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EFFECTIVE MEDICINAL PLANTS IN TREATING HEPATITIS B

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ABSTRACT: Medicinal plants and natural products have many applications in the treatment of viral diseases, due to much lower side effects. Different types of hepatitis, especially hepatitis B, are of the viral diseases whose treatment using herbal medicines is currently of great interest due to the limited availability of effective chemical drugs and having numerous side effects. Due to the attention paid to herbal drugs and their importance for the treatment of hepatitis B, we conducted this review to take a look at the evidence regarding the action mechanisms of viruses, antiviral herbal remedies and various herbal anti-hepatitis drugs and their therapeutic mechanism published until 2017. To provide data for conducting this review, the most up-to-date electronic journals including those indexed in the Pubmed, Elsevier, Institute for Scientific Information, Google Scholar and Scientific Information Database databases and various books, has been used. There are several plants for the treatment of viral diseases, including hepatitis B, which prevent or decrease infection via various mechanisms. Medicinal plants counteract viruses by various mechanisms, but most of them including *Ganoderma lucidum* and *Oenanthe javanica* inhibit the transcription of hepatitis B virus in hepatocytes. Most of action mechanism of medical plants exert an antiviral effect through inhibiting the transcription of HBV in hepatocytes; the need to study effective medicinal plants for treating different types of hepatitis, including hepatitis B and their action mechanisms have been intensified more than ever before, which makes this subject even more important.

INTRODUCTION: The liver is a vital organ of the body, which is also considered to be the largest gland. The liver plays a major role in the physiological processes of the body, which includes metabolism, secretion and storage. Detoxification of various drugs and xenobiotics is performed in the liver. Bile secretion is another task of the liver that plays a very important role in digestion [1, 2].

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Many toxic chemicals (certain antibiotics, chemotherapeutics, peroxidised oil, aflatoxin, carbon tetrachloride, acetaminophen, chlorinated hydrocarbons, *etc*.), food, alcohol, infections such as parasites, viruses, fungi or bacteria and also autoimmune disorders can cause liver diseases such as hepatitis, inflammatory liver disease, jaundice, hepatosis (non-inflammatory liver disease, cirrhosis (a digestive disorder that is the result of liver fibrosis), liver cancer, *etc*. [1, 3]

It is estimated that approximately 90% of hepatitis is of viral type, including hepatitis B, A, C, D (delta agents), E and G. Of these, hepatitis B often causes chronic liver disease and cirrhosis of the liver [3]. Hepatitis B virus (HBV) is a virus from the Hepadnaviridae family [4].

HBV is the cause of hepatitis B, which is transmitted to the virus through infected blood and fluids of the body. Although acute hepatitis is spontaneously healed, treatment for chronic cases is recommended because of the likelihood of cirrhosis of the liver. The hepatitis B vaccination program is being implemented in endemic countries, which reduces the cases of infection with this virus [5]. First, human beings were required to prepare the necessary medicines to cure their suffering and diseases from nature, especially plants. Chemical drugs are supplied worldwide for about 150 years.

A comparison of the use of chemical and herbal drugs shows that chemical drugs, while having good effects, have side effects some of which last until the end of life, and even in some cases, are transmitted to the next generation, while the side effects of herbal drugs are comparatively lower and in many cases, they lead to very few or no complications.

In the past decade, due to the problems that chemical drugs have caused for many people, the tendency to using and paying attention to plant-derived medicinal products have increased. Another important issue is that for certain diseases, herbal remedies have better effects, and for some others, only herbal remedies are available [6].

Due to the diversity of liver diseases, accurate diagnosis is very difficult and therefore a physician cannot do the exact and effective treatment for the disease. In most cases, treatment is symptomatic and supportive. On the other hand, current and modern drugs have high toxicity and it is therefore needed to replace these medications with high-value drugs with comparatively lower toxicity [1, 2].

Medicinal plants play an important role in maintaining health and survival of humans and animals. On the other hand, they contribute to the treatment of nontoxic liver disease [7, 8, 9, 10]. The purpose of this article is to investigate and identify effective medicinal plants in the treatment of viral diseases, especially hepatitis B, and the involved therapeutic mechanisms.

1. Medicinal Plants: Recently, a large proportion of the world population has turned to natural products to treat and prevent diseases. Influenced by this issue, pharmaceutical companies are developing new antimicrobial formulations that are derived from medicinal plants.

Currently, phytotherapy is widely used across the world, especially in developed countries including some European countries and the United States [11]. Approximately 45% of commercially available therapeutic products have been derived from medicinal plants or their derivatives [12]. Recently, a worldwide upsurge in the preparation of medicinal plants and the isolation of their active compounds has emerged in health care [13]. Many medicinal plants that are traditionally used have been reported to have antiviral properties, some of which are used to treat animals and people who suffer from viral infections [14, 15, 16].

In a research on post - World War II antiviral agents in 1952 in Europe, a pharmaceutical company in England tested the antiviral activity of 288 medicinal plants against influenza A virus in the egg embryo, showing that 12 of these plants prevented viral amplification [17]. Over the past 40 years, widespread programs around the world have begun to evaluate antiviral activity of medicinal plants *in-vitro* and *in-vivo*. Canadian researchers reported antiviral activity of grapes, apples, strawberries and other fruit juices against herpes simplex virus (HSV), poliovirus type 1, coxsackie virus B5 and Echovirus in the 1970s [18, 19, 20, 21].

Antiviral activity of 100 British Columbian medicinal plants against seven viruses was investigated [22]. At the tested concentrations of extract, 12 of the medicinal plants were found to have antiviral properties. The extracts of *Rosa nutkana* and *Amelanchier alnifolia* were very potent against enteric corona virus. *Potentilla arguta* root extract and *Sambucus racemosa* extract completely inhibit respiratory syncytial virus (RSV). It has been shown that the effect of *Ipomopsis aggregata* extract against the influenza type 3 virus is potent.

Lomatium dissectum root extract completely inhibits the cytopathic effects of rotavirus. In addition, the extracts of *Cardamine angulata*, *Conocephalum conicum*, *Lysichiton americanus*, *Polypodium glycyrrhiza* and *Verbascum thapsus* have antiviral activity against herpes virus type 1.

The extracts of 40 different plant species used in the traditional medicine have antiviral properties against human cytomegalovirus (HCMV), Ross River virus (RRV), two RNA viruses, DNA virus and poliovirus type 123. The human rotavirus (HRV), RSV and influenza A virus are susceptible to *Eleutherococcus senticosus* root extract, while DNA viruses, HSV type 1 virus (HSV-1) and adenoviruses are not inhibited by its extract [24]. Crude *Sanicula europaea* extract has antiviral properties against human parainfluenza virus type 2, whereas its ethanol extract does not have such property [25]. There are many medicinal plants with antiviral properties **Table 1**.

TABLE 1: ANTIVIRAL MEDICINAL PLANTS

Medicinal plant name	Product type	Viruses
Melaleuca alternifolia [26]	essential oils	HSV-1(herpes simplex virus-1), HSV-2(herpes simplex virus-2)
Santolina insularis [27]	essential oils	HSV-1 , HSV-2, herpes types
Santalum album [28]	essential oils	HSV-1
Sanicula europaea (L.) [29]	water-soluble extract	influenza
Nigella sativa [30]	black seed oil	murine cytomegalovirus (MCMV)
Eleutherococcus senticosus [31]	liquid extract	DNA viruses respiratory syncytial virus (RSV) adenovirus
Rosa nutkana [22]	extract	enteric corona virus
Amelanchier alnifolia [22]	extract	enteric corona virus
Ipomopsis aggregate [22]	extract	parainfluenza virus type 3
Lomatium dissectum [22]	root extract	rotavirus
Potentilla arguta [22]	root extract	respiratory syncytial virus (RSV)
Sambucus racemosa [22]	branch tip extract	respiratory syncytial virus (RSV)
Cardamine angulata [22]	extract	herpes virus type 1
Polypodium glycyrrhiza [22]	extract	herpes virus type 1
Verbascum Thapsus [22]	extract	herpes virus type 1
Conocephalum conicum [22]	extract	herpes virus type 1
Lysichiton americanum [22]	extract	herpes virus type 1
Dianella longifolia var. grandis (Liliaceae) [23]	root extract	poliovirus type 1
Pterocaulon sphacelatum (Asteraceae) [23]	extract	poliovirus type 1
Euphorbia australis (Euphorbiaceae) [23]	extract	human cytomegalovirus (HCMV)
Scaevola spinescens (Goodeniaceae) [23]	extract	human cytomegalovirus (HCMV)
Eremophila latrobei subsp. glabra (Myoporaceae) [23]	extract	Ross River virus (RRV)
Pittosporum phylliraeoides var. Microcarpa (Pittosporacea) [23]	extract	Ross River virus (RRV)
Sanicula europaea [25]	crude extract	Parainfluenza virus type 2
Myrcianthes cisplatensis [25]	extract	RSV، adenovirus serotype7، HSV-1
Azadirachta indica [32]	leaf extract	Smallpox, chicken pox, poxvirus, herpes viruses, poliomye litis
Opuntia streptacantha [33]	extract	HSV, equine herpes virus, pseudorabies virus, influenza virus
Bergenia ligulata [34]	extract	influenza virus, HSV
Nerium indicum [34]	ectract	influenza virus, HSV
Holoptelia integrifolia [34]	ectract	influenza virus, HSV

2. Hepatitis B Virus: Hepatitis B is one of the most important global health issues that lead to high morbidity and mortality, and two factors have contributed to the epidemiology of this disease; vaccination programs and migration. Nearly 240 million people worldwide have acquired chronic infection with this virus [35, 36, 37, 38]. HBV-related mortality rates are more likely to be due to chronic infection, including liver cirrhosis and hepatocellular carcinoma (HCC). HCC is the most common cancer in the world, with chronic HBV infection responsible for 50 - 90% of cases of this cancer [39]. HBV is a viral prototype of the Hepadnaviridae family that is double-stranded DNA genome [4] and is transcribed by the reverse transcription of the RNA pregenome [4, 40]. HBV had eight genotypes from A to H with different virological characteristics and geographical distributions [40, 41].

More than 8% of the nucleotide sequences of each genotype are different from each other. Considering these conditions, the likelihood of recombination between genotypes, especially B/C and A/D, increases. Depending on the genotype of the virus, the DNA genome is composed of 3182-3248 nucleotides [42]. HBV is the cause of hepatitis B that is transmitted through the blood or the body fluids (secretions) that contain this virus. Although there is self-healing in acute hepatitis, treatment of chronic cases is recommended because of the possibility of cirrhosis of the liver.

The hepatitis B vaccine program is implemented in endemic countries, which reduces the incidence of this virus [5]. HBV primarily infects humans, but there are also reports regarding the detection of this infection in chimpanzee, Chacma baboons and tree shrews contamination [43]. Most of the target cells of this virus are hepatocytes, but this virus is also found in other cells, such as those in the pancreas and kidney, bile duct lining cells and peripheral blood mononuclear cells [43].

HBV is an enveloped virus with a diameter of 42 - 47 nm. The envelope consists of a small amount of lipid and three surface proteins including: Small (SHB), medium (MHB) and large (LHB), which comprise disulfide-linked hetero and homodimers. In the serum of the people with the infection, two types of particle are found: Small spherical particles with approximately 20 nm diameter and filamentous particles with approximately 20 nm diameter [42]. The nucleocapsid is made up of nuclear protein that is composed of 185 - 188 amino acids depending on the genome. The N-terminal of 149 - 151 amino acids is responsible for the self assembly of nucleocapsids. This assembly has certain steps. The first step is the formation of homodimer links by disulfide bridges. The nucleocapsid contains poles that allow the nucleotide to bind during DNA synthesis. C-terminal amino acids in this core protein play the role of genome packet [44].

In the bloodstream of people with acute and chronic infections, high levels of HBV virions can be detected. Hepatocytes, which are the main target of this virus, are removed from the bloodstream by endothelial cells and kupffer cells, which are in direct contact with the sinusoids. Liver sinusoidal endothelial cells have a large cytoplasmic content of 50 - 100 nm in diameter. The virions of the bloodstream in the sinuses reach Dis space (the space between the endothelial cystic fibrosis and hepatocyte membrane).

Virions bind hepatocyte surface by the LHB protein, or perhaps by a lipid envelope [42, 43]. The nucleocapsid then releases into the cytoplasm and moves through the microtubules to the Micro-tubules - Organizing Center (MTOC) near the nucleus. Access to nucleus through nuclear pores is accomplished through the mediation of polymerase and heat shock proteins [42]. Then, transcription, translation steps and other steps are carried out.

3. Anti - Hepatitis Medicinal Plants: Due to the diversity of liver diseases, accurate diagnosis is very difficult, so a physician cannot do the exact and effective treatment of the disease. On the other hand, the only drugs used to treat chronic infections are lamivudine, interferon α, HBV, and adefovir dipivoxil. Most of these available drugs inhibit reverse transcriptase activity. Modern and currently used drugs have high toxicity. In addition, the emergence of resistant mutants during long-term treatments is another major problem with modern medicines.

It is, therefore, necessary to replace these medications with high-value ones with comparatively lower toxicity [1, 2]. Many medicinal plants that are traditionally used have antiviral properties, and some of them are used to treat animals and people suffering from viral diseases [45, 46]. Medicinal plants have several phytochemicals that have potent antioxidant properties including alkaloids, carotenoids, saponins, flavonoids (isoflavones, flavonones, anthocyanins, catechins, flavones, isocatechins and quercetin), terpenoids, polyphenols (ellagic acid, gallic acid and tannins), vitamins (A, C, E and K), carotenoids, minerals (manganese, selenium, copper, chromium, zinc and iodine), polysaccharides, enzymes (superoxide dismutase, catalase and glutathione peroxidase), lignins, saponins, xanthones an pigments [47, 48].

Antioxidants treat various diseases by protecting cells against free radical-induced damage [47]. Several medicinal plants are used to treat hepatitis or hepatotoxicity, and some of them have anti-HBV

activity. For example, *Curcuma longa* Linn. has antiviral properties against HBV, which inhibits the production of the constituents of HBV and HBV RNA in hepatocytes. The extract of this plant is indeed an inhibitor of transcription of HBV.

In addition, studies have shown that the antiviral activity of this plant is associated with an increase in the intracellular accumulation of the P53 protein, which is due to increased transcription of the P53 protein gene [49]. Another plant is *Ganoderma lucidum*. Studies have shown that ganoderic acid isolated from this medicinal plant inhibits HBV transcription in the HepG2215 hepatocytes, resulting in an antiviral activity against HBV [50].

TABLE 2: ANTIHEPATITIS MEDICAL PLANTS

Family	Medicinal plant name	Hepatitis
Zingiberaceae	*Curcuma longa* Linn.	Hepatitis B Virus [49]
Ganodermataceae	*Ganoderma lucidum*	Hepatitis B Virus [50]
Euphorbiaceae	*Phyllanthus amarus* or *Phyllanthus niruri*	Hepatitis B Virus [54, 55, 56, 57]
Euphorbiaceae	*Phyllanthusanus*	Hepatitis B Virus [55, 56, 57, 58]
Acanthaceae	*Acanthus ilicifolius* L	Hepatitis B Virus [52, 53]
Apiaceae	*Oenanthe javanica*	Hepatitis B Virus [59, 60]
Gentianaceae	*Swertia patens*	Hepatitis B Virus [61, 62]
Gentianaceae	*Swertia chirayita*	Hepatitis B Virus [61, 62]
Urticaceae	*Boehmeria nivea*	Hepatitis B Virus [63]
Rutaceae	*Citrus Sinensis*	Hepatitis C Virus [65]
Crassulaceae	*Rhodiola kirilowii*	Hepatitis C Virus [66]
Mimosoideae	*Acacia nilotica*	Hepatitis C Virus [64]
Burseraceae	*Boswellia carterii*	Hepatitis C Virus [64]
Myrsinaceae	*Embelia schimperi*	Hepatitis C Virus [64]
Fagaceae	*Quercus infectoria*	Hepatitis C Virus [64]
Apiaceae	*Trachyspermum ammi*	Hepatitis C Virus [64]
Piperaceae	*Piper cubeba*	Hepatitis C Virus [64]
Myrtaceae	*Syzygium aromaticum*	Hepatitis C Virus [64]
Zingiberaceae	*Zingiber officinale*	Hepatitis C Virus [67]
Asteraceae	*Silybum marianum*	Hepatitis C Virus [67]
Saxifragaceae	*Saxifraga melanocentra*	Hepatitis C Virus [68]
Lamiaceae	*Mentha longifolia*	Hepatitis A Virus [69]
Lamiaceae	*Ocimum basilicum*	Hepatitis A Virus [69]
Asteraceae	*Taraxacum Officinalis*	Hepatitis [70]
Brassicaceae	*Lepidium sativum*	Hepatitis [71]
Fabaceae	*Trigonella foenum graecum*	Hepatitis [72]
Meliaceae	*Azadirachta indica*	Hepatitis [73]
Fabaceae	*Glycyrrhiza glabra*	Hepatitis [74]
Euphorbiaceae	*Jatropha curcas* Linnaeus	Hepatitis [75]
Asteraceae	*Cynara scolymus*	Hepatitis [76]
Asteraceae	*Matricaria chamomilla*	Hepatitis [77]
Fabaceae	*Cassia fistula*	Hepatitis [78]
Marchantiaceae	*Marchantia thallus*	Hepatitis [79]
Asteraceae	*Silybum marianum*	Hepatitis [80]
Fabaceae	*Sophora flavescens*	Hepatitis [81]
Salicaceae	*Flacourtia indica* Governor's Plum	Hepatitis [82]
Rubiaceae	*Morinda citrifolia*	Hepatitis [83]

Clinical studies have indicated that phylantus species have positive effects on HBsAg in the clearance of serum from HBV carriers [51]. For example, *P. amarus* (L.) is an inhibitor of HBV polymerase activity and mRNA transcription [47]. Another plant that has antiviral activity against hepatitis is *Oenanthe javanica*. Studies have shown that this plant is helpful to treat HBV-induced infections by inhibiting transcription of HBV in hepatocytes [49]. *Acanthus ilicifolius* L. reduces HBV-induced liver damage by reducing transaminase [52, 53]. Other plants also have anti-hepatitis properties. In general, there is not enough information on the action mechanisms of medicinal plants on HBV, although there are effective natural products against HBV and the resulting infections **Table 2**.

CONCLUSION: Recently, due to the many side effects and the presence of medicinal residues of the chemical drugs for the treatment of viral diseases, especially hepatitis, attention has been paid to medicinal plant-derived products has increased.

It is, therefore, necessary, more than ever before, to address and study effective medicinal plants to treat different types of hepatitis, including hepatitis B, and their action mechanisms, which makes this subject even more important.

The action mechanism of a number of anti-hepatitis B drugs has been understood. Most of them exert an antiviral effect through inhibiting the transcription of HBV in hepatocytes; however, the action mechanism of many plants remains unknown and needs to be further studied. It should be noted that usually phenolic compounds in medicinal plants possess antimicrobial activities. Hence, other plants which have these compounds [84, 85] may possess anti-hepatitis activities, too, which worth examining.

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