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TOPIC HIGHLIGHT

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Medicinal plants against hepatitis C virus

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Abstract

Hepatitis C virus (HCV) is a global health concern which is responsible for most of the liver diseases. Currently, there is no vaccine available for prevention of HCV infection due to the high degree of strain variation. The current standard of care is a combination of pegylated interferon α with ribavirin and boceprevir/telaprevir. This treatment was partially effective and had significant side effects. Hence, there is a need to develop new antiviral agents that interfere with different stages of the HCV life cycle. Recent advances in the understanding of both the cellular and molecular mechanisms of HCV replication have provided the basis for novel therapeutic strategies. Several hundred plant species and their phyto-constituents have been isolated for screening against HCV, and some have been shown to have great medicinal value in preventing and/or ameliorating viral diseases in pre-clinical and clinical trials. This review summarizes medicinal plants and their phytochemicals which inhibit different stages of HCV life cycle and discuss their potential use in HCV therapy.

Key words: Hepatitis C virus; Medicinal plants; Anti-hepatitis C virus drugs

Core tip: Medicinal plants have always caught the attention of researchers to develop antiviral drugs against dreadful viral diseases. Many plant species are being tested against hepatitis C virus (HCV) to find a possible cure for it and, hopefully, in the future these medicinal plants can serve as an important source for developing anti-HCV drugs.

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INTRODUCTION

Hepatitis C virus (HCV) is a dreadful viral disease and has always been a global health issue. According to estimation, about 170 million people are affected, with the highest infection rates in Africa and Asia[1]. Each year approximately 3-4 million people are affected and > 350000 individuals die due to liver disease. HCV causes an acute infection which can eventually progress to chronic infection and can cause permanent liver damage, hepatocellular carcinoma (HCC), cirrhosis and death[2-5]. Acute to chronic progression is rapid in people who are older, human immunodeficiency virus (HIV) co-infected, consume more than 50 g of alcohol daily, or immunosuppressed and patients undergoing organ transplantation[6]. HCV belongs to the *Flaviviridae* family and has a positive single stranded RNA genome of 9.6 Kb. The genome of HCV has 5' untranslated region (UTR) which works as an internal ribosomal entry site (IRES). The 5' UTR is 324-341 in length and the IRES is considered important for Cap-independent translation of viral RNA[7,8]. This entry site (IRES) leads to the translation of an open reading frame (ORF) that encodes a 3010 amino acid poly protein precursor which

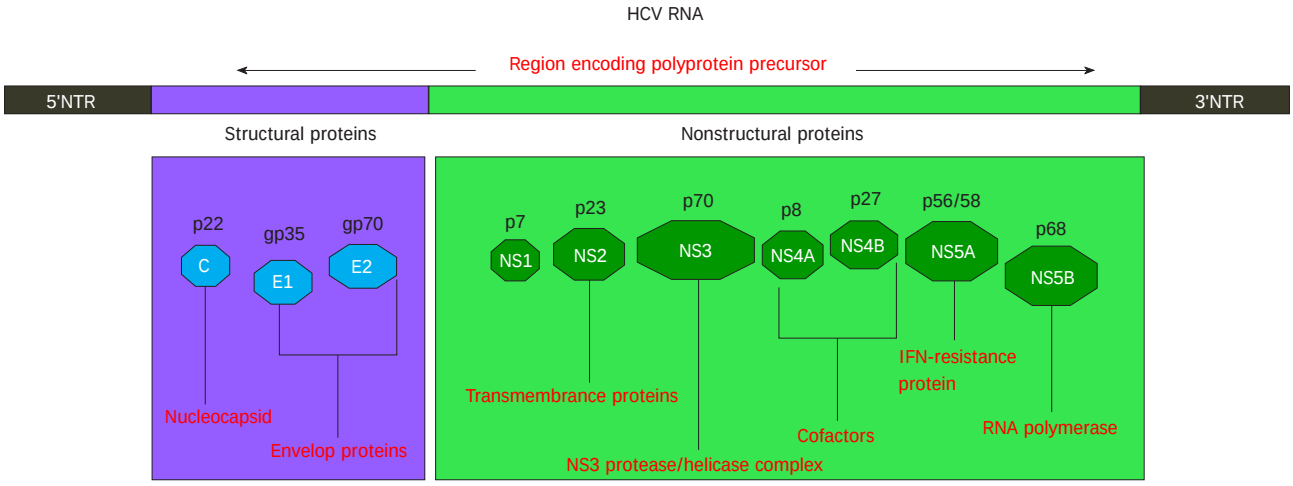

Figure 1 Hepatitis C virus genome organization. HCV: Hepatitis C virus; IFN: Interferon.

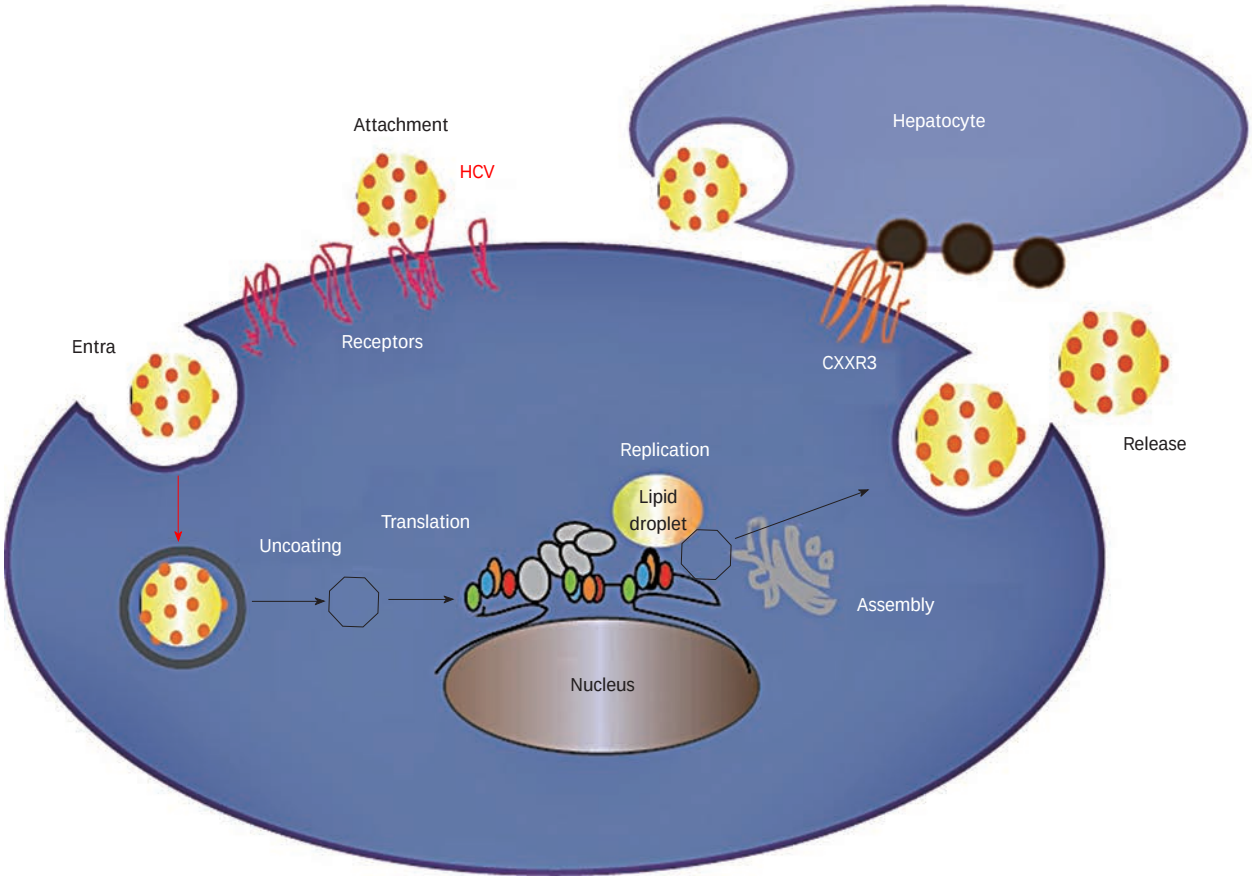

Figure 2 Hepatitis C virus life cycle.

is ultimately cleaved by host and viral proteases into 10 viral proteins in the order of NH (2) -Core-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-NS5B-COOH (Figure 1)[9]. According to past research, the structural proteins (Core, E and E2) and the nonstructural proteins (NS3 protease and NS5B RNA dependent RNA polymerase) have been considered the best targets to develop novel molecular inhibitors. Among these proteins, NS3 in association with NS4A has been hugely investigated due to its protease and helicase domains that are important in viral replication[1,10-12]. The life cycle of HCV is illustrated in Figure 2. HCV has six major genotypes with a series of subtypes[13]. In 2012, a new sequence has been found that is being named as subtype 7a[14]. The prevalence of genotype 3a is related to steatosis that leads to liver fibrosis[15,16].

To date, many medicinal plants have been tested against HCV and have proved beneficial as antiviral mediators. The reasons to prefer medicinal plants over traditional

medicines are their fewer side effects, low cost and multiple target activities[17]. The phytochemicals of the medicinal plants, such as limonoids, alkaloids, lignana, organosulfur, furyl, thiophenes, polylines, terpenoids, flavonoids, polyphenolics, sulphides, saponins, coumarins, chlorophyllins, are considered important due to their efficiency at hampering viral entry, blocking/limiting the RNA/DNA genome replication and their anti-oxidant activity[18]. Currently, there are few antiviral drugs that can efficiently work against HCV as most of the antiviral drugs show side effects and many of the viruses acquire resistance against them; thus, there is a strong need to develop antiviral compounds that can suppress HCV without side effects. Therefore, medicinal plants due to their magical powers are being investigated to discover antiviral agents that can efficiently target the entry or replication of HCV virus and are believed to be our future inhibitors for this dreadful disease.

CURRENT TREATMENT

HCV is a major concern worldwide and clearing it in its early phase to avoid liver cirrhosis and HCC has always been the target for researchers. To date, there is no authenticated vaccine available in the market and current approved treatment (standard of care) is a combination therapy having pegylated interferon alpha (PegIFN-α) injections and antiviral nucleoside analogue ribavirin (RBV) used for 24-48 wk depending upon the type of genotype. All the genotypes of HCV show different sustained virological response (SVR) and genotype 1 which is regarded as most problematic genotype shows the clearance of HCV in 50% of the cases. Similarly, genotype 2 infection shows clearance in only 80% of the cases[19-22].

This combination therapy has several considerable side effects such as fever, anemia, flu and depression[23]. Several combinations of IFN are in clinical trials, such as taribavirin which is a prodrug of ribavirin and albinterferon which is the combination of IFN-α and human albumin[24,25]. The side effects caused by current treatment raised the need to develop antiviral compounds that can suppress or eliminate the infection without toxicity and side effects. This directed the investigation to test antiviral agents against HCV viral proteins. HCV NS3 protease has been investigated as a drug target[26,27]. The inhibition of NS3/4A protease interferes with the replication of HCV genome and also restores the pathways of the innate immunity[28]. To date, several NS3/4A protease inhibitors have been investigated and recently, two NS3 protease inhibitors, boceprevir and telaprevir, have been approved by the Food and Drug Administration (FDA) as combination therapy along with PegIFN-α and RBV for HCV genotype 1 patients[29]. Despite the availability of current treatment, there is a dire need to screen antiviral agents that can target all four genotypes with the same efficiency and without any side effects. This increases the significance of the medicinal plants as antiviral agents as they are less toxic, less costly and are easily accessed.

MEDICINAL PLANTS AGAINST HCV

Viral infections with high mortality and morbidity rate are the leading cause of human deaths worldwide. All viruses start their life cycle through attachment and entry into the host cell and then increase their progeny by transcription and replication of the genome. The RNA viruses such as influenza, HIV and HCV have become a matter of concern as these are highly variable and lack an RNA dependent RNA polymerase proofreading mechanism[30]. Development of vaccines against viral diseases such as polio, mumps and smallpox have controlled these diseases but infections like HIV and HCV have been hard to target because of variation in genotypes. Infectious diseases have widely been treated using the medicinal plants and about 25% of current medicines have compounds from medicinal plants. There are plenty of plants that are known for their magical medicinal properties and these plants can serve as an important reservoir for drug discovery against infectious diseases. Current separation techniques have enabled researchers to find active compounds of plants as antiviral agents and to overcome the challenge of emerging infectious disease in human population. There is a wide range of medicinal plants which are being used to extract natural compounds that are being used for their antiviral activity. Liver diseases have been treated around the world using numerous medicinal plants and their formulations and this has given confidence to researchers to investigate the effect of these medicinal plants against HCV in more depth[31].

HCV infection is a leading cause of deaths among patients. To date, many drugs have been tested against HCV and many of them have successfully completed clinical trials but the problem of viral resistance against these drugs and side effects caused by these drugs have marked a question of developing better therapeutics against HCV[32]. At the present, drug discovery is being focused on medicinal herbs for HCV due to the lack of appropriate standard therapy. Acetonic and methanolic extracts of *Acacia nilotica* (AN) have shown novel inhibition of HCV titer *in-vitro* confirmed by real-time PCR[33]. Preclinical evaluation of the lyophilized juice of ginger and aqueous extracts of *Milk thistle* (MSE) has demonstrated anti HCV effects in the HepG2 cell line. Both of these plants have shown effective antiviral activity at concentrations of 300 μg/mL and 100 μg/mL respectively[34]. Recently, medicinal plants from Indonesia have been tested for their antiviral activity against HCV. Ethanolic extracts of Indonesian plants were analyzed in the Huh 7.5 cell line and HCV strains of 9 different genotypes namely 1a-71, 1b and 2b. Among the tested plants, *Toona sureni* leaves (TSL) showed IC_{50} value of 13.9, *Melicope latifolia* leaves (MLL) showed IC_{50} of 3.5, *Melanolepis multiglandulosa* stem (MMS) exhibited IC_{50} of 17.1 and *Ficus fistulosa* leaves (FFL) showed IC_{50} of 15.0. Among all of these, MLL, TSL, FFL and MMS exhibited antiviral activity against all genotypes of HCV and thus, it is suggested that these plants may prove good candidates to develop novel inhibitory drugs against

Table 1 Medicinal plant phytochemicals as anti- hepatitis C virus agents

Phytochemicals	Viral step	Effect
Diosgenin[43]	Replication	Inhibition of transcription factor 3 and signal transducer
Silymarin/silibinin[37,44,45]	Viral entry (viral attachment)	Inhibition of core protein and NS5 RNA-dependent RNA polymerase
	Replication	
Iridoids[46,47]	Viral entry	Blockage of E2 and CD81 contact
Naringenin[48,49]	Viral assembly	Suppression of core protein activity
EGCG[50,51]	Viral entry	Disturbance in glycoprotein activity and Inhibition of cell-cell transmission
Quercetin[52,53]	Replication	Inhibition of IRES activity and NS3 polymerase
Ladanein[54]	Post attachment entry step	Inhibition of receptor interactions, virus endocytosis, or membrane fusion
Luteolin and apigenin[55]	Replication	Inhibition of NS5B polymerase activity

IRES: Internal ribosomal entry site. EGCG: Epigallocatechin gallate.

HCV though, there is a need to further investigate these plants to develop drugs for the effective inhibition of HCV[35].

MEDICINAL PLANTS AGAINST HCV CORE

To date, many plants have been tested against HCV core protein and some of these plants have been found as a source of novel inhibitory drugs to suppress HCV infection. Some of these plants have been discussed in this review. In recent years, Pakistan has tested various medicinal plants *in vitro* and found significant inhibitory effects on HCV titer. Among these plants are glycyrrhizin (GL) which inhibited HCV titer in dose dependent mode and also exhibited synergistic effects when administered with interferon. GL inhibited the core protein of genotype 3a at the mRNA and protein level and thus has been suggested as a future drug that can help to decrease the viral titer of HCV[36]. Another plant *Silybum marianum* (SM) was tested by the same research group and two pure fractions of SM exhibited inhibition of HCV core protein of genotype 3a which was confirmed through western blotting. The research group suggested that the combination of SM with interferon shows promising results in treating HCV[37].

MEDICINAL PLANTS AGAINST NS3 PROTEASE

During the recent decades, advancements in drug discovery have revealed NS3/4A protease as an important drug target in overcoming HCV infection. Many inhibitors against NS3 have successfully entered clinical trials but there is still need to improve their functionality and efficiency. Various medicinal plants are also being investigated to develop anti HCV drugs that are not only efficient but are also easily available to developing countries due to their low cost[38]. Methanolic and water extracts of medicinal plants used in Sudanese traditional medicine such as *Boswellia carterii, Acacia nilotica*, *Quercus infectoria, Embelia schimperi*, *Trachyspermum ammi*, *Q. infectoria*, *Piper cubeba* and *Syzygium aromaticum* have been tested against HCV protease and showed more than 90% at 100 μg/mL[39]. An *in-silico* approach has been used to test *Accacia nilotica* phytochemicals against NS3/4A protease and found that they may serve as a potential drug candidate with relatively simple structural changes against HCV NS3/4A protease[40]. *Solanum nigrum* (SN) has also been tested against HCV and its methanolic and chloroform extracts exhibited significant inhibition against HCV protease in liver infected cells[41]. Recently, *Viola yedoensis* has been investigated to find an anti HCV compound targeting protease. Using the various chromatographic procedures, 3 coumarins have been isolated and characterized from *Viola yedoensis*. Among the isolated compounds, a dimeric coumarin 5, 5'-bi (6,7-dihydroxycoumarin) has significantly inhibited NS3/4A protease with IC_{50} value of 0.5 μg/ml. Thus, this dicoumarin can serve as an important molecular template to design novel anti HCV drugs[42].

MEDICINAL PLANT PHYTOCHEMICALS AS HCV INHIBITORS

Medicinal plants have shown potential against viral infections and investigation of their active compounds has taken antiviral research to a new horizon. Currently, there are many plant derivatives being tested against HCV and some of them have shown significant inhibition in entry, replication and assembly steps of the viral life cycle, described in Table 1.

Diosgenin (3β-hydroxy-5-spirostene), which is a plant-derived sapogenin, has effectively blocked the replication of the HCV subgenomic replicon system at both the mRNA and the protein level. A decrease in activator of transcription factor 3 and signal transducer has been observed. The EC_{50} value of diosgenin was 3.8 μmol with no cellular toxicity. In another antiviral system, it showed inhibition of viral replication at 20 μmol concentration[43].

Silymarin, which is isolated from *Silybum marianum* has been tested against HCV and is found to be effective in inhibiting the viral activity of HCV. Silymarin has been tested against the HCV core protein of genotype 3a and was found to be effective in inhibiting the core expression[37]. Silibinin, which is a combination of two diastereoisomers, is the major component of silymarin

responsible for anti HCV activity[44]. The antiviral effect of silibinin has been tested against NS5 RNA-dependent RNA polymerase with IC_{50} values of 75-100 μmol[45].

HCV entry has been blocked using different iridoids from *Lamium album* using HCVpp. The aqueous extract of *Lamium album* containing lamiridosins A/B (1/2) and iridoids aglycone epimers have reduced HCVpp entry by disturbing the contact of HCV envelope 2 proteins (E2) with the CD81 receptor[46]. The 4-[(1,2-dihydro-2-oxo-3*H*-indol-3-ylidene) amino]-*N* (4,6-dimethyl-2-pyrimidiny) benzene sulphonamide and its derivatives have also been evaluated for anti-HCV activity and have shown inhibitory effects. The replication of HCV RNA has been blocked by 5-fluoro derivative of Isatin in Huh 5-2 cells[47].

Naringenin is a predominant flavanone found in the grapefruit and has been tested on the HCV particles[48]. Naringenin has suppressed the activity of core protein in Huh 7 cells and has also effectively blocked the assembly of HCV particles. It showed maximum inhibition at 200 μmol concentration with IC_{50} value of 109 μmol[49].

Epigallocatechin-3-gallate (EGCG) is found in green tea extract and recently this compound has been found significant in inhibiting HCV entry. EGCG had no effect on HCV assembly, replication and release but it efficiently inhibited cell-culture-derived HCV (HCVcc) entry into hepatocellular cell lines and this effect was independent of the HCV genotypes[50]. The effect of EGCG on HCV entry blockage has also been confirmed by another research group using a new anti HCV molecule screening assay[51]. Thus, EGCG may serve as an important anti HCV drug by blocking the entry of virus into host cells.

Quercetin, present in vegetables, fruits, grains and leaves has been investigated as an anti HCV agent. Quercetin not only reduced IRES activity but also its augmentation by NS5A. Thus quercetin reduced viral production without any toxic effects[52]. Similarly, in another study quercetin suppressed RNA replication in a subgenomic RNA replicon and also inhibited replication in a model containing NS3 substrates suggesting that it may be related to NS3 protein of HCV and blocks replication by targeting the NS3 protease. The effects of quercetin were nontoxic and were significant[53].

Ladanein (BJ486K) is a flavone isolated from the *Marrubium peregrinum* L. (*Lamiaceae*). Ladanein has shown effective inhibition of the post attachment entry step of HCV with an IC_{50} value of 2.5 μmol. In combination with cyclosporine, it showed interesting synergetic results against all the genotypes of HCV. This provides clues to further investigate ladanein for its anti HCV potential in patients[54]. Luteolin and apigenin have also been identified as anti HCV agents with IC_{50} values of 4.3 μmol and 7.9 μmol respectively. Among both compounds, luteolin showed persuasive inhibition of NS5B polymerase activity with an IC_{50} of 1.12 μmol[55].

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