Plethora of opportunities as promising antiviral agents: Old Weapon Against New Enemy

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Plant based Terpenoid: Plethora of opportunities as promising antiviral agents.

ABSTRACT

Viruses cause a variety of human pathogeneses, including respiratory tract infections. However, few antivirals have been licensed for clinical use, and many viruses yet do not possess a viable vaccine. Antiviral drugs are significantly less effective since they are likely to produce drug-resistant mutants, especially when utilizing inhibitors of viral enzymes. In the unavailability of immunizations and standard treatments, it is urgent to identify novel antiviral medications that are both effective and cost-effective. Herbal remedies and purified natural materials are an abundant resource for the development of new antiviral drugs. Several studies have demonstrated the efficacy of herbal extracts as antiviral agents in animal feed or as preventatives and treatments. The identification of these natural agents' antiviral mechanisms has revealed knowledge on their interacts with both the virus life cycle, including viral entrance, multiplication, assembling, and release, as well as virus–host specific interactions. The current article will provide an overview of the antiviral properties of plant-based terpenoids found in a variety of herbal remedies and natural products against various well-known viral respiratory illnesses.

Keywords Antiviral drugs, Terpenoid, Viral infection, Virus, Molecular docking

1.0 Introduction

One of the most common human illnesses is viral respiratory infections [VRI] Human health has been impacted for decades by a number of life-threatening viruses, including hepatitis virus subtypes A, B, and C [HAV, HBV, and HCV], HIV, herpes simplex virus [HSV], influenza virus and others. Corona virus-2 has become a worldwide threat alongside these pre-existing viruses since 2019. Novel coronavirus illness [COVID-19], commonly referred to as coronavirus infection, is associated with serious acute respiratory symptoms and a significant fatality rate. [1, 2]. Viral infections can cause both acute, sometimes fatal clinical disorders (such as influenza and dengue) as well as chronic illnesses (such as HIV and hepatitis C), which require long-term treatment and are consequently expensive for the healthcare system. The potential for some of these viral illnesses to become pandemic is a serious concern these days [3]. Because viruses can change their genetic sequences and develop medication resistance, developing effective treatments and antiviral against them has become difficult. This fact necessitates a rapid and efficient method of drug discovery. In the

past few decades, computational techniques such as virtual screening have proved to be extremely useful in accelerating and reducing the cost of drug development [3]. Virtual screening (VS) against viral targets has a variety of applications in the drug development process. VS can rationalise and enhance the initial phases of target and lead structure identification, as well as subsequent phases such as compound development and optimization. Additionally, antiviral drugs have unfavorable side effects that harm people's health both directly and indirectly. This results in the development of natural medicines and herbal treatments with fewer side effects. [4]. Herbal remedies have long been employed to treat and reduce viral respiratory infections. Because the majority of the these plants have invulnerable and inflammation-modulating qualities, they can support the immune system's fight against infections while preventing immunological overreaction [cytokine storm] to VRI [4]. Patients suffering from the acute bronchitis, influenza, viral pharyngitis, and common cold can benefit greatly from herbal medicine. Viral infections have always been and will strive to be a persistent threat to civilization. [5].

Recently, one of the main areas of focus in the hunt for efficient medicines has been plant compounds and their bioactive metabolites and inexpensive drugs to meet the needs of the present. Several medicinal herbs have ethnomedicinal uses for treating infectious diseases like respiratory infections [6]. However, research programmes are necessary for validating traditional uses and providing evidence of the plant material's safety and quality. Furthermore, a number of natural or plant-derived compounds from various chemical groups have been investigated for antiviral activity. Active phytochemicals such as terpenoids, coumarins, polyins, polyphenols, thiophenes, chlorophyllins, proteins, and peptides organosulfur compounds, sulphides, lignans, alkaloids, limonoids, saponins, have proven therapeutic uses for a wide range of genetically and functionally diverse viruses [7]. The main ways bioactive compounds in medicinal herbs stop viruses from spreading are through antioxidant activity, scavenging, blocking DNA and RNA synthesis, stopping viruses from entering cells, or stopping viruses from making more copies of themselves [4].

Viruses contain RNA genome or DNA encased in a protein envelope and are dependent on their hosts. To replicate & survive, organisms must have the right metabolism and environment. The propensity of virus to enter and adopt evasion techniques is a major obstacle to the invention of antiviral drugs. [4].

Since plants contain phytoconstituents with a variation in the properties, they could be examined and used to tackle the antiviral challenges of evasion and drug resistance., thereby preventing viral spread [4]. There are multiple pathways that influence phytochemicals' antiviral action. The creation of innovative antiviral drugs can benefit greatly from the abundance of medicinal herbs and purified natural ingredients. Since these natural agents' antiviral mechanisms have been discovered, it is now possible to target interactions between viruses and their hosts as well as many stages of the life cycle of viruses, including viral entrance, their replication, assembling, and discharge [8]. Typically, fewer antivirus compounds that attach to the carbohydrate portion target the cell entry, for instance [9]. When vaccinations and conventional treatments are not available, there will be a crucial need to find innovative antivirals that are extremely active and affordable for managing of virus-related infections. This short article briefly discussed the antiviral effects of many terpenoid-containing natural remedies and herbal therapies for respiratory viral infections.

1.1 Role of Phytoconstituents in combating Viral infection

Antiviral medications are a specific class of medications used to treat viral infections. Antiviral medicines are pharmaceuticals used to combat virus-related infections. Viruses, one of the principal pathogens, are responsible for a wide variety of major diseases that affect humans, animals, and plants. Viruses are responsible for a vast array of human disorders, ranging from minor to catastrophic conditions. The development of antiviral medications focuses on two distinct strategies: targeting the host cell components or viruses itself.

Antiviral drugs that directly target the viruses include nucleotide and nucleoside reverse transcription inhibitors, virus integrase inhibitors, polymerase inhibitors, viral entryway blockers, virus uncoating inhibitors, and protease inhibitors. Darunavir, atazanavir and Ritonavir are protease inhibitors. Tenofovir, valacyclovir, acyclovir, and valganciclovir, are viral DNA polymerase inhibitors [10, 11].

In addition, because of increased worldwide travel and accelerated urbanization, epidemic outbreaks brought on by newly discovered or rediscovered viruses pose a serious risk to the public's health, especially when there are no existing prophylactic vaccines or antiviral treatments. Examples from recent times include the spread of the West Nile and dengue viruses, as well as the influenza, measles, and SARS [severe acute respiratory syndrome] viruses. However, many viruses do not currently have any effective immunization, and few antiviral medicines have been approved for clinical use. The possibility for drug-resistant mutants to emerge, particularly when utilising inhibitors of viral enzymes, further exacerbates the problem and drastically reduces treatment efficacy. Therefore, innovative antivirals that are highly effective and reasonably priced are urgently needed to manage and control viral infections in the absence of vaccinations and conventional treatments [10].

Herbal remedies and purified natural items are a valuable resource in order to develop innovative antiviral agent. Since these natural agents' antiviral mechanisms have been discovered, it is now possible to target interactions between viruses and their hosts as well as many stages of the cycle of a virus, which includes entrance, replication, assembling, and release [10].

In a 2018 report, Kazakova et al. looked at the antiviral efficacy of dihydroquinopimaric acid & betulin derivatives against by the type 1 HSV, HIV type 1ECHO 6 non-enveloped RNA virus, H7N1 influenza A and HIV type 1virusHIV type 1 . Betulic acid's alteration at carbons C3 and C28 demonstrated antiviral efficacy against HIV-1& HSV-1. Additionally, a dihydroquinopimaric acid changes positioned at C4 improved the anti-H7N1 activity. Due to the lack of a successful and affordable HCV cure as well as the lack of immunizations, researchers are turning their attention to the potential phytochemical-based therapy.

1.3 DNA virus:

Typically, viruses like poxviruses, herpes, adenoviruses, and papillomaviruses have single-digit DNA remains after double-stranded DNA. The DNA virus penetrates the nucleus of the cell and produces new viruses. [10].

1.4 RNA virus:

Single-descriptor RNA [ssRNA] viruses include mumps, measles, meningitis, influenza, colds, polio, arena viruses and retroviruses [AIDS, T-cell leukemia]. The cell nucleus is impervious to the RNA virus [in addition to the cold virus infection this season]. Then, viral RNA is used to produce a DNA copy of viral RNA, that is arranged by the host genome and afterwards retroviruses. [10].

1.5 The stages of viral infections

infection brought on by the replication of viral DNA once it enters a host cell as well as the discharge of fresh viruses. The six steps of viral replication include attachment, invading, endocytosis, replication, assembly, and release. Here we describe the processes of the life cycle of viruses that highlight the entry and exit of the virus. [10].

- The virus injects its genetic material into the host cell during in the attachments and penetration stage to cause infection. [10].
- The host cell's genetic material is then altered by the infected DNA or RNA, leading to viral genome replication. In this stage of the viral replication cycle, the virus uncoats, replicates, and assembles. [10].
- In the course of release, the host cell ruptures, dies, or sprouts newly generated viruses through the cell membrane. [10].

2.0 Methodology

This article presents a review of 20 plants that contain terpenoid and discusses the antiviral properties that these compounds possess. A thorough investigation of databases containing bibliographies, including Google Scholar, MEDLINE, PubMed, Scopus, Springer Link, and Science Direct, was conducted to find information on general plant descriptions, phytochemical analyses, and antiviral activity were compiled by using following keywords: terpenes, antiviral agent, respiratory syndrome. The research publications on anti-human coronavirus terpenes and derivatives that are covered in this manuscript were chosen from research published in English [9].

3.0 Terpenes and Terpenoids as promising Antiviral Agents

Terpenes, also known as isoprenoids, comprise the most numerous and structurally diverse class of naturally occurring compounds. [12]. Terpenoids are a group of naturally occurring compounds with simply modified terpenes with different functional groups in different positions [4]. They are biosynthesized from mevalonic acid [MVA] that include several isoprene [C5] structural units[13]. More than 50,000 terpenoids have been discovered in nature till date [13]. They are predominantly found in plants, but major class including terpene, such sterols and squalene, may also be seen in animals that possesses a variety of medicinal qualities. Terpene serves a range of roles among the natural ingredients that mediate antagonistic and positive interactions inside the organism [12]. Some terpenoids are important for plant growth and development. For example, gibberellin, which is a plant hormone, controls plant development, and carotenoids take part in photosynthesis [13]. Terpene protects microbes, animals, and plants against abiotic and biotic stressors [12]. Other terpenoids are involved in the interactions between plants and their environment, such as phytoalexins in plant defence mechanisms and interspecific sensing chemicals in interspecies competition. [13]. Terpene can repel infections, predators, and rivals. Terpene is used by living creatures for a variety of purposes, including medicine and communication regarding food, partners, or foes [12]. □ The terpene group, that can be produced from synthetic or natural substances, has been observed frequently among antiviral agents. [14].

3.1 Monoterpenes

Monoterpenes are the smallest type of terpenes. Monoterpene-containing essential oils are frequently employed in both the fragrance business and conventional medicine. The major elements of essential oils, including phenylpropanoids, monoterpenes and sesquiterpenes are responsible for the scent and biological properties of aromatic and medicinal plants. Gamma-terpinene, alpha-terpinene, p-cymene, alpha-pinene, alpha-terpineol, terpinen-4-ol, 1, 8-cineole thymol and citral which are important components of volatile oils, were tested for their antiviral activity against HSV-1 [herpes simplex virus type 1] in vitro.[15] The effectiveness of beta-pinene as an antiviral agent against the respiratory syncytial virus was investigated.[16]. This drug blocks viral DNA polymerase mainly during the viral replication, which is when new viral DNA is produced.[15],[17]

3.2 Diterpenes

Mevalonic acid biosynthesis results in the formation of di-terpenes. Diterpenes are composed of two molecules of isoprene. These chemicals are present in a variety of organisms, including mammals, fungi, coral, plants and algae. A number of kinds of diterpene chemicals including tiglilane, daphnane, tonantzitlolone, casbane, labdane, kaurene, jatrophane, pimarane, dolastane, prenylated guaiane diterpene and others. Antiviral diterpene compounds have pharmacological effects. Kirkinine, debromoaplysiatoxin briaexcavatolide U, jiadifenoic acids JP [anti-Coxsackie virus], genkwanine P, briaexcavatin L [anti-HCMV], excoecariatoxin [anti-HIV] and laurifolioside A [anti-HBV] are some diterpenes that have been shown to exhibit antiviral [anti-CHIKV] Diterpenes' molecular-level suppression of SARS-CoV via inhibition of the primary protease active location of the enzyme. Through the binding of diterpene molecule [ligand] and residues of amino acids on the active site of the

primary protease 3CL, the active site is predicted to provide a blueprint for the inhibitor of this enzyme.

3.3 Triterpenes

Six isoprene units make up triterpenes. Squalene, the fundamental building block, is biosynthesized to produce whether lanosterol or cycloartenol, the structural antecedents of all steroids.[18] Common natural product classes found in a variety of marine and terrestrial natural sources include steroids and triterpenes [e.g., plants, animals, and microorganisms][19]. The two triterpenoids had greater antiviral efficacy against influenza A [H1N1] virus, respiratory syncytial virus, herpes simplex virus type 1 and Coxsackie B3 virus according to an antiviral experiment utilising a cytopathic effect reduction approach [18]. Glycyrrhizin's antiHIV efficacy has been attributed to two different mechanisms: interfering to protein kinase C effect to prevent viral adsorption to target cells or disrupting the first stages of viral reproduction due to ineffective interactions between the molecule and the viral membrane. In vitro, some of the glycyrrhizin derivatives that had undergone chemical modification—salts, amides, and glycopeptides—were effective HIV-2 and HIV-1 inhibitors [18], [20]. Alphitolic acid is a pentacyclic ursan-type triterpene found from Rosa woodsii [F. Rosaceae]. The EC50 value for anti-HIV activity is 4 M.[19]

3.4 Tetraterpenes

Tetraterpenes are composed of eight isoprene units, and physiologically significant tetraterpenes include the monocyclic β-carotene, the bicyclic α- and β- carotenes and the acyclic lycopene[18]. Paclitaxel is a tetracyclic diterpenoid derived from taxus plants that has a positive therapeutic effect on diseases such as ovarian cancer and breast cancer.

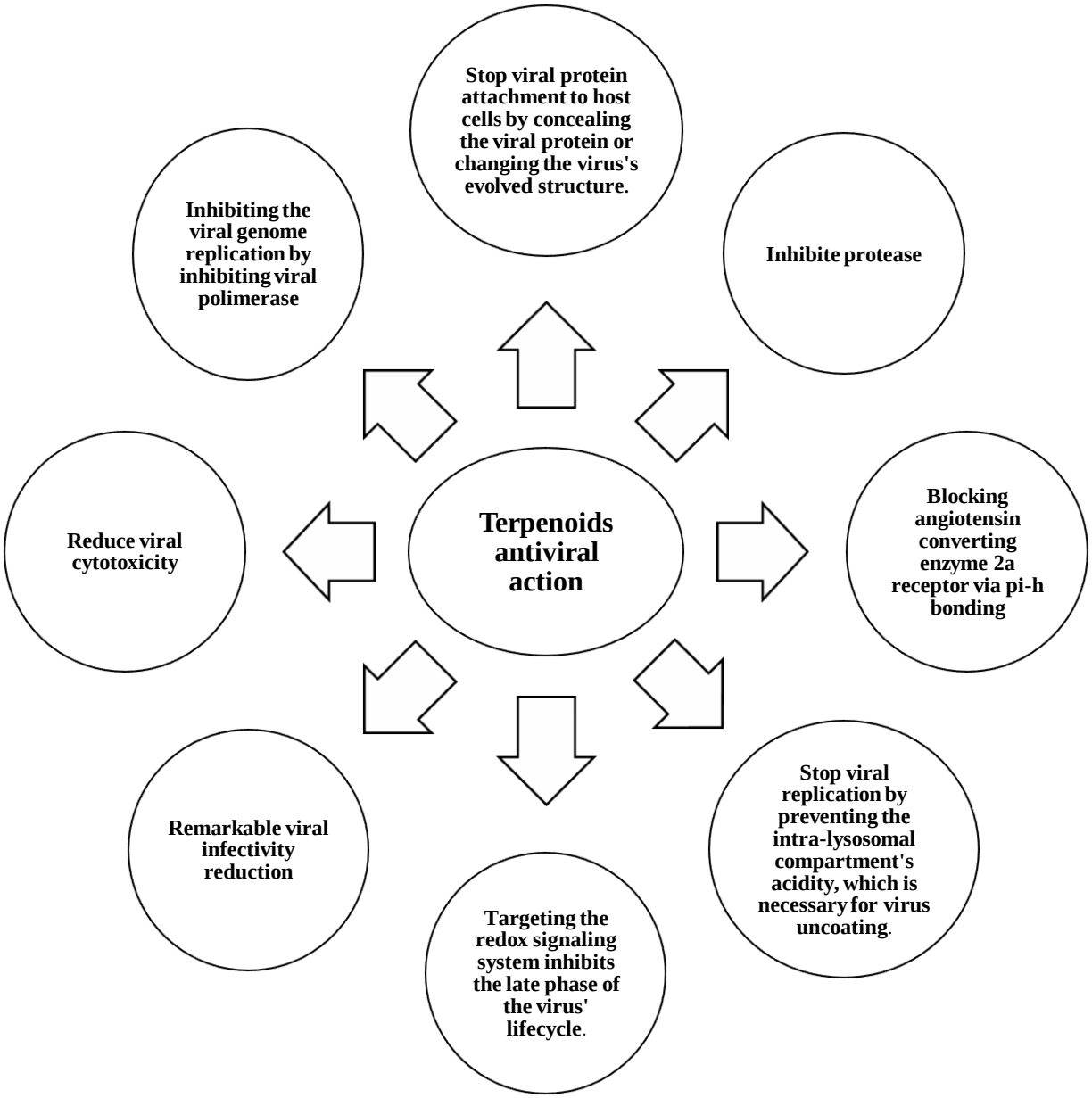

Fig no. 1: Terpenoids may have an antiviral effect through the above possible mechanism [66]

4.0 Anti-viral drug discovery strategies based on in silico virtual screening

Viral diseases continue to be a significant burden on public health despite the notable breakthroughs in medical and pharmacological research over the past few years. Virtual in-silico screening is repeatedly proved useful in addressing the unique challenges of antiviral drug development. Different computer screening techniques which include ligand-based similar searches, docking or pharmacophore-based screening, are used to filter large virtual compound libraries, lowering the number of candidate compounds to a more manageable number that is subsequently physiologically verified. This rational strategy helps the drug discovering process retains time and money as well as more goal-oriented.

4.1 Approaches to virtual screening

In silico VS describes the interactions between macromolecules and ligands using computational models. There are many different approaches that can be classified primarily into 2D and 3D approaches for this goal. Scalar molecular properties are estimated and compared as part of descriptor-based approaches (2D methods), which are used to find molecules that are comparable to one another in terms of those chemical characteristics.

The selection and weighting of descriptors pertinent to a particular target binding can be performed using machine-learning techniques, such as neural networks, or by linear correlation of measured biological activity (QSAR-quantitative structure–activity relationships) using calculated descriptors of interest. Most computational methods used recently to find anti-viral drugs focus on 3D techniques that try to characterise the steric and chemically complementarity of the 3D conformations of a macromolecular target and its binding ligand. There are two methods of creating 3D models: Design can be based on the (i) experimentally determined 3D structure of a disease-relevant macromolecular biological target (structure-based design) or (ii) a collection of ligands that are predicted to bind to the same target at the same position (ligand-based design). Xray crystallography is the primary information source for structure-based design, and the Protein Data Bank, also known as the PDB, is a great data source for such methods. When a ligand and the target structure are co-crystallized, the binding pocket position is ideally known beforehand. Contrarily, ligand-based design is used when there is no structural data on the target. It requires a group of already-known physiologically active compounds, whose shared binding site should be experimentally confirmed, such as , by mutational investigations. This makes it possible to find new potential ligands that exhibit a comparable 3D overlay in terms of molecular volume (molecular shape) or chemical activities (for example, hydrogen bond donors, acceptors, lipophilic regions, or charges). In terms of computing efficiency and applicability, 2D and 3D approaches are different: Due to their significantly faster calculation timeframes, 2D techniques are frequently employed as first classification filters to lessen the number of molecules that need to be screened later on. Structure-based 3D approaches position the putatively active ligand in the relevant binding site and are therefore frequently capable of providing suggestions for further chemical optimization of the compound (lead optimization). In some ways, ligand-based 3D techniques have the same advantage because they provide an overlay to known active compounds, which can be used to analyze factors crucial to lead optimization.

Table No. 1: Different types turpenoidal plants containing Antiviral activity:

Sr. No.	Plant name	Plant description	Phytoconstituents responsible for Antiviral activity	Virus	Reference
1	**Tulsi**	*Ocimum sanctum* [21] Family: Lamiaceae	Ursolic acid	Hepatitis B virus, adenoviruses, and herpes viruses [HSV]	[21, 22]
2	**Liquorice**	*Glycyrrhiza glabra*., Family: Leguminoseae	18 β-glycyrrhetinic acid, Glycyrrhizin, licochalcone A and E, liquiritigenin, glabridin	HSV, HRSV, DHV, HCV, Influenza virus, CVB3, H5N1,	[23], [24, 25],[26]
3	**Pomegranate**	*Punica granatum*, Family: Lythraceae	Punicic acid	influenza A viru	[27],[28],[29]
4	**Aaghada**	*Achyranthes aspera*, Family: Amaranthaceae	Ecdysterone, n-hexacos-14-enoic, triacontanol,	HSV-I & HSV-2 herpes	[30],[31],[32],[33]

			spathulenol, spina sterol, oleanolic acid, Achyranthine, triterpenoid-based saponins. and alkaloids, D-glucuronic, Betaine,	simplex virus type-I, & type-II,	
5	**Sweet flag**	*Acorus calamus* L. Family: Acoraceae [33, 34]	Asarone, α- and γ-asarone, asaronaldehyde, β-farnesene, calamenene, geranylacetate, borneol cis-methylisoeugenol, shyobunone, acorenone, calamenone, methyleugenol, epieudesmin, lysidine, [34]	HIV, Dengue	[33, 34]
6	**Garlic**	*Allium sativum*, [35]Family: Lilliaceae	Quercetin, allicin, thiosulfinates, ajoene	common cold virus, HIV, HSV-1, HSV-2, DENV, influenza virus A and B, human rhinovirus type 2, Newcastle Disease Virus [36]	[23], [35],[36],[33]
7	**Syzygium**	*Syzigium claviforum*,[37] Family: **Myrtaceae**	A pentacyclic triterpenoid betulinic acid	HSV-1, HSV-2,	[37]
8	**Hemp Marijuana, ganja and marihuana**	*Cannabis sativa* L [38]. Family:Cannabaceae [39]	terpenoids, hydrocarbons, cannabinoids, terpenes and phenolic compounds[39]	Newcastle disease virus [NDV], HIV-1[40]	[33],[41], [40, 42]
9	**Neem**	*Azadirachta indica*, Family:Meliaceae	Azadiractin	DEN-2 [Dengue virus type-2] [43] HSV	[43],[44]

				Measles, Chicken pox, and HIV[44]	
10	**Turmeric**	*Curcuma longa*, Family: Zinziberaceae	[1, 45]oids	Dengue virus Viral hemorrhagic septicemia virus, Human immunodeficiency virus, Zika virus [46], Chikungunya virus, Vesicular [14]	[1, 46], [45],[47],[48]
11	**Field marigold**	*Calendula arvensis* L. Family: Compositae [49, 50]	Sesquiterpene Glycosides[50]	active against two RNA viruses: the rhinovirus and the minus-strand RNA virus [HRV type 1B], vesicular stomatitis virus [VSV] , [49, 50]	[49, 50]
12	**Cinnamon**	*Cinnamomum zeylanicum* Blume Family:Lauraceae	eugenol [75–85%], linalool [1.6−8.5%], [E]−cinnamaldehyde [0.6−1.5%], [E]−cinnamyl acetate [0.7–2.6%], β-caryophyllene [0.5–6.7%], eugenyl acetate [0.1–2.9%], and benzyl benzoate [0.1–8.3%]	Influenza type A [H1N1], COVID-19	[62,63]
13	**Lemon**	*Citrus limonum*, Family: Rutaceae	Limonene, β-pinene and γ-terpinene	HSV-1	[62]
14	**Lemon grass**	*Cymbopogon flexuosus* [Nees] Family: Gramineae	geranial [48–54%] and neral [29–33%]	H1N1 [Influenza virus type A]	[62]
15	**Cynanchum**	*Cynanchum stauntonii* Family: Apocynaceae	2E,4E-decadienal, 3-isopropyl-1-	H1N1 [Influenza	[62]

			pentanol 5-pentyl-2[3H]-furanone and γ-nonalactone	virus type A]	
16	**Lavender**	*Lavandula angustifolia* Mill. Family: Lamiaceae	Linalool, lavandulol, β-caryophyllene, 1,8-cineole Linalyl acetate, geraniol, terpinene−4−ol and lavandulyl acetate	H1N1 [Influenza virus type A]	[64]
17	**Bitter orange**	*Citrus aurantium* L Family: Rutaceae	limonene, β-myrcene, α- β pinene.	Influenza type A [H1N1], COVID-19	[65]
18	**Ginger**	*Zingiber officinale* Family: Zingiberaceae [67]	Gingerols [68], zingiberene, zingerone, shogaols, and gingerols [67]	human respiratory syncytial virus **[HRSV]**	[67,68]
19	**April Rose**	*Camellia japonica* Family: Theaceae	Oleanane triterpenes 18β-hydroxy-28-norolean-12-ene3,16-dione, 3β,18βdihydroxy-28- norolean-12-en16-one [69]	Corona Virus	[69]
20	**Wormwood**	*Artemisia absentium*, Family: Asteraceae	Absinthin Artemisin Scopoletin Artamarin	Reduces coronavirus replication, HSV-1 and HSV-2, influenza virus A human herpes viruses HIV-1 and	[69]
21	**Ashwagandha**	*Withania somnifera*	Withanolide O, Withanolide P, Withanolide G, Withanolide F, Withanoside IV, Withanolide D, bsitosterol, and Somniwithanolide , Withanoside V		[83,84]

Plants containing terpenoids with antiviral activity:

1] Tulsi
Synonym: Holy Basil
Biological Source: *Ocimum sanctum* [21], Family: Lamiaceae
Phyto-constituents responsible for Antiviral activity: Ursolic acid, luteolin, luteolin-7-O glucuronide, apigenin, apigenin-7-O-glucuronide, molludistin and orientin additionally extracted from leaf extract [51]
Chemical structure:

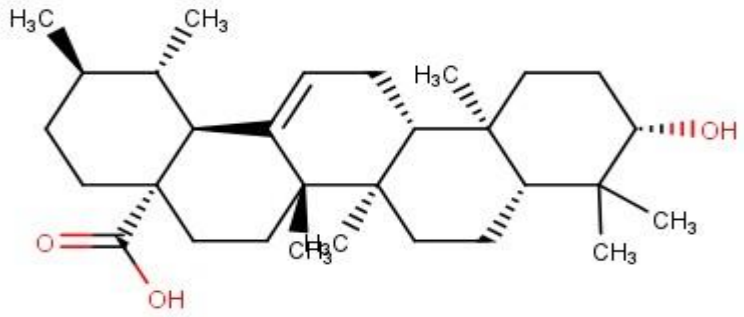

Figure 2. Ursolic acid

Mechanism of action: Hepatitis B virus, adenoviruses, and herpes viruses [HSV], as well as RNA viruses like enterovirus and coxsackievirus B1 [CVB1], are all effectively combated by O. basilicum [EV71] [22].

Molecular docking:
As per Priya Shree, Priyanka Mishra et.al. out of forty-six biologically active phytochemicals from O. sanctum (Tulsi), only three of the compounds, Vicenin (CID_3084407), Isorientin40 -O-glucoside 200-O-p-hydroxybenzoagte (CID_44257986), and Ursolic acid (CID_64945), demonstrated significant binding affinity compared to the built-in ligand N3 for SARS-CoV-2 Mpro. The binding energy of ursolic acid is 8.52 kcal/mol. It interacts with the residues Leu 271, Leu 288, and Tyr 239 to generate carbon and conventional hydrogen bonds as well as alkyl and p-alkyl interactions. Additionally, it generated a number of van der Waals interaction with the remaining residues (83).

2] Liquorice
Synonym: Gancao [25].
Biological Source: *Glycyrrhiza glabra L, Family: Leguminoseae* [25]
Phyto-constituents responsible for Antiviral activity: 18 β-glycyrrhetinic acid,Glycyrrhizin, licochalcone A and E, liquiritigenin, glabridin [[23]] The primary active ingredients with antiviral and antimicrobial properties include glabridin [GLD], 18-glycyrrhetinic acid [GA], licochalcone E [LCE], glycyrrhizin [GL], licochalcone A [LCA] [25].
Chemical structure:

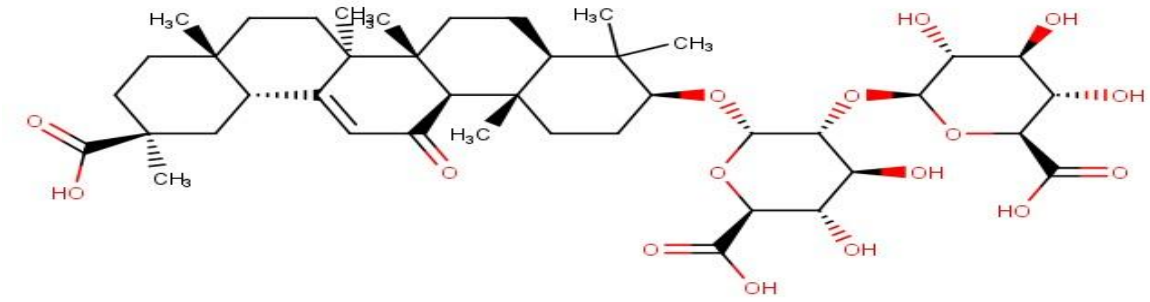

Figure 3. Glycyrrhizic acid

Mechanism of action: Reduce the levels of a viral proteins VP2, VP6, and NSP2 at the point of virus entry. 18 -glycyrrhetinic acid prevents viral attachment, internalisation, and promotes IFN release. [25]. Inhibit influenza virus polymerase and lessen HMGB1's ability to bind to DNA. [25].

Molecular docking: The ligand B (glycyrrhetinic acid) was docked with 4TWW.The same's docking scores were discovered to be -7.55. The best score for the water solubility characteristics (4.22) was observed for ligand B, which is glycyrrhetinic acid, out of all the evaluated phytochemical ligands (85).

3] Pomegranate

Synonym: Anar

Biological Source: *Punica granatum* L [28],[29], Family: **Lythraceae**

Phyto-constituents responsible for Antiviral activity: Punicic acid, ellagic acid, and fatty acids are all found in seed oil. The leaves include apigenin, punicafolin, punicalin, luteolin, and luteolin glucopyranosides.

The barks and roots contain ellagitannins and piperidine alkaloids, while the flowers contain punicaflavone, gallic acid, ursolic, asiatic, and maslinic acids [27].

Chemical structure:

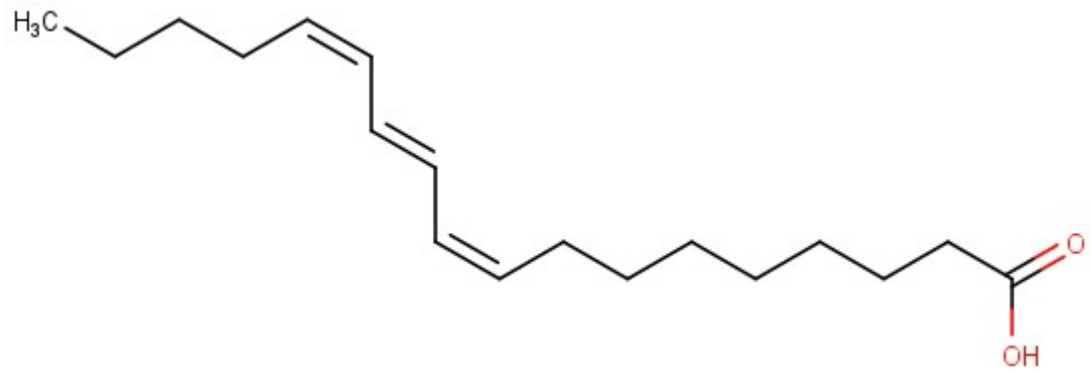

Figure 4. Punicic acid

Mechanism of action: Pomegranate polyphenol extract constituents punicalagin, caffeic acid, ellagic acid and luteolin, punicalagin has the strongest antiviral activity against influenza A virus through the viral RNA replication suppression [27].

Molecular docking:

Punicic acid can inhibit expression of IL-6, IL-8, IL-12, and TNF-α, by modulating PPAR-gamma, which restrains the expression of the NF-κB pathway

4] Aghada

Synonym: Apaamaarga [31],[32], Latjira [[33]]

Biological Source: *Achyranthes aspera* [30],[32]Family: Amaranthaceae [30],[32]

Phyto-constituents responsible for Antiviral activity: oleanolic acid [32]

Chemical structure:

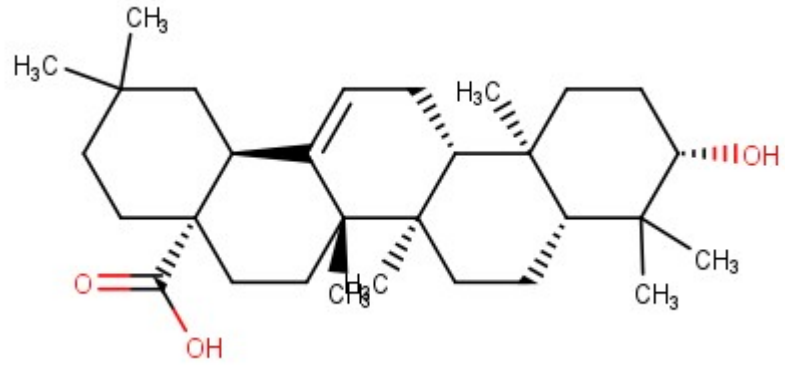

Figure 5. oleanolic acid

Mechanism of action:
Inhibits earlier stages of HSV multiplications.
Molecular docking:
Using AutoDock, a compound of oleanolic acid forms a complex with a binding energy of 6.0 kcal/mol. A hydrogen bond was created by the amino acid Gln189, while two other amino acids (Cys145 and His163) were implicated in hydrophobic interactions (87).

5] Sweet flag
Synonym: sweet flag, muskrat root
Biological Source: *Acorus calamus* L [33], Family: Acoraceae[34, 52]
Phyto-constituents responsible for Antiviral activity: α- and γ-asarone, β-Asarone, methyleugenol, calamenene, geranylacetate, n-heptanic acid, asaronaldehyde, cis-methylisoeugenol, shyobunone, calamenone, epishyobunone, calamendiol,β-farnesene, and isoshyobunone, acorenone[33].
Chemical structure:

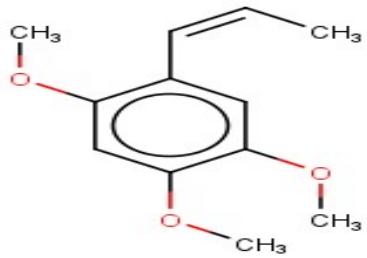

Figure 6. β-Asarone
Mechanism of action: A chemical derived from the plant exhibited unique antiviral action against Dengue Virus DENV2, inhibiting post-translation or early RNA production. Consequently, it could also be employed as an anti-Dengue Virus [DENV] lead compound. It also exhibited anti-HIV-1 reverse transcriptase enzyme activity.[33]
Molecular docking:
Diasarone-I may serve as an inhibitor of NS5's 2'O Methyltransferase, according to in silico study[88].

6] Garlic
Synonym: Lahsun
Biological Source: *Allium sativum*, [35]Family: Lilliaceae
Phyto-constituents responsible for Antiviral activity: Allicin [35],[36] methyl allyl thiosulfinate, alliin, allyl methyl thiosulfinate, ajoene, diallyl trisulfide, deoxyalliin, and diallyl disulfide, [36]
Chemical structure:

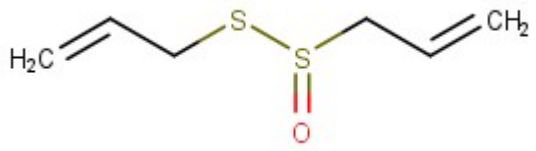

Figure 7. Allicin

Mechanism of action: Fresh garlic extract contains the highest concentration of thiosulfinate, which inhibits the adsorption or penetration of non-enveloped viruses, presumably by inhibiting the virus's replication.[36]

Molecular docking:

The best docked molecule from Autodock and CDocker was Allicin, which received scores of -3.9 for both programmes. Ajoene came in second with a top docked score of 85.658 for Libdock.Glu166, Cys145, Ser144, , His41, Met165, Pro168, and Leu167 were among the amino acid residues that interacted with the ligands via H-bond or Pi-Alkyl interactions.

7] Syzygium

Synonym: Syzygium

Biological Source: *Syzigium claviforum*,[37] Family: **Myrtaceae**

Phyto-constituents responsible for Antiviral activity: A pentacyclic triterpenoid betulinic acid

can interfere with viral fusion with cells and also decrease reverse transcriptase activity and virus assembly.[37]

Chemical structure:

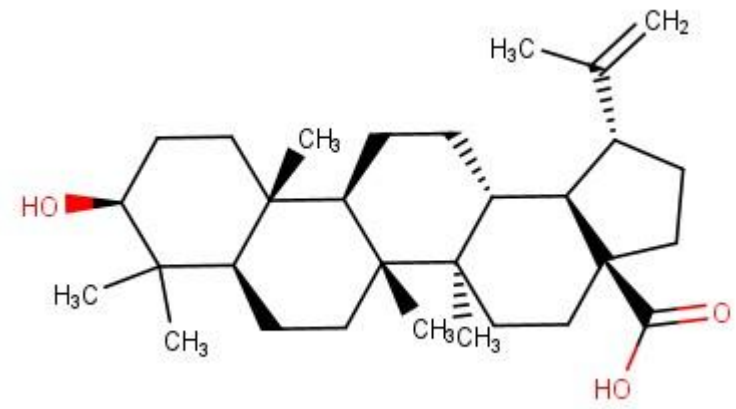

Figure 8. Betulinic acid

Mechanism of action: A pentacyclic triterpenoid betulinic acid

can interfere with viral fusion with cells and also decrease reverse transcriptase activity and virus assembly.[37]

Molecular Docking:

Based on having the lowest free energy value (-10.0 Kcal/mol) on the major COVID-19 protease, betulinic acid was placed first among the examined substances panel. The hydrophobic contacts, which produced ten pi-alkyl bonds between betulinic acid and the amino acids Leu 27, Cys 145, Met 49, His 41, and Met 165, were the other major type of interaction.

8] Hemp

Synonym: Cannabis

Biological Source: *Cannabis sativa* L[38]. Family: Cannabaceae

Phyto-constituents responsible for Antiviral activity: cannabidiol [CBD][42]

Chemical structure:

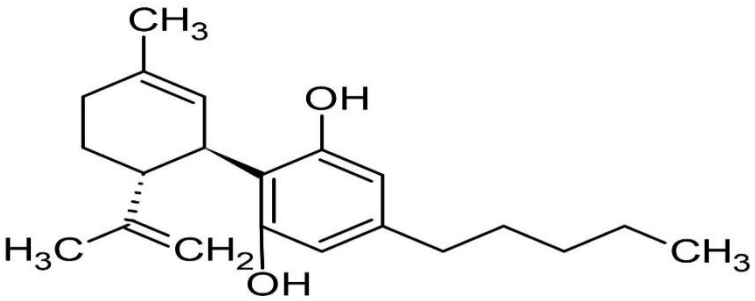

Figure 9. Cannabidiol

Mechanism of action: It potently inhibited viral replication under non-toxic conditions with EC50s ranging from 0.2-2.1 μM[42].

By inhibiting antiviral immune responses, in vitro and in vivo investigations shown that medicinal use of immunoregulating cannabis contributed to disease progression, increased morbidity, and even caused host mortality. Therefore, blocking CB2 receptors is just a therapeutic target for inhibiting immunosuppressive effects in specific viral infections.[40]

Molecular Docking:

When all 43 of the plant's cannabinoids and non-cannabinoids were docked with the ACE2 receptor, three potential ligands were found to have a higher affinity for the receptor than its well-known inhibitor MLN-4760 (7.1kcal/mol as binding energy) and to interact with the receptor in a nearly identical way[91]. Cannabinol, cannabinolic acid, cannabichromanon, and cannabicyclolic acid were among the substances tested, and they demonstrated significant activity as indicated by their best fitting scores within the binding sites of three key enzymes involved in viral replication and host invasion, SARS-CoV-2 MPro, SARS-CoV-2 PLpro, and ACE2[92].

9] Neem

Synonym: Nira, nimb

Biological Source: *Azadirachta indica* Juss [43],[44]. Family: Meliaceae

Phyto-constituents responsible for Antiviral activity: Azadirachtin, a complex tetranor-triterpenoid limonoid found in seeds, is primarily responsible for antifeedant and poisonous actions. [53].

Chemical structure:

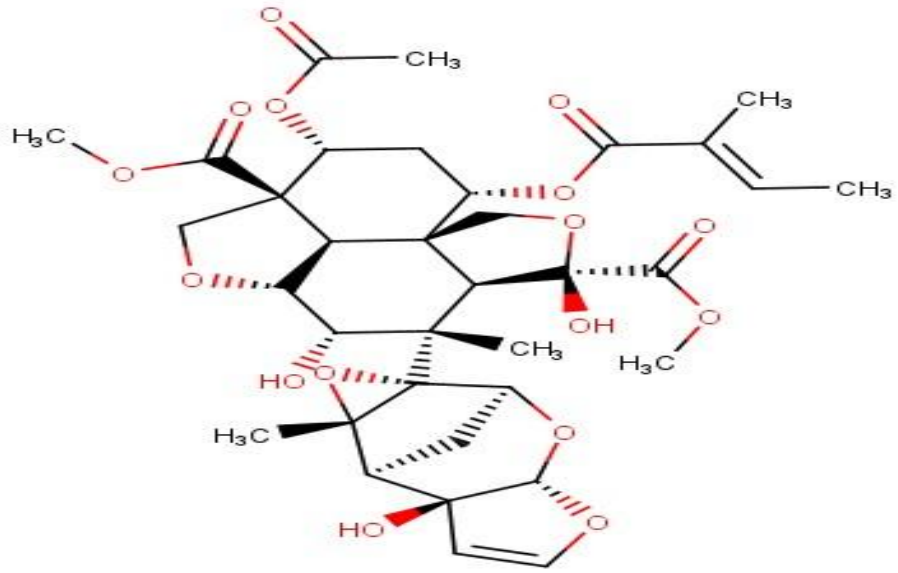

Figure 10. Azadirachtin

Mechanism of action: Neem has been used to treat numerous viral diseases, including HIV, chicken pox, HSV, measles, and chikungunya [Parida, Upadhyay et al. 2002]. At doses

between 50 and 100 g/mL, neem bark extract [NBE] substantially inhibited HSV-1 entry into cells.[53].

Molecular Docking:

With a binding free energy of 8.18 kcal mol1, azadirachtin H docks favourably at the spike RBD-ACE2. According to these docking studies, compound CID 16722121 exhibits a strong affinity for the pocket but not the catalytic site.

10] Turmeric
Synonym: Haldi,

Biological Source: *Curcuma longa*, Family: Zinziberaceae.

Phyto-constituents responsible for Antiviral activity: Curcumin,

Chemical structure: [46]

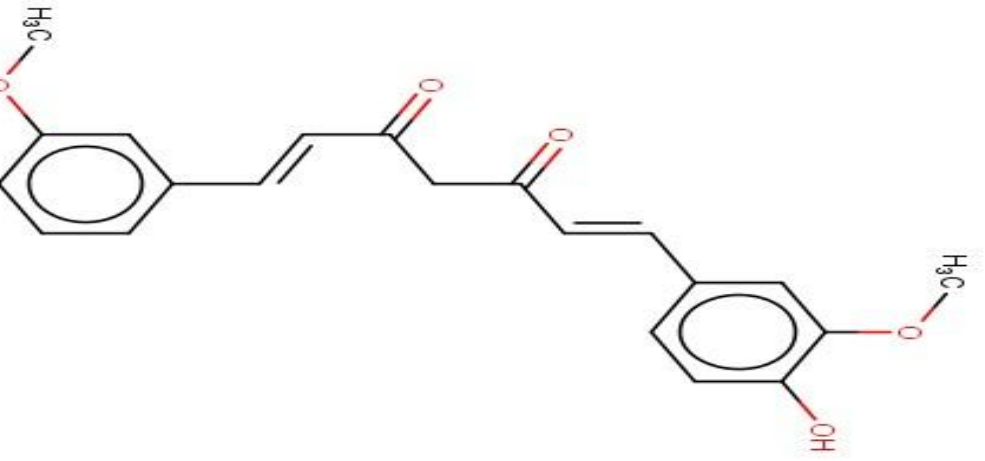

Figure 11. Curcumin

Mechanism of action: Through a variety of ways, curcumin and its derivatives can prevent the proliferation of a wide range of viruses which include viral entry inhibition, Protein expression & replication [1]. Curcumin [at 20 M and 40 M] exhibited strong anti-SARS-CoV action, as described. [45],[45, 47]

Molecular Docking:

With a score of 139.727, curcumin sulphate was determined to be the best docked ligand from the Libdock data. Asp623, Asn691, Arg555, and Ser682 were amino acid residues that were heavily involved in the hydrogen bonding with the majority of the ligands. Dihydrocurcumin's interactions with the RdRp protein are shown in Figure 8. There were contacts between the RNA's U20, A11, and U10 atoms[89].

11] Calendula
Synonym: Field marigold

Biological Source: *Calendula arvensis* L, Family: Compositae [49, 50, 54].

Phyto-constituents responsible for Antiviral activity: oleanolic acid glycosides 1—4 [49, 50, 54], Calendulaglycoside A [55]

Chemical structure: [49, 50, 54].

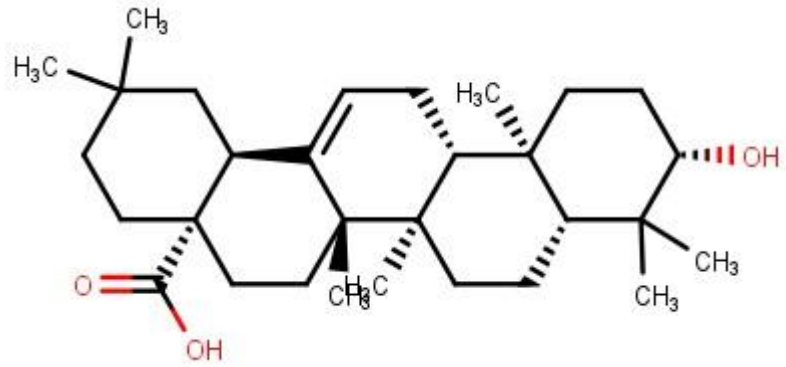

Figure 12. Oleanolic acid

Mechanism of action:
Inhibit the growth of several enveloped viruses. [De Tommasi, Pizza et al. 1990]
Molecular Docking:
Carvacrol, oleanolic acid, and ursolic acid have all demonstrated adequate interactions with a ctive site residues based on AutoDock binding affinity.
According to research, the binding energies of these substances are, respectively, -
4.0 kcal/mol, -6.0 kcal/mol, and -5.9 kcal/mol. From a biological perspective, the reported phytochemicals carvacrol, oleanolic acid, and ursolic acid are suggested as possible M pro inhibitors and have been shown in in vitro tests to have considerable antiviral action [94].

12] Cinnamon
Synonym: Kalmi dalchini
Biological Source: *Cinnamomum zeylanicum* Blume, Family:Lauraceae [62,63]

Phyto-constituents responsible for Antiviral activity: Eugenol, eugenyl acetat, linalool, [E]−cinnamaldehyde, [E]−cinnamyl acetate, β-caryophyllene, and benzyl benzoate.
Chemical structure:

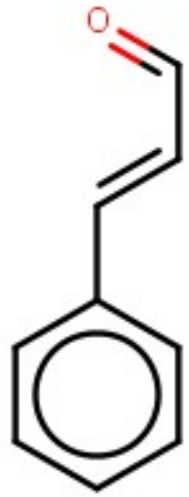

Figure 13. cinnamaldehyde

Mechanism of action:

In COVID-19, chronic obstructive pulmonary disease [COPD] and asthma the accumulation of inflammatory cells leads to respiratory tract blockage. Trypsin was inhibited by phenolic substances, cinnamic acid, caffeic acid, gallic acid, and eugenol isolated from Cinnamomum zeylanicum [a serine protease]. Cinnamic acid [IC50 = 53%] and caffeic acid [IC50 = 84%] exhibited the greatest ability to inhibit enzyme activity. [64]

Molecular Docking:

One of the phytochemicals with a high docking score that we have found is cinnamaldehyde, and when all the descriptors are taken into account, it gets the best score[95].

13] Synonym: Lemon

Biological Source: *Citrus limonum,* Family: Rutaceae

Phyto-constituents responsible for Antiviral activity: limonene [54.6%], β-pinene [14.5%] and γ-terpinene [19.1%].

Chemical structure:

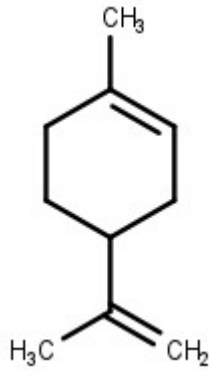

Figure 14. Limonene

Mechanism of action:

Essential oils may have biological effects, such as activating GABA and olfactory receptors, as well as transient receptor potential channels, and transmitting messages to the olfactory bulb and the brain.

Molecular Docking:

D-limonene exhibited high binding with the major protease, with a binding energy of -5.2 kcal/mol, with RNA dependent RNA polymerase, at -5.4 kcal/mol, and with the Spike receptor binding domain, at -7.1 kcal/mol[96].

14] Synonym: Lemon grass

Biological Source: *Cymbopogon flexuosus* [Nees]Family: Gramineae

Phyto-constituents responsible for Antiviral activity: geranial [48–54%] and neral [29–33%]

Chemical structure:

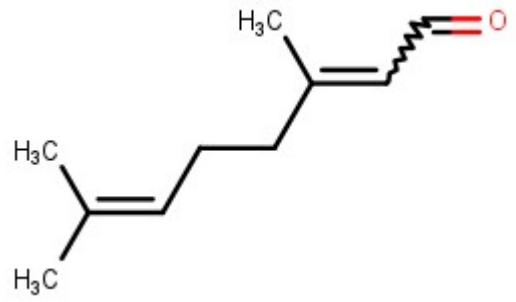

Figure 15. Geranial

Mechanism of action:
Inhibit the late stage of virus life cycle by targeting on redox signaling pathway. Inhibiting viral replication by inhibiting viral polymerases.
Molecular Docking:
In HT29 epithelial cells, geraniol also reduced the expression of the protein and mRNA for the ACE2 receptor. The researchers discovered that EOs from various plant families, including geraniol, carvacrol, cinnamaldehyde, anethole,-terpineol, thymol, and pulegone, all efficiently attached to the S1 RBD of the spike (S) glycoprotein[97].

15] Synonym: Cynanchum

Biological Source: *Cynanchum stauntonii [*Decne.] Family: Apocynaceae

Phyto-constituents responsible for Antiviral activity: [2E,4E]-decadienal, 3-isopropyl-1-pentanol, γ-nonalactone and 5-pentyl-2[3H]-furanone.

Chemical structure:

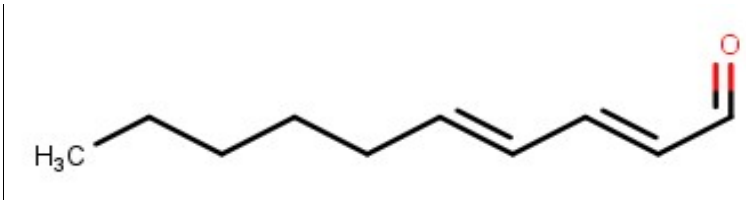

Figure 16. [2E,4E]-decadienal

Mechanism of action: inhibit viral host receptors.
In HT29 epithelial cells, geraniol also reduced the expression of the protein and mRNA for the ACE2 receptor. The researchers discovered that EOs from various plant families, including geraniol, carvacrol, cinnamaldehyde, anethole,-terpineol, [2E,4E]-decadienal,

thymol, and pulegone, all efficiently attached to the S1 RBD of the spike (S) glycoprotein[97].

16] Synonym: Lavender

Biological Source: *Lavandula angustifolia* Mill. Family: Lamiaceae

Phyto-constituents responsible for Antiviral activity: linalool, Linalyl acetate, β-caryophyllene, lavandulol, geraniol, terpinene−4−ol and lavandulyl acetate [66]

Chemical structure:

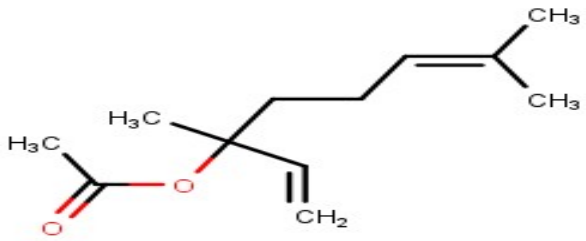

Figure 17. Linalyl acetate

Mechanism of action:

Stop binding to host cell by masking the viral protein or by modifying the virus envoloped structure.

Molecular Docking:

In HT29 epithelial cells, geraniol also reduced the expression of the protein and mRNA for the ACE2 receptor. The researchers discovered that EOs from various plant families, including geraniol, carvacrol, cinnamaldehyde, anethole,-terpineol, thymol, and pulegone, all efficiently attached to the S1 RBD of the spike (S) glycoprotein[97].

17] Synonym: Bitter orange

Biological Source: *Citrus aurantium* L, Family: Rutaceae

Phyto-constituents responsible for Antiviral activity: limonene,β-myrcene, α & ß pinene

Chemical structure:

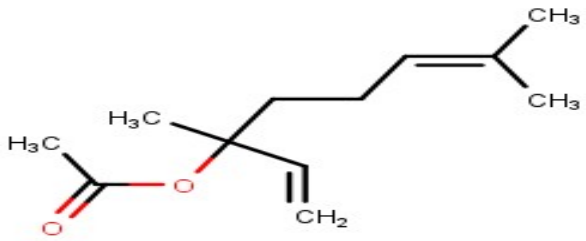

Figure 18. Linalyl acetate

Mechanism of action:

Stop binding to host cell by masking the viral protein or by modifying the virus envoloped structure.

Molecular Docking:

In HT29 epithelial cells, geraniol also reduced the expression of the protein and mRNA for the ACE2 receptor. The researchers discovered that EOs from various plant families,

including geraniol, carvacrol, cinnamaldehyde, anethole,-terpineol, thymol, and pulegone, all efficiently attached to the S1 RBD of the spike (S) glycoprotein[97].

18] Synonym: Ginger

Biological Source: *Zingiber officinale* Family: Zingiberaceae [67]

Phyto-constituents responsible for Antiviral activity: Gingerols [68], zingiberene, zingerone, shogaols, and gingerols [67]

Chemical structure:

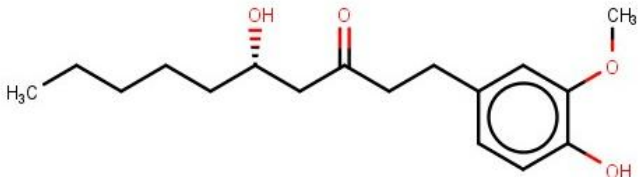

Figure 19. Gingerol

Mechanism of action:
G and F protein effects inhibit viral attachment, internalisation, and may stimulate IFN-b release. [68]

Molecular Docking:

The results of a flexible docking analysis using flexX software between COVID-19 viral targets and gingerol showed binding affinities and docking scores ranging from -2.8764 KJ/mol to -15.7591 KJ/mol. Gingerol binds to 5R7Y with the greatest affinity (-15.7591 KJ/mol). The COVID-19 viral spike glycoprotein interacts with gingerol in a molecular manner to establish hydrogen-bonded interactions with the residues Glu63, Arg89, Thr92, and Asp129 and non-bonded interactions with the residues Lys66, Glu63, Arg89, Thr92, Leu168, and Pro169[98].

19] Synonym: April Rose

Biological Source: *Camellia japonica* Family: Theaceae [69]

Phyto-constituents responsible for Antiviral activity: n-eicosane, α-linolenic acid neophytadiene, n-octacosane, all trans-squalene, 6,9-pentadecadien-1-ol, and n-hexadecanoic acid [69]

Chemical structure:

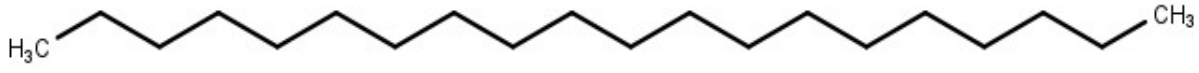

Figure 20. n-eicosane

Mechanism of action: Strong antiviral activity against the PEDV coronavirus Effects inhibiting the synthesis of critical genes and proteins during PEDV replication. Suppression of coronavirus [PEDV] skeleton protein leads to inhibition of viral growth. [72]
Molecular Docking:

In HT29 epithelial cells, geraniol also reduced the expression of the protein and mRNA for the ACE2 receptor. The researchers discovered that EOs from various plant families, including geraniol, carvacrol, cinnamaldehyde, anethole,-terpineol, thymol, and pulegone, all efficiently attached to the S1 RBD of the spike (S) glycoprotein[97].

20] Synonym: Wormwood

Biological Source: *Artemisia absentium* Family: Asteraceae [69]

Phyto-constituents responsible for Antiviral activity: Absinthin Artemisin Scopoletin Artamarin [69]

Chemical structure:

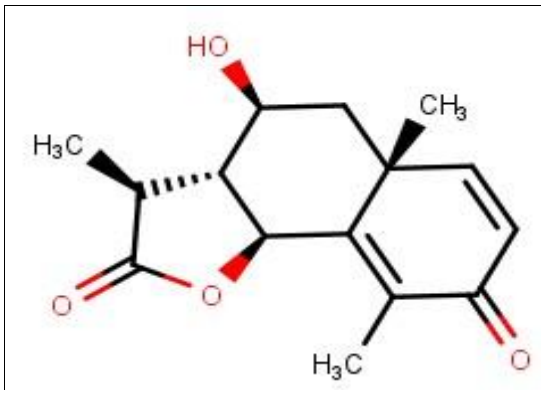

Figure 21. Artemisin

Mechanism of action: Reduces coronavirus replication. Viral replication and growth are inhibited by a variety of mechanisms, including the production of cellular ROS, Inhibition of the PI3K/Akt/p70S6K signalling pathway, binding to the NF-B/Sp1 transcription factor, and activation of an endocytosis inhibition mechanism.

Molecular Docking:
In addition, a molecular docking analysis was used to predict the binding affinities between artemisinin and the seventeen ACE2 variants that have been reported to bind with the coronavirus spike protein. The binding affinities were in the range of 4.9 to 8.2 kcal/mol. COVID-19 spike glycol protein residues Leu168,Arg89, Glu63, Thr92, Lys66, and Pro169

21) Ashwagandha
Synonym: Indian Ginseng
Biological Source: ***Withania somnifera***[83], Family: Solanaceae
Phyto-constituents responsible for Antiviral activity: Withanoside V withanolides (class of naturally occurring C28 steroidal lactone triterpenoids along with, steroidal lactones, alkaloids, tropine, Withanolide O, Withanolide P, Withanolide G, Withanolide F, Withanoside IV, Withanolide D, bsitosterol, and Somniwithanolide [83,84]
Chemical structure:

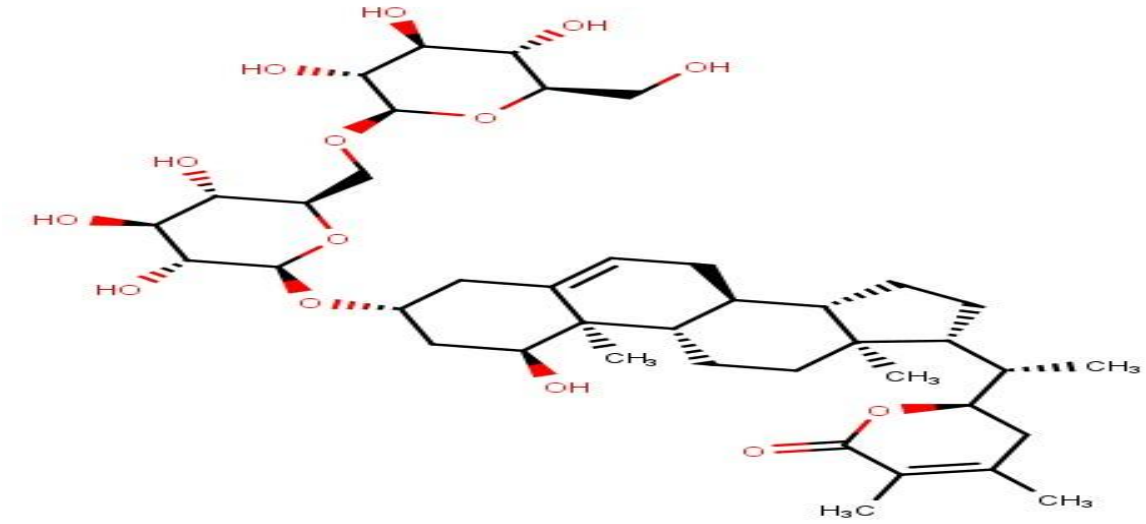

Figure 22. Withanoside

Mechanism of action: Withanolides may prevent the RBD of the SARS-CoV-2 S-protein from interacting with the ACE2 receptor. Because the interaction between the RBD of SARS-CoV-2 the S-protein and the ACE2 receptor is crucial for the entrance of the virus into the host cells during infection, bioactive compounds of Withania somnifera, like withanone and withaferin-A, may be useful in treating and managing the symptoms of COVID-19[84].

Molecular docking:

According to results from a molecular docking study, only two compounds from the W. somnifera (Ashwagandha) family, withanoside V (CID_10700345) and somniferine (CID_14106343), demonstrated a significant increase in binding affinity for the SARS-CoV2 Mpro virus when compared to native N3 (CID_146025593). The maximum binding energy was 10.32 kcal/mol for withanoside V[83].

Conclusions and Future Perspectives:

Traditional plants have conventionally been exploited in the healthcare profession to cure a variety of illnesses. Natural product-based therapies [phytochemicals] for human wellbeing are related to lower toxicity and fewer negative effects. As a result, scientists are working to clarify novel plant-based chemicals utilized in the treatment of a vast array of disorders. According to their antioxidant, anticancer, antibacterial, and antiviral properties, many plants secondary metabolites have been investigated and widely used in a variety of medical treatments.

There are several natural remedies for viral respiratory infections that are both safe and efficient. There is potential for photo-chemicals to be used to cure viral infections, according to numerous in vitro and in silico studies. Even though many have been verified through clinical trials, some require more confirmation. Several the modes of action include directly inhibiting several harmful viruses, affecting the inflammatory and immune response to the infection, and lowering symptoms. Terpenoid has received the most research attention and has been used to treat a range of viral infections among all phytochemicals. Additionally, some of the terpenoids showed promising antiviral property against influenza, dengue, chikungunya, and several other viruses, making them viable candidates that might be further processed to produce antivirals. Terpenoids have been the most extensively investigated and utilized phytochemicals to treat numerous viral infections.

Literature Study

For each portion of a manuscript, articles were chosen and located by searching for keywords and journal citations. After examining abstracts and raw data, related peer-reviewed scientific journal papers were selected from various journal depositories. [45-48, 56-58]

Declarations :

Author contribution statement :
All listed authors made substantial contributions to the conception and composition of this article.

Funding support:
This research did not receive any specific grants from funding sources or agencies in the public, commercial, or not-for-profit sectors.

Conflict of interests :
The authors have disclosed no conflicts of interest.

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