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Review Article

Complementary and Alternative Medicine for the Treatment of Hepatitis C Virus Infection

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Abstract

Hepatitis C virus (HCV) infection, a fatal infectious disease, is a grave issue from a global perspective. The current treatments with ribavirin, pegylated interferon, and direct-acting antivirals (DAAs) have been efficacious for years. However, toxicities, adverse drug reactions, and the development of resistance have created a need for discovering new molecules to treat HCV infection. Medicinal plants contain many constituents that provide potent activity against HCV. Natural remedies have given encouraging outcomes in terms of being reliable anti-HCV agents. Recently, *in-vitro* and *in-vivo* experiments have confirmed the anti-HCV potential of many phytochemicals, such as polyphenols, glycosides, and many other secondary metabolites. Many of these compounds prevent the entry of HCV into the liver cells, while some of them inhibit the viral replication process within the host cells. Silymarin is a significant discovery for HCV treatment from *Silybum marianum*. Epigallocatechin-3-gallate extracted from *Camellia sinensis*, Rutin obtained from *Prunus domestica*, and some other constituents have also provided propitious results with respect to their anti-HCV activity. Similarly, research is underway to discover more such natural products with potential activity against HCV without notable toxicity. The pharmacokinetics of these phytochemicals may be refined by applying nanomedicine to overcome the limitations of phytochemical therapy.

Keywords: Hepatitis C virus; phytochemicals; polyphenols; secondary metabolites; HCV infection; natural product; Nanomedicine.

1. Introduction

Hepatitis C is a deadly viral infection that contributes majorly to mortality around the world. According to the latest statistics of the World Health Organization (WHO), the death toll is approximately 0.3 million people yearly, while more than 3 million people of every age group are prey to chronic hepatitis C infection annually (WHO 2022). This disease is caused by the Hepatitis C virus (HCV), a single-stranded ribonucleic acid (RNA) virus that belongs to the Flaviviridae family of viruses (Gupta, Bajpai, and Choudhary 2014). It is a hepatotropic virus that majorly infects the liver by inducing chronic inflammation, leading to hepatic insults such as hepatic cirrhosis, hepatic fibrosis, liver failure, and hepatocellular carcinoma (Tanwar et al. 2020). The inflammatory responses lead to disruption of the hepatic cellular infrastructure, precipitating scar tissue formation and resulting in the loss of hepatic function (Laursen et al. 2020). HCV infections also have extrahepatic effects, including cryoglobulinemia, metabolic instabilities, diabetes mellitus, lymphoma, nephropathy, and cardiovascular disorders (Mohanty, Salameh, and Butt 2019).

Medicinal plants have been used for centuries due to phytochemicals' activity in treating various ailments (Astutik, Pretzsch, and Ndzifon Kimengsi 2019). Complementary and alternative medicine (CAM) has played a dominant role in conventional therapeutic remedies. The role of many phytoconstituents has been established as anti-infective chemical compounds. Many medicinal plants have shown antiviral activity in diseases such as hepatitis, influenza, human immunodeficiency virus (HIV), chikungunya, SARS-CoV-2, and many other viral infections (Ganjhu et al. 2015, Aanouz et al. 2021, Sharma et al. 2019). These plants contain many secondary metabolites with biological activities against the virus, i.e., they either inhibit its life cycle or block the pathways associated with viral-host cell interactions (Chojnacka et al. 2020). Hepatitis C, since its discovery, has been traditionally treated with many herbal remedies (Yan et al. 2019, Hussain et al. 2020). The current pharmacotherapy for hepatitis C includes antiviral drugs such as ribavirin, pegylated interferon, and direct-acting antivirals (DAAs) such as sofosbuvir, velpatasvir, ledipasvir, simeprevir etc. These treatment options have led to serious toxic effects, including nephrotoxic, anemic, teratogenic, neurological, and psychiatric effects that adversely impact the quality of life. (Vermehren et al. 2016, Asselah, Marcellin, and Schinazi 2018). This review aims to summarize the phytochemical-based therapeutic options and natural remedies to treat HCV infection that have minimal toxicity in addition to decent efficacy and may assist in alleviating the burden of this lethal infection. This review will also cover the epidemiology of HCV, its pathophysiological aspects at the molecular level, current pharmacotherapeutic strategies, the associated problems, and the reasons that make CAM therapy safer and more efficacious for HCV infections. This review may urge formulation scientists to develop nano-carrier-based drug delivery systems for phytochemicals to target HCV-infected cells more effectively.

2. Epidemiology of HCV Infection

Hepatitis C is a serious threat to global health, affecting more than 58 million people worldwide, with 1.5 million new active HCV infections and approximately 0.3 million deaths per year (WHO 2022). HCV infection is prevalent in developing countries with lower incomes and poor sanitation conditions. One of the key factors associated with a higher number of HCV infections is the lack of standards and measures for infection control. Transfusion of infected blood, sexual contact with infected people, and drug abusers reusing syringes are among other underlying causes (Nouroz et al. 2015). HCV has seven genotypic forms and many subtypes that mainly differ in their genetic material to some extent. Genotype 1 is most common in developed countries, genotype 2 is found mostly in African countries, and genotype 3 is most prevalent in India, Pakistan, and other eastern countries (Gower et al. 2014). Many studies were undertaken to assess the incidence of HCV infections among prisoners in various countries. The facts and figures generated from the population in prison demonstrated a high prevalence of HCV infection in Brazil, Australia, the United States, and some other countries (Defante Ferreto et al. 2021, Zampino et al. 2015). The neonates and children are at high risk of getting infected with HCV from their HCV-infected or HIV-hepatitis C co-infected mother. In adult population groups, tattooing has also been postulated as a significant risk factor for the spread of this infection (Jefferies et al. 2018). Several initiatives are being taken for the eradication of hepatitis C. The current therapies have helped control the disease's spread and overall prevalence, but many challenges remain, such as the incomplete coverage of preventive therapies for HCV infection, the absence of adequate data in developing countries, unaffordable treatments (DAAs), etc. These matters continuously demand the scientific community's attention to broaden their perspective regarding the control of HCV (Hajarizadeh et al. 2016).

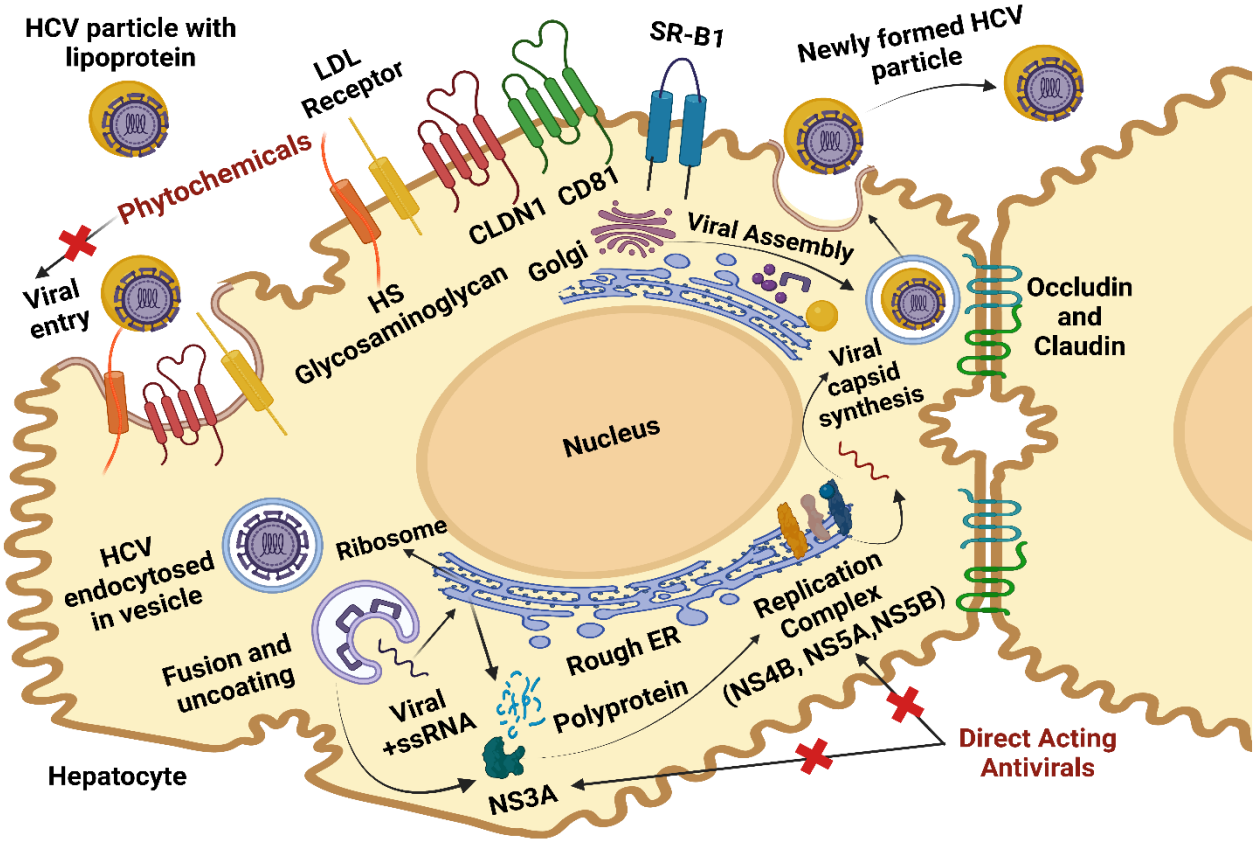

Figure 1: The figure demonstrates the molecular mechanism of HCV infection. The HCV particle with attached lipoprotein interacts with membrane receptors of hepatocytes such as Heparan Sulfate (HS) glycosaminoglycan, Cluster Differentiation (CD) 81, low density lipoprotein (LDL) receptor etc. This interaction mediates viral entry into the cell and membrane invagination forms a vesicle. The vesicle undergoes fusion with the viral envelope and releases the viral RNA, which afterwards is translated into viral polyprotein. This polyprotein is cleaved into non-structural proteins that form replication complex which completes the replication of viral genetic material, which is then encapsulated into newly synthesized viral capsid in endoplasmic reticulum and Golgi complex.

3. Pathophysiology of HCV Infection

HCV possesses single-stranded RNA with a 9.6 kilobase pair (kb) genome. After entering the body and evading the immune response, the virus reaches the liver cells and interacts with the receptors on these cells to gain entry within the cells (Zeisel et al. 2011). The HCV envelope proteins (E1 and E2) have specialized domains that are predominantly involved in interaction with receptors, including 'Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DG-SIGN)' expressed by the Kupffer cells (Sarma et al. 2020). The cell surfaces of hepatocytes are rich in surface heparan sulfate (HS) glycosaminoglycans (Gerold, Moeller, and Pietschmann 2020). The virus comes in contact with these molecules and attaches itself to the surface of hepatocytes to gain entry. HS glycosaminoglycans also facilitate the communication of viruses with other surface proteins in liver cells. E2 protein interacts with CD81 expressed on the surface of hepatocytes for entry into the cell (Dey et al. 2022). Liver cells also express a scavenger receptor, class B type 1 (SR-B1), that has an affinity for HCV envelope proteins

and mediates viral entrance into the liver cells (Deng et al. 2023, Yamamoto et al. 2016).

The HCV is endocytosed as a vesicle into the hepatocyte after membrane invagination. The viral positive-sense single-stranded RNA (ssRNA) is released from the vesicle after the uncoating of the capsid. The host ribosomes translate the RNA into HCV-polyprotein that is cleaved into separate non-structural proteins (most importantly NS3A and NS4A proteases, NS4B, NS5A, and NS5B) (Chen et al. 2017). These proteins form a replication complex on the surface of the endoplasmic reticulum of the host liver cell. This complex expedites viral positive sense ssRNA replication into negative sense ssRNA. This template is further replicated as multiple copies of positive-sense ssRNA to be encapsulated in the viral particle assembly produced in the host cell (Dustin et al. 2016).

The viral infection and replication in the hepatocytes lead to the expression of damage-associated molecular patterns (DAMPs) and the subsequent elicitation of inflammatory responses (Keenan, Fong, and Kelley 2019). Neutrophilic infiltration is followed by chemoattraction. and further cytokine release leading to liver damage and fibrosis. Hepatocellular carcinoma is the ultimate outcome of this inflammatory process. Besides mutations in the HCV genome, the exhaustion of T-lymphocytes is an important mechanism behind the impairment of T-cell responses in HCV infection (Sepulveda-Crespo and Resino 2020). Figure 01 illustrates the pathogenesis of HCV infection.

4. Current Treatments for HCV Infection

Before DAAs arrived, the treatment of choice for HCV infection consisted of ribavirin and pegylated interferon alpha. This combination provided improved patient outcomes but with some toxicity. Later on, combination therapy with DAAs boosted sustained virological response (SVR) rates against several HCV genotypes. The United States Food and Drug Administration (US FDA) has approved combinations of DAAs for the treatment of HCV, including ledipasvir/sofosbuvir, sofobuvir/velpatasvir, ombitasvir/paritaprevir/ritonavir, and some other combinations. (Scotto et al. 2019, Li and Chung 2019). On the other hand, pharmacotherapy with DAAs is also facing the development of resistance against the HCV genotypes due to resistance-associated substitutions (Soria et al. 2020).

4.1. Nucleoside Analogs

Ribavirin belongs to the pharmacological class of nucleoside analogs. Ribavirin is phosphorylated as ribavirin triphosphate. It mimics nucleotides and blocks the viral positive-sense single-stranded RNA replication process. Ribavirin, when monophosphorylated, also inhibits inosine-5′-monophosphate dehydrogenase, which catalyzes nucleotide synthesis. The inhibition of these enzymes will deplete guanosine nucleotides, thereby preventing viral RNA replication (Nyström et al. 2019).

A number of clinical studies have identified ribavirin as a promising agent for treating HCV infection. A clinical study has stated the role of the ribavirin and sofosbuvir combination in successfully treating adults suffering from HCV infection associated with genotypes 1 and 2. The advent of DAAs has lessened their use (Wirth et al. 2017).

4.2. Recombinant Interferon

Pegylated interferon -2a or 2b is recombinant human interferon -2a or 2b conjugated with polyethylene glycol (PEG). The pegylation process decreases the proteolysis of recombinant interferon and increases its half-life in circulation. Endogenously, interferon is secreted by viruses-infected tissue cells in response to interferon regulatory factors. Some genes encoding interferon are transcribed, leading to interferon production and subsequent antiviral signaling cascades. The pegylated interferon causes the activation of JAK-STAT signaling, causing the expression of genes responsible for synthesizing antiviral signaling molecules (Secombes and Zou 2017). Many clinical studies have proposed a pegylated interferon and ribavirin combination to

give good therapeutic results in patients with HCV infection. The combination of pegylated interferon with DAAs has also been explored, and better patient outcomes have also been recorded. DAAs have largely replaced recombinant interferon therapy (Petta and Craxì 2015).

4.3. NS3A/NS4A Inhibitors

NS3A and NS4A proteases are important for the mediation of the HCV life cycle in hepatocytes. NS3A is involved in cleaving the viral polyprotein into individual non-structural proteins that form 'the replication complex' for the replication of the RNA of HCV. NS4A facilitates the NS3A protease to perform its function. NS3A/4A inhibitors block these proteins and prevent the cleavage of vial polyproteins into further non-structural proteins, thereby terminating the HCV life cycle. Telaprevir, Bocepravir, and Simepravir are prominent members of this pharmacological class (Bakulin et al. 2014).

The therapeutic applications of NS3A/4A inhibitors in HCV infection are well-established in daily clinical practice. A meta-analysis has summarized the findings of many clinical studies that state the efficacy of NS3A protease inhibitors without developing any toxic effects. The combination of NS3A/NS4A inhibitors with any other DAA can achieve therapeutic outcomes in a more pronounced manner (Manzano-Robleda Mdel et al. 2015).

4.4. NS5A Inhibitors

The NS5A protein, in close association with NS4B, forms a replication complex in the membrane of the rough endoplasmic reticulum of the hepatocyte. This complex then facilitates the process of viral positive-sense single-stranded RNA replication. NS5A replication complex inhibitors block the function of the NS5A protein and prevent the formation of the replication complex for viral RNA replication(Gitto, Gamal, and Andreone 2017).

Many phases of clinical trials reported the efficacy of NS5A inhibitors, and FDA has also approved this class for the treatment of HCV. Many clinical studies have confirmed the efficacy of Daclatasvir in combination with Sofobuvir, an NS5B inhibitor, resulting in better patient outcomes (Pol, Corouge, and Vallet-Pichard 2016).

5. Medicinal Plants as Remedies for HCV Infection

5.1. Pterogyne nitens

Flavonoids are therapeutic entities with biological activity against various diseases (Sathishkumar et al. 2018, Karak 2019). Pterogyne nitens is a medicinal plant rich in flavonoids and other phytoconstituents that have vast activity in diseases such as the Zika virus and fungal infections (Lima et al. 2021, Lima et al. 2016). A study was conducted that screened the activity of flavonoids, pedalitin, and sorbifolin extracted from Pterogyne nitens leaves. The in-vitro assay was performed for anti-HCV activity in 'Huh-7.5 cell line' which is widely used to study HCV and hepatocellular carcinoma (Omura et al. 2019). The cell lines were pretreated with both flavonoids and infected with the JFH-1 HCVcc virus. The in-vitro experiment demonstrated that both flavonoids effectively blocked the entrance of HCV into the cell line, and the viral infectivity was reduced to a significant extent (Shimizu et al. 2017).

5.2. Prunus domestica

Prunus domestica, belonging to the Rosaceae family of plants, is found to have activity in ailments such as cancer, diabetes, and bacterial infections (Islam et al. 2017, Nayudu and Sowjanya 2017). Prunus domestica principle flavonoid, Rutin, was tested for its activity against HCV. The extract of Prunus domestica was obtained, fractionated, and characterized. Rutin was tested on 'Huh-7 cell line' infected with HCV-like particles derived from genotype 3a. Rutin acted directly upon the viral particle and blocked its entry into the cell, thereby preventing viral infection at very low concentrations (Bose et al. 2017).

5.3. Silybum marianum

Silymarin is a flavonolignan extracted from Silybum marianum, a plant conventionally known for its liver protective effects (Bahmani et al. 2015).

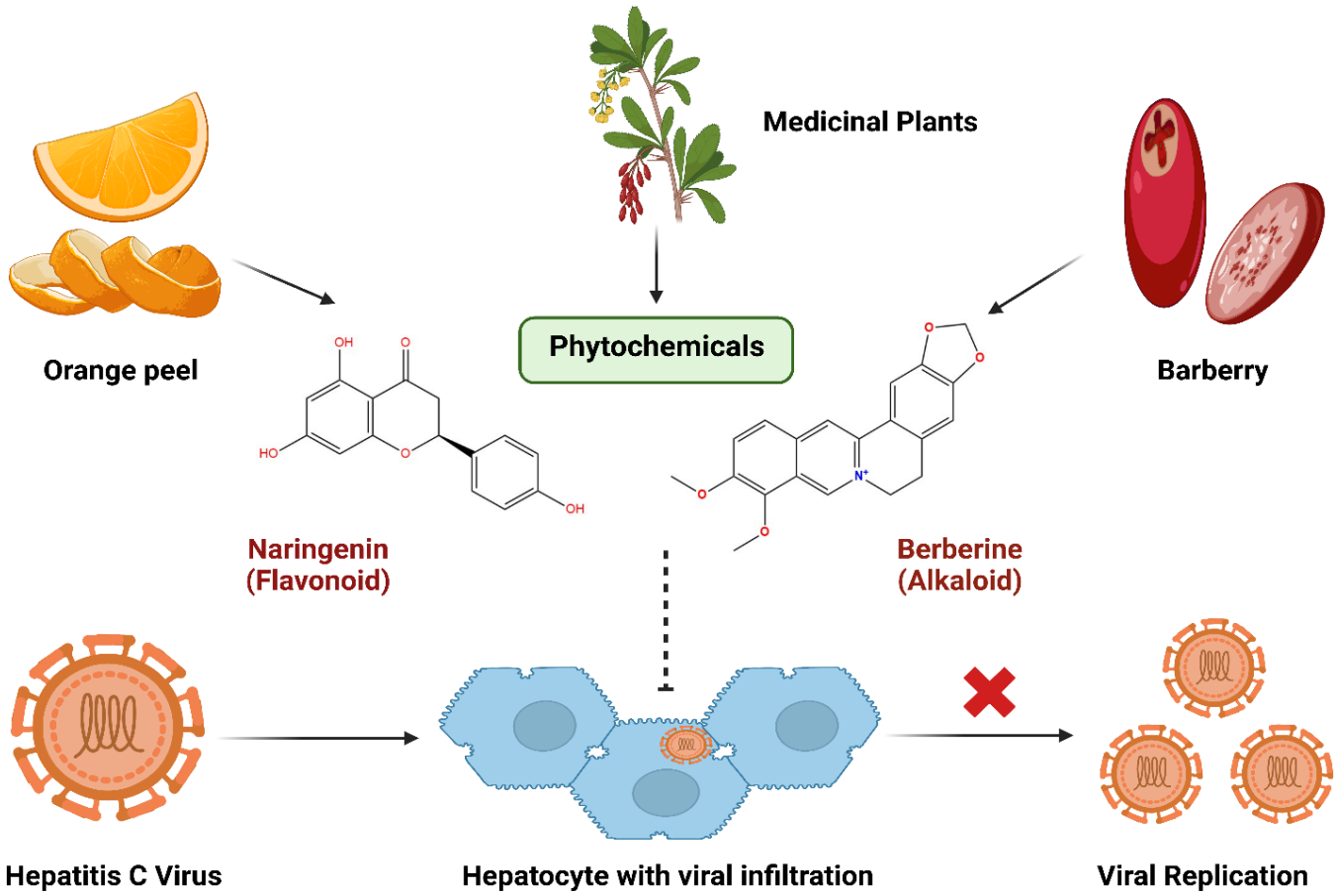

Figure 2: The figure shows the attenuation of viral replication and infection by the effect of phytochemicals such as polyphenols and alkaloids, acquired from medicinal plants and herbs.

A clinical trial was conducted that included patients diagnosed with primary HCV infection. The control group received Ribavirin 800mg and Sofosbuvir 400mg, while the test group was given the same doses of Ribavirin and Sofosbuvir along with Silymarin (400 mg per day). The results revealed that patient outcomes in the test group improved significantly. The liver enzymes and bilirubin levels were lower in the test group than in the control group. The levels of hemoglobin and glutathione were recorded to be higher in the test group as compared to those of the control group, reflecting the therapeutic efficacy of Silymarin with concomitant antiviral therapy (Ahmed et al. 2022).

HCV infection leads to hepatic fibrosis as a consequence of the inflammatory process (Khatun and Ray 2019, Tanwar et al. 2020). A research study was done to focus on the potential of Silymarin to halt the process of fibrosis preceded by HCV infection. A male BALB/c mice model was established, and hepatic fibrosis was induced using carbon tetrachloride. Silymarin doses were supplied to the mice at 100 mg per kg. The results showed the hepatoprotective effects of Silymarin, decreasing the levels of the alkaline transferase, aspartate aminotransferase, and other liver enzymes significantly. The histological studies disclosed that the Silymarin group did not develop fibrosis (Omar et al. 2022).

Silibinin is a related phytochemical that also exhibits anti-HCV activity. In a study, Silibinin nanoparticles were formulated using polyvinylpyrrolidone. The Huh-7 cell lines were infected with HCV particles that were derived from culture. The Silibinin nanoparticles provided antiviral effects with 100 % survival of the infected cells in-vitro. The luciferase reporter assay also rendered the same reports for Silibinin nanoparticles. An in-vivo analysis was also part of the study in which the safety of these nanoparticles was assessed. Sprague-Dawley rats were used in the model to evaluate the safety of Silibinin nanoparticles. The markers for hepatic damage were in the normal range, and no immune response was evident in rats for up to two weeks (Liu et al. 2017).

5.4. *Camellia sinensis*

Camellia sinensis (green tea) is a popular natural remedy used for antioxidant, anti-infective, anticancer, and anti-obesity effects **(**Aboulwafa et al. 2019**).** Its active constituents have an extensive range of biological activities. One of its constituents, epigallocatechin-3-gallate has vast pharmacological applications in ameliorating viral infections (Hsu 2015, Zhao et al. 2021). In-vitro experiment used polyinosinic-polycytidylic acid to induce an immune response in Huh cell line infected with the JFH-1 strain of HCV. Treating these cells with Epigallocatechin-3-gallate potentiated this immune response furnishing antiviral cytokine release in the cells by transcriptional up-regulation of interferon genes, confirmed through RT-PCR (Wang et al. 2017).

5.5. Sarcocornia fruticosa

Sarcocornia fruticosa plant has been studied for its therapeutic use in inflammation, Alzheimer's disease, and urinary system disorders (Megharbi and Kechairi 2021, Silvestre 2017). Sarcocornia fruticosa contains flavanol glycosides as active phytochemicals. These are rhamnazin 3-O-(6''-O-α-rhamnosyl)-β-galactoside, rhamnazin 3-O-rutinoside, and some related constituents. The methanolic extract of the leaves of Sarcocornia fruticosa was used in the HCV protease enzyme assay. The in-vitro analysis reported potent inhibition of the protease (Hawas et al. 2019).

5.6. Radix Bupleuri

Radix Bupleuri extract has been widely used in traditional medicine for several disorders (Yang et al. 2017). The plant extract is composed of saikosaponins, which are majorly responsible for the therapeutic activity of this herb. An in-vitro study was undertaken using the root extract of Radix Bupleuri on HEK 293T and Huh 7.5 cell lines. These cell lines were infected with HCV genotype 1b in a 96-well plate, and saikosaponin B2 was added to the wells. The saikosaponin B2 inhibited the HCV entry into the cells significantly, up to approximately 80 % of the cells. The translation of the viral proteins was also down-regulated with saikosaponin B2 (Lee et al. 2019).

5.7. Flakozid

Flakozid is a traditional Russian drug acquired from the extract of the medicinal plant Phellodendron amurense (Bortnikova et al. 2020). An in-vitro study employed the 'SPEV cell line' to screen the anti-HCV activity of Flakozid. Flakozid was compared with ribavirin for its antiviral actions. The cell line was grown in a well plate, and Flakozid was added to the wells (with a maximum concentration of 100 μg/ml) a day before infecting the cells with HCV. The cell lines treated with Flakozid displayed complete survival of the SPEV cells after a period of 24 hours. The activity of Flakozid was observed to be more potent as compared to ribavirin in this experiment (Fateeva et al. 2019).

5.8. Amphimedon spp.

Marine life provides a vast range of natural products that possess all the characteristics of a therapeutic entity (Jiménez 2018). The petroleum extract of marine sponge Amphimedon spp. was used in the formulation process of silver nanoparticles. The lyophilized sponge material was extracted with methanol and fractionated into aqueous and petroleum-ether fractions. This extract was employed in the HCV protease and helicase assays. The results showed that the extract was very promising in inhibiting the viral

enzymes. The mass spectroscopy identified several chemical compounds, including Hachijodine E, Amphimic acid A, Manzamine H, Manzamine L, and some other constituents. The molecular docking analysis reflected that the compounds had good binding affinities and positions towards the viral proteins of HCV proteins (Shady et al. 2020).

5.9. Curcuma longa

Curcumin is a polyphenolic compound obtained from Curcuma longa extract. It has been widely explored for its potential benefits as a remedy. Many studies have witnessed the anti-inflammatory, anti-infective, anti-Alzheimer, antioxidant, and anticancer effects (Yallapu et al. 2015, Giordano and Tommonaro 2019). It is well established that curcumin shows hepatoprotective activity by scavenging reactive oxygen species in the liver. It raises the levels of glutathione and other endogenous antioxidants. Curcumin can potentially inhibit liver fibrosis, preserving normal hepatic function (Pulido-Moran et al. 2016). A study revealed the potential of curcumin-loaded nanoparticles against HCV infection. The Huh 7 and Huh7.5 cell lines were assayed to evaluate the blocking of viral entry into the cells and inhibition of in-vitro viral replication. The results of this study showed that the curcumin-loaded chitosan nanoparticles effectively blocked the viral entry into the cells and inhibited in-vitro viral replication (Ali Mohamed 2018).

A study used green synthesis for formulating curcumin-platinum nanoparticles. These nanoparticles were tested for their potency to hinder the process of HCV-induced fibrosis in hepatic tissue. NIH/3T3 cells (a fibroblast cell line) were cultured and assayed for the anti-fibrotic activity of curcumin-platinum nanoparticles. A comparison was drawn between these nanoparticles and free curcumin. The curcumin-platinum nanoparticles successfully suppressed the excess collagen synthesis in liver cells, thereby preventing fibrosis **(**Yu et al. 2019**).**

6. . Quercetin Containing Medicinal Plants

Quercetin is a flavonoid found in many medicinal plants such as Gingko biloba, Morus alba, Achillea millefolium **L.,** Mentha spicata etc. **(**Grewal et al. 2021**)**. In a study, Huh 7.5 cell lines were infected with the HCV JFH1 strain to assess the biological activity of quercetin. RT- PCR pointed out that quercetin inhibited messenger RNA (mRNA) production for HCV and diacylglycerol acyltransferase (DGAT) enzyme in the infected cells. DGAT enzyme is thought to facilitate the life cycle of the HCV particle (Kim et al. 2018). Primary human hepatocyte cells were cultured and infected with the JFH1 HCV strain and quercetin 50 μM was supplied to the cultured cells. The results showed decreased mRNA production and subsequent relief from infection **(**Rojas et al. 2016**).**

6.1. ***Berberis vulgaris***

Berberis vulgaris extract is traditionally used as a herbal remedy for treating various infections, wounds, inflammation, rheumatism, gout etc. **(**Rahimi-Madiseh et al. 2017). Many studies have provided evidence regarding the hepatoprotective effects of Berberis vulgaris extract **(**Mehrzadi et al. 2018**,** Mohammadzadeh, Mehri, and Hosseinzadeh 2017**)**. Hepatitis was induced in a group of albino rats. High doses of lipopolysaccharides and paracetamol (LPS/PCM) were administered for a few days to induce hepatic inflammation in rats. Liver enzymes were markedly increased in rats with induced hepatitis. Later, these rats were administered an aqueous extract of Berberis vulgaris through the oral route. The extract significantly decreased the elevated levels of liver enzymes and all other biomarkers of hepatic inflammation. The study postulated that berberine, the principle component of Berberis vulgaris, provided major hepatoprotective effects in this rat model **(**Moustafa et al. 2021**).**

6.2. *Citrus sinensis*

Many studies have used the peel of Citrus sinensis to investigate its activity against various ailments, including diabetes mellitus, infections, hyperlipidemia, and hepatic inflammation (Kosasih et al. 2019, Hussain et al. 2015, Muhtadi et al. 2015). A study used a rat model involving hepatic inflammation induction using subcutaneous carbon tetrachloride injections. Citrus sinensis peels were obtained, dried in the shade, and converted into a fine powder. This powder was macerated with ethyl acetate for three days. The final extract was collected and orally administered to rats with induced hepatic inflammation. The hepatic inflammation was reduced to a greater extent which was further confirmed by histopathological analysis (Ammar et al. 2022). The study hypothesized that naringenin, the most important flavonoid imparts the hepatoprotective effects of Citrus sinensis peel extract.

Figure 02 displays the importance of phytochemicals in retarding the pathogenesis of HCV infection.

7. Opportunities and Challenges Associated With the Current and CAM Therapies for HCV Infection

Despite being efficacious, the current HCV therapy comprising ribavirin, interferon, and DAAs has many drawbacks. While anti-HCV therapy using phytochemicals is associated with many advantages, some shortcomings still need to be addressed regarding the pharmacokinetic profile of the phytoconstituents.

7.1. Problems associated with phytoconstituents and current HCV pharmacotherapy

The limitations of the current therapy for HCV infection create an opportunity for natural remedies to bridge the shortcomings in its pharmacotherapy. HCV infection is an issue of public health consideration. Research efforts have made us able to develop the current anti-HCV therapies. The affordability of these medicines and limited access to the healthcare system in countries with fewer resources are among the major challenges. Phytochemicals and their sources can serve as an inexpensive and readily available alternative.

The resistance-associated substitutions in HCV proteins make them refractory to the DAAs. This has increased the instances of therapeutic failure with current therapy for HCV infection and the chances of re-infection. Research is required to explore the viral-host cell interactions that could be maneuvered to avoid resistance to DAAs and to develop new molecules that may help combat the HCV infection more effectively. Frequent RNA mutations in HCV are also raising serious concerns for the current therapy. This demands further molecular exploration of HCV. As the immune response is impaired in HCV infection, the immune system becomes unable to provide an antiviral effect through chemokines or cytokines. Phytochemicals provide coherent immunomodulation and strengthen the immune responses against HCV (Bartenschlager et al. 2018).

The DAAs and other antivirals used in HCV infections interact with drugs for hyperlipidemia, antiepileptics, and drugs acting on the cardiovascular system. These interactions are associated with interference with the CYP-450 system of enzymes. On the other hand, phytochemicals are free of drug-associated interactions, making them even safer (Majumdar, Kitson, and Roberts 2016).

7.2. Unavailability of HCV Vaccine

The current therapy for HCV infection is not preventive and causes many toxicities. Despite exhaustive research efforts, the HCV vaccine remains one of the unfulfilled agendas of public health measures against HCV infection. Many contagious infections have been eradicated due to the advent of vaccines. More research is crucial for the discovery and development of protective vaccines to effectively prevent HCV infection and to lower the worldwide burden of the disease.

Despite current pharmacotherapy with DAAs like ribavirin, pegylated interferon, and CAM therapy, vaccine development against HCV should be the foremost priority. (Bailey, Barnes, and Cox 2019, Walker 2017).

8. Bioavailability of Phytoconstituents

An important challenge to successful treatment with natural products is their tendency to reach systemic circulation. Many phytochemicals, such as flavonoids and glycosides, may show low bioavailability due to decreased absorption when administered orally. The composition of gastric contents may affect the absorption of these compounds. For example, in the presence of monosaccharides, the absorption of quercetin from the gut is rapid. Fatty gastric contents may up-regulate the absorption of many natural products, leading to more bioavailability and efficacy for infections such as hepatitis C (Williamson, Kay, and Crozier 2018, Kamiloglu et al. 2021).

8.1. Metabolism of Phytochemicals

A major chunk of the phytochemicals are metabolized by CYP 3A4, CYP 1A2, CYP 2C19, catechol-O-methyl transferase, etc., before reaching the systemic circulation. Several in-vivo studies have highlighted the dominant role of phase II enzymatic machinery in metabolizing the phytoconstituents. Hence, this rapid metabolism may impact the therapeutic efficacy of natural products. This may affect the pharmacological response to HCV infection (Shi and Gu 2022, Chen et al. 2014).

8.2. Phytochemical Safety & Toxicity

Most of the phytochemicals involved in traditional remedies are very safe to use, as there are no serious adverse effects. In the case of HCV infection, they are hepatoprotective, immunomodulatory, antioxidant, and anti-infective. Many phytochemicals have a cytotoxic activity that can be utilized as a therapy for hepatocellular carcinoma. An in-vitro study using the extract of Ziziphus jujuba containing ursolic acid as an active constituent discovered that it modulates the cell cycle by inhibiting the anti-apoptotic proteins in the HepG2 cell line. Another study screened the ethanolic extract of Artemisia annua for its activity in hepatocellular carcinoma. Ex-vivo analysis was comprised of the HepG2 and Huh7 xenograft models. The extract retarded proliferation of cells by inhibiting pro-proliferative PI3K/AKT and mTOR pathways (Dietz et al. 2016, Jung et al. 2018, Rodriguez et al. 2021).

A clinical trial outlined its findings and proposed that irinotecan, a constituent of Camptotheca acuminate, was very effective in attenuating the hepatocellular carcinoma that resulted from HCV infection. The mechanism of irinotecan was assumed to be the regulation of DNA synthesis (Brandi et al. 2011).

8.3. Phytochemical Loaded Nanocarriers

Nanotechnology has significantly improved targeted drug delivery. The current review effort is overlapping anti-HCV therapy with nanotechnology. It is expected that the bioavailability issues regarding phytochemicals will be resolved using this approach. The phytochemicals, such as silibinin, have been loaded into nanoparticles and tested in vitro (on Huh-7 and MDA-MB-231 cell lines) and in vivo in a mouse model. The results showed that these nanoparticles possess antiviral and cytotoxic activity. Targeted therapy with nanoformulations of silibinin and related phytochemicals can serve as a novel CAM therapy option in modern pharmacotherapy for HCV infection and hepatocellular carcinoma (Singh et al. 2019, Kashyap et al. 2021).

9. Conclusion and Recommendations

Phytochemicals have massive potential for therapeutic utility in various ailments. Many of the medicines prescribed daily are chemical entities of plant origin. Along with other diseases, phytochemicals have shown auspicious activity against HCV infection. Many phytochemicals, including polyphenols, alkaloids, glycosides, etc., either restrict the entry of HCV into the liver cells or directly inhibit the viral replication to attenuate

the infection. This has brought hope for effective pharmacotherapy for HCV in the era of resistance arising against the current HCV therapy. Silymarin and silibinin extracted from Silybum marianum have exhibited their anti-HCV potential in vitro and in vivo. Quercetin, a principal component of Gingko biloba, inhibits the replication process of viral genetic material, leading to anti-HCV activity in human cell lines. Curcumin, an important constituent of Curcuma longa, has also proven very effective in diminishing viral replication in host cells. Continued exploration of the molecular mechanisms of HCV pathogenesis can further drive the drug discovery and development process for treating HCV infection. The coupling of phytochemistry with nanotechnology can further ease the process of discovering the most effective complementary and alternative medicine therapy for HCV infection.

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NA.

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