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Medicinal plants for treating Hepatitis B (A Review Article)

Research Project
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ABSTRACT

Medicinal plants and natural products have many applications in the treatment of different diseases including viral diseases. 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 their therapeutic mechanism. There are several plants for the treatment of hepatitis B virus, including Ganoderma lucidum and Oenanthe javanica.

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.

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1. INTRODUCTION

The liver is a vital organ of the body, which is also considered to be the largest gland and it is even considered as one of the most important glands working actively as it performs most of the vital functions in humans, but the problem with this organ is that it is one of the silent organs that She does not express her problem easily (Boyer and Lindor., 2016). 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 very important role in digestion (Thomas *et al*., 2011). Many toxic chemicals such (certain antibiotics, chemotherapeutics, peroxided 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, hepatitis (non-inflammatory liver disease), cirrhosis (a digestive disorder that is the result of liver fibrosis), liver cancer, etc.

It is estimated that approximately 90% of hepatitis is of viral type, including hepatitis A, B, C, D (delta agents), E. hepatitis B often causes chronic liver disease and cirrhosis of the liver (Kumar *et al*., 2011). HBV is the cause of hepatitis B, which is transmitted to the virus through infected blood and fluids of the body (Ni and Chen., 2010). 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 (Samani and Kopaei., 2018).

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 (Rabiei *et al*., 2015). 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 (Govind and Pandey.,2011) 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 (Pandey and Madhuri., 2010). 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.

2. LITERATURE REVIEW

2.1. Hepatitis

Hepatitis is a disease that can cause a range of health problems and can be fatal. There are five main strains of hepatitis virus, referred to as types A, B, C, D and E. While they all infect the liver, they differ in important ways, including means of transmission, severity of disease, geographic distribution, and methods of prevention . Types B and C, in particular, lead to chronic diseases in hundreds of millions of people, and are the most common causes of cirrhosis, liver cancer, and deaths associated with viral hepatitis. It is estimated that 325 million people worldwide suffer from hepatitis B and/or C (Khuroo and Sofi., 2020).

Hepatitis A virus (HAV) is one of the most common infectious etiologies of acute hepatitis worldwide. According to the WHO estimates (Havelaar *et al*., 2015). Rates of hepatitis A had declined by approximately 95% during 1996–2011; however, during 2016 – 2018, CDC received approximately 15,000 reports of HAV infections from U.S (Foster., 2019). HAV is primarily transmitted fecal-orally via contaminated food or water, or through close contact with an infected person (Havelaar *et al*., 2015).

Hepatitis C is a liver infection caused by the hepatitis C virus (HCV). HCV is a single-stranded RNA virus belonging to the Flaviviridae family (Lindenbach and Rice., 2005). The major routes of transmission are injection drug use, blood transfusion, hemodialysis, organ transplantation and less frequently sexual intercourse (Wasley and Alter., 2000).

Hepatitis D virus (HDV), also known as hepatitis delta virus, is a defective, hepatotropic pathogenic agent. The life cycle of HDV requires the hepatitis B surface antigen (HBs Ag) provided by hepatitis B virus (HBV). Like HBV, HDV is transmitted by the parenteral route through infectious body fluids; intravenous drug users are at highest risk for infection because of contaminated syringes (Rizzetto *et al*., 2016).

The hepatitis E virus (HEV) causes an infection of the liver, known as hepatitis E. The disease is more common in countries with inadequate sanitation and hygiene. Transmission usually occurs when people drink water contaminated with stool that contains HEV. Large outbreaks have occurred in refugee camps and other

environments prone to overcrowding. Occasionally, hepatitis E occurs in high-income countries and is associated with contaminated pork and other meat products. Symptoms of HEV infection include fever, nausea, vomiting, abdominal pain, fatigue, joint pains, dark urine, and jaundice (yellow eyes or skin) (Desai *et al*., 2020).

2.2. Hepatitis B

Hepatitis B virus (HBV) infection is the most common chronic viral infection in the world (Liaw and chu., 2009). HBV, a DNA virus transmitted percutaneously by sharing a needle in drug rituals and blood transfusions, sexually, or travel to countries where the disease is widespread, and perinatally, affects 1.25 million persons in the United States and 350 to 400 million persons worldwide. HBV infection accounts annually for 4000 to 5500 deaths in the United States and 1 million deaths worldwide from cirrhosis, liver failure, and hepatocellular carcinoma (Hoofnagle *et al*., 2007).

The distribution of hepatitis B infection varies greatly throughout the world. In areas where the prevalence is high, such as Southeast Asia, China, and Africa, more than half the population is infected at some time in their lives, and more than 8 percent are chronic carriers of the virus, the result of either neonatal transmission (vertical) or transmission from one child to another (horizontal). Areas with low levels of endemicity include North America, Western Europe, and Australia, where only a minority of people come into contact with the virus, as a result of horizontal transmission among young adults (Trépo *et al*., 2014). Most HBV infections in developed countries result from sexual activity, injection-drug use, or occupational exposure. Other, less frequent causes of infection include household contact, hemodialysis, transmission from a surgeon, and receipt of organs or blood products. No clear risk factors are found in 20 to 30 percent of patients, perhaps because of a reluctance to report high-risk behavior or possibly mucosal or other unrecognized routes of infection. Because HBV is present in serum in large quantities (108 to 1010 virions per milliliter), it is not surprising that HBV can also be detected in semen, saliva, cervical secretions, and leukocyte (Harpaz et al.,1996).

2.3. transmission of hepatitis B virus

HBV is transmitted parenterally by contaminated blood or other body fluids through blood vessels, skin or mucous membranes. The virus can be detected in all human body fluids, the virus concentration in the fluids is highest in the blood or serous exudates, and it is relatively low in saliva, semen, vaginal fluids (Kwon and Lee., 2011).The main transmission routes include perinatal infection, the skin and mucous membrane infections caused by contaminated blood or body fluids (blood transfusion, use of

contaminated syringes, hemodialysis, invasive tests or surgery), and sexual contacts. In world, the most important route is perinatal transmission in patients with chronic hepatitis B (Hwang et al., 2004).Although a very small amount of HBV is detected in breast milk, there is no evidence that hepatitis B is transmitted through breast milk.In a highly endemic setting, most cases of hepatitis B infection are due to vertical transmission (mother-to-child infection) and horizontal transmission (exposure to infected family members) (Zheng et al., 2018).In injection drug abuser, using the same syringe among injection drug users at the same time is the main transmission route of hepatitis B infection (Kwon and Lee., 2011).In addition, tattooing, ear piercing, acupuncture, dialysis, and even using a syringe can be the source of infection (Goldstein et al., 2002).In adolescents and adults in the countries with low and middle prevalence rates of hepatitis B, sexual contact is the major cause of HBV infection (Hoofnagle et al., 2007)The overall prevalence of HBsAg is 3.9% of the human population; however, it varies from country to country and depends on the complex interplay of behavioral, environmental, economic, geopolitical and host factors(Schweitzer et al., 2015).

2.4. Symptoms of hepatitis B infection

Not everyone has symptoms, they can range from mild to severe during the acute phase of infection, and may have also have symptoms (or not) with chronic infection(Liaw and chu., 2009).

Typical symptoms of infection include:
Fever, Loss of appetite, Nausea and vomiting, Abdominal pain ,Weakness and fatigue, Joint pain, Jaundice (yellowing of your skin and the whites of your eyes), Dark-colored urine, Light or clay-colored poop, Swelling with fluid in your belly or arms and legs (Boyer and Lindor.,2016).

With acute infection, symptoms of liver disease may indicate a more severe reaction than usual. Although many people clear the HBV without treatment, With chronic infection, mild or vague symptoms on an ongoing basis, or may not have symptoms at all for decades. When symptoms appear later, especially symptoms of liver disease, it may indicate the liver is beginning to fail(Bhat *et al.*, 2014).

HBV can live on surfaces outside of the body for at least seven days. So, used instruments that haven’t been sterilized can still carry the virus. This includes medical instruments and common items like a toothbrush or razor that may have provoked bleeding, besides blood, HBV also lives in other bodily fluids, including saliva. But unlike some viruses, hepatitis B isn’t easily transmitted through saliva, that means it aren’t likely to get it from sharing food or eating utensils or from someone coughing or sneezing (Hoofnagle *et al*., 2007).

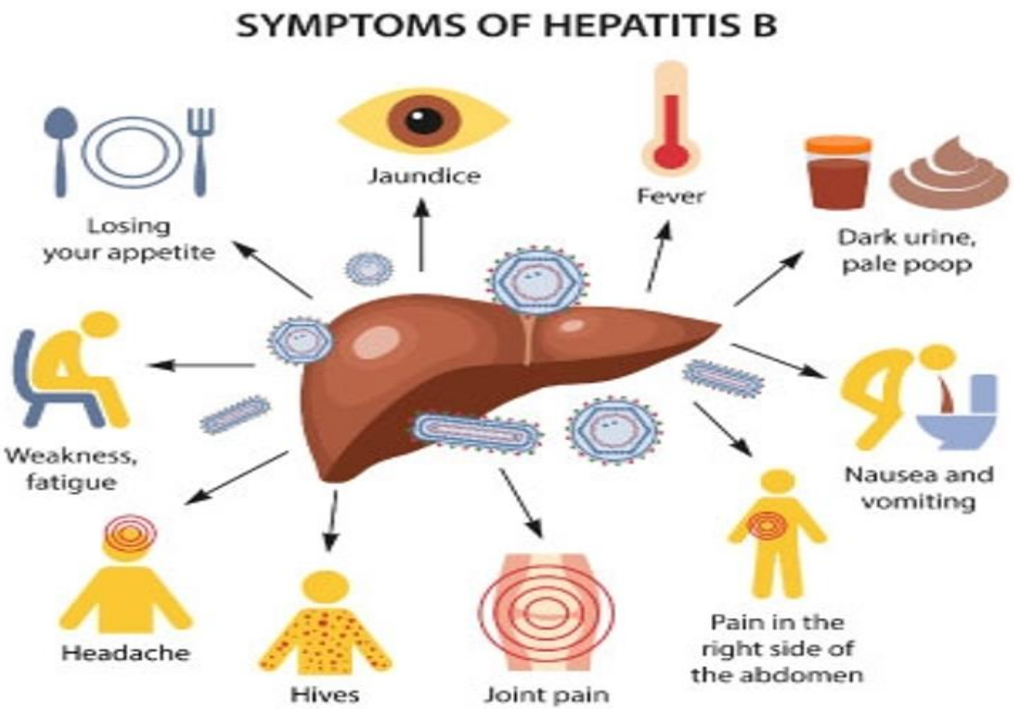

Figure 1. Symptoms of hepatitis B infection (Boyer and Lindor., 2016).

2.5. Virologic and Epidemiologic Factors

HBV, a DNA virus transmitted percutaneously, sexually, and perinatally (Hoofnagle *et al*., 2007). Hepatitis B surface antigen is found in the outside lipoprotein coat, often known as the envelope, (HBs Ag), which consists of proteins embedded in it that play the role of working to bind the virus to the receptors on the cells, and help it penetrate into the internal content of liver cells.

HBV genome and DNA polymerase, is contained within an inner nucleocapsid that is surrounded by HBs Ag. Which protects the internal genes of the virus and helps the virus infect cells (Alotaibi., 2023). Virus B is a very small virus, but there are many forms of it, such as, Dane particle (42 nm), spherical (20 nm) and filamentous (22 nm) particles are three different viral structures that were observed in serum of HBV-infected patients by electron microscopy . All the three particles have a common HBs Ag on their surface (Liang., 2009).

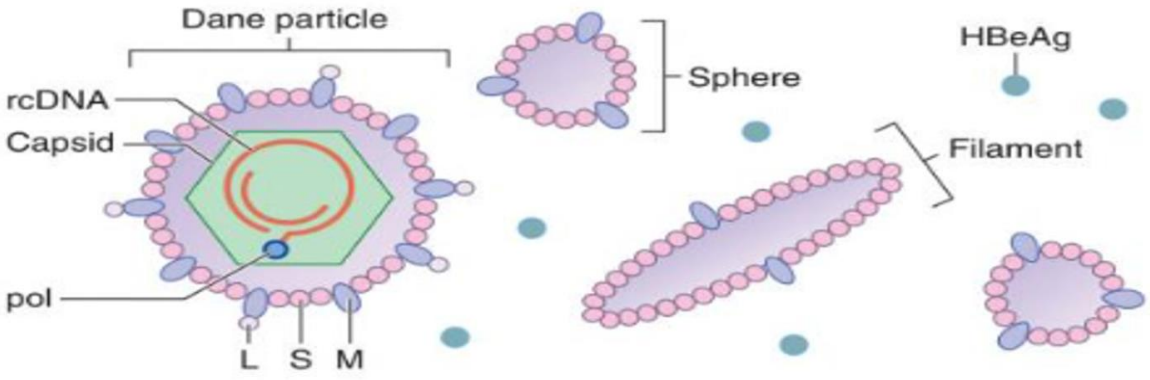

Figure 2. forms of the virus (Alotaibi., 2023).

The “B” virus is essentially of the “DNA” type, but it converts its genetic codes from “DNA” to “RNA” (reverse transcription from RNA to DNA) inside the human cell, using special enzymes for this work, so other viruses serve it to benefit from the energies of the human cell, and then it produces small Viruses, but in the form of “DNA” again, to secrete them outside to destroy healthy cells in the same manner (Doo and Ghany., 2010). Progression from acute to chronic HBV infection is influenced by the patient’s age at acquisition of the virus; age is also related to a dichotomy in the clinical expression of HBV infection between high-prevalence (e.g., Asian) and low-prevalence (e.g., Western) countries.

In the Far East, where HBV infection is acquired perinatally, the immune system does not recognize a difference between the virus and the host, and high-level immunologic tolerance ensues. The cellular immune responses to hepatocyte-membrane HBV proteins that are associated with acute hepatitis do not occur, and chronic, usually lifelong infection is established in more than 90% of persons who are infected (İnan and Tabak., 2015).

In contrast, in the West, most acute HBV infections occur during adolescence and early adulthood because of behaviors and environments that favor the transmission of blood borne infections, such as sexual activity, injection-drug use, and occupational exposure. In immunocompetent adults, a strong cellular immune response to “foreign” HBV proteins expressed by hepatocytes results in clinically apparent acute hepatitis, which, in all but approximately 1% of persons infected, affects clearance of the infection. Immunologic tolerance to HBV established during perinatal infection is profound and lifelong, but not complete; a low level of liver injury occurs and accounts for up to a 40% lifetime risk of death from liver disease among men. This risk is lower among women (Hoofnagle *et al*., 2007).

2.6. Life cycle of HBV in the human host

Under most circumstances, HBV is not cytopathic (i.e., it does not kill hepatocytes). An intact immune system is vital to cell injury and viral clearance. For practical purposes, the severity of the hepatocyte injury reflects the vigor of the immune response: the most complete immune response is associated with the greatest likelihood of viral clearance and the most severe liver injury (Lucifora and Zoulim., 2011). Ninety-five percent of infected neonates with immature immune systems be-come asymptomatic chronic HBV carriers, as com-pared with 30 percent of children infected after the neonatal period but before six years of age. Only 3 to 5 percent of adults remain chronically infected; the remainder have acute infections resulting in viral clearance. The first stage is characterized by immune tolerance. In the healthy adult, this incubation period lasts about two to four weeks. In contrast, with neonatal infection, this period often lasts for decades (Prange., 2012).

In most cases of HBV infection throughout the world, active viral replication continues despite little or no elevation in the aminotransferase levels and no symptoms of illness. In the second stage, an immunologic response develops or improves, leading to cytokine stimulation and direct cell lysis and the inflammatory process. Secretion of HBeAg still occurs in stage 2, but HBV DNA levels in serum drop as the number of infected cells declines. In patients with acute HBV infection, stage 2 is the period of symptomatic hepatitis and typically lasts three to four weeks. In patients with chronic disease, stage 2 may persist for 10 or more years, leading to cirrhosis and its complications. When the host is able to mount a response that eliminates infected cells or greatly diminishes their number, active viral replication ends and the third stage begins. In this stage, HBeAg is no longer present, and antibody to HBeAg becomes detectable. A marked decrease in viral DNA is observed, although many patients remain positive for HBV DNA as detected by PCR (Lee.,1997).

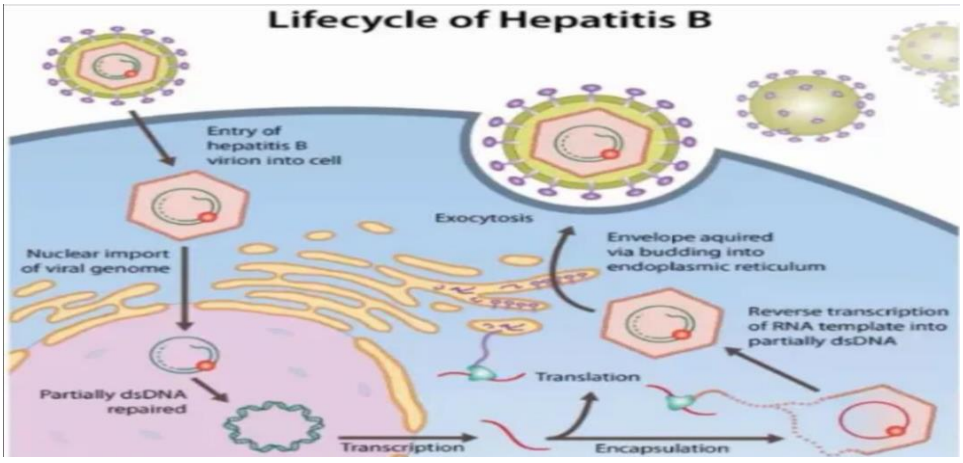

Figure 3. Life cycle of HBV (Liang., 2009).

2.7. Hepatitis B virus treatment

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 (Rabiei *et al*., 2015). 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 (Govind and Pandey., 2011). Medicinal plants play an important role in maintaining health and survival of humans and animals (Madhuri and Pandey., 2009).

2.8. 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 (Solati *et al*.,2017). Approximately 45% of commercially available therapeutic products have been derived from medicinal plants or their derivatives (Lahlou.,2013).

Recently, a worldwide upsurge in the preparation of medicinal plants and the isolation of their active compounds has emerged in health care (Ogbole *et al*.,2022). 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. 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 (Samani and Kopaei., 2018) .

2.9. 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, 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 (Govind and Pandey.,2011). 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 (Samani and Kopaei., 2018).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 (Govind.,2011) . 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 (Kim *et al*.,2009) .

Another plant is Ganoderma lucidum. Studies have shown that ganoderic acid isolated from this medicinal plant inhibits HBV transcription in the hepatocytes, resulting in an antiviral activity against HBV (Li and Wang., 2006).

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]

Figure 4. Anti - Hepatitis Medicinal Plants (Samani and Kopaei., 2018).

Clinical studies have indicated that phylantus species have positive effects on HBsAg in the clearance of serum from HBV carriers (Liu *et al*.,2001). For example, P. amarus (L.) is an inhibitor of HBV polymerase activity and mRNA transcription (Govind.,2011). 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 (Kim *et al*.,2009). Acanthus ilicifolius L. reduces HBV-induced liver damage by reducing transaminase (Wu., 2016). Other plants also have antihepatitis 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 (Samani and Kopaei., 2018).

Curcuma longa Linn

Ganoderma lucidum

Phylantus amarus

phyllanthusanus

Acanthus ilicifolius L

Oenanthe javanica

Swertia patens

Swertia chirayita

Boehmeria nivea

3. 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 may possess anti-hepatitis activities, too, which worth examining.

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