV induced liver damage Naseer & Wei et al. [18,19]. *Gymnema sylvestre* demonstrated antiviral activity and its active ingredients inhibited HBsAg binding and HBV DNA polymerase Subashini & Rajendran [20]. Methanolic extract of *Mimosa pudica* inhibited HBs Ag binding to its receptor at 5mg/ml (*in vitro*) which indicated that it had capability to act as novel entry inhibitor during HBV infection by using hepatitis B positive blood Rohan et al. [21]. Medicinal plants have certain components that targets different steps of life cycle of HBV see Figure 1.

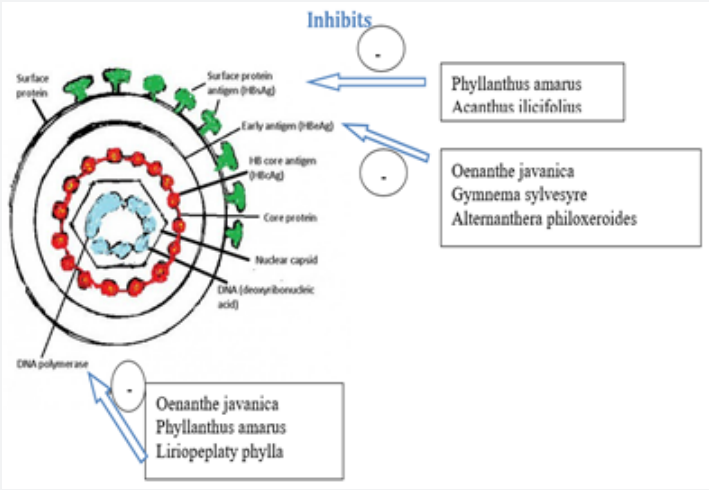

Figure 1: Medicinal plants targeting hepatitis B virus.

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The compound LPRP-Et acquired from *Liriope platyphylla* roots suppressed HBV by means of monitoring gene expression besides DNA replication via viral proteins which inhibited NF-kB (nuclear factor kappa B) pathway Saleem & Huang et al. [22,23]. Traditional Chinese medicinal plants such as *Phyllanthus, Salvia miltiorrhiza, Rheum palmatum L.* and *Radix astragali* and active ingredients such as oxymatrine, artemisinin and artesunate and wogonin also are effective against hepatitis B Cui et al. [24]. Active ingredients obtained from plants of different classes such as terpenoids, alkaloids, polyphenols, flavonoids and lignans have specific mechanism of action targeting at different steps of life cycle of hepatitis B as shown in Figure 2-5 & Table 1 [25-88].

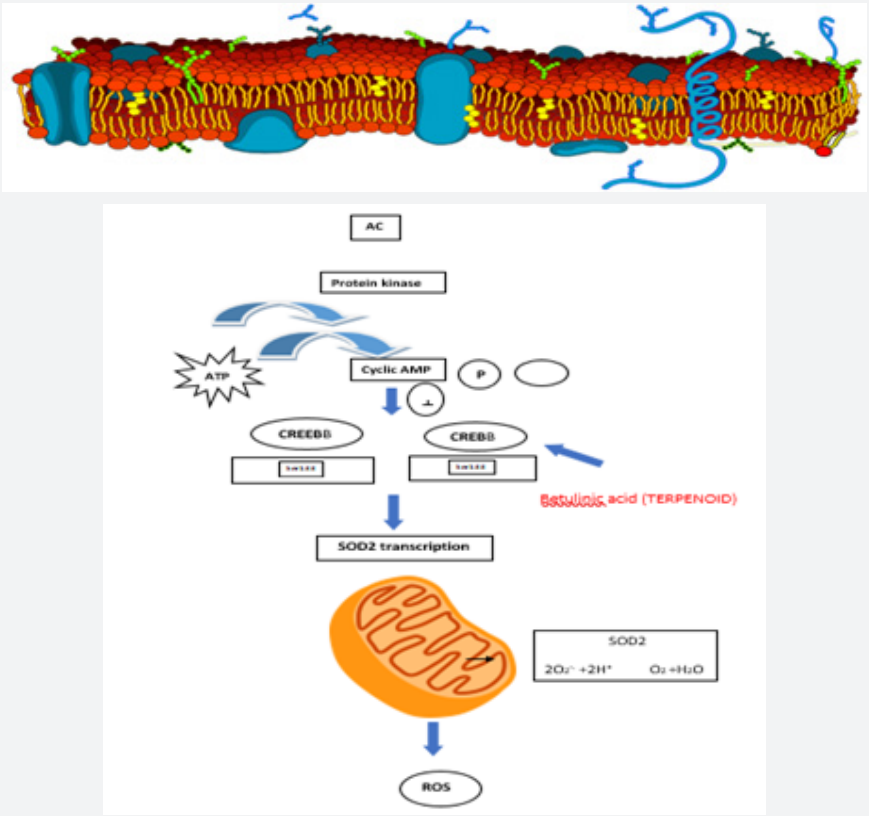

Figure 2: Betulinic acid acquired from *Pulsatilla chinensis* inhibited replication of HBV via depressing the manganese superoxide dismutase (SOD2) expression within transgenic mice result in formation of reactive oxygen species (ROS) as well as its dysfunction in mitochondria. Newer investigation exhibited that SOD2 expression was reduced via betulinic acid induced dephosphorylation of cAMP response element binding protein (CREB) at Ser133 which transcription factor for SOD2 is transcription. Yao et al. [26].

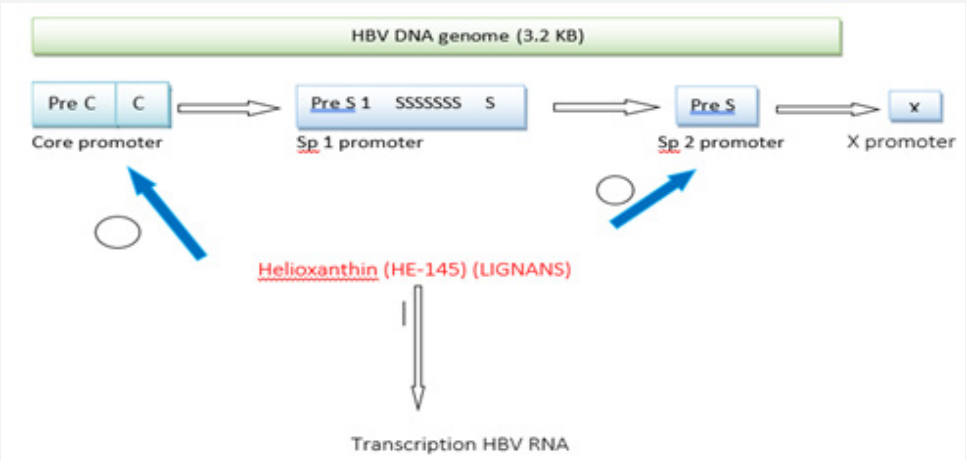

Figure 3: HE-145 inhibited selectively core promoter (CP) and surface antigen promoter II (SPII) but had no effect on X gene promoter (Xp) and surface antigen promoter I (SPI). Thus, blocks HBV RNA Tseng et al. [42].

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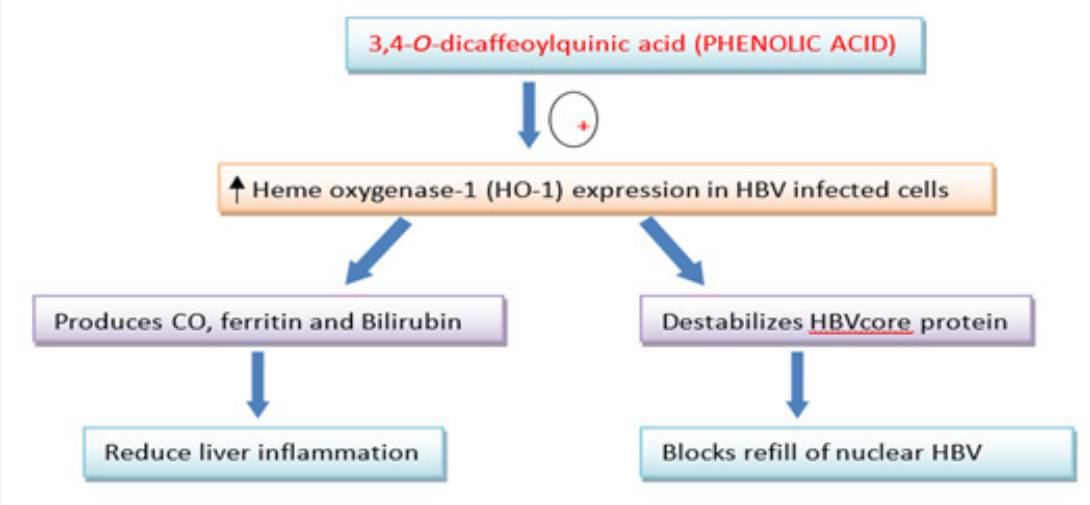

Figure 4: 3,4-O-dicaffeoylquinicacid distinctly reduced hepatitis B viral cccDNA content and considerably increased heme oxygenase-1 (HO-1) expression in HepG 2.2.15 cells and HBV transgenic mice. Because HO-1 can weaken the HBVcore protein and thus prevents refill of nuclear HBV cccDNA Kim et al. [49].

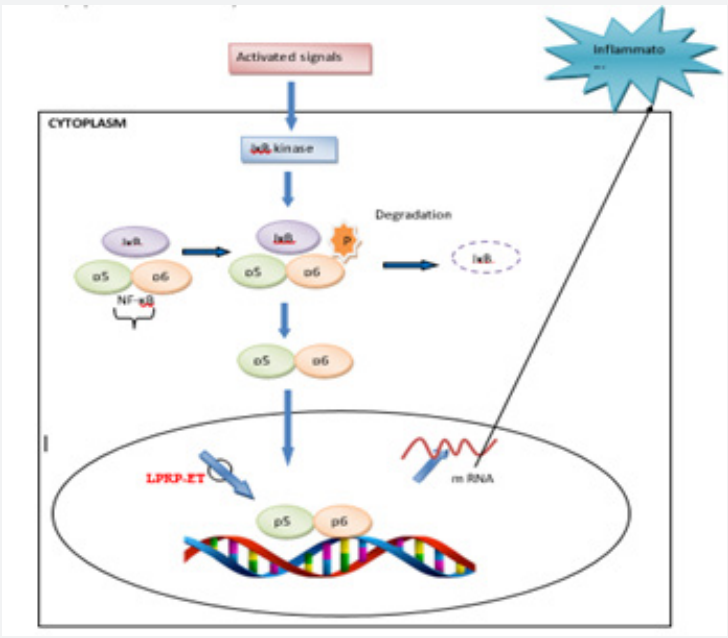

Figure 5: LPRP-Et declinined nuclear expression of p50 as well as p65 proteins from nuclear factor kappa B (NF-κB) and improved level of IκBα protein without distressing the expression within HBV non transfected cells Huang et al. [53].

Conclusion

Although there are many drugs available for treatment of hepatitis B and vaccination is also effective against virus but due to side effects and resistance associated with these drugs, there is need to explore safer and most potent drugs. Natural products are considered good candidates with strong anti-hepatitis B activity. This review illustrates the description of medicinal plants used to treat hepatitis B. Forthcoming energies should be dedicated to enhancing and progress these principal complexes into effective anti HBV agents for experimental claims. There is limited data available illustrating mechanism of action of medicinal plants with anti-hepatitis B activity. Thus, mechanisms of function and safety of herbs remain incomprehensive and even controversial. The toxicological data for screening the safety of medicinal plants is not discussed and people have blind faith in herbal treatment. For determination of activity of medicinal plants against hepatitis B, various HBV animal models for instance HBV transgenic mice and duck model have been used thus, are very expensive but these representations can only describe a portion of the mechanism of anti-hepatitis B medicines. In several findings, cell lines such as HepG 2 2.2.15 within mice were recognized to mimic the occurrence of HBV viremia, for the reason that viruses produced from HepG 2 2.2.15 cells have been defined to be transmittable.

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