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A mini-review of anti-hepatitis B virus activity of medicinal plants

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ABSTRACT

Medicinal plants are of undoubted value, as they have been used for centuries to treat various diseases and health disorders in almost every part of the world. In several studies, the use of medicinal plants was found effective in treatment of infectious and non-infectious diseases. The World Health Organization has been working for many years to identify all surviving medicinal plants on the earth. An important step has also been taken by the Natural Health Product Regulation of Canada for promotion and usages of natural products. At present, the rapidly growing population of the world is facing many challenges from various infectious diseases that are associated with hepatitis A, B and C virus, human immunodeficiency virus, influenza virus, dengue virus and new emerging viruses. Hepatitis B virus causes a severe and frequently transmittable disease of the liver. Millions of people worldwide suffer from hepatitis B virus (HBV) infection. The drugs available on the market for the treatment of hepatitis B are not sufficient and also cause side effects in patients suffering from HBV infection. The pharmaceutical companies are searching for suitable alternative and natural inhibitors of HBV. Therefore, it is important to explore and use plants as a source of new medicines to treat this infectious disease, because single plants contain a priceless pool of active ingredients which could help in the production of pharmaceutical-grade peptides or proteins. However, the knowledge of the antiviral activity of medicinal plants is still limited.

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Introduction

Since time immemorial, humans are known to have used plants as a source of medicine for the cure of diseases. Historically, by 1980, at least 121 phytochemicals of known structure had been extracted from plants that have medicinal properties [1]. Nowadays, the modern society is shifting towards alternative medicines, and western physicians are searching for alternative methods when they are unable to find a suitable therapy for the health disorders of a suffering patient. Most of the world population relies mainly on medicinal plants for health care, and more than 30% of the total plant species were used for medicinal purposes. Today, people around the world are becoming very conscious about their health, and their blind dependence on allopathic medicine is decreasing day by day. Thus, people are returning to naturals with hope of safety and security. Therefore, medicinal plants and derived medicines are widely accepted worldwide and the demand for such products is increasing rapidly in the pharmaceutical industry. According to Mukhtar et al. [2], 25% of the commonly used drugs have compounds extracted from plants, and based on the estimations of the World Health Organization (WHO), medicinal plants and derived medicines provide the health care demands of 80% of the world's population.

Herbal therapy is an old tradition in Arabian regions, and phytomedicine has a significant value for this area's heritage [3]. According to Hasan et al. [4], the Arabian Peninsula is the place of origin of herbal therapy. However, medicinal plants grown particularly in Saudi Arabia have received little international attention as compared to other countries like China, India, Japan, Thailand, Africa and Egypt. From the available literature, there are 2250, 600, 1204, 2088 and 2367 plants found in Saudi Arabia, the United Arab Emirates (UAE), Oman, Egypt and Palestine, respectively [5], and their antiviral properties are still unknown. However, only less than 10% of these medicinal plants have been identified for their medicinal use in

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the Gulf region [3]. Nearly 300 species in Saudi Arabia and 99 species in UAE have been identified as medicinal plants [3]. Therefore, UAE took a good initiative step to establish the Zayed Complex for Traditional and Herbal Medicine, a state-of-the-art centre that focuses on the identification and characterization of native herbs. Moreover, most of the species are a rich source of new bioactive compounds with priceless properties. Therefore, more studies are needed for elucidation of the properties of medicinal plants active against viruses causing various diseases (e.g. influenza, acquired immune deficiency syndrome, hepatitis, dengue fever, etc.) in humans. According to Farnsworth and Bingel [6], pharmaceutical companies use only 25% of the medicines derived from plants. The Food and Agriculture Organization (FAO) reported that 52,885 of 422,000 plant species have been identified and used as medicinal plants [7]. However, China, India, Indonesia and Malaysia use 18.9%, 20%, 4.4% and 7.7% of the medicinal plants of the world as a source of drugs in traditional medicine, respectively. In Saudi Arabia, only 300 of 2250 species (just 12% of the total species in the flora), belonging to 72 families, have been identified as medicinal plants and the remaining 1950 species in 142 families need to be investigated for their medicinal values [8–10]. The Medicinal, Aromatic and Poisonous Plant Research Center (MAPPRC), King Saud University, Riyadh, Saudi Arabia, took a good initiative to identify medicinal plants, as the flora of Saudi Arabia includes a large number of medicinal plants. It is important to explore and use plants as a source of new medicines because single plants contain a priceless pool of active constituents which could help in the production of pharmaceutical-grade peptides or proteins [11,12].

Distribution of hepatitis B virus

There are different types of hepatitis viruses, i.e. A, B, C, D and E, and exposure to them leads to acute infection and inflammation of the liver. However, hepatitis B virus (HBV) and hepatitis C virus (HCV) are unique types in that they cause chronic infection. HBV is the prototypic member for a family of viruses known as Hepadnaviridae [13]. Worldwide, millions of people suffer from chronic HBV infection, despite the availability of a safe and effective vaccine [14]. Chronic infection with HBV is more likely to lead to development of primary hepatocellular carcinoma (HCC) [15,16]. Globally, hepatitis B is one of the major threats to human health. About 90% of HBV infections develop into acute hepatitis and 10% into chronic hepatitis, cirrhosis and HCC. About 350 million people worldwide are HBV carriers [17]. According to WHO, Saudi Arabia has one of the highly endemic chronic HBV populations as shown in Figure 1. Therefore, it is important to search for suitable HBV natural inhibitors and the strategies should be aimed at eradication of HBV transmission. This is particularly important because the present antiviral drugs, i.e. alpha-interferon (interferon alpha-2a and interferon alpha-2b), lamivudine and adefovir, are effective, but not sufficient for all patients, and some of them are slow-acting and even frequently causing adverse effects, such as fever, malaise, fatigue, depression, hair loss, neutropenia and thrombocytopenia [19,20].

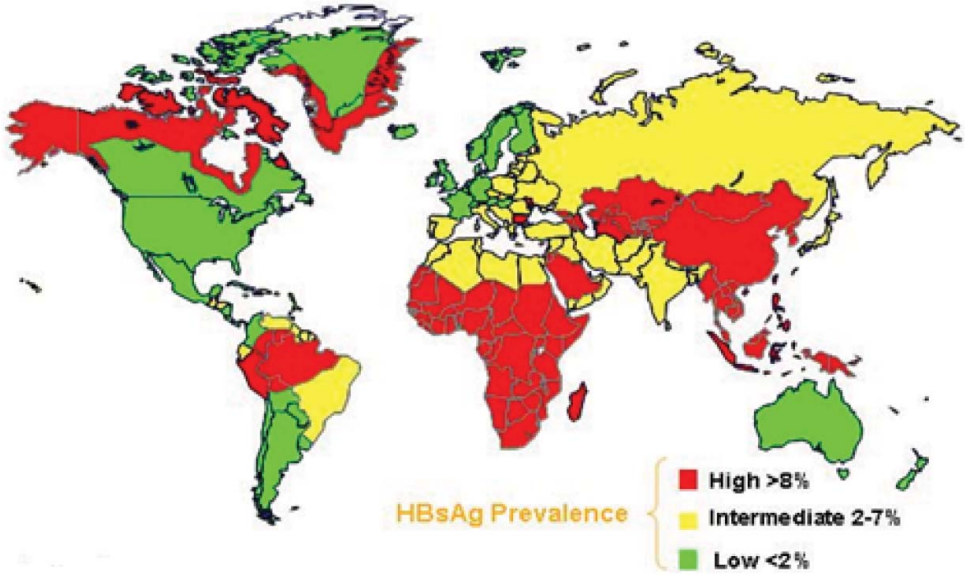

Figure 1. Geographical distribution of chronic HBV infection [18].

A high endemicity of HBV in Saudi Arabia was reported in 2003 [21]; 5%–10% of the population were infected and the southern part of the country was highly infected. In Saudi Arabia, liver cancer accounts for 6.1% of all newly diagnosed cancers [22]. Saudi males are affected with the second most common cancer, HCC, and it is the eighth most common cancer-affecting females, with an overall age standardized rate of 4.5/100,000 population. The male-to-female ratio is 279:100. In Saudi Arabia, HCC accounts for 87.6% of all liver cancers [22,23]. Currently, interferon α, lamivudine and adefovir dipivoxil are the only drugs approved for the treatment of chronic HBV infection. Most of the currently available drugs inhibit the reverse transcriptase activity of HBV as shown in Figure 2.

For these reasons, traditional medicinal plants may offer an alternative for the treatment of infectious diseases. Several thousands of plant species have antiviral properties and some have already been utilized to treat patients suffering from viral infection [24]. It is well established that several medicinal plants are a rich source of natural ingredients, including alkaloids, flavonoids, furyl compounds, terpenoids, polyphenolics, lignans, coumarins, proteins and other groups of substances. These phytochemicals are active against the formation of viral DNA or RNA, and facilitate DNA repair and enhance the immune function. Isoquinoline alkaloids show effective antiviral activity against HBV [25]. At the molecular level, the mechanism of action of plant extracts against the viral activities varies among different viruses. Saudi Arabia has a long history of using traditional medicinal plants to treat a range of diseases. HBV infection is epidemic in Saudi Arabia. Therefore, exploiting the antiviral potential of these medical extracts to treat HBV infection in the Saudi population can provide alternative treatments in reducing the health care costs.

Medicinal plants

Plants have been used as a weapon against various pathogens in the past. However, the Boots drug company (Nottingham, England) was the first to screen 288 plants and find antiviral activity against influenza virus [26] (reviewed in [2]). Since viral infections are still a major threat to human health worldwide, medical practitioners are shifting towards new medicines derived from plants that may have fewer side effects on patients and higher effectiveness against viruses. Herbal medicines, or herbal remedies (phytomedicines), derived from higher plants are used worldwide, especially in developed countries, e.g. in European countries and the United States [27]. The pharmaceutical companies are growing fast and show a great interest in phytomedicines because of their popularity and demand on the market. According to a recent market report, the global nutraceuticals product market reached US$165.62 billion in 2014 and is predicted to reach US$278.96 billion by the end of 2021 [27]. There is a growing body of literature demonstrating that plants are a rich source of biologically active constituents and that they show antiviral activity against different viruses. Nearly 45% of the therapeutic products available on the market are derived from plants or their derivatives [28] (Table 1).

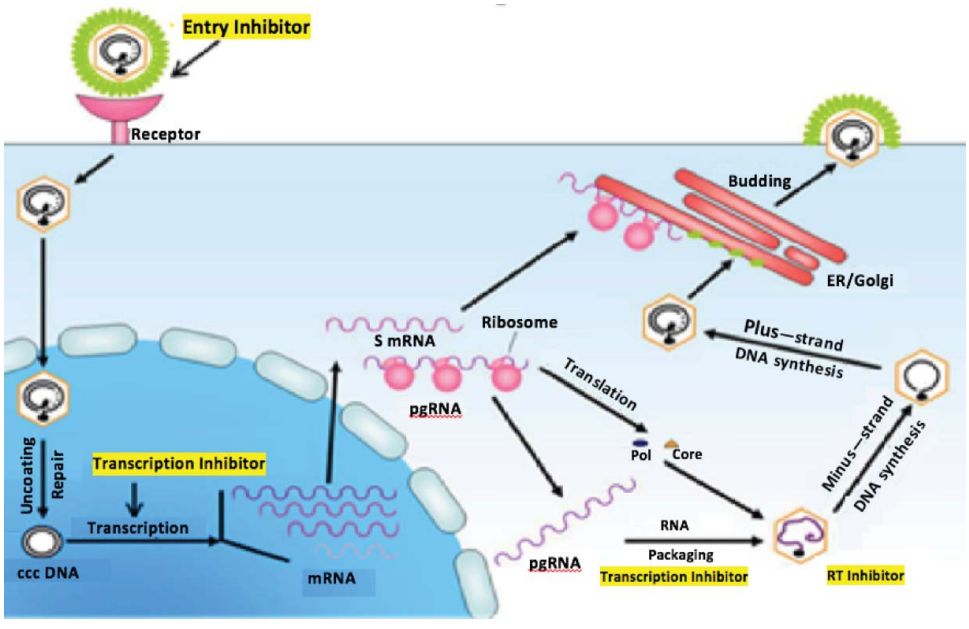

Figure 2. Life cycle of HBV and potential antiviral targets.

Table 1. Medicinal plants and their activity against different viruses.

Family	Medicinal plant used	Viruses	References
Asteraceae	*Pterocaulon sphacelatum*	Poliovirus	[29]
Liliaceae	*Dianella longifolia*	Poliovirus	
Euphorbiaceae	*Euphorbia australia*	Cytomegalovirus	
Goodneniaceae	*Scaevola spinescens*	Cytomegalovirus	
Myoporaceae	*Eremophila latrobei* subsp. *glabra*	Ross River virus	
Pittosporaceae	*Pittosporum phylliraeoides*	Ross River virus	
Apocynaceae	*Carissa edulis*	Herpes simplex virus	[30]
Myrtaceae	*Eugenia jambos*	Vesicular stomatitis virus	[31]
Compositae	*Santolina oblongifolia*		
Malvaceae	*Chiranthodendron pentadactylon*		
Cistaceae	*Tuberaria lignosa*	Herpes simplex virus (type 1)	
Phyllanthaceae	*Phyllanthus urinaria*	Herpes simplex virus	[32]
Geraniaceae	*Geranium sanguineum*	Influenza virus	[33–35]
Meliaceae	*Azadirachta indica*	Dengue virus type-2 (DEN-2)	[36]
Sterculiaceae	*Guazuma ulmifolia*	Poliovirus	[37]
Polygonaceae	*Poygonum punctatum*	Respiratory syncytial virus	[38]
Anacardiaceae	*Lithraea molleoides*	Respiratory syncytial virus	
Myrtaceae	*Myrcianthes cisplatensis*	Respiratory syncytial virus	
Guttiferae	*Hypericum mysorense*	Herpes simplex virus	[39]
Hypericaceae	*Hypericum hookerianum*	Herpes simplex virus	
Usneaceae	*Usnea complanta*	Herpes simplex virus	
Euphorbiaceae	*Phyllanthus amarus*	Human immunodeficiency virus	[40]
	Phyllanthus urinaria	Herpes simplex virus	[32]
Caprifoliaceae	*Sambucus nigra*	Influenza virus	[41]
Pandanaceae	*Pandanus amaryllifolius*	Influenza virus (H1N1)	[42]
		Herpes simplex virus	
Apocynaceae	*Carissa edulis*	Herpes simplex virus	[30]

HBV and medicinal plants

Medicines are limited by poor long-term response, the high frequency of adverse side effects and the emergence of resistant mutants during long-term therapy [43,44]. Therefore, the discovery of safe and effective anti-HBV drugs is still considered a serious challenge. Herbal medicines have long been used for the treatment of liver disorders all over the world, and a number of them exhibit anti-HBV activity, which has been proved experimentally in preclinical and clinical studies. Meta-analysis in clinical trials showed that extracts from *Phyllanthus* species have a positive effect on the clearance of serum hepatitis B surface antigen (HBsAg) in HBV carriers [45]. For example, *P. amarus* (L.) has been shown to exert its antiviral effect via interaction with HBV enhancer I and C/EBP alpha and beta transcription factors, thus inhibiting the HBV polymerase activity and mRNA transcription [46,47]. In fact, various studies have reported that plants have antiviral properties against hepatitis virus. For example, *Oenanthe javanica* has been shown to be helpful in the treatment of HBV infection and to inhibit HBsAg and HBeAg secretion *in vitro* [48]. Jacob et al. [49] investigated that KYH-1 (an aqueous extract of herbal formulation) showed potent antiviral activity and suppressed HBV replication in a human hepatoplastoma cell line. Thus, the use of medicinal plants becomes an interesting target for research to substitute the conventional drugs and chemicals. More research is needed to focus on the screening of the antiviral activity of Saudi medicinal plants on HBV (Table 2).

According to Wu et al. [60], there are few studies regarding the novel mode of action of natural products against HBV. For example, *Acanthus ilicifolius* L. reduces HBV-induced liver damage by lowering the transaminase [61]. *Gymnema sylvestre* R. Br. shows antiviral activity and its phytoconstituents inhibit HBsAg binding and HBV DNA polymerase [62]. Also, the extract from *Phyllanthus* reduces HBV DNA synthesis and HBsAg and HBcAg secretion by replicating cells harbouring HBV wild-type

Table 2. Medicinal plants and their activity against hepatitis virus.

Family	Medicinal plant used	Viruses	References
Lamiaceae	*Mentha longifolia*	Hepatitis A virus	[50]
Lamiaceae	*Ocimum basilicum*		
Urticaceae	*Boehmeria nivea*	Hepatitis B virus	[51]
Euphorbiaceae	*Phyllanthus amarus*,		[46,47]
	Phyllanthusanus		[52]
Mimosoideae	*Acacia nilotica*	Hepatitis C virus	[53]
Burseraceae	*Boswellia carterii*		
Myrsinaceae	*Embelia schimperi*		
Fagaceae	*Quercus infectoria*		
Apiaceae	*Trachyspermum ammi*		
Piperaceae	*Piper cubeba*		
Myrtaceae	*Syzygium aromaticum*		
Asteraceae	*Silybum marianum*		[54]
Zingiberaceae	*Zingiber officinale*		
Saxifragaceae	*Saxifraga melanocentra*		[55]
Gentianaceae	*Swertia patens*,	Hepatitis B virus	[56,57]
	Swertia chirayita		
Euphorbiaceae	*Euphorbia sikkimensis*	HIV	[58]
Oleaceae	*Ligustrum purpurascens*	Influenza virus	[59]

and LMV-resistant mutants, may be by inducing the expression of interferon-beta, cyclooxygenase-2 and interleukin-6 via activation of extracellular signal-regulated kinases and c-jun *N*-terminal kinases [63]. Two new important C-boivinopyranosyl flavones (luteolin-6-C-β-d-boivinopyranosyl-3′-*O*-β-D-glucopyranoside and chrysoeriol-6-C-β-D-boivinopyranosyl-4′-*O*-β-D-glucopyranoside) of *Alternanthera philoxeroides* exhibited significant anti-HBV activities by reducing HBsAg secretion in HepG2.15 [64]. Curcumin inhibits HBV gene expression and DNA replication, mediated by down-regulation of PGC-1α, a starvation-induced protein that initiates the gluconeogenesis cascade and that may robustly co-activate HBV transcription [65]. The compound LPRP-Et-97543, isolated from *Liriope platyphylla* roots, inhibits the mode of action of HBV by controlling gene expression and DNA replication by viral proteins, which interferes with the nuclear factor NF-κB pathway [66]. Traditional Chinese medicine plants (*Phyllanthus*, *Salvia miltiorrhiza*, *Rheum palmatum* L. and *Radix astragali*) and active constituents (oxymatrine, artemisinin and artesunate and wogonin) also have promising and potent anti-HBV activities [67]. Overall, there are not sufficient studies on the mechanism of action of active constituents of plants against HBV, although many natural products have been found effective against HBV inhibition in many studies.

Conclusions

Flora of world is rich in a wide variety of plant species with various active ingredients that deserve more international attention. The medicinal potential of the world flora is still unidentified. Therefore, rigorous studies on the medicinal properties of plants against different viruses, including HBV, are very important in order to uncover the priceless medicinal value for the cure of infectious diseases. Some medicinal plants are already widely used by the pharmaceutical and herbal companies for making drugs and cosmetic products, and plant-derived medicine has gained international reputation. The knowledge of active constituents associated with the medicinal properties of a particular plant could help to provide valuable information for the discovery of powerful remedies to cure diseases. However, there have been no significant attempts made yet on revealing the antiviral activity of medicinal plants by molecular techniques. By detailed elucidation of the antiviral activity of medicinal plants, it would be possible to increase the phytochemical and toxicological knowledge for discovery of effective anti-HBV drugs in due course.

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References

[1] ITC. Market for selected medicinal plants and their derivatives. Geneva: International Trade Centre/UNCTAD/GATT; 1982. p. 206.
[2] Mukhtar M, Arshad M, Ahmad M, et al. Antiviral potentials of medicinal plants. Virus Res. 2008;131:111–120.
[3] Amin A, Mousa M. Merits of anti-cancer plants from the Arabian Gulf region. Cancer Ther. 2007;5:55–66.
[4] Hasan MY, Das M, Behjat S. Alternative medicine and the medical profession: views of medical students and general practitioners. East Mediterr Health J. 2000;6:25–33.
[5] Migahid AM. Flora of Saudi Arabia. 4th ed. Riyadh: King Saud University Press; 1996.
[6] Farnsworth NR, Bingel AS. Problems and prospects of discovering new drugs from higher plants by pharmaceutical screening. In: Wagner H, Wolff P, editors. New natural products and plant drugs with pharmacological or therapeutical activity. Berlin: Springer Verlag; 1977. p. 1–22.
[7] Schippmann U, Cunningham AB, Leaman DJ. Impact of cultivation and gathering of medicinal plants on biodiversity: global trends and issues, case study no. 7. In: Biodiversity and the ecosystem approach in agriculture, forestry and fisheries. Satellite event on the occasion of the Ninth Regular Session of the Commission on Genetic Resources for Food and Agriculture. Proceedings; 2002 Oct 12–13; Rome. Rome: FAO Inter-departmental Working Group on Biological Diversity for Food and Agriculture; 2003. Available from: http://www.fao.org/DOCREP/005/Y4586E/y4586e08.htm.
[8] Rahman MA, Mossa JS, Al-Said MS, et al. Medicinal plant diversity in the flora of Saudi Arabia 1: a report on seven plant families. Fitoterapia. 2004;75:149–161.
[9] Mossa JS, Al-Yahyu MA, Al-Meshal IA. Medicinal plants of Saudi Arabia. Vol. 1. Riyadh: King Saud University Press; 1987.
[10] Mossa JS, Al-Yahya MA, Al-Meshal IA. Medicinal plants of Saudi Arabia. Vol. 2. Riyadh: King Fahad National Library Publication; 2000.
[11] Koprowski H, Yusibov V. The green revolution: plants as heterologous expression vectors. Vaccine. 2001;19:2735–2741.
[12] Glenz K, Warzecha H. New medicinal plants for the production of vaccines. J Verb Leb. 2006;1:126–130.
[13] Hollinger FB, Liang TJ. Hepatitis B virus. In: Knipe DM, Howley PM, editors. Fields' virology. Philadelphia (PA): Lippincott Williams and Wilkins; 2001. p. 2971–3036.
[14] Mast EE, Alter MJ, Margolis HS. Strategies to prevent and control hepatitis B and C virus infections: a global perspective. Vaccine. 1999;17:1730–1733.
[15] Okuda K. Hepatocellular carcinoma. J Hepatol. 2000;32:225–237.
[16] Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295:65–73.

[17] Meddrey WC. Hepatitis B: an important public health issue. J Med Virol. 2000;61:362–366.
[18] CDC, Hepatitis Branch. Epidemiology and prevention of viral hepatitis A to E: an overview [slide set]. U.S. Department of Health and Human Services, Public Health Service. Atlanta (GA): Centers for Disease Control and Prevention; 1995. Available from: http://virology-online.com/viruses/HepatitisB.htm
[19] Lavanchy D. Hepatitis B virus: epidermiology, disease burden, treatment and current and emerging prevention and control measures. J Viral Hepatitis. 2004;11:97–107.
[20] Dusheiko GM, Roberts JA. Treatment of chronic type B and C hepatitis with interferon alfa: an economic appraisal. Hepatology. 1995;22:1863–1873.
[21] Al-Faleh FZ. Changing pattern of hepatitis viral infection in Saudi Arabia in the last two decades. Ann Saudi Med. 2003;23(6):367–371.
[22] Abdo AA, Karim HA, Al Fuhaid T, et al. Saudi gastroenterology association guidelines for the diagnosis and management of hepatocellular carcinoma: summary of recommendations. Ann Saudi Med. 2006;26:261–265.
[23] Jassim SAA, Naji MA. Novel antiviral agents: a medicinal plants perspective. J App Microbiol. 2003;95:412–417.
[24] Aljofan M, Netter HJ, Aljarbou AN, et al. Anti-hepatitis B activity of isoquinoline alkaloids of plant origin. Arch Virol. 2014;159:1119–1128.
[25] Chantrill BH, Coulthard CE, Dickinson L, et al. The action of plant extracts on a bacteriophage of *Pseudomonas pyocyanea* and on influenza A virus. J Gen Microbiol. 1952;6:74–84.
[26] Dutra RC, Campos MM, Santos ARS, et al. Medicinal plants in Brazil: pharmacological studies, drug discovery, challenges and perspectives. Pharmacol Res. 2016;112:4–29.
[27] TMR. Nutraceuticals market-global industry analysis, size, share, growth, trends, and forecast 2015–2021 [Internet]. Albany (NY): Transparency Market Research; cTMR [published 2015 Sep 23]. Available from: http://www.transparencymarketresearch.com/globalnutraceuticals-product-market.html
[28] Lahlou M. The success of natural products in drug discovery. Pharmacol Pharm. 2013;4:17–31.
[29] Semple SJ, Reynolds GD, O'Leary MC, et al. Screening of Australian medicinal plants for antiviral activity. J Ethnopharm. 1998;60:163–172.
[30] Tolo FM, Rukunga GM, Muli FW, et al. Anti-viral activity of the extracts of a Kenyan medicinal plant *Carissa edulis* against herpes simplex virus. J Ethnopharm. 2006;104:92–99.
[31] Abad MJ, Bermejo P, Villar A, et al. Antiviral activity of medicinal plant extracts. Phytother Res. 1997;11:198–102.
[32] Yang CM, Cheng HY, Lin TC, et al. The *in vitro* activity of geraniin and 1,3,4,6-tetra-O-galloyl-beta-d-glucose isolated from *Phyllanthus urinaria* against herpes simplex virus type 1 and type 2 infection. J Ethnopharm. 2007;110:555–558.
[33] Pantev A, Ivancheva S, Staneva L, et al. Biologically active constituents of a polyphenol extract from *Geranium sanguineum* L. with ant-influenza activity. Z Naturforsch C. 2006;61:508–516.
[34] Serkedjieva J. Anti-infective activity of a plant preparation from *Geranium sanguineum* L. Pharmazie. 1997;52:799–802.
[35] Serkedjieva J. Combined antiinfluenza virus effect of a plant preparation and a bacterial protease inhibitor. Biotechnol Biotechnol Equip. 2009;23(Suppl. 1):589–593.
[36] Parida MM, Upadhyay C, Pandya G, et al. Inhibitory potential of neem (*Azadirachta indica Juss*) leaves on dengue virus type-2 replication. J Ethnopharm. 2002;79:273–278.
[37] Felipe AM, Rincao VP, Benati FJ, et al. Antiviral effect of *Guazuma ulmifolia* and *Stryphnodendron adstringens* on poliovirus and bovine herpes virus. Biol Pharm Bull. 2006;29:1092–1095.
[38] Kott V, Barbini L, Cruanes M, et al. Antiviral activity in Argentine medicinal plants. J Ethnopharm. 1999;64:79–84.
[39] Vijayan C, Raghu C, Ashok G, et al. Antiviral activity of medicinal plants of Nilgiris. Indian J Med Res. 2004;120:24–29.
[40] Notka F, Meier G, Wagner R. Concerted inhibitory activities of *Phyllanthus amarus* on HIV replication *in vitro* and *ex vivo*. Antiviral Res. 2004;64:93–102.
[41] Barak V, Halperin T, Kalickman I. The effect of sambucol, a black elderberry-based, natural product, on the production of human cytokines: I. Inflammatory cytokines. Eur Cytokine Netw. 2001;12:290–296.
[42] Ooi LS, Sun SS, Ooi VE. Purification and characterization of a new antiviral protein from the leaves of *Pandanus amaryllifolius* (Pandanaceae). Int J Biochem Cell B. 2004;36:1440–1446.
[43] Wong DKH, Cheung AM, O'Rourke K, et al. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. Ann Inter Med. 1993;119:312–323.
[44] Zoulim F. A preliminary benefit-risk assessment of lamivudine for the treatment of chronic hepatitis B virus infection. Drug Safety. 2002;25:497–510.
[45] Liu J, Lin H, McIntosh H. Genus *Phyllanthus* for chronic hepatitis B virus infection: a systematic review. J Viral Hepatitis. 2001;8:358–366.
[46] Lee CD, Ott M, Thyagarajan SP, et al. *Phyllanthus amarus* down-regulates hepatitis B virus mRNA transcription and replication. Eur J Clin Invest. 1996;26:1069–1076.
[47] Ott M, Thyagarajan SP, Gupta S. *Phyllanthus amarus* suppresses hepatitis B virus by interrupting interactions between HBV enhancer I and cellular transcription factors. Eur J Clin Invest. 1997;27:908–915.
[48] Huang ZM, Yang XB, Cao WB. Effects of Qin ling ke li in the treatment of 90 patients with chronic hepatitis B. Pharm J Chinese People's Lib Army. 2001;17:41–44.
[49] Jacob JR, Korba BE, You JE, et al. Korean medicinal plant extracts exhibit antiviral potency against viral hepatitis. J Altern Complement Med. 2004;10:1019–1026.
[50] Al-Ali KH, El-Badry AA. Anti-viral activity of two labiatae plants [naana (hassoi, habak) and basil (rahan)] of Al-Madiah Al-Munawarah. J Med Biomed Sci. 2010;2:67–73.
[51] Chang JM, Huang KL, Yuan TTT, et al. The anti-hepatitis B virus activity of *Boehmeria nivea* extract in HBV-viremia SCID mice. Evid Based Complement Alternat Med. 2010;7:189–195.
[52] Lam WY, Leung KT, Law PT, et al. Antiviral effect of *Phyllanthus nanus* ethanolic extract against hepatitis B virus (HBV) by expression microarray analysis. J Cell Biochem. 2006;97:795–812.
[53] Hussein G, Miyashiro H, Nakamura N, et al. Inhibitory effects of Sudanese medicinal plant extracts on hepatitis C virus (HCV) protease. Phytother Res. 2000;14:510–516.

[54] El-Adawi H, El-Demellawy M, El-Wahab AA. Some medicinal plant extracts exhibit potency against viral hepatitis C. J Biosci Tech. 2011;2:223–231.
[55] Zuo GY, Li ZQ, Chen LR, et al. *In vitro* anti-HCV activities of *Saxifraga melanocentra* and its related polyphenolic compounds. Antivir Chem Chemother. 2005;16:393–398.
[56] He K, Geng CA, Cao TW, et al. Two new secoiridoids and other anti-hepatitis B virus active constituents from *Swertia patens*. J Asian Nat Prod Res. 2016;18(6):528–534.
[57] Zhou NJ, Geng CA, Huang XY, et al. Anti-hepatitis B virus active constituents from *Swertia chirayita*. Fitoterapia. 2015;100:27–34.
[58] Jiang C, Luo P, Zhao Y, et al. Carolignans from the aerial parts of *Euphorbia sikkimensis* and their anti-HIV activity. J Nat Prod. 2016;79(3):578–583.
[59] Hu XP, Shao MM, Song X, et al. Antiinfluenza virus effects of crude phenylethanoid glycosides isolated from *Ligustrum purpurascens* via inducing endogenous interferon-γ. J Ethnopharmacol. 2016;179:128–136.
[60] Wu YH. Naturally derived anti-hepatitis B virus agents and their mechanism of action. World J Gastroenterol. 2016;22:188–204.
[61] Wei PH, Wu SZ, Mu XM, et al. Effect of alcohol extract of *Acanthus ilicifolius* L. on anti-duck hepatitis B virus and protection of liver. J Ethnopharmacol. 2015;160:1–5.
[62] Subashini MS, Rajendran P. *In vitro* screening of anti HBV and anti HIV properties of *Gymnema sylvestre R.Br* leaves from Kolli Hills, Tamilnadu, India. Int J Curr Microbiol Appl Sci. 2015;4:542–547.
[63] Jung J, Kim NK, Park S, et al. Inhibitory effect of *Phyllanthus urinaria* L. extract on the replication of lamivudine-resistant hepatitis B virus *in vitro*. BMC Complement Altern Med [Internet]. 2015 [cited 2016 Apr 12];15:255. Available from: http://bmccomplementalternmed.biomedcentral.com/articles/10.1186/s12906-015-0792-3.
[64] Li B, Guo QL, Tian Y, et al. New anti-HBV C-boivinopyranosyl flavones from *Alternanthera philoxeroides*. Molecules [Internet]. 2016 [cited 2016 Apr 12];21:336. Available from: http://www.mdpi.com/1420-3049/21/3/336.
[65] Rechtman MM, Har-Noy O, Bar-Yishay I, et al. Curcumin inhibits hepatitis B virus via down-regulation of the metabolic coactivator PGC-1alpha. FEBS Lett. 2010;584:2485–2490.
[66] Huang TJ, Tsai YC, Chiang SY, et al. Anti-viral effect of a compound isolated from *Liriope platyphylla* against hepatitis B virus *in vitro*. Virus Res. 2014;192:16–24.
[67] Cui X, Wang Y, Kokudo N, et al. Traditional Chinese medicine and related active compounds against hepatitis B virus infection. BioScience Trends. 2010;4(2):39–47.