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Review Article

The long and stumble way to find potential active compounds from plants for defeating hepatitis B and C: review

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Abstract

Hepatitis is a liver illness caused by virus such as hepatitis A virus, hepatitis B virus and hepatitis C virus. Hepatitis B and C are considerably more usual and induce more cirrhosis and dead worldwide than hepatitis A. Although drugs that are currently often used in the medication of hepatitis B and C, the finding of recent drug from various resources including herbal has been intensively developed. Therefore, the purpose of this review is to consider the possibility of plant's compounds as anti-HBV and anti-HCV. From the results of a review of several articles, several plant's compound have shown effectiveness againts HBV and HCV by *in silico*, *in vitro* and *in vivo* studies. In conclusion, several plant's active compounds are possibility to be developed as anti-hepatitis B and C.

Keywords

plant's active compound, anti-HBV, anti-HCV

Introduction

Hepatitis is an inflammatory liver disease which is a solemn infectious illness in the world. Hepatitis can progress to liver cancer and cirrhosis. Hepatitis B and C are types of hepatitis that can usually develop into chronic hepatitis, cirrhosis or liver cancer. The cause of hepatitis A is the picornaviridae family virus that is hepatitis A virus (HAV) while the cause of hepatitis B is the hepatitis B virus (HBV) including the DNA virus of the hepadnavirus family and the cause of hepatitis C is the hepatitis C virus (HCV) which belongs to the flaviviridae family that is an enveloped virus (Liang 2009; Lemon et al. 2018; Morozov and Lagay 2018).

Based on WHO data, the case of hepatitis B is quite elevated in the worldwide. Some places in Asia, Africa and the Pacific shave the highest prevalence of HBV. Drugs that are presently often used in the medication of hepatitis B are the nucleoside or nucleotide group and the interferon group (Tang et al. 2018). However, these drugs have many limitations, namely treatment using interferon-α has a fairly high side effect and poor efficacy. Then treatment using nucleoside/nucleotide analogues with a long duration will cause drug resistance to develop due to viruses that can mutate. In addition, because of hepatitis B treatment is quite expensive, it becomes a challenge in treatment by the poor (Parvez et al. 2019).

Hepatitis C also has been spread over the globe, approximately beyond than 180 million humans have been infected by hepatitis virus C (Jardim et al. 2018). Several countries such as Egypt, Pakistan and China are countries with the giant number of hepatitis C sufferers in the worldwide that the cases number of hepatitis C in Egypt was 15%, Pakistan was 4.8% and China was 3.2% in 2012. Hepatitis C can spread rapidly in these countries it is suspected through injection needles that may have been contaminated by the virus. The surprising thing is that more than 75% of patients infected with the virus can progress to chronic and more than 60% of patients with chronic disease will cause cirrhosis so that it can cause the possibility of death from cirrhosis up to 5% and it is estimated that 25% of liver cancer patients are caused by this virus infection (Alhawaris 2019).

This review article is supposed to provide scientific explanation about the active compounds in plants that have the potential as antiviral of hepatitis B or C using *in silico*, *in vivo* and also *in vitro* testing methods.

Materials and method

In this review article the data presented is based on data collection in the form of journals and scientific articles both national and international journals or scientific articles obtained from search results online by entering the keywords "anti-HBV", "anti-HCV", "anti-hepatitis B virus" and "anti-hepatitis C virus" in Science Direct, Elsevier, Research Gate, and Google Scholar, then after scientific journals are collected, conducted screening of scientific journals that have relevance to the antiviral of plants compounds for the last 10 years (2012–2022).

Hepatitis B and C: an introduction

It is guess that beyond than 350 million humans with hepatitis B are caused by infection with the HBV in the world, where it is estimated that deaths from HBV infection reach more than 750,000 deaths per year so that hepatitis B is a top priority to be overcome in the world. Although there is a vaccine to prevent HBV, the role of the community is very important in preventing the transmission of hepatitis B. In addition, the use of interferon alpha drugs has been widely applied to treat hepatitis B, the usage of this drugs has unwanted side effects for patients (Lavanchy 2004).

Hepatitis C virus (family flaviviridae) is one of RNA virus. The proteins involved in the existence cycle of HCV are non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, NS5B), proteins C, E (1 and 2), and p7. The proteins C, E1, E2, and p7are used to infect host cells so commonly called with infectious particles in viruses, while non-structural proteins are used in the multiply process. Non-structural proteins and RNA of the virus are found in the liver because replication of the virus occurs in there (Bartenschlager and Lohmann 2000).

About 80% of humans with acute hepatitis C will develop into chronic. Sex factors, age, asymptomatic, obesity, ethnics, HIV disease, immunosuppression conditions, alcohol, and diabetes being points that can escalate the risk of becoming chronic (Chen and Morgan 2006).

Detection of acute hepatitis C can be made if anti-HCV of patient is positive, due to the absence of serological markers that can indicate acute infection of hepatitis C virus. Although 80% of acute hepatitis C infections are symptom-free, if a person with appropriate symptoms for example alanine aminotransferase (ALT) higher than 10 times from the normal limit value without a history of hepatitis, it can be suspected as hepatitis C acute (Mutimer et al. 2014).

Hepatitis C patients should check the amount of hepatitis C virus RNA before receiving drug therapy in IU/mL units using real-time PCR technique. Genotype examination is needed to assign the duration of medication, therapeutic regimen and determine various techniques such as sequence analysis, hybrization and PCR. Currently the examination of 6 genotypes in chronic hepatitis C infection can be accurately identified (Chevaliez and Pawlotsky 2008).

Hepatitis B and C drugs therapy

Treatment of HBV infection uses various drugs, one of which is tenofovir which is commonly prescribed to pregnant women infected with HBV (Trépo et al. 2014). The drugs that can be given to patients with hepatitis B is interferon, where interferon can be a physiological inflammatory mediator of the body that functions in defense against viruses, then lamivudine which works by inhibiting the binding site, viral polymerase, competes with nucleosides or nucleotides and terminates DNA chain elongation. Adefovir dipivoxil (ADV) can act as an anti-HBV by competing with cAMP nucleotides for binding to viral DNA and inhibiting polymerase and reverse transcriptase thereby breaking the HBV DNA strand. Entecavir works by inhibiting reverse transcription of negative DNA strands, viral DNA polymerase priming, and positive DNA chain synthesis, entecavir has the advantage of good long-term effects but lifelong administration of entecavir in patients who are HBeAg negative should be considered. Furthermore, telbivudine is a hepatitis B drug that works by impeding the multiply of the hepatitis B virus, this drug has an effectiveness comparable to lamivudine (Lok et al. 2003; Lai et al. 2007; Leung 2008; Gish et al. 2009; Shouval et al. 2009; Yuen et al. 2011; Tang et al. 2018).

Recuperation of hepatitis C is often focus on the chronic condition. In chronic hepatitis C therapy can be given antivirals in order to avoid the emergence of complications of cancer in the liver, death, and HCC (hepatocellular carcinoma). The target of antiviral therapy is SVR (Sustained Virological Response) so that the presence of RNA of hepatitis C virus should be checked. Antiviral administration of hepatitis C using an amalgam of DAA regimen *(*Direct Acting Antiviral*)* can achieve SVR12 more than 90% in all genotypes in people with chronic hepatitis C and consumption of Peg-IFN and ribavirin (Poordad et al. 2008).

Most of hepatitis C treatments using DAA drugs nowdays. The first generation DAA is boceprevir. There are many new generations of DAA such as simeprevir, sofosbuvir, elbasvir, ledipasvir, daclatasvir, and grazoprevir. This new generations of DAA has several advantages, such as give higher SVR12 number than interferon drugs, available in oral preparations and has minimal side effects with shorter duration of treatment (Tamori et al. 2016).

The mechanism of work of each drug in hepatitis C therapy varies with the drug itself. The mechanisms of drugs in hepatitis C therapy are:

a) Mechanism of work of Pegylated Interferon (Peg-IFN).
   Interferon that can be immunomodulator has mechanism of works such as inhibit viral replication, the virus entry, synthesis of mRNA and also protein in hepatitis C virus. *Pegylated* usually added in the drug formula in order to has good stability, durable in the body, low toxicity and good solubility (Ahad et al. 2004).
b) Mechanism of work of ribavirin.
   Even information about how ribavirin works is still limited but several hypotheses tell that ribavirin can inhibit the inosine monophosphate dehydrogenase enzyme, replication of virus, increase the viral RNA mutagenesis and immune response of T-helper-1 (Th1). Ribavirin is metabolized in the kidneys, widely distributed throughout the body after administration is taken and can be absorbed quickly with a half-life of about 2 hours (Chung et al. 2008).
c) DAA Mechanism of Work.
   There are three main working mechanism groups of DAA drugs such as:
   The first group are inhibitors of NS3/4A (ending in -previr). They suppress the multiply process of hepatitis C virus by inhibiting the work of NS3 serine protease and NS4A as cofactors. There are two kind of these drugs, namely the first generation with linear forms and low genetic barriers such as boceprevir and telaprevir; and the second generation faldaprevir, simeprevir, asunaprevir, vaniprevir, paritaprevir, grazoprevir, and sovaprevir which have macrocyclic forms and intermediate or high genetic barrier (Tamori et al. 2016).
   The second group are inhibitors of NS5A (ended -asvir) such as daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir (Tamori et al. 2016).
   The third group are inhhibitors of NS5B in the hepatitis C virus (ended -buvir), for example : becalbuvir, dasabuvir, and sofosbuvir (Tamori et al. 2016).

Patients who have chronic cirrhosis liver may be given antiviral as long as there are no contraindications. This aims to achieve SVR12 and reduce the incidence of various complications due to liver cancer (cirrhosis of the liver). Some existing studies show the achievement of SVR12 in patients with compensatory liver cirrhosis decreases the incidence of hepatocellular carcinoma and decompensated liver cancer. However, people with hepatitis C with cirrhosis have a lower chance of achieving SVR12 (Singal et al. 2010; Van der meer et al. 2012).

Because of cirrhosis patient usually have hypertension, hypersplenism, low platelet, low leucocyte level and also side effects of drugs so that intense monitoring should be done during therapy (Schmid et al. 2005).

Potential active compound from plant for defeating hepatitis B and C

The following is a table (Table 1) of active compounds present in plants that have been studied to have anti-HBV and anti-HCV activity with various mechanisms.

From the table it can see that there are many plants that have anti-hepatitis B and C by *in silico*, *in vivo* and *in vitro* studies. The following are an explanation of the plant's active compounds that have anti-hepatitis B and C activity.

4-pyridone glucoside and polyacetylene glucoside compounds contained in *Artemisia Scoparia* extract in a experimentation run by Geng et al. (2015) showed anti-hepatitis B activity by *in vitro* test by inhibiting HBV DNA with a percentage of inhibition value of 49.3 ± 9.7%, HBsAg with a percent inhibition value of 36.5 ± 8.1% and HBeAg with a percent inhibition value of 25.0 ± 6.7% with tenofovir as a control.

The compound 8-epi-kingiside (8-Epik) contained in *Jasminum officinale* var. Grandiflorum based on research by Zhao et al. (2013) has anti-hepatitis B activity. In the *in vitro* test, HBsAg was inhibited with 19.4 ± 1.04 µg/mL (as IC_{50} value) at a concentration of 50 µg/mL with Lamivudine as a control. While *in vivo* test, at a concentration of 80 mg/kg can suppress 46.1% of DHBV DNA replication in ducks.

Based on anti-hepatitis B research conducted by Yang et al. (2017), the alkaloid and polysaccharide group compounds contained in the 95% ethanol extract of *Sophora flavescens* can inhibit HBsAg by 57.97 ± 6.79% and HBeAg by 51.53 ± 26.57% at 500 µg/mL by *in vitro* test and can inhibit HBsAg by 20.58% and HBeAg by 21.22% at a concentration of 100 mg/kg in mice by *in vivo* tests.

The lectin compounds, polysaccharides and alkaloids contained in *Viscum coloratum* (Kom.) *Nakai* have anti-hepatitis B activity by *in vitro* test based on the research of Chai et al. (2019) with Lamivudine as a control. In this study, at 10 mg/mL the % inhibition of HBsAg was 5.676 ± 0.012% and % inhibition of HBeAg was 4.880 ± 0.010%.

The curcumin compound has anti-hepatitis B activity based on a journal reported by Wei et al. (2017). In this experiment, it was found that curcumin at a concentration of 20 µmol/L can reduce 57.7% HBsAg by *in vitro* test.

Based on experiment run by Liu et al. (2017), the compound of the diterpenoid group, namely ent-cauranoids contained in *Rabdosia japonica*, has anti-hepatitis B activity by inhibiting HBsAg by 59% at the 20 µg/mL by *in vitro* test. In this study, adefovir was used as a control.

Table 1. Active compounds present in plants that have been studied to have anti-HBV and anti-HCV activity.

Active Compounds	Plant's Name	Test Method	Anti-HBV / Anti-HCV	References
1,2,3,4,6-Pentagalloyl glucose	*Terminalia Chebula*	*in silic*o	Anti-HCV	(Patil et al. 2022)
3-hydroxy caruilignan C	*Swietenia Macrophylla*	*in vitr*o	Anti-HCV	(Wu et al. 2012)
4-pyridone glucoside and polyacetylene glucoside	*Artemisia scoparia*	*in vitro*	Anti-HBV	(Geng et al. 2015)
8-epi-kingiside (8-Epik)	*Jasminum officinale* var. grandiflorum	*in vitro, in vivo*	Anti-HBV	(Zhao et al. 2013)
Alkaloids and polysaccharides (SFP-100)	*Sophora flavescens*	*in vitro, in vivo*	Anti-HBV	(Yang et al. 2018)
Alkaloids, lectins and polysaccharides	*Viscum coloratum*	*in vitro*	Anti-HBV	(Chai et al. 2019)
Apigenin	Plants that contain apigenin compound	*in vitro*	Anti-HCV	(Shibata et al. 2014)
APS	*Maytrenus ilicifolia*	*in vitro*	Anti-HCV	(Jardim et al. 2015)
Azadirachtin	Plants that contain azadirachtin compound	*in silico*	Anti-HBV	(Parvez et al. 2019)
Baccatin III	Plants that contain baccatin III compound	*in silico*	Anti-HBV	(Parvez et al. 2019)
Caffeine	Plants that contain caffeine compound	*in vitro*	Anti-HCV	(Batista et al. 2015)
Chebulagic Acid	*Terminalia Chebula*	*in silico*	Anti-HCV	(Patil et al. 2022)
Curcumin	Plants that contain curcumin compound	*in vitro*	Anti-HBV	(Wei et al. 2017)
Delphinidin	Plants that contain delphinidin compound	*in vitro*	Anti-HCV	(Calland et al. 2015)
Detarium microcarpum stem extract	*Detarium microcarpum (Caesalpinaceae)*	*in vitro*	Anti-HCV	(Galani et al. 2015)
Dimocarpus longan extract	*Dimocarpus longan (Sapindaceae)*	*in vitro*	Anti-HCV	(Apriyanto et al. 2016)
Embelia ribes root extract	*Embelia ribes* (*Primulaceae*)	*in vitro*	Anti-HCV	(Lin et al. 2015)
Embelin	Plants that contain embelin compound	*in silico*	Anti-HBV	(Parvez et al. 2019)
Ent-cauranoid (1 and 2) and ent-cauranoid type diterpenoids	*Rabdosia japonica*	*in vitro*	Anti-HBV	(Liu et al. 2017)
Epigallocatechin-3-gallate	*Camellia sinensis*	*in vitro*	Anti-HCV	(Chen et al. 2012; Calland et al. 2012;)
Epigallocatechin gallate (EGCG)	Plants that contain EGCG compound	*in silico*	Anti-HCV	(Mathew et al. 2014)
Ficus fistula leaves extract	*Ficus fistula* (*Moraceae*)	*in vitro*	Anti-HCV	(Wahyuni et al. 2013)
Flavonoid	*Cudrania cochinchinensis* or *C. Tricuspidata, Acanthus ilicifolius, Phyllodium pulchellum*	*in vitro and in vivo*	Anti-HBV	(Zhao et al. 2019)
Gallic Acid	*Limonium sinense*	*in vitro*	Anti-HCV	(Jardim et al. 2018)
Garcinia mangostana L fruit peels extract	*Garcinia mangostana* L (*Clusiaceae*)	*in vitro*	Anti-HCV	(Choi et al. 2014)
Glycosides longumoside A and B	*Piper longum*	*in vitro*	Anti-HBV	(Jiang et al. 2013)
Glycyrrhiza uralensis root extract	*Glycyrrhiza uralensis (Fabaceae)*	*in vitro*	Anti-HCV	(Adianti et al. 2014)
Griffithsin	*Griffithsia sp*	*in vitro*	Anti-HCV	(Takebe et al. 2013)
Hesperidin	Plants that contain hesperidin compound	*in silico*	Anti-HBV	(Parvez et al. 2019)
Honokiol	*Magnolia Officiais*	*in vitro*	Anti-HCV	(Lan et al. 2012)
Ladanein	*Marrubium peregrinum L*	*in vitro*	Anti-HCV	(Haid et al. 2012)
Ladanein	Plants that contain ladanein compound	*in silico*	Anti-HCV	(Mathew et al. 2014)
Ligustrum lucidum fruit extract	*Ligustrum lucidum* (*Oleaceae*)	*in vitro*	Anti-HCV	(Kong et al. 2013)
Limonium sinense root extract	*Limonium sinense (Plumbaginaceae)*	*in vitro*	Anti-HCV	(Hsu et al. 2015)
Lupeol	Plants that contain lupeol compound	*in silico*	Anti-HBV	(Parvez et al. 2019)
LPRP-Et-97543	*Liriope platyphylla*	*in vitro*	Anti-HBV	(Huang et al. 2014)
Melanolepis multiglandulosa stem extract	*Melanolepis multiglandulosa* (*Euphorbiaceae*)	*in vitro*	Anti-HCV	(Wahyuni et al. 2013)
Melicope latifolia leaves extract	*Melicope latifolia* (*Rutaceae*)	*in vitro*	Anti-HCV	(Wahyuni et al. 2013)
Menisdaurin	Plants that contain menisdaurin compound	*in silico*	Anti-HBV	(Parvez et al. 2019)
Monoterpenes, (japopenoid A, B, C, and caffeoliquinic acid derivatives	*Lonicera japonica*	*in vitro*	Anti-HBV	(Ge et al. 2019)
Morinda citrifolia leaves extract	*Morinda citrifolia* (Rubiaceae)	*in vitro*	Anti-HCV	(Ratnoglik, et al. 2015)
Naringenin	Plants that contain naringenin compound	*in silico*	Anti-HCV	(Mathew et al. 2014)
Niranthin and nirtetralin B	*Phyllanthus niruri L.*	*in vitro* and *in vivo*	Anti-HBV	(Liu et al. 2014)
Norbisabolan sesquiterpenes	*Phyllantus acidus*	*in vitro*	Anti-HBV	(Gu et al. 2019)
Oxymatrine (OMT)	*Sophora tonkinensis* Gagnep	*in vivo*	Anti-HBV	(Sang et al. 2017)
Phenolic compound, organic acid and terpenoids	*Boehmeria nivea*	*in vitro*	Anti-HBV	(Wei et al. 2014)
Phyllanthin, ellagic acid and hypophyllanthin	*Phyllanthus rheedei*	*in vitro*	Anti-HBV	(Suresh et al. 2014)
Pinus massoniana bark extract	*Pinus massoniana (Pinaceae)*	*in vitro*	Anti-HCV	(Wang et al. 2015)
Platycodon grandiflorum root extract	*Platycodon grandiflorum* (*Campanulaceae*)	*in vitro*	Anti-HCV	(Kim et al. 2013)
Plumbagin	*Plumbago indica L.*	*in vitro*	Anti-HCV	(Hassan et al. 2016)
Polysaccharides	*Isatis indigotica* Fortune	*in vitro*	Anti-HBV	(Wang, et al. 2020)
Polysaccharides	*Saussurea laniceps*	*in vitro*	Anti-HBV	(Chen et al. 2019)
Pragmanthera capitata leaves extract	*Pragmanthera capitata* (*Loranthaceae*)	*in vitro*	Anti-HCV	(Galani et al. 2015)

Active Compounds	Plant's Name	Test Method	Anti-HBV / Anti-HCV	References
Psoralen	Plants that contain Psoralen compound	*in silico*	Anti-HBV	(Parvez et al. 2019)
Quercetin	*Embelia ribes*	*in vitro*	Anti-HCV	(Bachmetov et al. 2012; Pisonero-Vaquero et al. 2014)
Quercetin	Plants that contain quercetin compound	*in silico*	Anti-HBV	(Parvez et al. 2019)
Quercetin and myricetin-3-O-rhamnoside	*Guiera senegalensis*	*in vitro*	Anti-HBV	(Parvez et al. 2020)
Ruta angustifolia leaves extract	*Ruta angustifolia* (*Rutaceae*)	*in vitro*	Anti-HCV	(Wahyuni et al. 2014)
Rutin	Plants that contain rutin compound	*in silico*	Anti-HBV	(Parvez et al. 2019)
Saikosaponin b2	*Bupleurum kao*	*in vitro*	Anti-HCV	(Jardim et al. 2018)
Saponin	*Abrus Cantoniensis*	*in vitro* and *in vivo*	Anti-HBV	(Yao et al. 2020)
Saponins (asiaticoside)	*Hydrocotyle sibthorpioides* Lam	*in vitro* and *in vivo*	Anti-HBV	(Huang et al. 2013)
Scytovirin	*Scytonema varium*	*in vitro*	Anti-HCV	(Takebe et al. 2013)
Secoiridoid glycosides	*Swertia cincta*	*in vitro*	Anti-HBV	(Jie et al. 2015)
Sesquiterpenes	*Cyperus rotundus*	*in vitro*	Anti-HBV	(Parvez et al. 2019)
Silibinin	*Silybum marianum*	*in vitro*	Anti-HCV	(Blaising et al. 2013)
Silybin	Plants that contain Silybin compound	*in silico*	Anti-HCV	Mathew et al. 2014
Silymarin Extract	*Silybum marianum*	*in vitro*	Anti-HCV	(Blaising et al. 2013)
Swertisin	*Iris tectorum* Maxim	*in vitro, in vivo*	Anti-HBV	(Xu et al. 2020)
Toona sureni leaves extract	*Toona sureni* (*Meliaceae*)	*in vitro*	Anti-HCV	(Wahyuni et al. 2013)
Trichilia dregeana root extract	*Trichilia dregeana* (*Meliaceae*)	*in vitro*	Anti-HCV	(Galani et al. 2015)
Triterpenoid	*Iris confusa*	*in vitro*	Anti-HBV	(Chen et al. 2018)
Ursolic acid	*Cynomorium Songaricium*	*in vitro*	Anti-HCV	(Kong et al. 2013)
Xanthohumol	*Humulus lupulus* L	*in vitro*	Anti-HCV	(Lou et al. 2014)
β Sitosterol	Plants that contain β Sitosterol compound	*in silico*	Anti-HBV	(Parvez et al. 2019)

Based on research conducted by Zhao et al. (2019), the flavonoid compounds contained in a mixture of three plants, that are *Acanthus ilicifolius*, *C. tricuspidata* and *Phyllodium pulchellum* with a ratio of 5:3:2 have anti-hepatitis B activity. In the *in vitro* test, the mixture of the three plants at a concentration of 200 µg/mL could inhibit HBsAg well. Meanwhile, in the *in vivo* test, the inhibition of DHBsAg was significantly inhibited at a concentration of 12 g/kg/day. In this study, Lamivudine was used as a control.

Several glycoside and alkaloid compounds contained in the 90% ethanol extract of *Piper longum* have anti-hepatitis B activity *in vitro* according to the research of Jiang et al. (2013). In this study, Lamivudine was used as a control. Based on the results of the HBsAg and HBeAg inhibition tests, *Piper longum* extract was able to inhibit HBsAg and HBeAg with IC_{50} above 14 mM.

The compound LPRP-Et-97543 contained in 95% ethanol extract of *Liriope platyphylla* has anti-hepatitis B action based on research conducted by Huang et al. (2014). At 10 µg/mL extract can inhibit HBsAg 3.82 µg/mL (as IC_{50} value) and HBeAg 2.58 µg/mL (as IC_{50} value) by *in vitro* test and lamivudine was used as a control.

Monoterpene group compounds, namely caffeoliquinic acid derivatives, japopenoids (Types A, B and C) contained in *Lonicera japonica* have anti-hepatitis B activity *in vitro* based on research conducted by Ge et al. (2019). At a concentration of 25 µg/mL it can inhibit HBsAg by as much as 39.39 ± 5.25%, inhibited HBeAg by 15.64 ± 1.25% and inhibited HBV DNA by 16.13 ± 4.10%.

Niranthin and nirtetralin B compounds contained in *Phyllanthus niruri* have anti-hepatitis B action based on research conducted by Liu et al. (2014). In an *in vitro* test of 93.1% HBsAg and 80% HBeAg can be inhibited at concentrations 129.7 µM of *Phyllanthus niruri*. Meanwhile, in the *in vivo* test, 64.29% HBsAg and 54.55% HBeAg can be inhibited at the 100 mg/kg/day with lamivudine as a control.

Based on experiment run by Chen et al. (2019), compounds from the sesquiterpene group, namely norbisabolan, such as phllanthacidoid N1, phllanthacidoid A1, phyacidusin A, and phyacidusin B contained in *Phyllanthus acidus* have anti-hepatitis B activity by *in vitro* test with 11.2 ± 0.01 µM as IC_{50} value in inhibiting HBsAg and an IC_{50} of 57.1 ± 0.02 µM in inhibiting HBeAg compared with Lamivudine as a control.

Oxymatrine compounds contained in *Sophora tonkinensis* Gagnep have anti-hepatitis B activity *in vivo* based on research by Sang et al. (2017) in mice. In this study *Sophora tonkinensis* can inhibit HBV replication at 20 mg/kg and is more efficient than entecavir as a control.

Based on the *in vitro* research of Wei et al. (2013), terpenoids, organic acids and phenolic compounds contained in the ethyl acetate fraction of 70–80% ethanol extract of *Boehmeria nivea* (Linn.) at a concentration of 200 mg/L have anti-hepatitis B activity with a percent inhibition of HBsAg inhibition value of 89.95 ± 2.26% with an IC_{50} value more than 39 mg/L then the percentage of HBeAg inhibition value more than 98%. In this study, lamivudine was used as a control.

Based on the *in vitro* research conducted by Suresh et al. (2014), *Phyllanthus rheedei* have anti-hepatitis B activity. In this study, *Phyllanthus rheedei* at 200 mg/mL

could inhibit HBsAg by 70.5%. In this study, Lamivudine was used as a control.

Based on the *in vitro* research by Wang et al. (2020), the polysaccharide group compounds contained in 95% ethanol extract of *Isatis indigotica* has anti-hepatitis B activity with an inhibition value of 65% (HbsAg) and 38% (HbeAg) at 200 μg/mL. Lamivudine was used as a control.

The polysaccharide compound SL-4 compounds in the 95% ethanol extract of *Saussurea laniceps* has anti-hepatitis B activity by *in vitro* test according to Chen et al. (2015) using Lamivudine as a control. In this study *Saussurea laniceps* can inhibit HBsAg by 32.81% and HBeAg by 60.75% at 500 μg/mL.

Quercetin and myrisetin-3-O-ramnoside compounds contained in the 96% ethanol extract of *Guiera senegalensis* have anti-hepatitis B activity by inhibiting HBsAg by 60% at 50 μg/mL based on research conducted by Parvez et al. (2019) that used lamivudine as a control.

The presence of soyasaponin Bb and soyasaponin Be compounds in *Abrus cantoniensis* Hance have anti-hepatitis B activity. Experiment run by Yao et al. (2019) showed that at the 60 μg/mL *Abrus cantoniensis* extract could inhibit HBsAg by 30% and HBeAg by 50% by *in vitro*. At the concentration of 77 mg/kg/day, it can inhibit HBsAg by 75% and inhibit HBeAg by 31.8% in mice in the *in vivo* test.

Based on research by Huang et al. (2013), Saponin compound that is asiaticoside contained in 80% ethanol extract of *Hydrocotyle sibthorpioides* has anti-hepatitis B activity by inhibiting HBsAg 56.9 μM (as IC_{50} value) and HBeAg 84.2 μM (as IC_{50} value) by *in vitro* test with Lamivudine as control. In this study, *in vivo* test was also conducted that ducks given 20 mg/kg of 80% ethanol extract of *Hydrocotyle sibthorpioides* were able to reduce DHBV expression well.

In vitro test, Secoiridoid glycosides group compounds, namely swertiasida, 9-epi swertiamarin, swericinctoside, swertianoside E contained in 90% ethanol extract of *Swertia cincta* have anti-hepatitis B activity based on research of Jie et al. (2015). In this study the extract can inhibit HBsAg 151.5 μg/mL (as IC_{50} value), inhibiting HBeAg 53.7 μg/mL (as IC_{50} value) and inhibiting replication of HBV DNA with 21.9 μg/mL (as IC_{50} value) using tenofovir as a control.

Another study reported by Parvez et al. (2019), compounds from the sesquiterpene group such as cyperotundon, cyperenoic acid, triacetic sugetriol, guaidiol A, sugebiol, valencene epiguaidiol, and nootkatone contained in the extract of *Cyperus rotendus* the 100 mg/mL has anti-hepatitis B activity with a percentage of HBsAg inhibition of 48% and a percentage of HBeAg inhibition of 40%. In this study, lamivudine was used as a control.

The Swertisin compound contained in the 95% ethanol extract of *Iris Tectorum* has anti-hepatitis B activity according to the research of Xu et al. (2020), which at a concentration of 5 μM extract, it can prevent HBsAg by 70.82% then HBeAg by 50.99% by *in vitro* test with entecavir as a control. In this study, *in vivo* test was also conducted that at the 5 mg/kg the extract could inhibit HBsAg by 55% and HBeAg by 32% in mice.

Based on the research of Chen et al. (2018), the triterpenoid group compounds, namely 17-hydroxyl27-ene-iridal, isobalamcabdal and spirioiridoconfal A-C contained in the 70% ethanol extract of *Iris confusa* at the 40 μg/mL can inhibit HBV DNA replication of hepatitis B virus with 84.6 μM (as IC_{50} value). In this study, tenovofir was used as a control.

There are many of plants active compound as anti-HCV have been reported. Griffithsin, Scytovirin, Saikosaponin b2, Ladanein, Delphinidin, Silibinin, root extract of *Trichilia dregeana*, stem extract of *Detarium microcarpum*, *Embelia ribes* root extract and *Pragmanthera capitate* leaves extract work as anti-HCV by inhibiting viral entry of hepatitis C virus. Then epigallocatechin-3-gallate, xanthone extract, 3-hydroxy caruilignan C, plumbagin, xanthohumol, apigenin, caffeine, APS, quercetin, ursolic acid, honokiol, silymarin extract have anti-HCV activity by inhibiting replication of HCV. On the other hand several plants extract also can inhibit HCV J6/JFH1 specifically such as *Melanolepis multiglandulosa* stem extract, *Ruta angustifolia* leaves extract, *Glycyrrhiza uralensis* root extract, leaves extract of *Toona sureni*, leaves extract of *Melicope latifolia*, leaves extract of *Ficus fistula*, *Morinda citrifolia* leaves extract with IC_{50} between 2.0 μg/mL to 17.1 μg/mL. (Bachmetov et al. 2012; Calland et al. 2012; Chen et al. 2012; Choi et al. 2012; Haid et al. 2012; Lan et al. 2012; Blaising et al. 2013; Kong et al. 2013; Takebe et al. 2013; Wahyuni et al. 2013; Adianti et al. 2014; Lou et al. 2014; Pisonero-vaquero et al. 2014; Shibata et al. 2014; Wahyuni et al. 2014; Batista et al. 2015; Calland et al. 2015; Galani et al. 2015; Jardim et al. 2015; Lin et al. 2015; Ratnoglik et al. 2015; Hassan et al. 2016; Jardim et al. 2018)

Ligustrum lucidum fruit extract, *Platycodon grandiflorum* root extract, *Garcinia mangostana L* fruit peels extract, and *Pinus massoniana* bark extract can inhibit HCV replication. *Limonium sinense* root extract can also inhibit viral entry of HCV to the cell. Extract of *Dimocarpus longan* can also inhibit HCV (Kim et al. 2013; Kong et al. 2013; Choi et al. 2014; Hsu et al. 2015; Wang et al. 2015; Apriyanto et al. 2016).

In silico studies, experiment run by Mathew et al. 2014 showed that epigallocatechin gallate, ladanein, naringenin and silybin as phytocompound have good interaction energy with capsid strain of hepatitis C virus such as HCV-3, HCV-3b and HCV-3g so that they potentially can be as inhibitor of hepatitis C virus.

Another study reported by Parvez et al. 2019, plant-derived compounds such as flavonoids compounds (quercetin, rutin, hesperidin) lupeol, azadirachtin, betasitosterol, psoralen, embelin, menisdaurin and baccatin III have good interaction with hepatitis B virus active site residues and negative value of binding free energy by *in silico* study so that they potentially can be anti-hepatitis B. In this study, lamivudine was used as a control.

Based on research by Patil et al. 2022, Compounds that contained in *Terminalia chebula* pottentially can be inhibitor of NS3/4A protein of HCV with value of binding energy were Chebulagic acid -8.6 kcal/mol and 1,2,3,4,6-Pentagalloyl glucose -7.7 kcal/mol, respectively by *in silico* study.

Conclusion

From the results of a review of several articles, it can be concluded that there are many active compounds in plants that potentially can be developed as anti-hepatitis B and C. Although there is a need for further research related to the anti-hepatitis B and C activities of plant's active compounds, the development and discovery of active compounds from plants as an alternative to anti-hepatitis B and C must always be explored.

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Conflict of interest

This study has no conflict of interest.

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