OCTAHEDRON
Drug Research
Vol. 7
Review Article

Brief review focuses on the green synthesis approaches employed in the development of key anti-HCV medications

Rogy R. Ezz Eldin[a,b*], Aya T. Goda[a,b*] Sarah K. Al-banna[c], Shrouk S. Mokhtar[c], Ghada H. Abdo[c], Shahd A. Abdelaziz[c], Arwa S. Nashat[c], Habiba G. Badawi[c], Marvin T. William[c], Mazen K. Elnaggary[c], Habiba E. Salah[c], Mohammed A. AbdelMajeed[c], Shahinaz A. Elammary[c], Yomna A. Elsegai[c], Abdelrahman A. Elgazar[c], Roaa S. Yahia[c], Amira A. Elbadry[c], Eman E. Refai[c], Shahenda A. Elkady[c], Mariam G. Ahmed[c], Youmna M. Hosny[c], Hoda E. Awad[c], Mariam H. Elghznawy[c], Abdelaty M. Sleem[c], Fatma A. Mubarak[c], Ahmed O. Elshiekh[c], Ahmed R. Elsholhy[c], Samar R. Sabiha[a,b*]

[a] Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, East Port Said National University, Port Said 42526, Egypt; [b] Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Port Said University, Port Said 42526, Egypt.; [c] Faculty of Pharmacy, East Port Said National University, Port Said 42526, Egypt.
Correspondence: rogy.reda@pharm.psu.edu.eg

ARTICLE INFO

Article history :
Received 30 April 2025
Received in revised form
7 May 2025
Accepted 9 May 2025
Available online xxxx

Keywords: Hepatitis C Virus (HCV), Green chemistry, nanoparticles, microwave

ABSTRACT

One of the leading causes of illness in the globe is the hepatitis C virus (HCV), especially because it can lead to chronic liver disorders. The pharmaceutical industry has undergone radical change because of recent developments in green chemistry, which have introduced efficient, economical, and environmentally friendly synthesis methods. This review emphasizes the use of green synthesis techniques in the creation of anti-HCV medications such as daclatasvir, ribavirin, and elbasvir. In terms of increasing yield, decreasing toxicity, and using less energy, methods including chemoenzymatic reactions, continuous-flow synthesis, and microbial biotransformation have shown remarkable results. The contributions of particular green techniques, such as Pd/C-catalyzed microwave-assisted processes and nanoparticle-based sensing systems, to the optimization of antiviral production and development of important anti-HCV drugs with the goal of striking a balance between environmental responsibility and therapeutic efficacy are examined. These strategies highlight how important it is to combine sustainability with innovative therapeutics in the battle against HCV.

Introduction

Worldwide, the Hepatitis C virus (HCV), that is a member of the family Flaviviridae, is still the primary cause of liver-related illness and death. Although most cases lead to Prolonged liver conditions such as carcinoma of the liver, fibrosis, and hepatitis, acute infections can sometimes go away on their own[1]. Scientific advancements since the 1989 discovery of HCV have made major strides possible in both detection and treatment. After a period when interferon (IFN)-based therapy predominated, targeted medications, often referred to as direct-acting antiviral drug

Doi: 10.21608/odr.2025.380593.1052

(DAA)-based therapy—were created[2]. Within groups of patients that been previously challenging to manage (such as individuals with compensating hepatic disease, individuals with HIV and HCV concurrent infections, and those with impaired kidney function), Most individuals with persistent HCV infection are healed by these regimens[3]. A cure is characterized by the absence of recognizable HCV RNA levels in bloodstreams for twenty1-four weeks or, lately, for twelve weeks beyond the completion of treatment, or a sustained virological response (SVR)[4]. Since DAAs can generate significant levels of sustained virological reaction (SVR) even with complex patient groups, they have supplanted interferon-based treatments[5]. When compared to previous IFN-based regimens, DAA treatment improves patients' quality of life (QOL)[6]. Diagnostic tools include genotyping, resistance-associated substitutions (RAS) analysis, blood HCV RNA levels, and anti-HCV antibody testing[7]. Novel DAA-based treatment regimen failures are molecularly caused by RASs, which are viral RNA amino acid changes[8]. Green chemistry, which emphasizes sustainability, efficiency, and safety, is being used by the pharmaceutical industry to transform the way drugs are discovered, made, and delivered. It aims to reduce the adverse environmental effects of pharmaceutical manufacturing while upholding the highest standards of patient care and safety[9]. Green chemistry is a cutting-edge field that encourages the creation of safer, cleaner, and more sustainable chemical processes, and the pharmaceutical sector is adopting it concurrently[10]. development of important anti-HCV drugs with the goal of striking a balance between environmental responsibility and therapeutic efficacy[11]. This approach benefits the environment and raises the cost-effectiveness and ethical standards of drug manufacturing. Green chemistry encourages the adoption of innovative synthetic production processes that minimize waste and hazardous material usage[12]. For instance, traditional drug manufacturing usually involves several energy-intensive processes that produce dangerous byproducts[13]. Green chemistry uses catalytic techniques to ensure that reactions are more efficient, clean, and selective[14]. This reduces energy consumption and the production of harmful emissions, which benefits pharmaceutical companies financially[15]. This review paper will discuss the applying of green chemistry in the production of anti HCV drugs, including lamivudine, ribavirin, silver entecavir, elbasvir, and ombitasvir. This review focuses on the green synthesis approaches employed in the development of key anti-HCV medications, aiming to balance therapeutic efficacy with environmental responsibility.

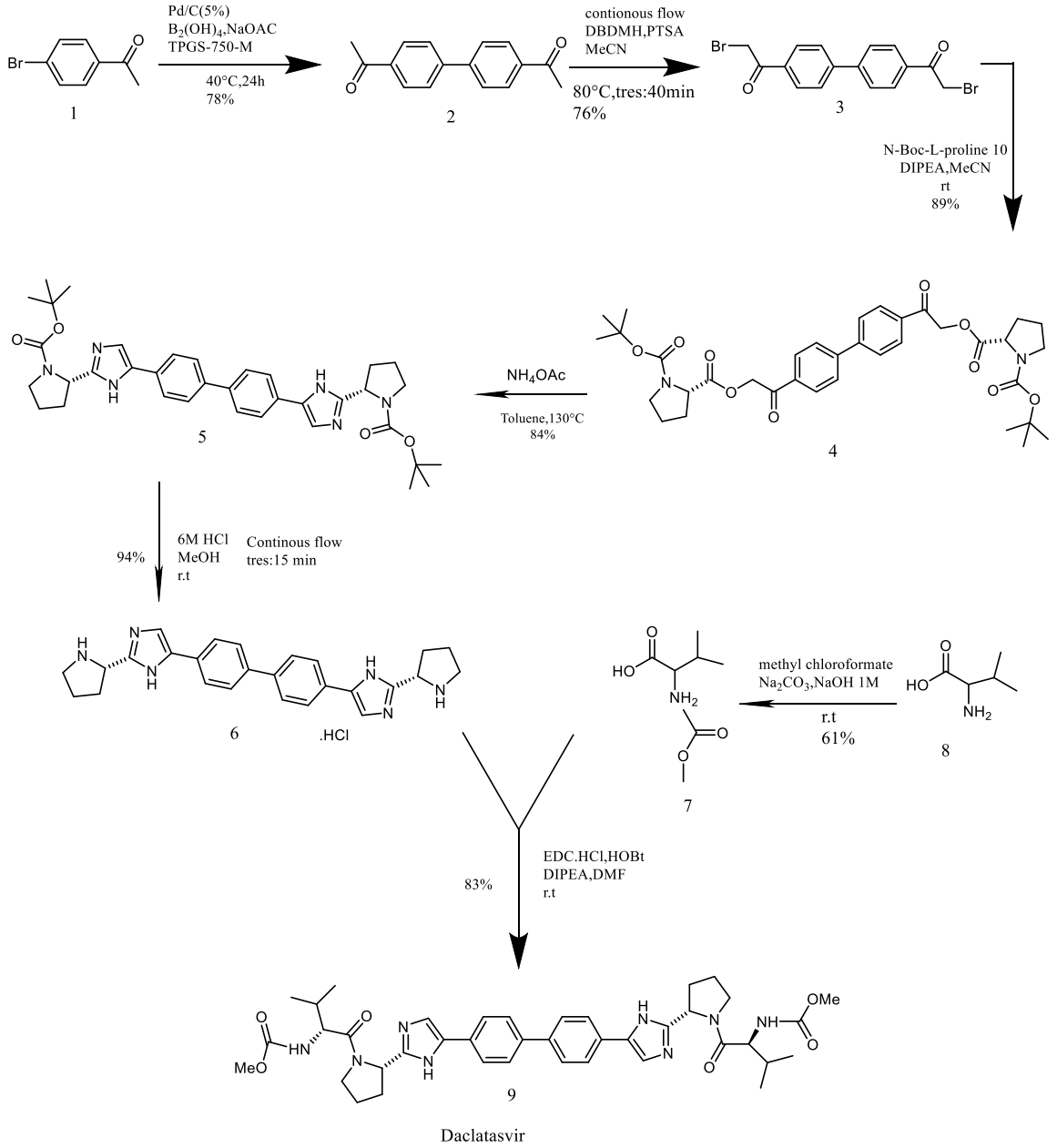
Green Synthesis

Phase transfer catalysts are activated using ligand-free Pd/C and microwave assistance for the sustainable synthesis of diaryl compounds and the antiviral medication daclatasvir in water. A novel, sustainable, Pd/C without ligands-catalyzed process of the diaryl compound production in water with reduced loading of catalysts has been created. With a mild reaction temperature of 40°C, 56–81% of the required diaryl compounds were produced. Phase transfer activation catalyst when exposed to microwave radiation accelerated the reaction and shortened its duration from 24 hours to 30 minutes. This technique was brilliantly used to create the antiviral medication daclatasvir in conjunction with continuous-flow bromination and Boc deprotection processes [16]. Using this approach, the synthesis of daclatasvir began with 4-bromacetophenone, yielding the required dimer product 8b in 78%. Using a modified process, the bromo compound 3 was produced in a 76% yield. Using NBS, Kappe and colleagues carried out the daclatasvir bromination phase. Since two moles of bromine might be released by one mole of DBDMH, creating an atom economy. method, we chose to employ it instead of NBS. To increase yield and shorten cycle time, A flow reactor was used to test this procedure. Our lab is developing innovative synthesis techniques including continuous-flow API synthesis techniques. At RT, the reaction was initially carried out in a flow reactor; however, it was unable to produce the intended product. The intended When the reaction temperature was increased to 80 °C and the residence time was adjusted to 40 minutes, dibromo compound 3 was generated in a 76% yield. N-Boc-L-proline and bromo compound 9 interacted to form compound 4 (89% yield), per a reported procedure, which was then cyclized to produce compound 5 (84% yield) [25]. The 6 M HCl was used to deprotect the Boc-group of 5, and the procedure was conducted in a flow reactor with residence duration of 15 minutes (94%). The target chemical 6 was separated. reactor for this reaction and the 94% yield of the desired free amine compound 6. When amine compound 6 and amino acid 7 were coupled with EDCI and HOBt, the intended daclatasvir was formed in an 83% yield[16]

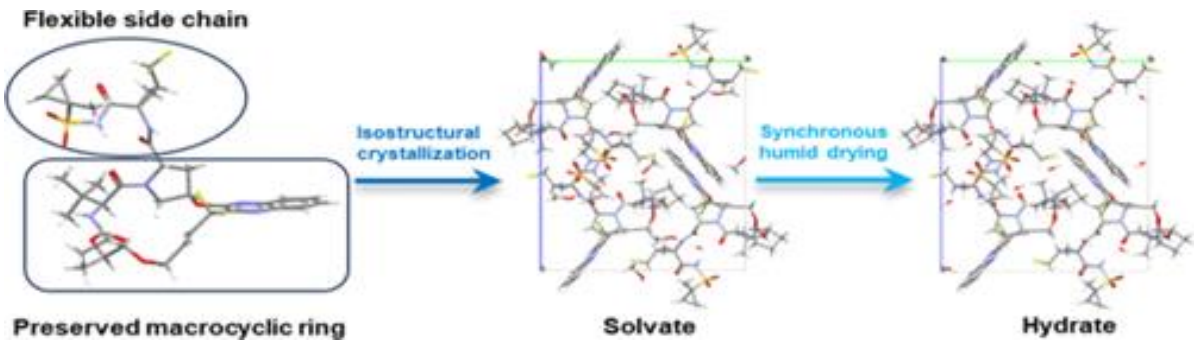
Moving forward with the Continuous Production of Daclatasvir

Doi: 10.21608/odr.2025.380593.1052

Here, we present a continuous flow synthesis of imidazoles modified with 1H-4. at high temperature and high pressure, beginning with carboxylic acids and a-

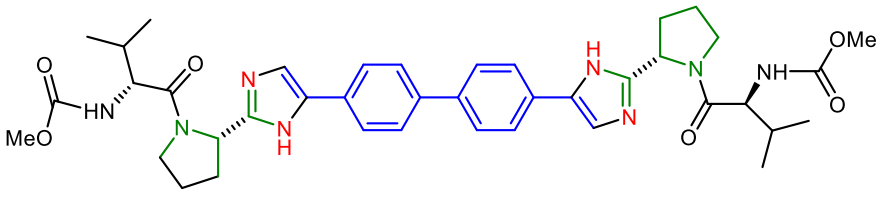


SCHEME 1. Key processes in the synthesis of daclatasvir include the continuous-flow bromination of 8b, the deprotection of amine 12, and the Pd/C-catalyzed homocoupling reaction in water. 1,3-Dibromo-5,5-Dimethylhydantoin (DBDMH)

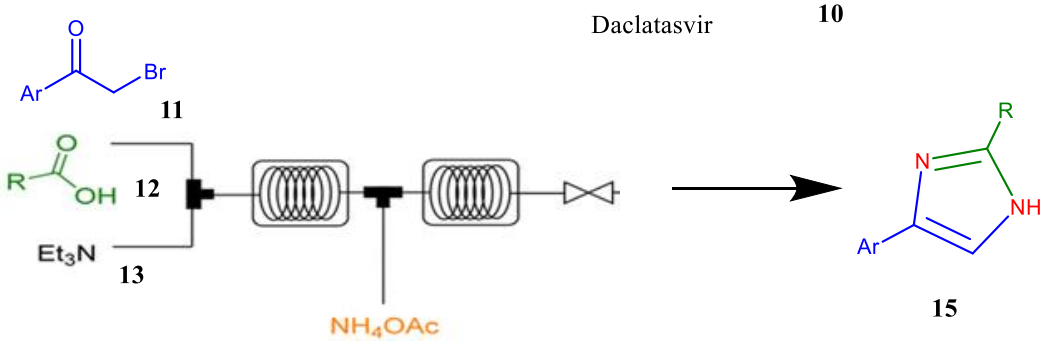


Doi: 10.21608/odr.2025.380593.1052

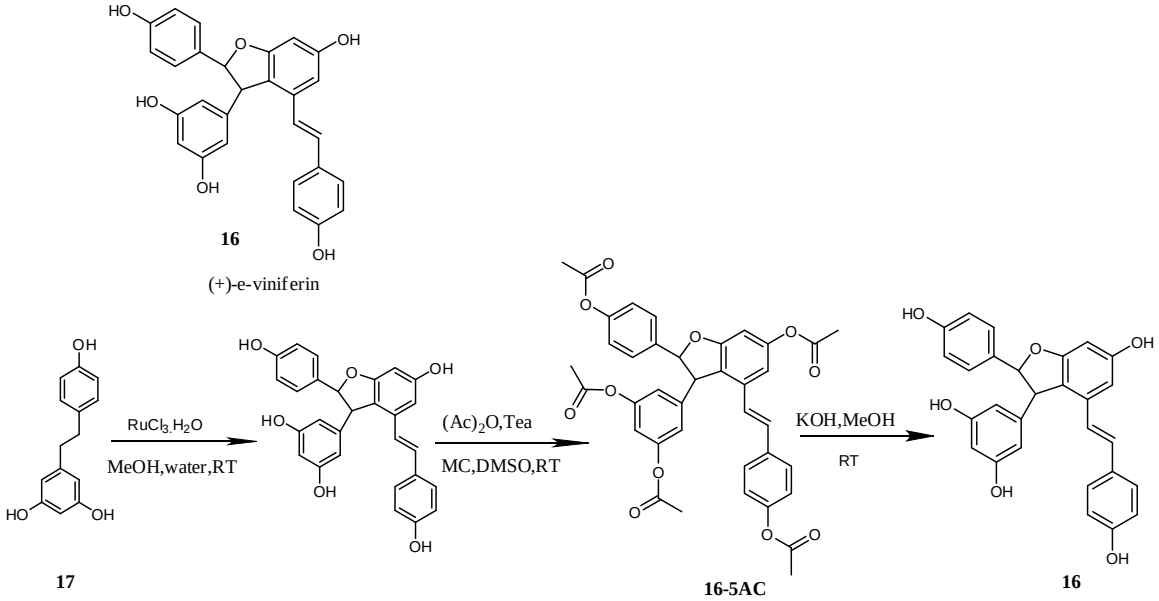
FIGURE 1. Experimental techniques in the development of drying processes and the selection of marketable solid forms. Purification from Plants, Chemical Synthesis, and In Vitro/In Vivo Assessment of Viniferin, a Resveratrol Dimer, as an Inhibitor of HCV Replication



Daclatasvir **10**



SCHEME 2. The formation of the α-acyloxy ketone from bromoacetophenone and the carboxylic acid marked the beginning of the reaction cascade.



SCHEME 3. (16) (+)-ε-viniferin's chemical structure, three distinct forms of (+)-ε-viniferin which were chemically synthesized with either penta-acetylation (16-5Ac) or no acetylation (16) and one that was extracted from the grapevine root (EVF) (C) The technique of making SVF-5Ac and SVF from resverat organically the anti-hepatitis B virus properties of therapeutic herbs.

bromoacetophenones. Important components used in the production of NS5A inhibitors, the most well-known of which being daclatasvir, are 1H-4-aryl imidazoles. The reaction chain started when the carboxylic acid and a-bromoacetophenone combined to generate the a-acyloxy ketone. The following condensation was carried out to the

Doi: 10.21608/odr.2025.380593.1052

1H-4-substituted imidazole using ammonium acetate in a high-temperature stainless steel coil reactor. For this reaction to yield the high-purity imidazole that is required, high temperatures (> 150 °C) were necessary. One of the most important enabling technologies for improving processes and lessening The amplification of chemical reactions in continuous flow reactors is one way that chemical processes affect the environment[17]. The

Table 1. Medicinal plants and their activity against hepatitis virus[20].

Family	Medicinal plant used	Viruses
Lamiaceae	Mentha longifolia	Hepatitis A virus
Lamiaceae	Ocimum basilicum	
Urticaceae	Boehmeria nivea	Hepatitis B virus
Euphorbiaceae	Phyllanthus amarus, Phyllanthusanus	
Mimosoideae	Acacia nilotica	Hepatitis C virus
Burseraceae	Boswellia carterii	
Myrsinaceae	Embelia schimperi	
Fagaceae	Quercus infectoria	
Apiaceae	Trachyspermum ammi	
Piperaceae	Piper cubeba	
Myrtaceae	Syzygium aromaticum	
Asteraceae	Silybum marianum	
Zingiberaceae	Zingiber officinale	
Saxifragaceae	Saxifraga melanocentra	
Gentianaceae	Swertia patens, Swertia chirayita	Hepatitis B virus
Euphorbiaceae	Euphorbia sikkimensis	HIV
Oleaceae	Ligustrum purpurascens	Influenza virus

necessary temperature was swiftly reached by heating the reaction mixture thanks to the continuous flow configuration. Additionally, headspace was removed, and the liquid phase's volatile chemical content was raised by operating at a higher pressure (17 bar). After barely two to five minutes of residence, the imidazole synthesis was finished in the coil reactor. A straightforward extraction process was used to isolate the very pure compounds following the two-step reaction. The optically pure chemicals were imidazoles made from chiral amino acids. As possible prodrugs, 25 new Analogues (8a–8y) of imidazole N–H substituted Daclatasvir (BMS-790052, DCV) were developed and synthesized. Potency and pharmacokinetic (PK) characteristics were enhanced through structural alterations. A replicon of the hepatitis C virus (HCV) genotype 1b was used to test each target drug. The anti-HCV activity of compound 8t, which was replaced with 2-oxoethyl acetate, was comparable to that of Daclatasvir, the lead chemical (EC50 = 0.08 nM). Additionally, when prodrugs were administered in vivo, the parent compound's exposure was comparable, demonstrating the usefulness of prodrug 8t. Prodrug 8t was the best option for a slower and longer-acting version of daclatasvir, according to PK studies[17].

1- Glecaprevir Development: Crystal Structures, Conformations, and Effective Solid-Solid Conversion for a Highly Polymorphic

A powerful NS3/4A protease inhibitor with 18 members, glecaprevir (GLE) is used to cure infections caused by the hepatitis C virus (HCV). This work uses a combination of advanced computational and experimental approaches to assess the molecular conformations, polymorphism, and importance of crystal structural features of GLE in the context of commercial solid form selection and drying process development. The presence or lack of an intramolecular hydrogen bonding interaction between the side chain and macrocyclic ring of GLE is found to significantly influence its capacity to adopt various conformations. Thus, two different distinct solvents can cause distinct kinds of GLE forms to crystallize. due to two different molecular conformations, bound-chain and free chain[18].Furthermore, because the core macrocyclic ring conformation is preserved from solution to solid phases, isostructural forms of GLE, such as those that are highly relevant to drug O mixed solvate Form 2, crystallize readily. Detailed 2substance process hydrate form 1 and MeOH/H evaluations of dynamic vapor sorption isotherms and energetics of host–guest solvent interactions are used to develop a comprehensive understanding of the desolvation and hydration behavior of GLE crystals. An efficient and dependable synchronous humid drying method that achieves constant form control and direct solid-solid conversion from Form 2 to Form 1 with fewer process-induced issues is developed by completely utilizing the properties of isostructural solvates and hydrates[18].

1- Building a thorough grasp of Two advantages of the knowledge gathered from this study are the development of an efficient and trustworthy isolation and drying process as well as the correlations between the structure and properties of crystalline macrocycle medicines. The new DAA glecaprevir/pibrentasvir (G/P; 300 mg/120 mg) has anti-hepatitis C viral qualities.[18]. **Viniferin, a resveratrol dimer, is purified from plants,**

Doi: 10.21608/odr.2025.380593.1052

chemically synthesized, and evaluated in vitro and in vivo as an inhibitor of HCV replication.

A class of resveratrol multimers known as oligostilbenoid molecules exhibits several antimicrobial properties by blocking vital host and viral enzymes and neutralizing harmful oxidants. We found a number of oligostilbenoid substances to be powerful in our earlier investigation[19]. Replication inhibitors for the HCV or hepatitis C virus. Vitisin B, a resveratrol tetramer, showed the most anti-HCV action by inactivating the viral helicase NS3 (IC50 = 3 nM) (EC50 = 6 nM and CC50 > 10 μM). However, its development as a potential treatment for HCV was halted due to its inherent issues, which include limited in vivo absorption, low water solubility, and poor stability. To obtain around these restrictions, we looked at the resveratrol dimer (+)-ε-viniferin as a substitute[19].Using a recently developed synthesis process, we created three distinct forms Of (+)-ε-viniferin, two were chemically synthesized with either no acetylation (SVF) or penta-acetylation (SVF-5Ac), and one was isolated from the grapevine root (EVF)[19]. Used HCV replicon cells of genotypes 1b and 2a to verify their minimal cytotoxicity and anti-HCV replication activity. Because of their anti-HCV replication action, they also markedly reduced the expression of viral proteins. Furthermore, in vitro confirmation of EVF's anti-HCV NS3 helicase activity was obtained. The last thing we demonstrated was that SVF outperforms vitisin B in terms of pharmacokinetic characteristics. All things considered, these three viniferin formulations' advantageous pharmacokinetic and antiviral characteristics call for additional research on them as potential members of a novel class of anti-HCV medications[19]. Another important step in promoting and using natural products is the Natural Health Product Regulation of Canada. The world's rapidly growing population is today facing several infectious diseases that are connected to hepatitis A, B, and C viruses, human immunodeficiency virus, influenza virus, dengue virus, and newly emerging viruses. A dangerous and frequently spread liver disease is caused by hepatitis B virus. The hepatitis B virus (HBV) infects millions of individuals worldwide. Patients with an HBV infection have adverse side effects and ineffectiveness from the hepatitis B drugs now available on the market. Pharmaceutical firms are searching for suitable and natural HBV inhibitors. Since individual plants have a valuable pool. Researching and using plants as a source of novel treatments for this infectious disease is essential because they contain active compounds that may help produce pharmaceutical-grade peptides or proteins. Nevertheless, nothing is now known about medicinal plants' antiviral properties[20].

The world's flora is abundant in many different plant species with a range of active components that merit greater international attention. The world flora's potential for medicine is currently unknown. Therefore Comprehensive studies on the medicinal properties of plants against different viruses, including HBV, are necessary to uncover the priceless therapeutic value for the treatment of infectious disorders, is crucial[20].

Pharmaceutical and herbal companies currently use a variety of medicinal plants to make medications and cosmetics, and plant-derived medicine has become well-known worldwide. Knowing the active ingredients linked to a plant's therapeutic qualities may assist in revealing important details for the development of potent disease-curing treatments. However, there haven't been any noteworthy attempts to use molecular approaches to uncover the antiviral properties of therapeutic plants yet. More phytochemical and toxicological knowledge could be gained for the eventual discovery of potent anti-HBV medications by thoroughly elucidating the antiviral properties of therapeutic herbs [20].

Conclusion

The integration of green chemistry into the synthesis of anti-HCV drugs offers a promising pathway toward sustainable and ethical pharmaceutical development. Through the adoption of microbial biotransformation, continuous-flow synthesis, and environmentally friendly reagents, the industry can significantly reduce its ecological footprint while maintaining high therapeutic standards. Continued exploration and optimization of green methods are essential for ensuring future antiviral therapies are not only effective but also aligned with global sustainability goals.

Ethical consideration

All the participants in this study gave their informed permission.

Conflicts of Interest

No conflicts of interest are disclosed.

The authors reported no potential conflict of interest

References

[1] El-Feky, S., *Hepatitis C virus (HCV) infection afflicts many million people worldwide, with the great majority of patients with acute hepatitis C developing chronic hepatitis C infection. It can result in liver cirrhosis, hepatitis C failure or hepatocellular carcinoma (HCC), which are responsible for many thousands of deaths each year. In Egypt, HCC contributes about 2.3% of all cancers with a median age of 53 years.*

Doi: 10.21608/odr.2025.380593.1052

[2] Florian, J., et al., *Direct-acting antiviral drugs for the treatment of chronic hepatitis C virus infection: Interferon free is now.* Clinical Pharmacology & Therapeutics, 2015. **98**(4): p. 394-402.
[3] Bonacci, M., et al., *Challenges in special populations: HIV/HCV coinfection, liver transplantation and patients with end-stage renal disease.* Digestive Diseases, 2016. **34**(4): p. 317-326.
[4] Pearlman, B.L. and N. Traub, *Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more.* Clinical infectious diseases, 2011. **52**(7): p. 889-900.
[5] Meshram, R.J., G.H. Kathwate, and R.N. Gacche, *Progress, evolving therapeutic/diagnostic approaches, and challenges in the management of hepatitis C virus infections.* Archives of Virology, 2022. **167**(3): p. 717-736.
[6] Lanini, S., et al., *Impact of new DAA therapy on real clinical practice: a multicenter region-wide cohort study.* BMC infectious diseases, 2018. **18**: p. 1-12.
[7] Naseer, M., H. Chela, and A. AlJuboori, *Laboratory and Molecular Diagnosis of Hepatitis C and Resistance Testing.* Viral Hepatitis: Chronic Hepatitis C, 2019: p. 25-58.
[8] Onorato, L., et al., *Virological factors associated with failure to the latest generation of direct acting agents (DAA) and re-treatment strategy: a narrative review.* Viruses, 2021. **13**(3): p. 432.
[9] Watson, W.J.W., *How do the fine chemical, pharmaceutical, and related industries approach green chemistry and sustainability?* Green Chemistry, 2012. **14**(2): p. 251-259.
[10] Welton, T., *Cutting-edge research for a greener sustainable future.* Green Chem, 2013. **15**: p. 550-583.
[11] Craxi, L., et al., *Prioritization of high-cost new drugs for HCV: making sustainability ethical.* European review for medical and pharmacological sciences, 2016(20): p. 1044-1051.
[12] Ncube, A., et al., *Circular economy and green chemistry: the need for radical innovative approaches in the design for new products.* Energies, 2023. **16**(4): p. 1752.
[13] Ogbuagu, O.O., et al., *Sustainable pharmaceutical supply chains: Green chemistry approaches to drug production and distribution.* IRE Journals, 2024. **8**(4): p. 761-767.
[14] Meurig Thomas, J. and R. Raja, *Designing catalysts for clean technology, green chemistry, and sustainable development.* Annu. Rev. Mater. Res., 2005. **35**(1): p. 315-350.
[15] Richie, C., *Environmental sustainability and the carbon emissions of pharmaceuticals.* Journal of Medical Ethics, 2022. **48**(5): p. 334-337.
[16] Swain, S.P. and M. Mhate, *Ligand-free Pd/C-catalysed and microwave-assisted activation of phase transfer catalysts for sustainable synthesis of biaryl compounds and antiviral drug daclatasvir in water.* 2024.
[17] Carneiro, P.F., et al., *Process intensified flow synthesis of 1 H-4-substituted imidazoles: Toward the continuous production of daclatasvir.* ACS Sustainable Chemistry & Engineering, 2015. **3**(12): p. 3445-3453.
[18] Chen, S., et al., *Development of Glecaprevir: Conformations, Crystal Structures, and Efficient Solid–Solid Conversion for a Highly Polymorphic Macrocyclic Drug.* Crystal Growth & Design, 2024. **24**(20): p. 8270-8284.
[19] Lee, S., et al., *Plant-derived purification, chemical synthesis, and in vitro/in vivo evaluation of a resveratrol dimer, viniferin, as an HCV Replication inhibitor.* Viruses, 2019. **11**(10): p. 890.
[20] Siddiqui, M.H., et al., *A mini-review of anti-hepatitis B virus activity of medicinal plants.* Biotechnology & Biotechnological Equipment, 2017. **31**(1): p. 9-15.

Doi: 10.21608/odr.2025.380593.1052