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Investigation of Terpenoid derivative as Potent Inhibitor of SARS-CoV-2 Nsp13 Helicase: Grid Based Docking Approach

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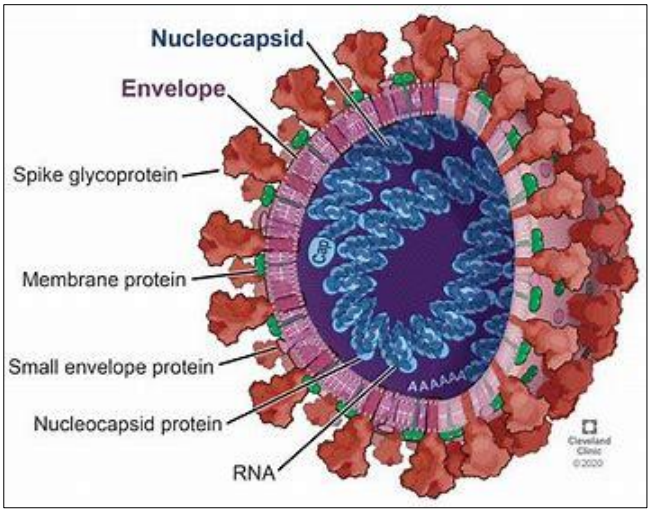
Abstract
The coronavirus (COVID-19) is an enveloped RNA virus with varied origins in humans and wildlife. Six distinct species have been identified as the causative agents of human disease. Viral infections substantially affect human health, with the recent global epidemic being the introduction of the novel coronavirus. The SS-RNA virus belonging to the enveloped coronavirus family is responsible for the potentially fatal Severe Acute Respiratory Syndrome (SARS). In numerous countries worldwide, illness is proliferating rapidly. As of March 26, 2020, there have been 462,684 confirmed cases and 20,834 recorded fatalities internationally. The World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020. A multitude of pharmacological research are currently under progress, with several yielding favorable outcomes. The sole method to combat the virus is through preventative measures, as no immunization exists. The objective of the present work was to employ a molecular docking methodology to assess terpenoid derivatives as possible agents against SARS-CoV-2 infection. Clarification of the suggested mechanism of action of natural terpenoids (terpein-4-ol, terpinolene, and beta-sesquiphellandrene) in combating SAR-CoV-2 infection.

Keywords: SARS-CoV-2 Nsp13 Helicase, terpenoid, Molecular Docking & Prevention measures

Introduction
The novel coronavirus (SARS-CoV) is responsible for the initial significant global epidemic of the new millennium. The repeated development and outbreaks of CoV pose a significant risk for public health. The likelihood increases that newly found coronaviruses may transmit between humans and from animals to humans. Ongoing ecological and climatic alterations heighten the probability of future epidemics of these illnesses. The COVID-19 coronavirus has created issues in 188 countries and territories globally. A study indicated that the coronavirus was responsible for 31,200 total infections and 13,071 recorded deaths [1]. Research is ongoing about SARS caused by the coronavirus, as the optimal therapy remains contentious. Immune modulation, supportive therapy, and antiviral agents [2]. Nearly a decade following SARS, Middle Eastern nations have witnessed the introduction of the highly perilous Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [3]. The order Nidovirales encompasses the families Coronaviridae, Arteriviridae, and Roniviridae, primarily consisting of viruses identified as coronaviruses (CoVs) [4]. A coronavirus is an enveloped, single-stranded RNA virus characterized by surface spikes measuring between 9 and 12 nm in length. Fever, cough, and dyspnea are among the symptoms [5-6].



Structure of CoV

Mode of transmission [6]

- The transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between individuals is mostly believed to occur through respiratory droplets.
- Infection may occur if an individual contacts a contaminated surface and subsequently touches their eyes, nose, or mouth.

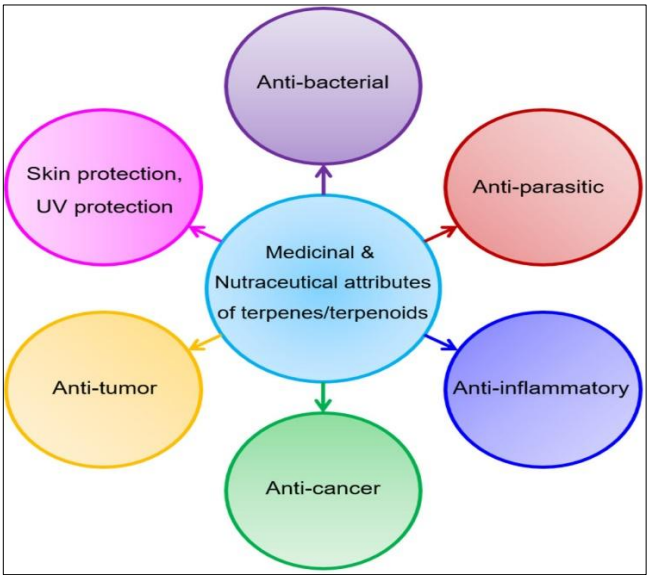
Co-morbidity associated with CO-V 19

- An analytical examination of CoV cases indicates that diabetes and hypertension are prevalent in roughly 50% of the patients. Coronary heart disease (CHD) is observed in 30% of instances, while obesity is prevalent in 16%. These conditions diminish the production of pro-inflammatory cytokines and compromise the host's innate and humoral immune responses [6].

Prevention of COVID-19 [7]

- Cleanse your hands; utilize a hand sanitizer with a minimum of 60% alcohol content.
- Avoid contact with your eyes, nose, and mouth using unwashed hands.
- Refrain from proximate interaction
- Conceal your mouth and nose
- Don a facemask
- Daily clean and disinfect surfaces that are often touched.

Terpenes, or terpenoids, represent the largest and most diversified category of naturally occurring chemicals. They are classed as mono-, di-, tri-, tetra-, and sesquiterpenes based on the quantity of isoprene units present. They predominantly occur in plants and provide the primary component of essential oils derived from them. Terpenes serve significant and diverse functions among natural compounds that confer medical benefits to organisms. Common botanical sources of terpenes include tea, thyme, cannabis, Spanish sage, and citrus fruits such as lemon, orange, and mandarin. Terpenes possess numerous medical applications, with considerable anti-plasmodial activity, as their mode of action resembles that of the widely used antimalarial medication, chloroquine. Monoterpenes are extensively researched for their antiviral properties. Given the increasing prevalence of cancer and diabetes in contemporary society, terpenes may also function as anticancer and antidiabetic medicines. In addition to these features, terpenes provide flexibility in administration routes and mitigate negative effects. Specific terpenes were extensively utilized in traditional folk medicine. Curcumin is a terpene that possesses anti-inflammatory, antioxidant, anticancer, antiseptic, antiplasmodial, astringent, digestive, diuretic, and various other characteristics [8].



Pharmacological Potential of Terpenoid

Description of Selected Lead molecules [9-11]

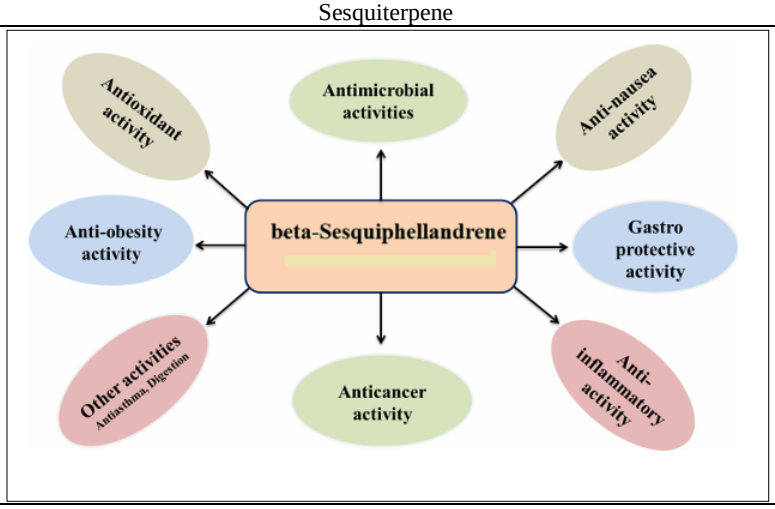
Terpien-4-ol

S. No.	Description	
1.	Molecular formula	$C_{10}H_{18}O$
2.	Molecular weight	154.25 g/mol
3.	Synonym	• Terpinen-4-ol • 4-Carvomenthenol • 562-74-3 • 4-Terpineol • p-Menth-1-en-4-ol
4.	Category	Cyclic terpenes
5.	Pharmacology	• Antibacterial agent • Antioxidant • Anti-inflammatory agent • Antiparasitic agent • Antineoplastic agent • Apoptosis inducer

Terpinolene

S. No.	Description	
1.	Molecular formula	$C_{10}H_{16}$
2.	Molecular weight	136.23 g/mol
3.	Synonym	• Terpinolene • Isoterpinene • Terpinolen • alpha-Terpinolene
4.	Category	Monoterpene
5.	Pharmacology	• Anti-Inflammatory and Pain Management • Potential Anti-Anxiety Effects • Neuroprotection and Anticancer Properties • Anti-Microbial and Anti-Fungal Effects

β-Sesquiphellandrene

S. No.	Description	
1.	Molecular formula	$C_{15}H_{24}O$
2.	Molecular weight	204.35 g/mol
3.	Synonym	beta-Sesquiphellandrene (-)-beta-Sesquiphellandrene 20307-83-9 (-)-(6R,7S)-sesquiphellandrene (3R)-3-[(2S)-6-methylhept-5-en-2-yl]-6-methylidenecyclohexene
4.	Category	Sesquiterpene
5.	Pharmacology	

Experiment Work

Selection of Lead molecules

Terpenoids are prevalent in microorganisms, marine organisms, plants, insects, and fungus. This class comprises several terpenoids and isomers. Research has highlighted their diverse pharmacological effects and significant biological activity, including potential as hypoglycemic, anti-inflammatory, antiviral, and anticancer agents. Recent studies have increasingly emphasized the potent antiviral properties of terpenoids. Previous literature studies demonstrated that diterpenes (tanshinone and carnosic acid) and sesquiterpene lactone (arteminins) exhibit inhibitory activity against SARS-CoV-2 [12].Recent literature on Terpien-4-ol indicates its diverse pharmacological properties, including antibacterial, antivirulent, antioxidant, anti-inflammatory, antihypertensive, and anticancer effects [13].Research has revealed terpinolene as a bioactive compound with significant pharmacological capabilities, including its antifungal, antioxidant, and insecticidal effects. β-sesquiphellandrene is regarded as a notable contributor to the anticancer properties of ginger and has exhibited *in vitro* antiviral activity against rhinovirus 1B [15].

In the present study, several new terpenoid derivatives, namely terpinen-4-ol, terpinolene, and β-sesquiphellandrene were evaluated for their anti-SARS-CoV-2 efficacy.

Selection of Target Protein

The coronavirus nonstructural protein 13 (nsp13) encodes an RNA helicase (nsp13-HEL) with many enzymatic functions, including unwinding and nucleoside triphosphate (NTP) hydrolysis activities. Research aimed at enzymatic inactivation has recognized nsp13-HEL as a crucial enzyme for viral replication and a primary target for antiviral investigation. Helicases have exhibited several functions outside their conventional ATPase and unwinding responsibilities; however these activities are just now being explored in the context of coronavirus biology. Recent genetic and biochemical research, together with studies on structurally similar helicases, has provided evidence that supports new hypothesis concerning the helicase's likely role in coronavirus reproduction [16].

Designed of *In-Silico* molecular docking analysis

This study aims to conduct molecular docking, molecular dynamics studies, and predict the ADMET properties of

selected promising antiviral terpenoid drugs. The study clarifies biomolecular interactions to understand the inhibitory mechanism and spatial arrangement of the assessed ligands, along with the identification of essential amino acid residues in the substrate-binding pocket relevant for structure-based drug design. We performed molecular docking studies of terpie-4-ol, terpinolene, and β-sesquiphellandrene against Nsp13 helicase to assess their potential as anti-SAR-CoV-2 drugs. In-silico analyses, encompassing molecular docking, dynamics, and drug-like property prediction of the natural compound, were performed using Nsp13 helicase as the target protein.

Molecular docking studies

Ligand Preparation

The 2D structures of ligands such as terpein-4-ol, terpinolene, and beta-sesquiphellandrene were created using ChemSketch. These two-dimensional structures were subsequently transformed into their three-dimensional counterparts, optimized for 3D geometry. The optimized structures were preserved in PDB format for compatibility with AutoDock. The fundamental structures of the synthesized ligands are presented below:

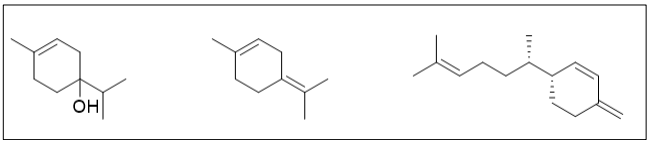


Fig 1: 2D structure of terpein-4-ol, terpinolene and beta-sesquiphellandrene

Preparation of the grid file: The regions of interest utilized by Autodock were delineated by constructing a grid box encompassing the active sites. The grid box is crucial in the docking process as it encompasses all amino acids in the active sites required for binding, excluding those found in the receptor. The grid box contains three thumbwheel widgets that allow for the adjustment of points in the x, y, and z directions. The spacing between grid points can be modified using an additional thumbwheel, with a value of 0.458 Å. The number of points evaluated is 50 in each dimension (x, y, and z), with centers at -13.606, 25.925, and -70.215 for x, y, and z, respectively [18-20].

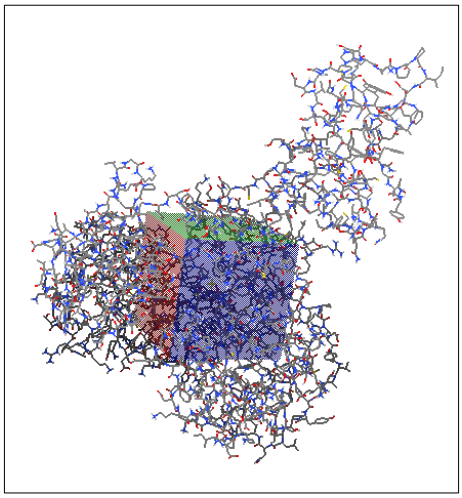


Fig 2: Grid box covering all active sites in NSP13 helicase enzyme

Preparation of the docking file

All computations were conducted with Autodock 4.2 as the docking tool. The visualization and other requisite programs for docking investigations were executed using Pymol, Chimera, DS Visualizer, and MMP Plus [21-24].

Docking of beta-tubulin with Quercetin

Crystal structure: The crystal structure of the NSP13 helicase enzyme is obtained from the Protein Data Bank. All principal information pertaining to the receptor and structure (6zsl.pdb) recorded in the Protein Data Bank was utilized [25-27].

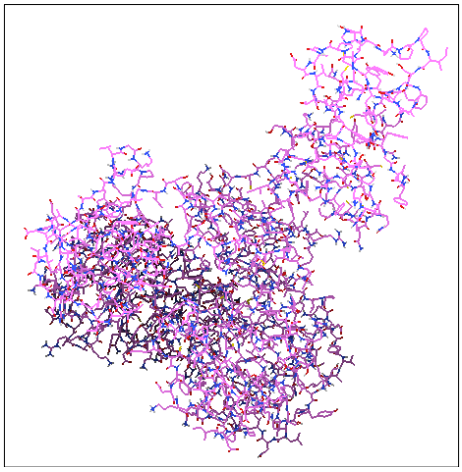


Fig 3: Crystal structure of NSP13 helicase enzyme (PDB ID-6zsl)

Processing of Protein

The downloaded receptor protein consists of two chains, namely chain A and chain B. Chain B was chosen for experimental purposes, whereas the other chains were discarded. The bound ions were isolated from the macromolecular complex utilizing Chimera software [28-29].

Molecular Docking Simulation Studies

Docking of ligands such as terpein-4-ol, terpinolene, and beta-sesquiphellandrene against the viral NSP13 helicase enzyme was conducted using Autodock. All bonds of each ligand were maintained in a flexible state, whereas no residues in the receptor were rendered flexible [30-33].

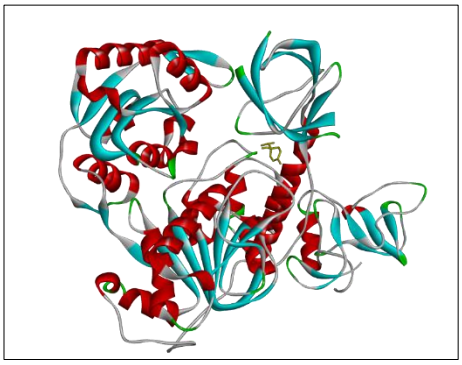


Fig 4: Binding mode of terpein-4-ol within the active site of viral NSP13 helicase enzyme

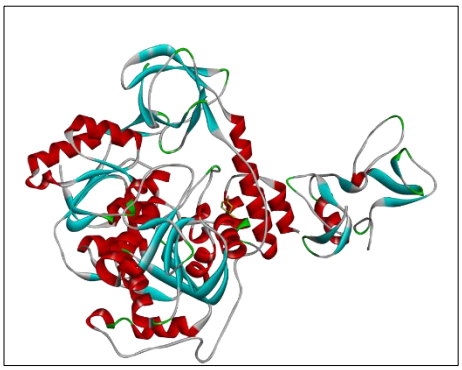


Fig 5: Binding mode of tepinolene within the active site of viral NSP13 helicase enzyme

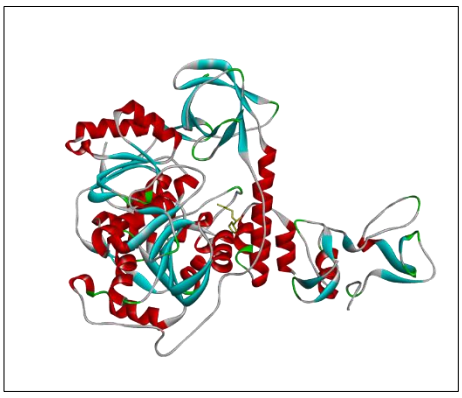


Fig 6: Binding mode of beta-sesquiphellandrene within the active site of viral NSP13 helicase enzyme

Toxicity & ADME-T Studies

The ligand compounds, namely terpein-4-ol, terpinolene, and beta-sesquiphellandrene, were analyzed using the online tool OSIRIS to anticipate the presence of any hazardous groups and assess their ADME-T characteristics [35].

Results and Discussion

The novel coronavirus (SARS-CoV) represents the inaugural significant outbreak of the new millennium across many nations globally. CoV epidemics and recurring outbreaks provide a risk to public health. This indicates the potential for transmission of CoV between animals and humans, as well as between humans themselves. Ongoing alterations in ecosystems and climate heighten the probability of such illnesses occurring in the future. The novel coronavirus, COVID-19, impacts 188 nations and territories globally. The study reports a total of 312,002 coronavirus infections and 13,071 fatalities. Treatment for coronavirus-related SARS is progressing, and there is no agreement on the ideal therapeutic protocol. Therapeutic therapies for SARS including broad-spectrum antibiotics, supportive care, antiviral medication, and immunomodulatory treatment. Approximately a decade following SARS, another virulent coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV), has emerged in the Middle East, alongside Arteriviridae and Roniviridae. Coronaviruses are enclosed, single-stranded ribonucleic acids characterized by surface spikes measuring 9-12 nm in length. Symptoms including fever, cough, and dyspnea. The coronavirus nonstructural protein 13 (nsp13) encodes an RNA helicase (nsp13-HEL) that possesses many enzymatic capabilities, including unwinding and nucleoside triphosphate (NTP) phosphatase activity. Efforts to achieve enzymatic inactivation have identified nsp13-HEL as an essential enzyme for viral replication and a primary target for antiviral research. Helicases have several functions outside their traditional ATPase and unwinding activities; however, these roles are only beginning to be investigated in the context of coronavirus biology. Recent genetic and biochemical investigations, along with studies on structurally analogous helicases, have yielded information that bolsters new hypotheses regarding the helicase's putative function in coronavirus reproduction. Potential helicase inhibitors can be classified into four categories based on their binding sites on the CoV nsp13-HEL: zinc-binding domain inhibitors, nucleic acid-binding site inhibitors, nucleotide-binding site inhibitors, and inhibitors with unidentified binding sites. Nucleic acid-binding site inhibitors seek to obstruct helicase-RNA interactions, hence impeding RNA unwinding and helicase movement along the nucleic acid strand. These inhibitors comprise helicase-specific non-G-quadruplex aptamers, which are small, single-stranded RNA molecules. Terpenoids are a varied category of phytochemicals originating from isoprene units, demonstrating considerable promise as antiviral drugs. Mechanistic insights into their antiviral effect encompass disruption of viral entrance, replication, and modulation of host immunological responses. Their complex methods of action provide them appealing candidates for the treatment of viral infections and present chances for synergy with current antiviral medications. Studies have emphasized their varied pharmacological effects and notable biological activities, including their potential as hypoglycemic, anti-inflammatory, antiviral, and anticancer medicines. Recent research has progressively highlighted the powerful antiviral activities of terpenoids. These chemicals exhibit the capacity to obstruct viral adsorption and penetration into host cells

during the initial phases of infection, hence inhibiting viral replication post-cell entry. The result of molecular docking was tabulated in table 1, showing binding energy -4.77,-5.42,-6.08 kcal/mol for terpinen-4-ol, terpinolene, and β-sesquiphellandrene respectively. The binding mode showed in fig.4-6 whereas 2D &3D binding interaction was shown in fig.7-12. The IC50 showing 0.13,0.11 & 0.10 for terpinen-4-ol, terpinolene, and β-sesquiphellandrene respectively. All selected lead molecules showed good interaction with selected ligand but highest binding interaction displayed by terpinolene with viral NSP13 helicase enzyme having drug-likeness score 0.46. The binding interaction of lead molecules are as follows:

Lead molecule	Vanderwaal's	CH bounding	Pi-Sigma	Alkyl
Terpine-4-ol	Thr 410 Lys 146 Thr 179	Val181 ASN179	Thr180	Leu227
Terpinolene	Arg409 Thr 380 Glu142 Thy 382 ASN 381 ASN124	--------	--------	Ala135 Leu138 Lys139 Thy120 Ala123
β-sesquiphellandrene	Glu142 Tyr382 Thr380 Arg409 Tyr120 Pro408 ASN 124 ASN381	--------	--------	Leu138 Ala407 Lys139 Ala135

The pharmacokinetic profiling of the *terpinen-4-ol, terpinolene, and β-sesquiphellandrene* ligand has revealed that it is having good pharmacokinetic profile associated without the presence of major toxic effects like reproductive effects, irritant effect, and tumorogenic properties, but shows the presence of some mutagenicity. The pharmacokinetic and toxicity profiling results of lead molecule was shown in fig.13-15 & table. 2-5.

Summary and Conclusion

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), referred to as "the novel coronavirus" because to its genomic divergence from previously recognized coronaviruses, is a positive-sense RNA virus and the causative agent of COVID-19. SARS-CoV-2 belongs to the viral family Coronaviridae and the subfamily Coronavirinae, comprising large, enveloped, single-stranded RNA viruses ranging from 65 to 125 nm in diameter. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly transmissible and pathogenic coronavirus that arose in late 2019, resulting in a pandemic of acute respiratory disease known as 'coronavirus disease 2019' (COVID-19), posing significant risks to human health and public safety.Terpenoids are small secondary metabolites in plants and are undoubtedly the most prevalent category of natural goods. Terpenoids exhibit a variety of pharmacological effects, including antiviral, antibacterial, antimalarial, anti-inflammatory, hypoglycemic, and anticancer actions. Terpenoids represent the most extensive category of phytochemicals, comprising a variety of molecules with significant structural diversity. A literature review revealed that the selected lead compounds exhibit a variety of pharmacological activities, including antioxidant, antibacterial, antiviral, apoptosis-inducing, and anti-inflammatory actions. This study aims to evaluate the efficiency of flavonoids and elucidate the suggested mechanism of action against SARS-CoV infection. The precise antiviral mechanism of flavonoids against SARS-CoV-2 remains undisclosed. To suggest the most likely mechanism of action of flavonoids, a docking-based computational analysis has been conducted against antiviral medication targets such as SARS-CoV helicase. The SARS-CoV-2 helicase Nsp13 possesses both ATPase and helicase functions, as it unwinds RNA helices in an ATP-dependent fashion. Nsp13 is seen as a promising target for antiviral medication development due to its significant sequence conservation among the coronavirus family. Furthermore, it has been demonstrated that the SARS-CoV-2 helicase Nsp13 is capable of hydrolyzing all varieties of NTPs, including ATP, to facilitate the unwinding of RNA helices. The established ATP-binding location of the helicase Nsp13 represents a viable target for potent inhibition. The investigation into docking analysis, chemical interactions, and physicochemical pharmacokinetic profiling has demonstrated that the terpenoid exerts its antiviral effect by inhibiting SARS-CoV helicase, thereby obstructing ATPase and helicase activity as it unwinds RNA helices in an ATP-dependent manner. The finding revealed that selected terpenoids i.e. terpein-4-ol, terpinolene and β-sesquiphellandrene are potent inhibitor of SARS-CoV-2 helicase Nsp13 in following manner: terpein-4-ol > terpinolene > β-sesquiphellandrene.

Theoretically, all ligand compounds exhibit promising docking scores and can be anticipated as effective inhibitors of the viral Nsp13 helicase enzyme.

A literature review revealed that the selected lead compounds exhibit a variety of pharmacological activities, including antioxidant, antibacterial, antiviral, apoptosis-inducing, and anti-inflammatory actions.

Divulgence of Investigation

The present study examined the prevalent presence of terpenoids in medicinal plants and their role in combating COVID-19. Terpenoids may exhibit possible inhibitory effects against SARS-CoV-2 by binding to essential viral sites required for entry and/or replication, as indicated by computational studies. The proposed mechanism of action are as follows:

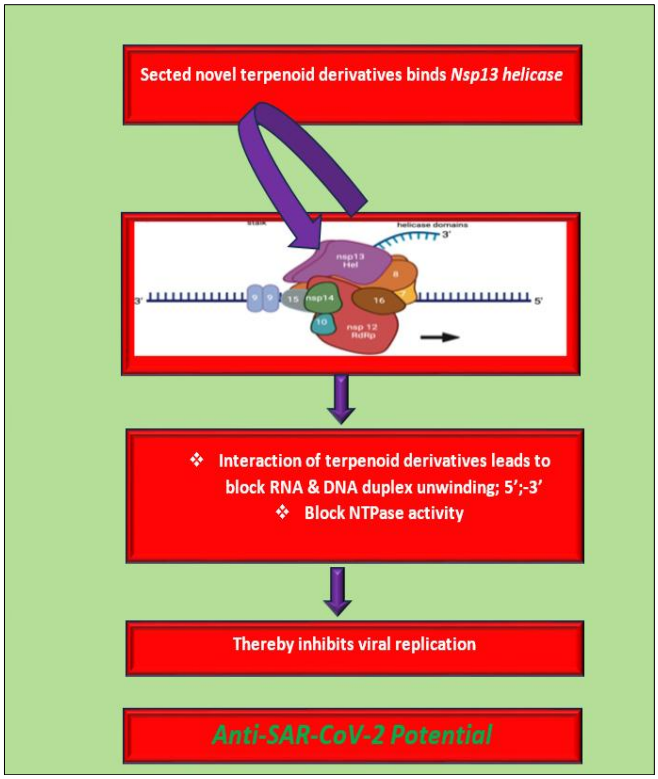
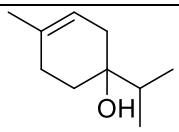
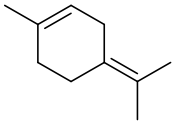
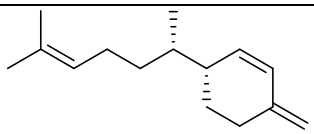


Table 1: Results of docking of ligands like terpein-4-ol, terpinolene, and beta-sesquiphellandrene against viral NSP13 helicase enzyme

Sl. No	Compound Name	Structure	Binding Energy (Kcal/mole)	Ki	IC50
1	Terpein-4-ol		-4.77	7.9	0,13
2	Terpinolene		-5.42	9.14	0.11
3	Beta-sesquiphellandrene		-6.08	10.26	0.10

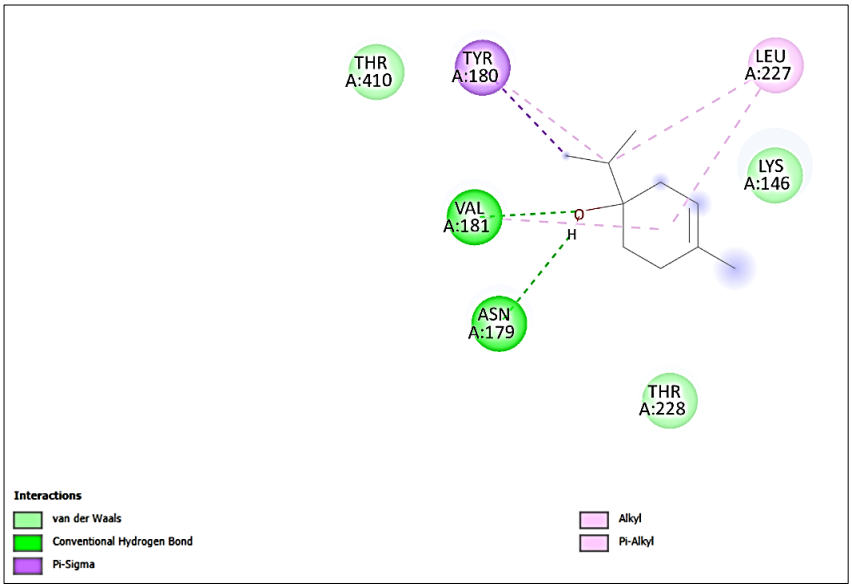


Fig 7: Two-dimensional binding mode of terpein-4-ol within the active site of viral NSP13 helicase enzyme

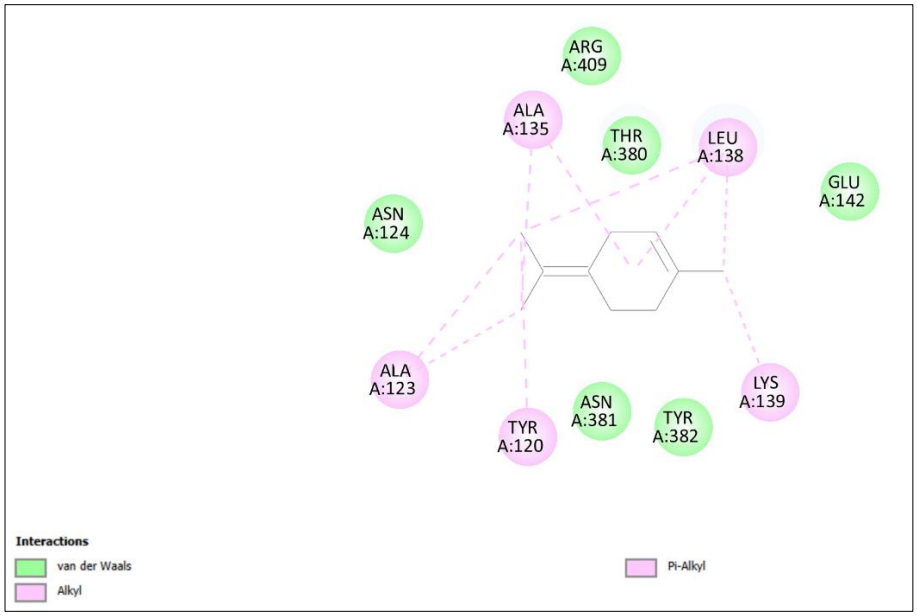


Fig 8: Two-dimensional binding mode of terpinolene within the active site of viral NSP13 helicase enzyme

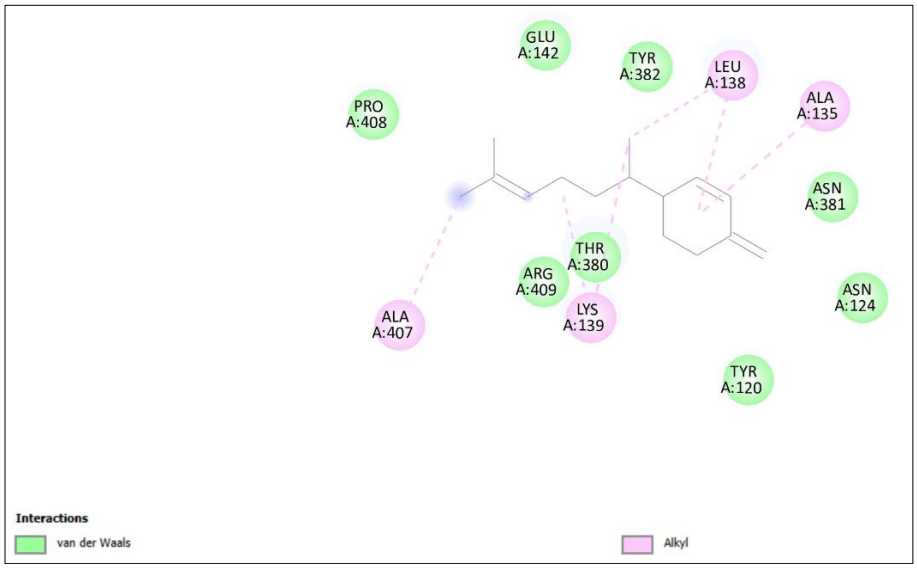


Fig 9: Two-dimensional binding mode of beta-sesquiphellandrene within the active site of viral NSP13 helicase enzyme

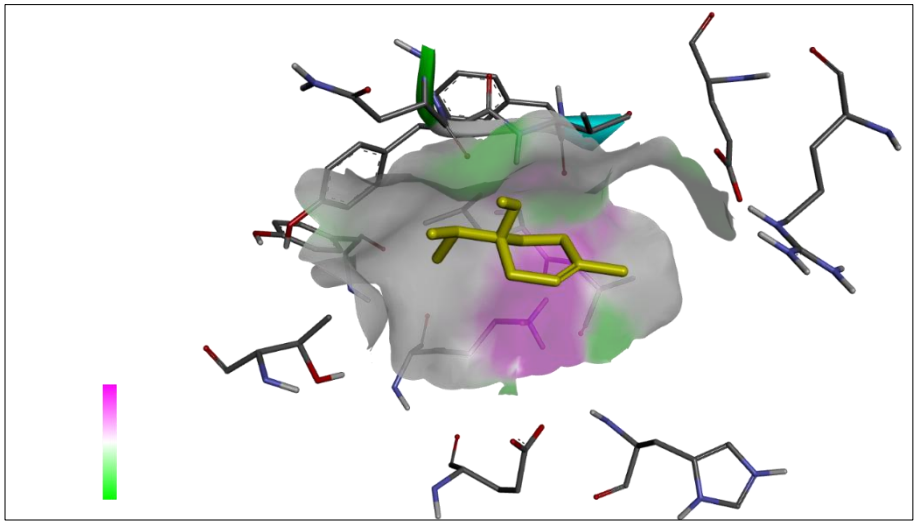


Fig 10: Three-dimensional binding conformation of terpein-4-ol within the active site of viral NSP13 helicase enzyme

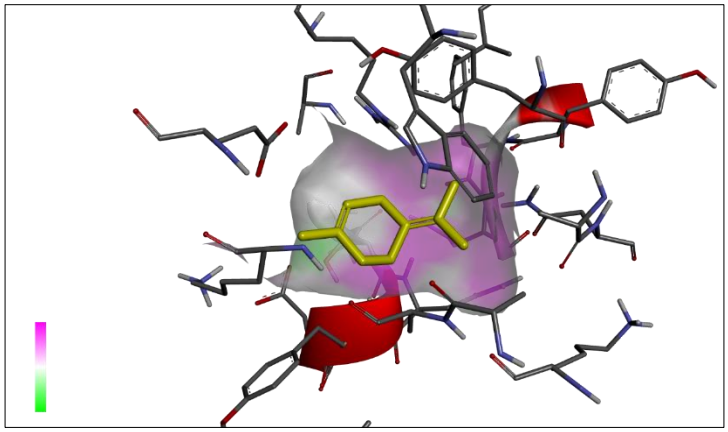


Fig 11: Three-dimensional binding conformation of terpinolene within the active site of viral NSP13 helicase enzyme

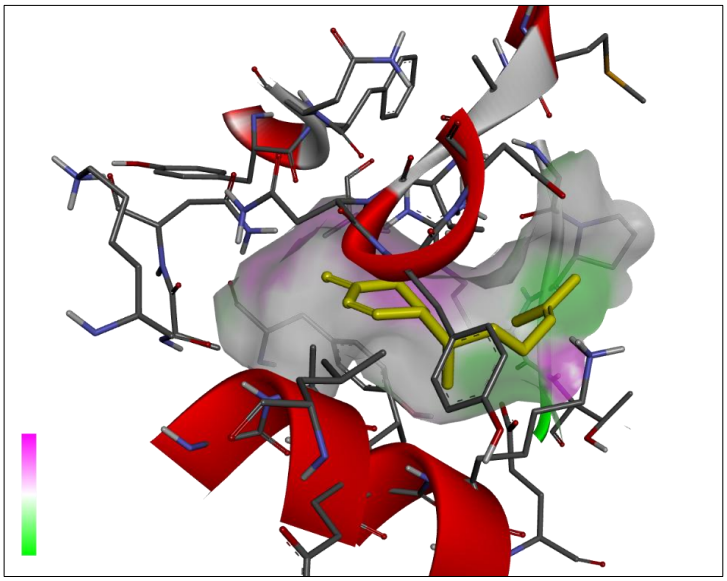


Fig 12: Three-dimensional binding conformation of beta-sesquiphellandrene within the active site of viral NSP13 helicase enzyme

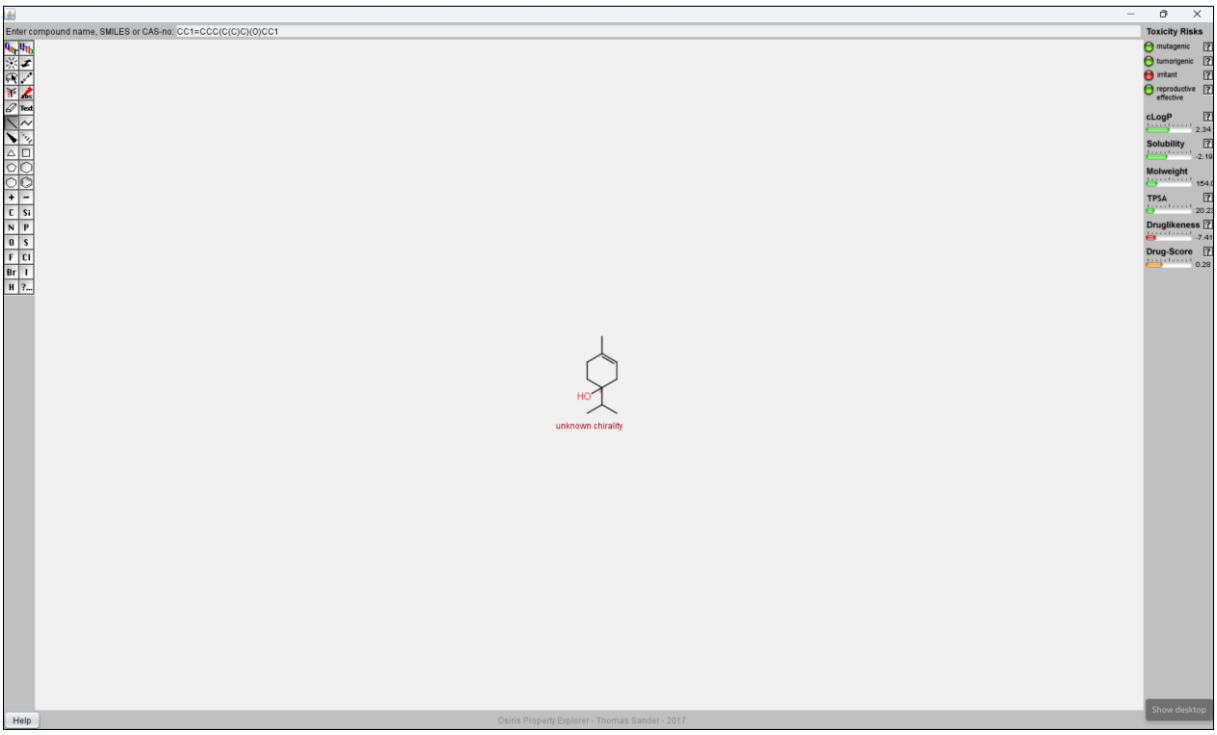


Fig 13: Pharmacokinetic and toxicity profiling of terpein-4-ol

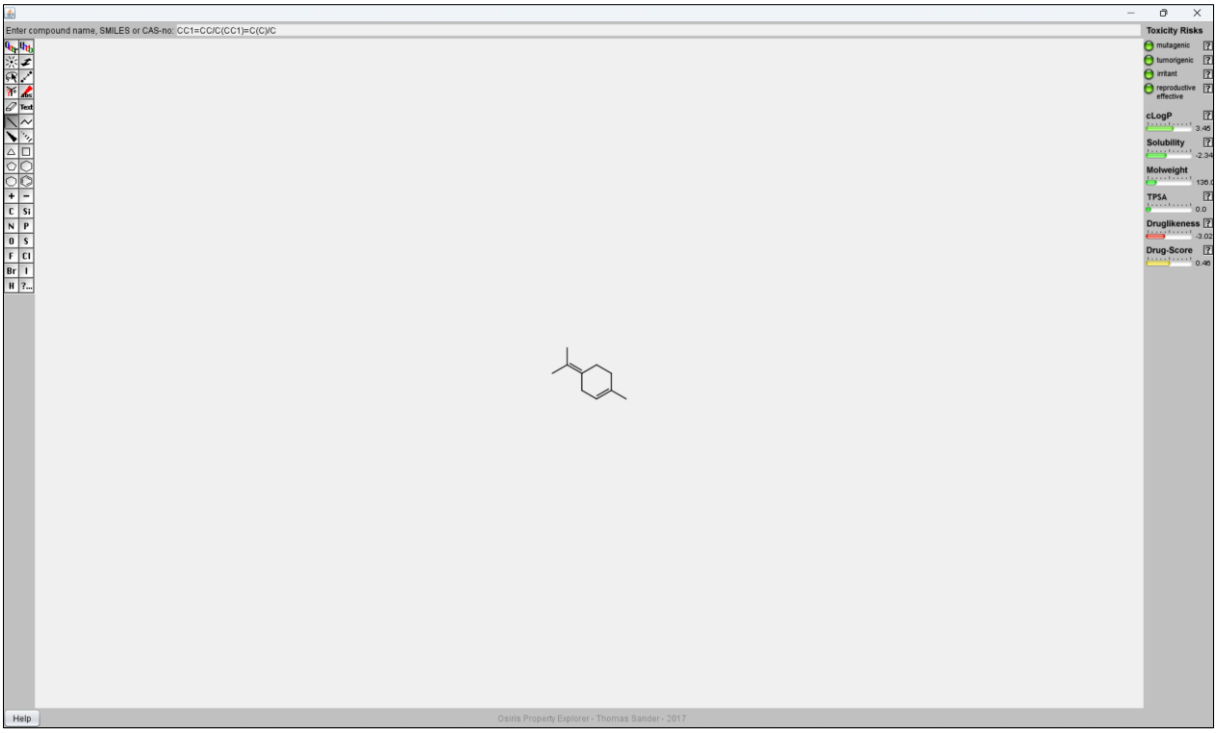


Fig 14: Pharmacokinetic and toxicity profiling of terpinolen

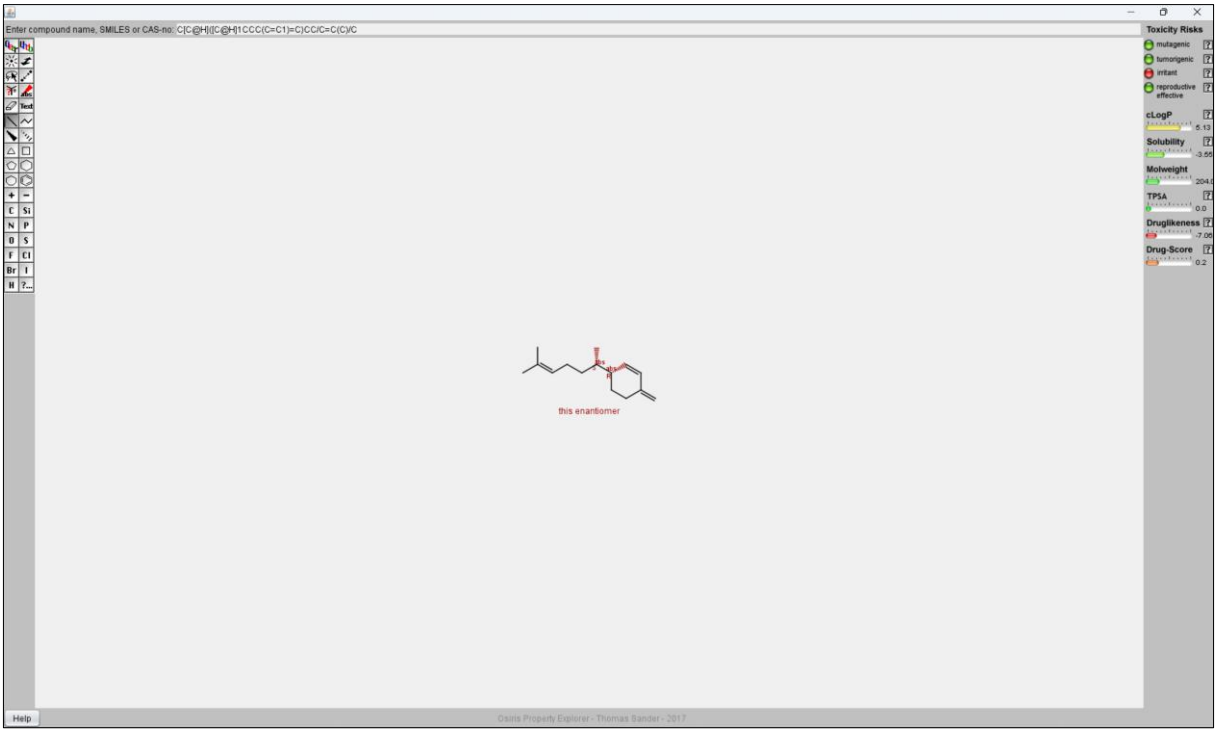


Fig 15: Pharmacokinetic and toxicity profiling of beta-sesquiphellandrene

Table 2: Pharmacokinetic Profiling of lead molecules

Compound	ADMET			
	Mutagenic	Tumorigenic	Irritant	Reproductive effectivity
terpein-4-ol	NO	NO	Yes	NO
Terpinolene	NO	NO	NO	No
beta-sesquiphellandrene	NO	NO	NO	No

Table 3: Lipinski Properties of lead molecules

Compound	*cLogP*	Solubility	Mol.wt.	TPSA	Drug likeness	Drug score
terpein-4-ol	2.34	-2.10	154	20.21	-7.4	0.26
Terpinolene	3.45	-2.3	136	10.1	-3.02	0.46
beta-sesquiphellandrene	5.13	-2.5	204	0.1	-7.02	0.2

Table 4: Drug likeness of lead molecules

Compound	Lipinski rule of five	H bond donar(<5)	H bond acceptor (<10)
terpein-4-ol	Yes	1	1
Terpinolene	Yes	0	0
beta-sesquiphellandrene	Mild	0	0

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