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Boosting the human antiviral response in conjunction with natural plant products

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The increasing prevalence of viral infections and the emergence of drug-resistant or mutant strains necessitate the exploration of novel antiviral strategies. Accumulating evidence suggests that natural plant products have significant potential to enhance the human antiviral response. Various plant natural products (PNPs) known for their antiviral properties have been evaluated for their ability to modulate immune responses and inhibit viral infections. Research has focused on understanding the mechanisms by which these PNPs interact with the human immune system and their potential to complement existing antiviral therapies. PNPs control compounds such as alkaloids, flavonoids, terpenoids, and polyphenols to promote antiviral cytokine synthesis, increase T-cell and macrophage activity, and activate antiviral genes. Studies have investigated the molecular interactions between PNPs, viruses, and host cells, exploring the potential of combining PNPs with conventional antiviral drugs to enhance efficacy. However, several challenges remain, including identifying, characterizing, and standardizing PNP extracts, optimizing dosages, improving bioavailability, assessing long-term safety, and navigating regulatory approval. The promising potential of PNPs is being explored to develop new, effective, and natural antiviral therapies. This review outlines a framework for an integrative approach to connect the full potential of PNPs in combating viral infections and improving human health. By combining natural plant products with conventional antiviral treatments, more effective and sustainable management of viral diseases can be achieved.

KEYWORDS

secondary metabolite, human pathogen, virus, antiviral response, immunity, plants

Introduction

Infectious diseases have shaped human civilization, with urbanization and trade increasing zoonotic pathogen spread. Major pandemics like SARS-CoV, MERS-CoV, and COVID-19 have highlighted the global health burden and socioeconomic conditions of viral infections, with COVID-19 alone causing over 180 million cases and 4 million deaths (World Health Organization, 2021), Despite advancements in immunization and drug development, many viruses still lack preventive vaccines and effective antiviral treatments, often undermined by viral escape mutants (Lin L.-T. et al.,

2014). Therefore, discovering new antiviral drugs is crucial, and natural products offer a valuable resource for these discoveries. Natural products from plants, animals, or microbes offer pharmacological benefits beyond nutrition and have long been used as medicines, hallucinogens, food additives, and fragrances.

Plants are the primary source of natural products that serve as a key source of human medicines and play a pivotal role in drug discovery and design. Various traditional medicinal practices, such as Ayurveda, traditional Chinese medicine, Kampo, traditional Korean medicine, and Unani medicine, have enlisted several kinds of plant species used for treating human diseases. Identifying active compounds in these medicines remains a source of modern drug discovery. Interestingly, the FDA approved 1,562 drugs till 2019, of which 586 (37%) are natural products or their derivatives (Newman and Cragg, 2020). Of these approved drugs, only 53 are antiviral drugs, classified into biological molecules, natural product derivatives, and mimics of natural compounds (Newman and Cragg, 2020). However, antiviral drug discovery acts slowly compared to antibiotics, probably due to the "one drug one virus" dogma. Viruses are obligatory parasites, and most naturally derived antiviral compounds inhibit viral replication and target virus-host interactions. Some natural compounds can inhibit the growth of multiple viruses that utilize a similar pathway or host factor, acting as a source for the "one drug multiple virus" consortium. Thus, the pharmaceutical industry's focus on natural products can accelerate antiviral drug discovery. In addition to aiding in drug discovery, plant natural products (PNPs), can improve human immunity. Consuming PNPs as probiotics and functional foods helps combat infections due to their bioactive compounds. These foods, rich in flavonoids, phenolics, carotenoids, vitamins, and minerals, can eliminate or inactivate viruses, boost immunity, and improve overall health. Regular intake may prevent viral replication, reduce symptom severity, low mortality rate, and speed recovery. Furthermore, PNPs function as probiotics to prevent viral infections by adhering to them and hindering host-cell communication (Singh S. et al., 2021; Saddiqa et al., 2024).

PNPs are involved in innate immunity response modulation, B-lymphocyte proliferation, and the generation of cytotoxic chemicals such as nitric oxide free radicals, T-lymphocytes, and phagocytosis activation (Vieira et al., 2024). Various *ex-vivo* and *in vivo* measures have proven that consuming PNPs enhances immunity against viruses (Elshafie et al., 2023). In this review, we discussed the role of bioactive natural products in antiviral drug discovery and highlighted their action against viral invasion based on insights from previously published studies.

Plant natural products (PNPs): an insight

PNPs have high structural diversity and unique pharmacological or biological activities due to the natural selection and evolutionary processes that have shaped their utility over hundreds of thousands of years. PNPs include a wide range of compounds, for example, Alkaloids (Nicotine, morphine, quinine), Phenolics (Flavonoids, tannins, lignans), Terpenoids (Essential oils, carotenoids, saponins), Glycosides (Cardiac glycosides, cyanogenic glycosides), Polysaccharides (Beta-glucans, pectins) (Kaur et al., 2021; Prakash et al., 2021; Thomas et al., 2021; Kumar A. et al., 2022; Al-Khayri et al., 2023; Bhatla and Lal, 2023). PNP compounds are often divided into two major classes: primary and secondary metabolites (Figure 1). Primary metabolites are vital for survival, forming key macromolecules like nucleic acids, amino acids, and sugars. Secondary metabolites, though not essential for survival, aid in the organism's competitiveness within its environment. (Bhardwaj et al., 2021; Elshafie et al., 2023). Plants produce a wide array of secondary metabolites with complex chemical compositions. These compounds are synthesized in response to various stresses and serve crucial physiological functions (Srivastava et al., 2014; Pandey et al., 2016; Srivastava et al., 2018; Pandey et al., 2019; Mishra et al., 2020; Bajpai et al., 2023; Elshafie et al., 2023). Plant secondary metabolites are classified into four major classes depending on their biosynthetic pathway: (i) phenolic groups; (ii) terpenes and steroids (iii) nitrogen-containing compounds; and (iv) sulfur-containing compounds (Prakash et al., 2021; Kumar A. et al., 2022; Al-Khayri et al., 2023; Bhatla and Lal, 2023). Due to their bioactive qualities, which can have toxicological or pharmacological impacts on humans as well as animals, many of these secondary metabolites are relevant to the drug manufacturing sector. Plant secondary metabolites have various health benefits, including immune system support, antioxidant, anti-inflammatory, neutralizing free radicals, allergy relief, cardiovascular health, neurodegenerative diseases, pain-relieving effects, and anti-carcinogenic properties (Elshafie et al., 2023).

Viral infections and human immunity

Human viral infections can seriously negatively influence society and the economy. Human viral diseases are a major global health concern due to their high morbidity and mortality rates, frequency, and potential for outbreaks (Luo and Gao, 2020; Baker et al., 2022). Viruses are tiny entities with either RNA or DNA as their genetic material, and they cannot exist without a host. Structurally, a typical virus has a lipid membrane called the viral envelope, covering a protein coat called a capsid that surrounds the genetic material (MW, 2014; Luo and Gao, 2020). Viruses reproduce by inserting their genome into the host cell, making multiple copies, and assembling new viral components within the infected cell (Roossinck, 2011; Hull, 2014). The etiologies vary due to distinct viruses, such as RNA viruses (e.g., influenza, coronaviruses) and DNA viruses (e.g., poxviruses, herpesviruses). The dsDNA (double standard DNA) viruses that infect humans have genome sizes ranging from 5 to 1,180 kb, linked to the stability of dsDNA and a low replication error rate (Payne, 2017). At the same time, ssDNA (single standard DNA) viruses have smaller genomes (2–7 Kb) and are generally non-enveloped with icosahedral capsids. Retroviruses, which include families like Retroviridae (e.g., HIV) and Hepadnaviridae (e.g., Hep B), challenge the Central Dogma of human biology (Gelderblom, 1996; Tramontano et al., 2019). Human viral infections can present with a wide variety of symptoms, from mild flu-like signs to severe respiratory distress, neurological disorders, and potentially premature death. These viral infections may be progressive, cancer-causing, latent, revived, acute, or chronic. The specific health problems vary based on the infection's progression, cellular affinity, and host cell resistance.

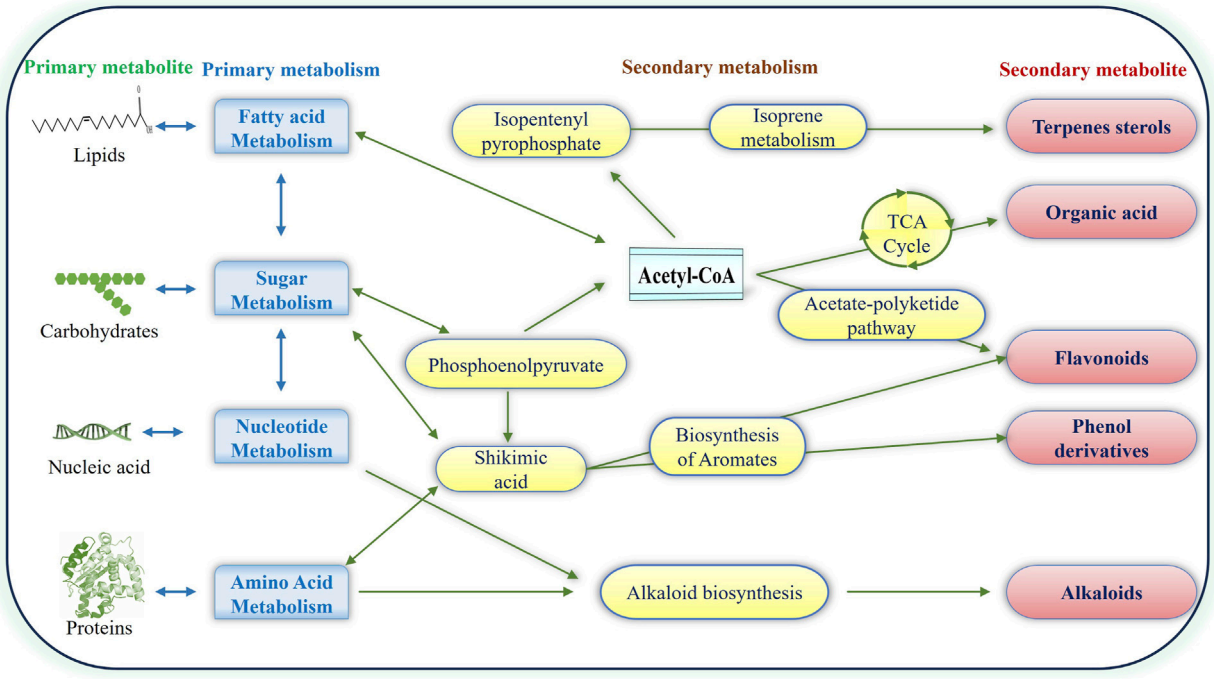

FIGURE 1
Illustration of Plant Natural Products: primary and secondary metabolites. Pathways from primary metabolites contribute to the production of terpenes, flavonoids, phenolics, alkaloids and organic acids, forming distinctive major classes of secondary metabolites.

Because of their high rates of morbidity and mortality, high frequency, and potential for outbreaks and pandemics, human viral diseases have become a major global health concern (Morales-Sánchez and Fuentes-Pananá, 2014; Prasad et al., 2017). The illnesses' etiologies differ because of distinct viruses, such as RNA viruses (e.g., G. influenza, and coronaviruses) and DNA viruses (e.g., G. Poxviruses, Herpesviruses, etc.) (Payne, 2017; Rampersad and Tennant, 2018).

The defense against pathogens is broadly classified into innate and adaptive immunity. Innate immunity is non-specific and serves as the first line of defense such as inflammatory responses and the complement system (Smith et al., 2019; Pal and Chakravarty, 2020). Adaptive immunity is specific and acquired over time, involving antibodies, lymphocytes, antigen presentation and immunological memory. Human viral infections can range from mild symptoms, like the flu, to severe respiratory issues, neurological disorders, or even death. The health impact of viral infections depends on factors like infection progression, cellular affinity, and host resistance, with infections potentially being acute, chronic, latent, or cancer-causing. (Silva et al., 2022; Brown et al., 2023).

Multiple consequences of viruses on human immunity frequently result in a compromised immune system and increased vulnerability to new infections. For example, HIV targets and destroys $CD4^+$ T cells, causing immunosuppression, while the measles virus induces "immune amnesia" by depleting memory T and B cells (Mueller and Rouse, 2008; McNab et al., 2015; Sette and Crotty, 2021). Through antigenic variation and latency, viruses have developed evasive ways to avoid the immune system being recognized. For instance, Viruses like HIV and influenza evade immunity through antigenic variation, continually mutating their surface proteins. Herpesviruses, such as HSV and EBV, enter latency within host cells, reactivating periodically to avoid detection by the immune system (Yewdell and Hill, 2002; Paludan et al., 2011; White et al., 2012; Silva et al., 2024).

Certain viruses generate proteins that directly disrupt the host's immune system, resulting in the suppression of immunological responses. Hepatitis C and other viruses produce proteins that inhibit interferon synthesis. In chronic infections like Hepatitis B and C, viruses also disrupt immune checkpoints to suppress effective T-cell responses. (Gokhale et al., 2014; Karamichali et al., 2022; Zheng et al., 2023). Prolonged viral infections result in chronic or persistent immunological activation, which could have negative consequences. Persistent infections, like Hepatitis B and C, leading to liver damage and cirrhosis (Marcellin and Boyer, 2003; Baseke et al., 2015; Ferrari, 2015). Persistent immune activation in HIV is linked deterioration of immune function (Gobran et al., 2021). Some viral infections may induce the immunopathology condition where the immune system causes tissue destruction. For example, Severe COVID-19 can trigger a "cytokine storm," causing widespread inflammation and tissue damage (Gour et al., 2021; Que et al., 2022; Panteleev et al., 2023).

Viral infections can impact various components of both the innate and adaptive immune systems. For instance, Viruses like HIV and dengue impair dendritic cell function, disrupting antigen presentation and adaptive immunity (St. John and Rathore, 2019; Constant et al., 2022; Lee et al., 2022). Some also reduce natural killer (NK) cell activity by downregulating activating ligands. HIV and Hepatitis C cause T cell exhaustion, lowering functionality, while Epstein-Barr virus (EBV) infects B cells, increasing lymphoma risk (Rouse and Sehrawat, 2010; Carty et al., 2021; Singh H. et al., 2021).

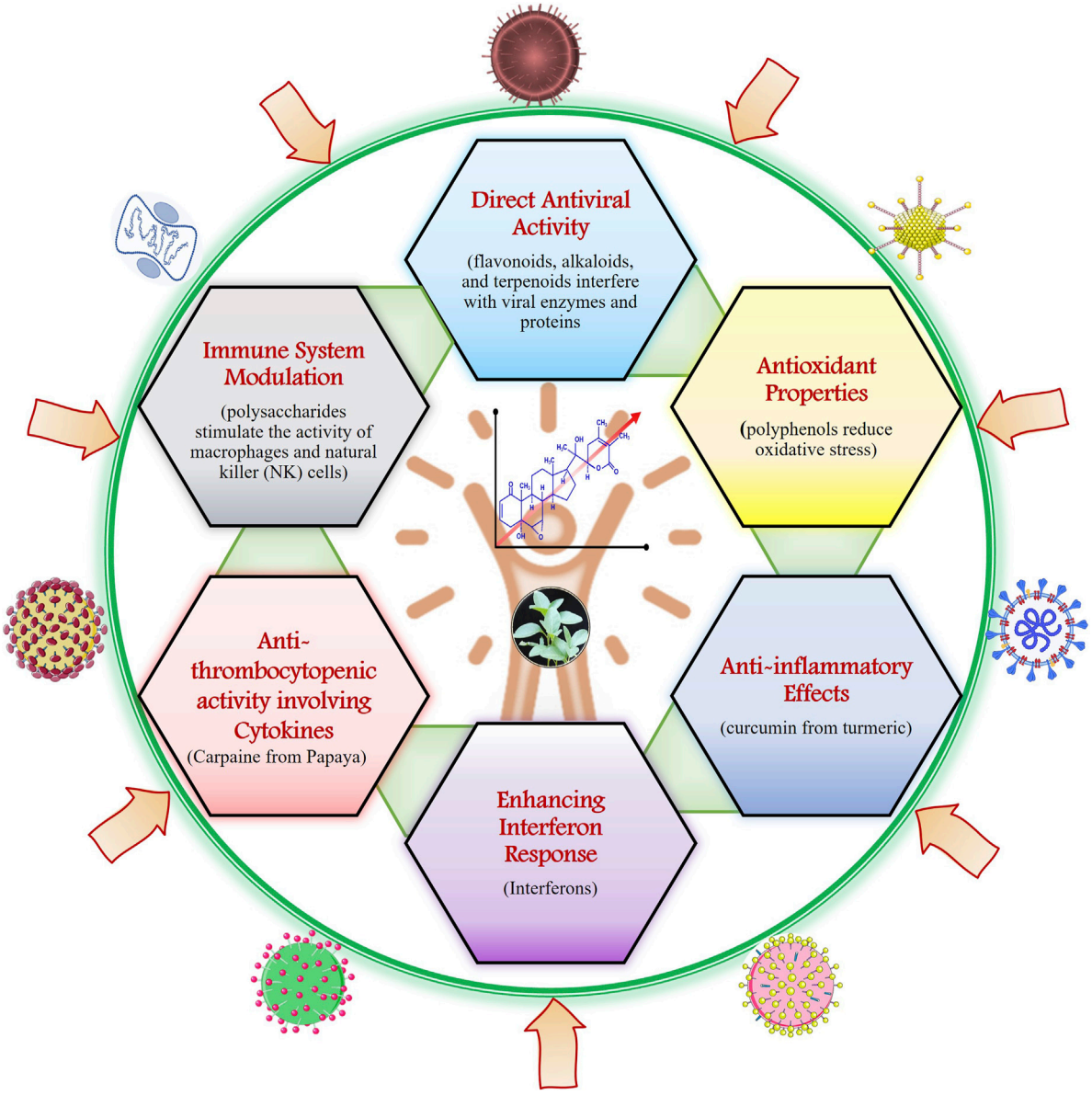

FIGURE 2
The image illustrates various mechanisms by which natural products contribute to antiviral activity and enhance immune function in the human.

Mechanisms of plant-natural products on human immunity

Plant-based natural products have been used in traditional medicine for centuries to address various health issues, including viral infections. Plant natural products (PNPs) have a significant impact on human immunity through their various bioactive compounds (Hu et al., 2024). Recently, scientific research has delved into understanding how these natural compounds boost the human antiviral response. Those mechanisms can be broadly categorized in direct antiviral activity, immune system modulation, antioxidant properties, anti-inflammatory effects, enhancement of interferon response, and anti-thrombocytopenic properties, as depicted in Figure 2 and Table 1. Firstly, direct antiviral activity involves plant compounds that inhibit viral replication. For instance, flavonoids, alkaloids, and terpenoids have been shown to interfere with viral enzymes and proteins crucial for the virus's lifecycle (Table 1). Secondly, immune system modulation is achieved by plant-derived compounds that enhance the immune system's ability to fight off infections. Some PNPs can modulate immune responses by enhancing or suppressing specific immune system components. PNPs can enhance the adaptive immune response by promoting the production and activity of T-cells and B-cells. Green tea catechins improve the proliferation and differentiation of T-cells. For example, Plant Ginseng whose active component is Ginsenosides enhances both innate and adaptive immunity and increases the activity of macrophages, NK cells, and T-cells (Ferrucci et al., 2024; Nikiema et al., 2024).

Polysaccharides from plants such as Echinacea, for example, can stimulate macrophages and natural killer (NK) cells. PNPs play a crucial role in modulating the immune system through their anti-

TABLE 1 Detail of some plant products use to control the human affecting viral diseases.

Compound	Plant source	Metabolite class	Plant organ	Virus against working	Antiviral activity	References
Alkaloid extract	*Haemanthus albiflos*	Alkaloids	Bulbs	HRV	Inhibited RNA synthesis	Husson et al. (1994)
Anisotine	*Justicia adhatoda* L.	Alkaloids	Leaf	SARS-CoV-2, HSV	Inhibit Mpro of SARS-CoV-2 which mediates the cleavage of polyprotein to matured and acquire infectivity	Chavan and Chowdhary (2014), Ghosh et al. (2021)
Berberine	*Berberis vulgaris*	Alkaloids	Plant roots, Rhizomes, and Stem bar	IAV	Impairing the export of ribonucleotides	Botwina et al. (2020)
Camptothecin, a quinoline alkaloid	*Camptotheca acuminata*	Alkaloids	Bark	EV71	Protein expression was suppressed	Wu et al. (2004)
Harman alkaloid	*Ophiorrhiza nicobarica*	Alkaloids		Herpes virus	Inhibition of replication, inhibits plaque formation and delays the eclipse phase of	Gurjar and Pal (2024)
Isoquinoline alkaloid thalimonine	*Thalictrum Simplex* L	Alkaloids	Aerial parts	Influenza A virus	by reducing the expression of virus-specific protein synthesis	Serkedjieva and Velcheva (2003)
Lycorine	*Lycoris radiate* L.	Alkaloids	Bulbs	SARS-CoV, H5N1	Block assembly, Inhibiting viral RNA-dependent RNA polymerase activity	Li et al. (2005), He et al. (2013), Jin et al. (2021)
Piperine	*Piper longum* L.	Alkaloids	Seed	VSV-IN, PIV, and HBV	Inhibit the secretion of HBsAg and HBeAg of HBV	Jiang et al. (2013), Kumari and Priya (2017)
Skimmianine	*Zanthoxylum chalybeum*	Alkaloids	Seed	Swartz and Edmonston measles virus	Suppresses virus	Olila et al. (2002)
Solamargine and michellamine B, glycoalkaloids	*Solanum khasianum*	Alkaloids	Berries	HIV.	Prevent virus multiplication	Gurjar and Pal (2024)
Oils	*Fortunella margarita*	Essential Oils	Fruit	H5N1 IAV	Antiviral plant natural products	Ibrahim et al. (2015)
Sandalwood oil	*Santalum album* Linn.	Essential Oils	Heartwood	HSV-1	Prevent adsorption	Khan Yusuf and Sen Das (2023)
Tea tree oil	Tea tree (*Melaleuca alternifolia*)	Essential Oils	Leaves	IAV	Viral adsorption inhibited	Garozzo et al. (2011)
Silvestrol is a flavagline compound	*Aglaia foveolata*	Flavaglines	Fruits and Twigs	Ebola virus, human coronavirus, MERS-CoV, Human rhinovirus A1 and poliovirus, Zika virus	Preventing protein translation	Müller et al. (2018)
5,7-dihydroxy −3,6,4-trimethoxy, flavone-7-O-α-L xylopyranosyl (1→3)-O-α-L arabinopyranosyl-(1→4)-O-β-D galactopyranoside	*Butea monosperma* (Lam.) Taub.	Flavonoids	All plant part	EV-71	Inhibit virus activity	Panda et al. (2017), Tiwari et al. (2019)
Baicalein and baicalin, flavonoids	*Scutellaria baicalensis* Georgi	Flavonoids	Dried root	HIV	It interacted with HIV envelope glycoproteins and chemokine coreceptors to prevent virus entrance into CD4 cells and limit HIV-1 replication	Li et al. (2000)

(Continued on following page)

TABLE 1 (*Continued*) Detail of some plant products use to control the human affecting viral diseases.

Compound	Plant source	Metabolite class	Plant organ	Virus against working	Antiviral activity	References
bioflavonoid quercetin	*Carica papaya*	Flavonoids	leaves	DENV	Antiviral and platelet-protective properties	Shrivastava et al. (2022)
Calanolide A	*Calophyllum lanigerum*	Flavonoids	Leaves and twigs	HIV-1	Inhibits reverse transcriptase	Buckheit et al. (1999)
Camelliiatannin	*Camellia japonica*	Flavonoids	Pericarp	HIV	Prevent virus attachment and penetration.	Park et al. (2002)
Epigallocatechin-3-gallate, epicatechin gallate, epicatechin and catechin	Camellia sinensis (L.) Kuntze	Flavonoids	Leaf	HIV, HSV-I, IAV, HCV, HBV, VSV, Reovirus, DENV, JEV, CHIKV, ZIKV, TBEV, EV71, Rotavirus	Inhibit influenza virus replication Inhibit reverse transcriptase	Song et al. (2005), Xu et al. (2017)
Flavonol iridoid glycosides luteoside	*Barleria prionitis*	Flavonoids	Leaves	RSV	Inhibit virus actvity	Chen et al. (1998), Gurjar and Pal (2024)
Hesperidin, luteolin, and vitamin C	*Citrus sinensis* (L.) Osbeck	Flavonoids	Fruit	HAV, SARS-CoV-2	Inhibit, spike protein formation	Battistini et al. (2019), Bellavite and Donzelli (2020), Goyal et al. (2020)
Kaempferol-3-O-(6″-O-Ep- coumaroyl)- β-D-glucopyranoside	*Bombax ceiba* L.	Flavonoids	Flower	RSV, SARS-CoV-2	Inhibit cytopathic effect of RSV	Zhang et al. (2003), Schwarz et al. (2014)
Mangiferin	*Mangifera indica* L.	Flavonoids	Fruit	Human influenza virus, HSV-I, HIV	Inhibit HSV-1 virus duplication	Al-rawi et al. (2019)
(+)-cycloolivil-4′-O-β-dglucopyranoside, swertiachiralatone A, swertiachoside A, swertiachirdiol A, and swertiachoside B	*Swertia angustifolia* var. pulchella (D. Don) Burkill	Glycosides	Whole plant	HBV, HSV-I	Inhibit HBsAg and HBeAg secretion and HBV DNA replication	Verma et al. (2008), Zhou et al. (2015)
(+)-pinoresinol 4-O-(6″-O-vanilloyl)-β-D-glucopyranoside 6′-O-vanilloyltachioside 6′-Ovanilloyl- isotachioside	*Calotropis gigantean* (L.) Dryand.	Glycosides	Latex	H1N1	Inhibit NF-κB pathway and viral ribonucleoproteins	Parhira et al. (2014)
Forsythoside A	*Forsythia suspensa*	Glycosides	Fruit	H1N1	Inhibitory of viral replication	Law et al. (2017)
Geraniin and 1,3,4,6-tetra-O-galloyl-betad- glucose (1346TOGDG)	*Phyllanthus urinaria*	Glycosides	Acetone extract	HSV-1, HSV-2	Suppressed virus multipliaction	Yang et al. (2007)
Maltol 60-b-D-apiofuranosyl-b-Dgluco- pyranoside, and grevilloside G	*Hedyotis scandens* Roxb.	Glycosides	Whole plant	RSV	Inhibit virus actvity	Wang et al. (2013)
Phyllanthin, and hypophyllantin	*Phyllanthus niruri* L.	Glycosides	Whole plant	HBV, WHV, HCV	Bind to protein of HCV leading to interference in viral entry to host cells	Tan et al. (2013), Wahyuni et al. (2019)
Podophyllotoxin	*Podophyllum peltatum* L.	Glycosides	Aquous extract	HSV-1		Bedows and Hatfield (1982)
Progoitrin	*Isatis indigotica*	Glycosides	Sun-dried roots	H1N1	Neutralize the influenza virus strain	Nie et al. (2020)
Torvoside H	*Solanum torvum*	Glycosides	Fruit	HSV-1	Inhibit virus activity	Arthan et al. (2002)
Anolignan A Anolignan B	*Anogeissus acuminata* (Roxb. Ex DC.) Wall. ex Guillem. & Perr	Lignans	Stem	HIV	Inhibit HIV-I reverse transcriptase	Rimando et al. (1994), El-Ansari et al. (2020), Bachar et al. (2021)

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TABLE 1 (*Continued*) Detail of some plant products use to control the human affecting viral diseases.

Compound	Plant source	Metabolite class	Plant organ	Virus against working	Antiviral activity	References
Lignans like Schizarin B, Taiwanschirin D, and Rhinacanthin E and F	*Justicia procumbens*, *Pelargonium peltatum*, *Kadsura matsudai*	Lignans	Different plant part	HIV, Hepatitis B, Influenza A	Preventing the virus from replicating.	Bekhit and Bekhit (2014), Gurjar and Pal (2024)
Matairesinol and harman	*Symplocos setchuensis*	Lignans	Stems	HIV	Prevent virus replication	Ishida et al. (2001)
Strictinin, shephagenin, and hippophaenin	*Shepherdia argentea*	Lignans	Leaf	HSV-1, HIV	Reverse transcriptase inhibitors and inactivating transport proteins	Yoshida et al. (1996), Gurjar and Pal (2024)
Trychnobiflavone	*Strychnos pseudoquina*	Lignans	Stem bark	HSV-1	Reduced HSV-1 protein expression	Thomas et al. (2021)
Shuanghuanglian	Chinese traditional medicine extracted from the herbs *Lonicera japonica*, *Scutellariia baicalensis* and *Forsythia suspense*	Mixture	Mixture of many plants	SARSCoV-2	Antiviral activities in a cell-based system	Su et al. (2020)
Meliacine, a cyclic peptide	*Melia azedarach*	Peptides	leaf	Foot and mouth disease virus VSV, and HSV-I	Inhibition of foot and mouth disease virus	Wachsman et al. (1998)
(+)-catechin, and protocatechuic acid	*Albizia procera* (Roxb.) Benth.	Phenolics	Bark	HIV	Inhibit integrase enzyme of human influenza virus-I	Panthong et al. (2015)
Chrysophanate and chrysophanic acid	*Pterocaulon sphacelatum* and *Dianella longifolia*	Phenolics		Poliovirus 2 and 3	Impede the replication	Gurjar and Pal (2024)
Coumarins (2H-chromen-2-on)	Tonka beans, liquorice, cassia, etc	Phenolics	Different plant part	HSV-1	Stimulate macrophages	Hassan et al. (2016)
Coumestan	*Eclipta prostrata* L.	Phenolics	Leaf	HCV	Inhibit HCV NS5B protein leading to RNA replication	Kaushik-Basu et al. (2008)
Curcumin	*Curcuma longa*	Phenolics	Rhizome	HBV, SARS-CoV-2, HIV, IAV, DENV, CHIKV, VSV, ZIKV, Kaposi sarcoma associated HSV, RSV	Inhibiting HCV protein expression, and replication of other viruses	Kim et al. (2009), Chen et al. (2012), Jennings and Parks (2020), Sharifi et al. (2020), Bachar et al. (2021), Thimmulappa et al. (2021)
Eugeniin	*Syzygium aromaticum* L.	Phenolics	Clove	HSV-1, COVID-19	-	Vicidomini et al. (2021), Gurjar and Pal (2024)
Feralolide, 9-dihydroxyl-2-O-(z)- cinnamoyl-7-methoxy-aloesin, aloeresin, quercetin, catechin hydrate, and kaempferol	*Aloe vera* (L.) Burm.f.	Phenolics	Leaf	SARS-CoV-2, H1N1, H3N2	Inhibit the main protease (3CLpro) responsible for the replication of SARS-CoV-2	Choi et al. (2019), Mpiana et al. (2020)
Geraniin	*Phyllanthus amarus*	Phenolics	Leaf	HIV	Blocks reverse transcriptase	Notka et al. (2004)
Honokiol	*Magnolia officinalis*	Phenolics	Bark	HCV	Interfering with the HCV life cycle	Gurjar and Pal (2024)
Hypericin	*Hypericum perforatum* L.	Phenolics	Leaves	SARS-CoV-2	Direct virus-blocking effect against SARS-CoV-2 virus particles	Mohamed et al. (2022)
Indole-3-carboxylic acid, dihydroxyoleanoic acid, and Begonanline	*Begonia nantoensis*	Phenolics	Rhizome	HIV	Inhibit virus replication	Wu et al. (2004)

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TABLE 1 (*Continued*) Detail of some plant products use to control the human affecting viral diseases.

Compound	Plant source	Metabolite class	Plant organ	Virus against working	Antiviral activity	References
Oligophenols	*Stylogne cauliflora*	Phenolics	Plant extract	HCV	Inhibit protease activity	Cadman (1959), Hegde et al. (2003), Gurjar and Pal (2024)
Oxyresveratrol	*Artocarpus lakoocha* and *Millettia erythrocalyx*	Phenolics	Heartwood and leaves	HSV, HIV-1	Effective inhibitor of poliovirus genomic	Likhitwitayawuid et al. (2005)
Phenanthrene	*Bletilla striata*	Phenolics	Rhizomes	H3N2	Reduction in transcription of viral matrix protein mRNA	Shi et al. (2017)
Polyphenols	*Geranium sanguineum* L.	Phenolics	Plant extract	SARS-CoV-2, Herpes virus	Hindering viral replication by inhibiting enzymes like DNA polymerase and reverse transcriptase	Abarova et al. (2024), Gurjar and Pal (2024)
Polyphenols and proanthocyanidins	*Hamamelis virginiana*	Phenolics	Bark	HSV-1, HIV-1	Exhibit reverse transcriptase activity	Erdelmeier et al. (1996)
Proanthocyanidin A-1	*Vaccinium vitis-idaea*	Phenolics	Dried whole plants	HSV-2	Attachment and infiltration	Cheng et al. (2005)
Eugenol, 1,8- cineole and, rosmarinic acid	*Ocimum tenuiflorum* L.	Phenolics	Aerial part	HSV-I, II	Inhibit replication of HSV-I and II	Caamal-Herrera et al. (2016), Tshilanda et al. (2020)
L-galactan hybrid C2S-3	*Cryptonemia crenulata*	Polysaccharides	Red alage	Dengue virus	Anti-viral activity	Talarico et al. (2007)
Polysaccharides	*Rhizophora mucronata*	Polysaccharides	Bark and leaves	HIV	Budding prevented	Asres et al. (2005)
Cyanovirin N (CV-N) (an 11-kDa protein)	*Nostoc ellipsosporum.*	Proteins	Blue green alage	HIV-1	Inhibiting HIV infection	Boyd et al. (1997)
Griffithsin	*Griffithisia* sp.	Proteins	Red alage	HIV, MERS-CoV	Antibody-dependent neutralization of HIV-1 particles	Emau et al. (2007), Millet et al. (2016)
Hydrolysed peptides AIHIILI and LIAVSTNIIFIVV	*Quercus infectoria*	Peptides	Fruit and peel	HIV-1	Against RT	Seetaha et al. (2021)
Lectins like MAP30, GAP31 and jacalin	*Momordica charantia*, *Gelonium multiflorum*, *Artocarpus heterophyllus*	Proteins	Leaf and fruit	HIV, CMV	Ribosomal binding and other activty	Amirzadeh et al. (2023), Gurjar and Pal (2024)
Garlic oil, alliin, garlicin, and lectin, etc	*Allium sativum* L.	Sulfur Compounds	Bulb	ADV-3, SARS-CoV-2, HSV-I, H1N1, HIV-1	Inhibit virus by diminishing inflammation by suppressing oxidative stress	Rouf et al. (2020), Bachar et al. (2021)
Tannins	*Bergenia ligulata*, *Phaseolus vulgaris*	Tannins	Rhizome and leaf extracts	Influenza, HIV	Suppress RNA and protein synthesis in a dose-dependent way	Gurjar and Pal (2024)
Andrographolide	*Andrographis paniculata* (Burm.f.)	Terpenoids	Leaf	HSV-I, HIV, and EBV	Inhibit the expression enveloped glycoproteins, induce lymphocyte	Jayakumar et al. (2013)
Arganine C, a triterpene	*Tieghemella heckelii*	Terpenoids	Fruit	HIV	Inhibits HIV entry	Gosse et al. (2002)
Essential oil (Humulene epoxide, and caryophyllene oxide)	Cyperus rotundus L.	Terpenoids	Rhizome	SARS-CoV-2, HAV HSV-I, CVB	Inhibit four target proteins of SARS-CoV-2 such as spike, glycoprotein, papain-like protease (	Samra et al. (2020), Amparo et al. (2021)

(Continued on following page)

TABLE 1 (*Continued*) Detail of some plant products use to control the human affecting viral diseases.

Compound	Plant source	Metabolite class	Plant organ	Virus against working	Antiviral activity	References
Eucalyptus oil and terpinen-4-oil	Eucalyptus species	Terpenoids	Fresh leaves	HSV-1, HSV-2	Prevent adsorption	Mieres-Castro et al. (2021)
Gedunin, pongamol, and azadirachtin	*Azadirachta indica* A.Juss.	Terpenoids	Bark and leaf	HSV-I, HBV, SARS-CoV-2	Inhibit NS3 RNA polymerase and NS3 protease helicase	Alzohairy (2016), Rao and Yeturu (2020), Nesari et al. (2021)
Gingeronone A	*Zingiber officinale* Roscoe	Terpenoids	Rhizome	SARS-CoV-2	Inhibit SARS-CoV-2	Pandey et al. (2021)
Guaiol	*Piper nigrum* L	Terpenoids	Seed	VSV-IN, PIV, and SARS-CoV-2	Inhibit 6LU7 and 7JTL of SARS-CoV-2	Kumari and Priya (2017), Pandey et al. (2021)
Illic acid	*Laggera pterodonta*	Terpenoids	Total plants	H1N1, H3N2, H6N2	inhibits the early stage of the virus replication.	Wang et al. (2015)
Pandanin	*Pandanus amaryllifolius* Roxb.	Terpenoids	leaves	HSV-1, H1N1		Ooi et al. (2004)
Phorbol ester, hop-8	*Ostodes katharinae*	Terpenoids	Dried leaves	HIV-1 and HIV-2	Vif-mediated degradation	Chen et al. (2017)
Flacourtosides A and E, betulinic acid 3β-caffeate, and scolochinenoside D	*Flacourtia indica* (Burm.f.) Merr.	Triterpenoids	Stem bark	DENV, CHIKV	Inhibit RNA polymerase	Bourjot et al. (2012)
Glycyrrhizin	*Glycyrrhiza uralensis*	Triterpenoids	Root	SARS-CoV	Replication and block assembly	Cinatl et al. (2003)
Oleanolic acid	*Achyranthes aspera* L.	Triterpenoids	Leaf	HSV-I and II	Inhibited the early stage of multiplication and protease enzyme activity	Mukherjee et al. (2013), Tshilanda et al. (2020), Bachar et al. (2021)
Triterpene vaticinone	*Vatica cinerea*	Triterpenoids	Leaves and Stem	HIV-1	Prevent adsorption and replication	Zhang et al. (2003)
Triterpenoid betulinic acid	*Caesalpinia minax*	Triterpenoids	Seed	HIV, Parainfluenza 3 virus	Anti-viral activity	Chattopadhyay and Naik (2007)
Ursolic acid	*Geum japonicum*	Triterpenoids	Whole plant	HIV	Inhibits the action of the HIV-1 protease enzyme	Xu et al. (1996)

inflammatory, antioxidant, immunomodulatory, antimicrobial, and adaptive immunity-enhancing properties (Ferrucci et al., 2024; Nikiema et al., 2024). Plant antioxidants, such as polyphenols, can mitigate oxidative stress and protect cells from viral damage. Quercetin, found in apples and onions, is a potent antioxidant that enhances the function of the immune system. Anti-inflammatory effects also play a role, as chronic inflammation can weaken immune responses. The PNPs exhibit anti-inflammatory properties by modulating the production of pro-inflammatory cytokines and enzymes, which remain the main mechanisms of their action (Alarabei et al., 2024; Wu et al., 2024). Compounds like curcumin from turmeric help maintain immune balance by reducing excessive inflammation. The active component of Curcumin from turmeric shows anti-inflammatory, antioxidant, and enhances antibody responses. For example, curcumin from turmeric inhibits the activity of nuclear factor-kappa B (NF-κB), a key regulator of inflammation. PNPs, particularly flavonoids and phenolics, scavenge free radicals, reducing oxidative stress and protecting immune cells from damage (Hooda et al., 2024). Furthermore, some plant compounds enhance the production and activity of interferons, which are essential for the antiviral immune response. Carpaine, an alkaloid from papaya leaves, has demonstrated notable anti-thrombocytopenic activity, offering potential for managing Dengue Virus (DENV) by modulating cytokine responses and platelet levels. Studies indicate that carpaine significantly increases blood platelet counts in DENV-infected individuals by upregulating the expression of platelet-activating factor receptor and arachidonate 12-lipoxygenase genes (Zunjar et al., 2016; Anjum et al., 2017; Kapoor, 2017; Sarker et al., 2021; Munir et al., 2022). Advanced phytochemical analyses have identified several metabolites in Carica papaya leaf extract, including quinic acid, malic acid, caffeoyl malate, quercetin, p-coumaroyl malate, clitorin, rutin, feruloyl malate, nicotiflorin, and carpaine (Kasture et al., 2016; Ayodipupo Babalola et al., 2024). The diverse bioactive compounds of PNPs interact with various components of the immune system, making them valuable in promoting overall health and resilience against diseases (Frazzoli et al., 2023; Gasmi et al., 2023; Kussmann et al., 2023). However, it is crucial to note that the PNP dosage intake, effectiveness, and safety can all vary, and further investigation is needed to understand their processes and possible therapeutic uses properly.

Application of PNP to control human viral infection

Plant-derived natural products play a crucial role not only in drug discovery but also in enhancing human immunity against

pathogens. As challenges in developing chemical-based antiviral treatments continue, plant extract or fraction are increasingly recognized as safe and affordable alternatives to traditional antiviral medications (Elshafie et al., 2023). These compounds offer a range of antiviral properties and contribute to bolstering the immune system. Several studies highlight the potential of plant-derived compounds in the prevention and treatment of viral infection (Pebam et al., 2022). For instance, according to Chassagne et al. (2021), natural compounds that have been extracted from a variety of plants may help improve the development flow and yield novel drugs (Chassagne et al., 2021). Studies have shown that several medicinal plants with antiviral properties, including Andrographis paniculata, Lindera chunii, Dioscorea bulbifera, Wisteria floribunda, Xanthoceras sorbifolia, and Aegle marmelos, exhibit significant anti-HIV activity (Kaur et al., 2020). Additionally, various plant-derived compounds from different chemical groups have demonstrated potential anti-HBV activity (Wu, 2016). Unlike conventional antivirals and antibiotics that target pathogens broadly, plant-based medications may offer more specific mechanisms of action against viruses. For instance, quercetin, a well-known flavonoid available as a dietary supplement, is commonly used to boost immunity, manage allergies, and improve general health. It has been shown to inhibit the replication of several viruses, including influenza, herpes simplex, and hepatitis C viruses (Agrawal et al., 2020).

Despite the availability of antiviral medications and vaccines, effectively controlling infections remains challenging due to the unique characteristics of each virus and the limited number of approved antiviral drugs (Adamson et al., 2021; Cheung et al., 2024; Mahmoudieh et al., 2024). This has driven increased interest in plant-based treatments, as PNPs exhibit diverse bioactive properties, including antiviral effects. Research supports the use of plant-based medications in treating viral infections (Chassagne et al., 2021). Advances in genetic engineering and molecular breeding in plantations have facilitated the development of potential treatments for viruses such as SARS-CoV-2. Recent studies indicate that plant extracts possess therapeutic potential against the COVID-19 strain (Jalal et al., 2021; Mukherjee et al., 2024), suggesting that the therapeutic effects of plant extracts on COVID-19 highlight their significance in managing viral infections.

Even though, the presence of over 220 identified human viruses and the limited number of clinical approvals for antiviral drugs are major concerns (Adamson et al., 2021; Cheung et al., 2024). Each virus's unique characteristics and behaviors require customized medications or therapies, which can be challenging. Additionally, rapid viral genome evolution contributes to the emergence of several mutants in the virus leading to antiviral resistance and complicating treatment efforts (Ghaebi et al., 2020). Research on compounds such as K22, which has demonstrated strong anti-CoV activity by reducing endoplasmic reticulum zippering, offers promising insights into overcoming these challenges (Bills et al., 2023).

Humans have used herbs and supplements to treat illnesses since ancient times. Even today, influenza and coronavirus vaccinations are not 100 percent effective, so the immune system can use all the help it can get from antiviral herbs. Some of the best antiviral herbs and supplements have been used therapeutically to manage symptoms of coronavirus (Saddiqa et al., 2024). Some prevalent plant natural products that help ameliorate the effects of viral infections in humans include quercetin, resveratrol, echinacea, allicin, and epigallocatechin gallate (Lin L. T. et al., 2014; Adeosun and Loots, 2024) (Table 1).

Polyphenols prevent viral infection of host cells by disturbing virus adsorption and attachment and by suppressing reverse transcriptase and RNA polymerase activity in HIV and influenza virus attacks (Chojnacka et al., 2021). Resveratrol, is a potent polyphenolic compound, found in grapes and red wine, exhibits antiviral properties against several viruses, including influenza and herpes simplex virus, by inhibiting viral protein synthesis (Abba et al., 2015). Baicalein and luteolin are two flavones, a family of polyphenolic compounds, whose antiviral properties have also been well studied. Baicalein substantially effect viral DNA synthesis and reduced human cytomegalovirus (HCMV) early and late protein levels (Croft, 1998). Luteolin exhibits antiviral activity against viruses like the poliovirus and coxsackievirus and has antimicrobial properties that help fight bacterial and viral infections (Zakaryan et al., 2017). Polyphenols Epigallocatechin gallate, derived from green tea, has potent antiviral effects against viruses such as hepatitis B and C, influenza, and herpes, partly through inhibiting viral entry and replication (Wang et al., 2021). *Echinacea* is widely used in traditional medicine and contains various secondary metabolites, primarily phenolics (such as caffeic acid derivatives) and polysaccharides, which can boost immune function. It has also been shown to reduce the duration and severity of colds and other respiratory infections (Karsch-Völk et al., 2014). Curcumin, a natural polyphenolic compound and the primary ingredient in turmeric, is known for its ability to eliminate human viruses such as H5N1, SARS-CoV-2, HIV-1 & HIV-2, influenza, HSV-1 & HSV-2, coxsackievirus, hepatitis B, and other pathogens. (Babaei et al., 2020; Bormann et al., 2021; Sahoo et al., 2021; Srivastava et al., 2022). The basil (*Ocimum sanctum*), or tulsi, contains many flavonoids such as orientin, vicenin, eugenol, rosmarinic acid, and luteolin, which contribute to its medicinal properties. Tulsi's antiviral properties make it a valuable herbal remedy for managing and preventing viral infections by inhibiting viral replication, modulating the immune system, reducing inflammation, and providing antioxidant support including Influenza-A, flu A subtype H9N2, HSV1, HSV2, ADV-8, CVB1, EV71, ADV-3, ADV-II, HIV-1, HIV-2, HPV, HCV, DEN-1 & 2, DNA, and RNA viruses, and SARS-CoV-2 (Bhattacharya et al., 2024; Jayashankar et al., 2024; Rani, 2024; Sao et al., 2024). Coumarins from *Calophyllum lanigerum* and *C. inophyllum* have been shown to inhibit reverse transcriptase and are effective against HIV-1 (Sharapov et al., 2023). Black tea phenolics such as tannic acid, 3-isotheaflavin-3-gallate, and theaflavin-3,3′-digallate, as well as phenolics from *Isatis indigotica* like hesperetin, and have exhibited inhibitory effects against various viruses (Salasc et al., 2022b; Sezer et al., 2022; Gamil and Abeer, 2023). Strychnobiflavone is a bioactive flavonoid compound derived from the bark of Strychnos pseudoquina, known for its ability to inhibit HSV-1 virus and its associated disease (Thomas et al., 2021).

Different alkaloids like Isoquinoline alkaloid thalimonine, berberine, Camptothecin, Harman, Gingeronone A, alkaloid isolated from *Zanthoxylum chalybeum*, *Thalictrum Simplex* L, *Berberis vulgaris*, *Camptotheca acuminata*, *Ophiorrhiza nicobarica*, *Camellia sinensis* (L.) Kuntze, *Zingiber officinale*

Roscoe, used to control the viral diseases like Swartz and Edmonston measles virus, Influenza A virus, IAV, EV71, Herpes virus (Olila et al., 2002; Serkedjieva and Velcheva, 2003; Wu et al., 2004; Song et al., 2005; Xu et al., 2017; Botwina et al., 2020; Pandey et al., 2021; Gurjar and Pal, 2024). Lycorine is a natural alkaloid from *Lycoris radiata L.*, showed anti-SARS-CoV activity (Li et al., 2005). Sanguinarine, alkaloid derived from the bloodroot plant (*Sanguinaria canadensis*), has potential antiviral effects against hepatitis C virus (HCV) and herpes simplex virus (HSV) by inhibiting viral RNA synthesis and blocking viral protein expression, enhancing the host's immune response to viral infections (Croaker et al., 2016; Wink, 2020).

Artemisinin, a terpenoid derived from *Artemisia annua*, is used in treating malaria and has shown antiviral activity against hepatitis B and C viruses (Uzun and Toptas, 2020). Oregano (*Origanum vulgare*), a popular herb from the mint family, has medicinal properties. Its oil's active components, such as carvacrol and thymol, possess antiviral properties and disrupt the lipid envelopes of viruses, leading to the inactivation of the virus, allowing it to treat murine norovirus (MNV) (Gilling et al., 2014; Solis-Sanchez et al., 2020; Mohanty and Murhekar, 2024). Andrographolide, a diterpene lactone found in *Andrographis paniculata*, has shown antiviral properties against influenza, hepatitis C, and dengue viruses (Kaushik et al., 2021). Components like Andrographolide, Oleanolic acid, Phorbol ester, hop-8, etc., isolated from the leaf of *A. paniculata*, *Justicia adhatoda* L., *Achyranthes aspera* L., *Ostodes katharinae*., protect against viruses like HSV-I, HIV, SARS-CoV-2, and EBV (Jayakumar et al., 2013; Mukherjee et al., 2013; Chavan and Chowdhary, 2014; Chen et al., 2017; Tshilanda et al., 2020; Bachar et al., 2021; Ghosh et al., 2021). Bel (*Aegle marmelos*), plant is an important ethanobotanical use in Indian culture. Seselin, a compound isolated from *A. marmelos* (L.) Corrêa showed effective against SARS-CoV-2 (Bachar et al., 2021; Nivetha et al., 2022). Licorice, known as "sweet grass," has been used in traditional Chinese medicine. The plant's root is the primary source of its antiviral and antibacterial properties. Licorice, frequently used in folk food systems during cold and cough, contains glycyrrhizin from *Glycyrrhiza uralensis.* Glycyrrhizin, a triterpenoid saponin compound derived from the licorice plant (*Glycyrrhiza glabra*), has shown activity against a range of viruses, including herpes simplex, hepatitis C, HIV, and SARS-CoV-2, by interfering with virus replication and boosting the immune response (Cinatl et al., 2003; Rizzato et al., 2017; Tseng et al., 2017; Gomaa and Abdel-Wadood, 2021). Celastrol, a quinone methide triterpene obtained from *Tripterygium wilfordii* root extracts, has shown promise to prevent HCV replication by targeting on the JNK/Nrf2/HO-1 pathway, providing a viable strategy to fight HCV infection (Tseng et al., 2017).

Garlic (*Allium sativum L.*) has been used for centuries in food and medicine and has been shown to heal viral infections in humans, animals, and plants (Tesfaye, 2021). Studies indicate that garlic can help treat the common cold, flu, viral hepatitis, and even warts (Sasi et al., 2021). Allicin, a sulfur-containing compound derived from garlic, has broad-spectrum antiviral activity, inhibiting viral RNA synthesis and boosting immune cell activity. Bulb of *A. sativum* L., produces garlic oil, garlicin, and lectin, etc., protects against L. ADV-3, SARS-CoV-2, HSV-I, H1N1, HIV-1 (Rouf et al., 2020; Bachar et al., 2021). Another sulfur-containing compound Progoitrin, a glucosinolate, isolated from the root of *I. indigotica* protect against H1N1 (Nie et al., 2020).

Essential oils, concentrated extracts from plants, contain various bioactive complex mixture of terpenes, phenolics, and other secondary metabolites that can exert antiviral effects. Some essential oils can directly inactivate viruses by disrupting their lipid envelopes, denaturing proteins, or interfering with viral entry into host cells. They can also inhibit viral replication within host cells by interfering with viral RNA or DNA synthesis and disrupting viral enzyme activity. Additionally, essential oils can enhance the immune response and reduce inflammation associated with viral infections. Different plant oils, such as those from lavender, camphor, peppermint, cinnamon, eucalyptus, tea, and thyme, contain compounds used for antiviral activity (Mohammed Ail, 2021). Specific essential oils with antiviral properties include tea tree oil (*Melaleuca alternifolia*), which contains compounds like terpinen-4-ol and alpha-terpineol that disrupt viral envelopes and inhibit viral replication of HSV, influenza, and HPV. Eucalyptus oil (Eucalyptus globulus) contains eucalyptol (1,8-cineole), which inhibits viral replication and enhances immune responses against influenza, HSV, and RSV (Garozzo et al., 2009). Peppermint oil (*Mentha piperita*) has menthol and other compounds that exhibit antiviral activity against HSV, influenza, and adenovirus. Lavender oil (*Lavandula angustifolia*) contains linalool and linalyl acetate, which can inactivate viruses and reduce inflammation during HSV and influenza infections (Abou Baker et al., 2021). Oregano oil (*O. vulgare*) is rich in carvacrol and thymol, which have strong antiviral, antibacterial, and antifungal properties, disrupting viral envelopes and inhibiting replication of HSV, rotavirus, and norovirus. Lemon balm oil (*Melissa officinalis*) part of the mint family, possesses antioxidant, antihistamine, anti-cancer, antibacterial, antifungal, and antiviral properties. Contains compounds like citral and citronellal, which have antiviral effects by inhibiting viral attachment and entry of HSV and enterovirus. Studies indicate that lemon balm essential oil helps treat the influenza virus (Behzadi et al., 2023; de Sousa et al., 2023). Lemon balm also relieves muscle spasms and may slow down HSV-1 (Mazzanti et al., 2008; Astani et al., 2012; Gurjar and Pal, 2024). Different oils viz., Sandalwood oil, Eucalyptus oil, Essential oil (Humulene epoxide, and caryophyllene oxide) Tea tree oil and Terpinen-4-ol from different plants like *Cyperus rotundus* L. *Fortunella margarita,* Tea tree (*M. alternifolia*), *Santalum album* Linn use against different viral disease. Eucalyptus species are used to control the disease of SARS, HAV, HSV, etc (Garozzo et al., 2011; Ibrahim et al., 2015; Battistini et al., 2019; Bellavite and Donzelli, 2020; Goyal et al., 2020; Samra et al., 2020; Amparo et al., 2021; Khan Yusuf and Sen Das, 2023).

More than 200 extracts from different plants, such as *L. radiata*, *A. annua*, *Pyrrosia lingua*, and *Lindera aggregate*, have been analyzed and found to have anti-SARS-CoV effects (Omrani et al., 2021; Perera et al., 2021; Salasc et al., 2022a; Gamil and Abeer, 2023; Pal and Lal, 2024; Sezer et al., 2024). Aqueous extract of Carica papaya leaves to treat Dengue fever (Shrivastava et al., 2022). Extracts from folk medicinal plants like *Heracleum maximum, Plantago major Linn*., and *Sambucus nigra L.* possess antiviral effects by stimulating macrophage activation (Barak et al., 2001;

Chiang et al., 2003; Webster et al., 2006; Mukhtar et al., 2008). Similarly, anti-HCV activity has been observed in methanolic and aqueous extracts of *Boswellia carterii*, *Acacia nilotica L.*, *Embelia schimperi, Trachyspermum ammi L., Quercus infectoria*, *Piper cubeba L.*, and *Syzygium aromaticum L.* (Mukhtar et al., 2008). Astragalus root, a medicinal plant from Asia, is an antiviral agent used to treat avian influenza H9 (Shkondrov et al., 2023). Plant-derived zinc components boost the immune system and have effective antiviral properties, helping to protect the body from HPV, HIV, Picornavirus, Togavirus (Chikungunya), flu, coronavirus, and herpes (Murakami et al., 2007; Read et al., 2019; Khabour and Hassanein, 2021) Ginger (*Z. officinale*) is a spice packed with antioxidants beneficial to the human immune system's health. It possesses antimicrobial properties and can fight off various human viruses in diseases such as Chikungunya, Dengue (DENV), SARS-CoV-2, and the human respiratory syncytial virus (HRSV) (Chang et al., 2013; Aboubakr et al., 2016; Kaushik et al., 2020; Mukherjee et al., 2024); Black elderberry (*S. nigra*), a popular medicinal shrub in Europe, possesses antioxidant properties and boosts the immune system. *In vitro* studies have shown that black elderberry can slow the spread of influenza A and B, as well as some bacterial lung (Charlebois et al., 2010; Hawkins et al., 2019; Torabian et al., 2019; Seymenska et al., 2023). The tubers of various *Dioscorea* species have been used to treat different viruses, including herpesvirus, poxvirus, and picornavirus. These extracts work against viruses by binding to the virion particles, preventing their penetration into cells, modifying the cell wall surface to prevent the release of viral replicates, and interfering with the intracellular replication of viruses (Ganjhu et al., 2015). Leaf extracts of *Azadirachta indica* have shown antiviral activity against several RNA and DNA viruses (Gurjar and Pal, 2024). Aqueous extract from the roots of *Carissa edulis* (Forssk.) V showed anti-HSV activity (Tolo et al., 2006), while the ethanolic extract of *Phyllanthus* (*Phyllanthus nanus*) showed anti-HBV activity (Lam et al., 2006). Whole plants of *Cynodon dactylon* L. and the leaf of *Rosa centifolia* L. show inhibitors of viruses like BCoV and HIV respectively (Nalanagula, 2020; Palshetkar et al., 2020; Bachar et al., 2021). Supplemented liquid fermented broth of *Ganoderma lucidum* with aqueous extract of *Radix Sophorae* flavescentis strongly showed anti-hepatitis B virus activity (Mukhtar et al., 2008). Hot water extracts of *Stevia rebaudiana* L. blocked the entry of various infectious HRV viruses (Takahashi et al., 2001).

Not only higher plant products but lower plant-like products of blue-green algae and red algae also help in managing the human attacking viruses. Cyanovirin N (CV-N), an 11-kDa protein product of cyanobacterium *Nostoc ellipsosporum,* and Griffithsin a red marine algae (*Griffithisia* sp.) product can develop anti-HIV-1 effect. These molecules neutralize the HIV viruses by inhibiting their infection and antibody based HIV particle neutralization processes (Boyd et al., 1997; Emau et al., 2007; Millet et al., 2016). DL-galactan hybrid C2S-3 derived from different algae *Cryptonemia crenulata* help to protect the human body from Dengue viruses (Talarico et al., 2007).

Peptides like Meliacine and Hydrolysed peptides AIHIILI and LIAVSTNIIFIVV isolated from *Melia azedarach* and *Q. infectoria* leaf and fruit part protect the human body from Foot and mouth disease virus VSV, and HSV-I, HIV-1 viruses (Wachsman et al., 1998; Alché et al., 2003; Seetaha et al., 2021). Lectins of *S. nigra*, which can administer either orally or parenterally in liquid composition inhibit the activity of several enveloped viruses (Ganjhu et al., 2015). Rhizome of *Bletilla striata* produce Phenanthrene to inhibit virus H3N2 propagation (Shi et al., 2017). Fruits of *Mangifera indica* L. and *Forsythia suspensa* produce Mangiferin and Forsythoside A which work as antiviral compounds against HSV, HIV and H1N1 (Law et al., 2017; Al-rawi et al., 2019).

These plant-derived substances have provided opportunities for creating novel antiviral treatments. However, it is crucial to remember that while many of these substances have shown antiviral activity in laboratory conditions, further clinical research is required to determine their safety and effectiveness in humans.

Limitation and toxicity of PNPs

PNPs have shown promise in antiviral drug discovery, but they also have several limitations during viral infections (Figure 3). PNPs often exist as complex mixtures with multiple active compounds. The chemical composition of PNPs can vary significantly depending on the source, growing conditions, and extraction methods. Isolating and identifying the specific components responsible for antiviral activity can be challenging, making standardization difficult. This variability can affect the consistency and reliability of the therapeutic effects (Raskin et al., 2002; Kusumawati, 2021). Many PNPs suffer from poor bioavailability, as they are not easily absorbed, distributed, or maintained in effective concentrations within the body (Kumar S. et al., 2022). This can limit their therapeutic effectiveness. For example, the pharmacokinetics of quercetin in humans showed a low oral bioavailability (~2%) after a single dosage (Li et al., 2016). The approval process for natural products as therapeutic agents is indeed intricate and lengthy. Regulatory authorities require extensive evidence to validate the efficacy, safety, and quality of PNPs, which can significantly delay their clinical availability. One major challenge is the limited scientific data on the safety profiles of many PNPs, especially concerning long-term use and their effects on vulnerable populations such as pregnant women, children, and the elderly. This lack of comprehensive safety information increases uncertainty about potential toxicity. Furthermore, while numerous PNPs demonstrate promising antiviral effects *in vitro*, the transition to robust clinical trials is often insufficient. This gap between preclinical findings and clinical validation hinders the acceptance of PNPs as mainstream antiviral therapies.

The potential for toxicity in PNPs is an important consideration when using these substances for therapeutic purposes. Many PNPs are safe at low doses but can become toxic when consumed in larger quantities or when used over long periods. For instance, high doses of raw garlic extract given over an extended period of time could potentially interfere with blood coagulation, cause liver toxicity, and create gastrointestinal problems (Banerjee and Maulik, 2002). Several studies indicate that coumarin-induced hepatotoxicity is relatively infrequent in humans. Clinical research, however, suggests that coumarin therapy may be associated with liver damage, which is frequently seen as high transaminase levels (Pitaro et al., 2022). The safety profile of these compounds must be thoroughly evaluated to avoid adverse effects during treatment. Some individuals may have allergic reactions to specific PNPs. These reactions can range from

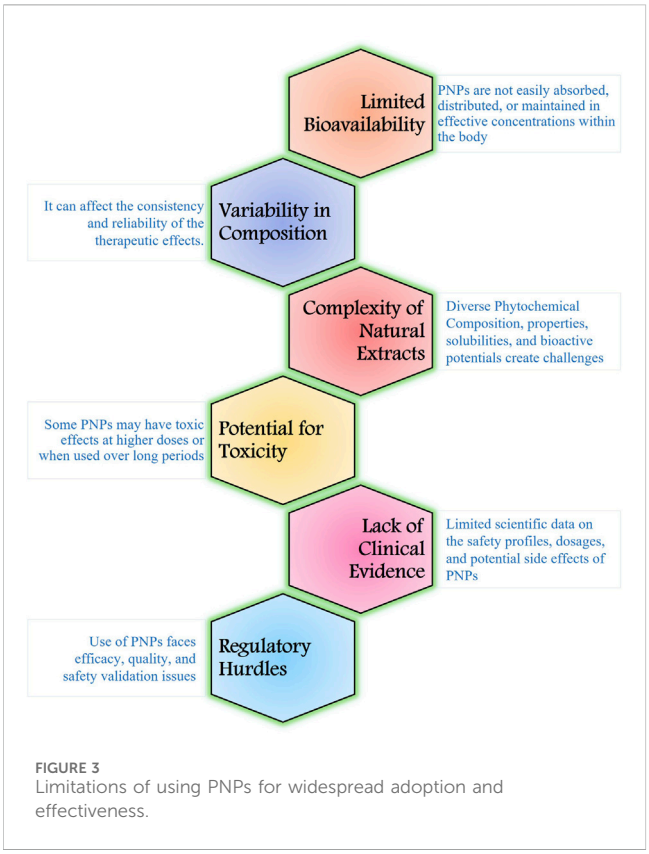

FIGURE 3
Limitations of using PNPs for widespread adoption and effectiveness.

mild symptoms like rashes or itching to severe anaphylactic reactions such as sesquiterpene lactones, found in plants like chamomile and arnica, these compounds can cause contact dermatitis in sensitive individuals (Paulsen, 2017). Addressing these limitations will enhance the credibility and therapeutic potential of PNPs, paving the way for their integration into modern antiviral treatments.

Conclusion and perspective

Plant-extract products with antiviral activity are gaining attention as safe and affordable alternatives to traditional antiviral medications. These plant-extract products, which include flavonoids, alkaloids, terpenoids, and phenolic compounds, have the ability to inhibit viral lifecycles and stimulate cellular immune responses, making them useful in fighting viral infections. Despite their potential, therapeutic use of PNPs faces several challenges: low natural concentrations, difficulty in identifying active components, slow plant growth rates, environmental dependence, and extinction risks. Addressing these limitations is essential, particularly in the current scenario of rapid viral infections. Biotechnological platforms, such as plant cell and tissue culture technologies, offer crucial solutions for producing large volumes of plant-derived compounds. Enhancing our understanding of biosynthetic pathways and improving supply chains for commercial production are key steps in this process.

Standardization and rigorous quality control are essential for ensuring the consistency and safety of plant-derived products in clinical applications. Research into these compounds not only aids in the development of new antiviral drugs but also helps design more effective treatments by understanding their mechanisms. Combining PNPs with conventional antiviral medications can enhance efficacy and reduce the risk of resistance, offering a synergistic approach to therapy. In-depth studies and clinical trials are necessary to fully explore the antiviral potential of these compounds. Researchers are investigating the relationship between phytochemical structures and antiviral activity through bioassays, but identifying active components in complex natural extracts remains challenging. Effectiveness may also vary within the human body, emphasizing the need for further validation. The ongoing exploration of PNPs holds significant promise for developing innovative antiviral therapies. By enhancing human antiviral responses and providing new pharmacological options, PNPs could play a crucial role in improving public health. Their nutraceutical and therapeutic properties position them as valuable candidates for combating a range of viruses, making continued research into their mechanisms, efficacy, and safety vital for the future of antiviral medicine.

Author contributions

RS (1st author): Resources, Writing–original draft, Data curation, Methodology, Visualization. ND: Data curation, Methodology, Visualization, Writing–original draft. MS: Data curation, Writing–original draft. HK: Writing–review and editing. RB: Writing–review and editing, Conceptualization. RS (6th author): Conceptualization, Data curation, Visualization, Writing–original draft, Writing–review and editing.

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Conflict of interest

Author RS (6th author) was employed by Helix Biosciences.

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