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In silico studies of essential oil components from Indian herbal formulation against RdRp enzyme in Covid-19 virus

Abstract

Ayush Kwath (AK), a traditional herbal remedy from India, is used to treat viral and bacterial infections of the respiratory tract. A GC-MS analysis of essential oils isolated from AK revealed 52 components, of which 10 had known medicinal uses. These substances included α-zingiberene, α-curcumene, cinnamaldehyde, β-caryophyllene), β-bisabolene, β-sesquiphellandrene, D-limonene, β-eudesmene, β-elemene and -copane. A simulation of *in silico* molecular docking was run to target the SARS-CoV-2 RNA dependent RNA polymerase (RdRp) enzyme. In comparison to other compounds, β-eudesmene has the highest binding energy (-7.3 Kcal/mole), and ADMET predictions are promising for its medicinal potential. As a result, it was concluded that the β-eudesmene component of AK ligand's essential oil may have the ability to prevent SARS-CoV-2 replication via the RdRp enzyme.

Keywords: *ayush kwath*, herbs, essential oils, molecular docking, β-eudesmene, RdRp, SARS-CoV-2, Covid-19

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Abbreviations: RdRp, RNA dependent RNA polymerase; SDF, structure data format; EO, Essential oil; TIC, total peak area; AK, Ayush Kwath; RI, retention index

Introduction

Essential oil (EO) is generally made up of a combination of monoterpenes, sesquiterpenes, and their oxygenated derivatives, which have a variety of chemical structures and multifaceted bioactivities that include antibacterial, antiviral, and anticancer properties.[1] Recent research suggests that EO may have promise as a treatment for SARS-CoV-2.[2] Traditional Indian medicine uses the herbal remedy *Ayush Kwath* (AK) to treat viral respiratory infections. The herbs utilized in AK, including *Ocimum sanctum* (leaf),[3] *Zingiber officinale* (rhizome),[4] *Cinnamomum zeylanicum* (stem bark)[5] and *Piper nigrum* (fruit)[6] are regarded as rich sources of EO and immunomodulatory properties. According to reports, *O. sanctum* suppresses the NF-β classical pathway and functions as a key defensive mechanism to boost immunological response to infection.[7] Additionally, *C. zeylanica* blocks anti-CD3-induced p38, JNK, ERK1/2, and STAT4 activation, changing the inflammatory responses mediated by T-cells.[8] *Z. officinale* prevented the multiplication of viruses.[9] Furthermore, *P nigrum* promotes T and B cell proliferation while inhibiting GATA3 and demonstrating immune-stimulating effects.[10]

In addition to *in vitro* investigations, other researchers suggest that certain chemicals found in different EOs may have anti-Covid-19 infection properties.[11] The replication of RNA from an RNA template typically requires the enzyme RNA dependent RNA polymerase (RdRp), and there is a strong sequence similarity (96%) between SERS-CoV and SARS-CoV-2 for RdRp.[12] The agents that target the RdRp of SARS-CoV may therefore also target RdRp of SARS-CoV-2. Remdesivir is a frontline medication for SARS-CoV-2 infection and a possible RdRp inhibitor.[13] In light of this, the current investigation was carried out for the first time to identify and quantify the bioactive components of EOs from AK and evaluate their antagonistic potentialities against the RdRp enzyme from the SARS-CoV-2 virus using *in silico* molecular docking.

Materials and methods

Extraction of essential oil

Highly pure *O. sanctum* (leaves), *C. zeylanicum* (stem bark), *Z. officinale* (rhizome) and *P. nigrum* (fruit) were purchased from a nearby market to prepare AK. The materials were combined into a fine powder in a 4:2:2:1 (w/w) ratio, which was then stored at 4ºC in a sterile container. Essential oil (EO) extraction was performed by hydro-distillation method using Clevenger's apparatus. In brief, 25g AK was boiled with water at 100°C for 3h. EO was dried over anhydrous sodium sulphate and stored in amber glass vial at 4ºC for further investigation.

GC-MS analysis of essential oil

GC-MS was carried out to isolate and identify the constituents of AK essential oil (Agilent 7890B GC with 5977A MSD, Agilent, USA). An effective separation was achieved using HP-5ms (5% diphenyl-95% dimethyl polysiloxane) capillary column (30m x 0.25mm ID and 0.25µm film thickness). The optimal oven temperature was programmed to start at 80°C for 2minutes, then rise to 220°C at a rate of 4°C/min, and lastly to 280°C at 5°C while maintaining the ultimate temperature for 5minutes. The flow rate of the carrier gas, helium, was kept constant at 1ml/min. The temperature of the MS transfer line was set at 280°C while the injector was set at 220°C. 1µl of EO samples were injected with a 10:1 split ratio. Prior to injection, EO samples were dissolved in 10% v/v hexane. The 70ev ion source

was used in EI mode to achieve fragmentation within the mass range of 50-550m/z. By matching the mass spectra to those in the NIST 14.1 library, all the components of essential oils were identified. By using the instrument software MassHunter, the abundance of EO components was quantified as a relative percentage of the total peak area (TIC). By analysing EO using GC-FID under the same conditions as GC-MS, each component's retention index (RI) was calculated. Chromatography of a mixture of homologous series of n-alkanes C6–C24 was also carried out at the same time.

In silico molecular docking and dynamics

Using the SAVES 6.0 server, the crystal structure of the SARS-CoV-2 RdRp complex with Remdesivir was obtained and verified.[14] The crystal structure of receptor protein RdRp (PDB:7B3B) of SARS-CoV-2 presented in Figure 1A, the Ramachandran plot of SARS-CoV-2 RdRp PDB:7B3B VADAR (Volume, Area, Dihedral Angle Reporter) shown in Figure 1B, and the PDB:7B3B structure validation by Verify3D presented in Figure 1C. The structural quality of the target protein was determined using PROCHECK server. The CASTp website was used to assess whether amino acids were present in the active site. The selected EO bioactive chemicals' structure data format (SDF) was obtained from the PubChem database and then converted to PDB format using Open Babel.[15] Chem sketch data are presented in Figure 2. Using Autodock 4.2 tools, the protein and ligands were converted to PDBQT format.[16] The common drug Remdesvir, which has demonstrated inhibitory actions against RdRp, was downloaded and compared. Using Autodock 4.2 and AutodockVina, all separated chemicals were docked into a 3D X-ray structure.[17] The Broyden-Fletcher-Goldfarb-Shanno algorithm was used by AutodockVina. Finally, Bovia Discovery Studio Visualizer was used to display the binding complexes. Additionally, the SwissADME website measured Adsorption, Distribution, Metabolism, and Excretion (ADME) characteristics and pHCSM measured toxicity level.[18]

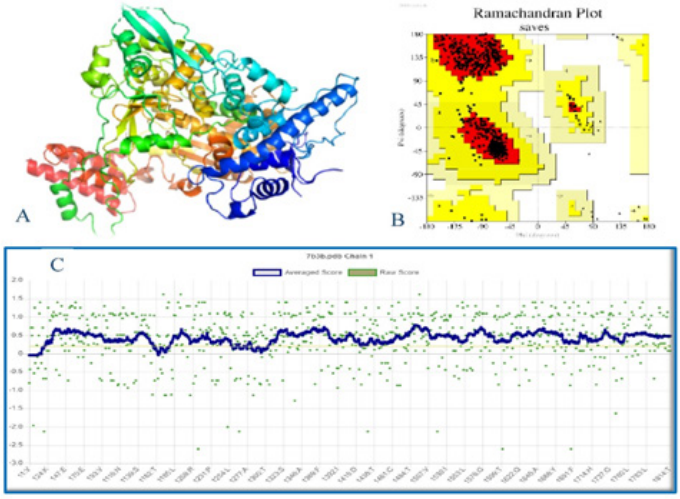

Figure 1 The crystal structure of receptor protein RdRp of SARS-CoV-2.

A=Ramachandran plot of SARS-CoV-2 RdRp; B=Volume, Area, Dihedral Angle Reporter; C=structure validation by Verify3D

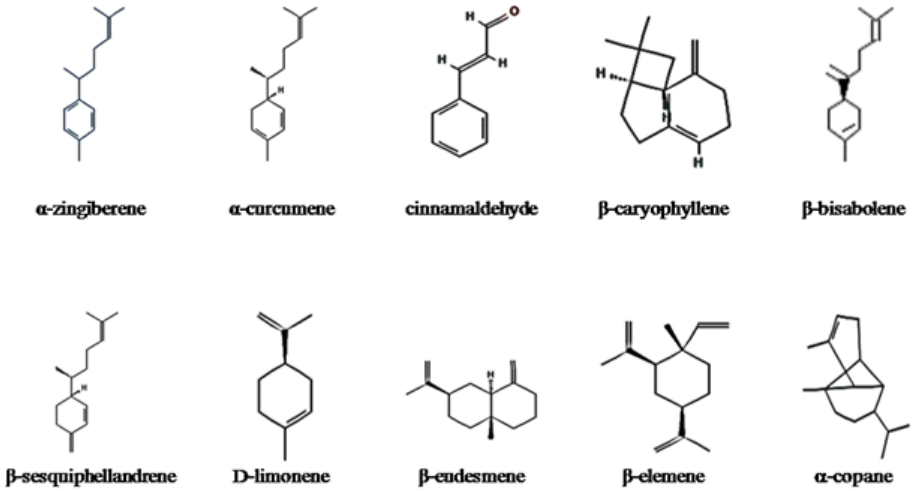

Figure 2 Structure of selected compounds as ligands for SARS-CoV-2 RdRp enzyme.

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Results

GC-MS of essential oil

The yield of EO from AK was 0.33% (w/w), and GC-MS analysis revealed a total of 52 components for EO (Table 1). The primary constituents that were determined to be present included α-zingiberene (12.3%), α-curcumene (9.2%), cinnamaldehyde (6.7%), β-caryophyllene (6.2%), β-bisabolene (6.1%), β-sesquiphellandrene (4.9%), D-limonene (4.1%), β-eudesmene (3.9%), β-elemene (3.4%) and α-copane (3.5%). The GC-MS chromatogram is given in Figure 3.

Table 1 Identification of bioactive components presents in essential oils of *Ayush Kwath* (AK)

No.	Name	Class	RIa	EO (%)	No.	Name	Class	RIa	EO (%)
1	α-Pinene	MH	942	0.48	27	α-Farnesene	SH	1509	0.82
2	Camphene	MH	953	0.6	28	β-Bisabolene	SH	1512	6.1
3	β-Pinene	MH	981	0.65	29	γ-Cadinene	SH	1518	3.53
4	D-Limonene	MH	1032	4.16	30	L-calamenene	SH	1524	1.07
5	γ-Terpinene	MH	1063	0.33	31	Cadina-1(10),4-diene	SH	1527	2.27
6	Linalool	OM	1101	0.57	32	β-Sesquiphellandrene	SH	1529	4.91
7	Camphol	OM	1169	0.88	33	α-Calacorene	SH	1545	0.63
8	Terpinen-4-ol	OM	1179	0.63	34	Elemene	OS	1550	2.76
9	α-Terpineol	OM	1191	0.72	35	Germacrene B	SH	1560	0.47
10	α-Citral	OM	1272	0.36	36	trans-Nerolidol	OS	1565	1.29
11	Cinnamaldehyde	OM	1284	6.77	37	Caryophyllene oxide	OS	1582	1.53
12	δ-Elemene	MH	1340	0.39	38	trans-Sesquisabinene hydrate	OS	1583	0.68
13	Eugenol	OM	1359	0.65	39	β-Copaen-4α-ol	OS	1590	1.39
14	Cyclosativene	MH	1371	0.32	40	Viridiflorol	OS	1593	0.57
15	α-Copaene	MH	1378	3.56	41	Zingiberenol	OS	1621	1.12
16	β-Elemene	SH	1393	3.4	42	Ledene oxide-(II)	O	1632	0.69
17	β-Caryophyllene	SH	1419	6.26	43	Cubenol	OS	1644	0.43
18	Aromandendrene	SH	1441	0.38	44	δ-Cadinol	OS	1647	1.56
19	α-Caryophyllene	SH	1457	1.02	45	α-Eudesmol	OS	1655	0.64
20	γ-Gurjunene	SH	1475	0.53	46	α-Cadinol	OS	1658	0.47
21	γ-Muurolene	SH	1478	1.53	47	7-epi-trans-sesquisabinene hydrate	OS	1675	1.31
22	α-Curcumene	SH	1486	9.23	48	Aromadendrene oxide	OS	1679	0.66
23	β-Eudesmene	SH	1489	3.91	49	α-Bisabolol	OS	1687	0.67
24	β-Guaiene	SH	1493	0.7	50	Benzyl Benzoate	OS	1766	1.13
25	Epicubebol	OS	1495	0.94	51	β-Costol	OS	1782	1.15
26	α-Zingiberene	SH	1497	12.33	52	Gerany-p-cymene	OS	1981	0.48
Total identified [No.]				52					
Total identified [%]				99.63					
Monoterpene hydrocarbons (MH)[%]				8.6					
Oxygenated monoterpenes (OM)[%]				10.58					
Sesquiterpene hydrocarbons (SH)[%]				57.45					
Oxygenated sesquiterpenes (OS)[%]				21.21					
Others (O)[%]				1.79					

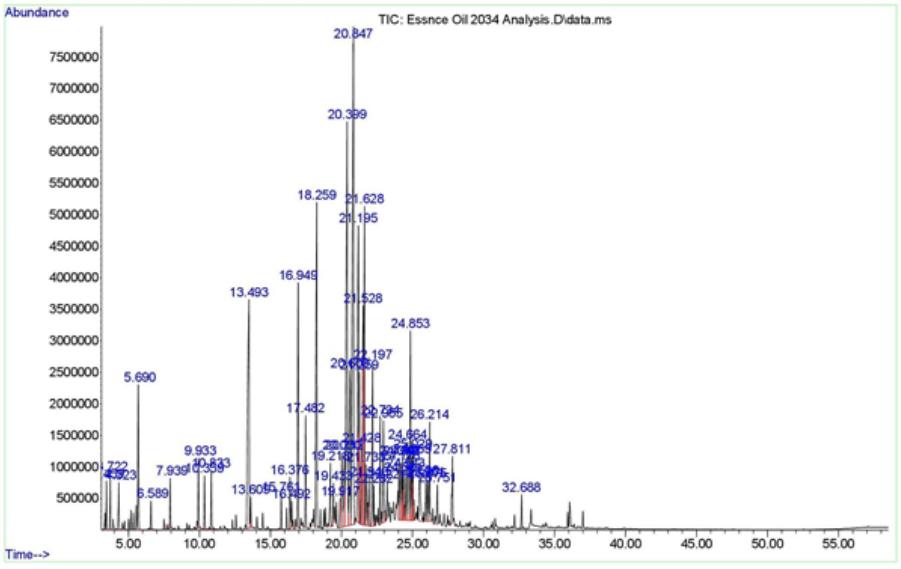

Figure 3 GC-MS chromatogram of essential oil.

Molecular docking

The binding affinity of selected EO compounds namely α-curcumene, β-caryophyllene, α-zingiberene, cinnamaldehyde, β-bisabolene, α-copaene, β-eudesmene, D-limonene, β-sesquiphellandrene, and β-elemene, range between -5.4 kcal/mol and -7.3 kcal/mol (Figure 4). Among the ten chemicals docked, β-eudesmene displayed the highest binding energy (-7.3), compared to Remdesivir although interacts with three amino acid residues of corona virus RdRp such as LEU371, ALA375 and TRP509. In the RdRp binding site, the β conformation with alkyl and pi-alkyl interactions was seen for β-eudesmene (Figure 5). Key residues were depicted in a violet colour ball and stick model, and the compound was depicted in a green colour ball and stick model to reflect the RdRp structure (Figures 5A & B). With a pink dotted line, the β-eudesmene illustrating hydrogen, hydrophobic, and van der Waals interactions inside active binding sites of RdRp are displayed in Figure 5C.

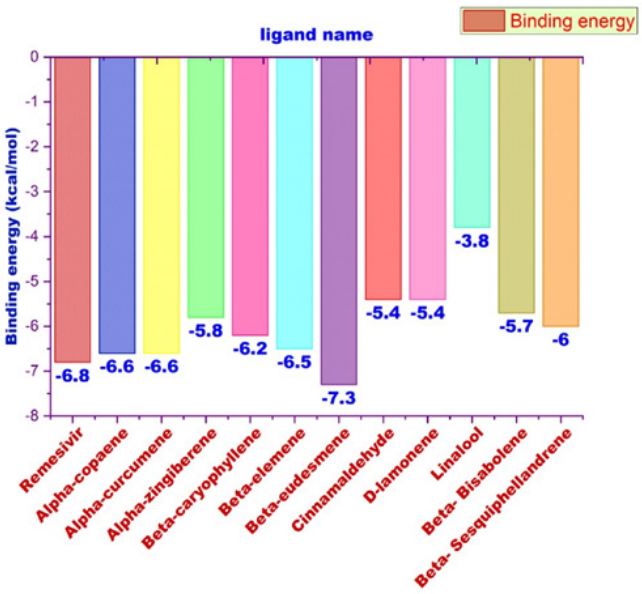

Figure 4 Binding energy of selected essential oils with RdRp.

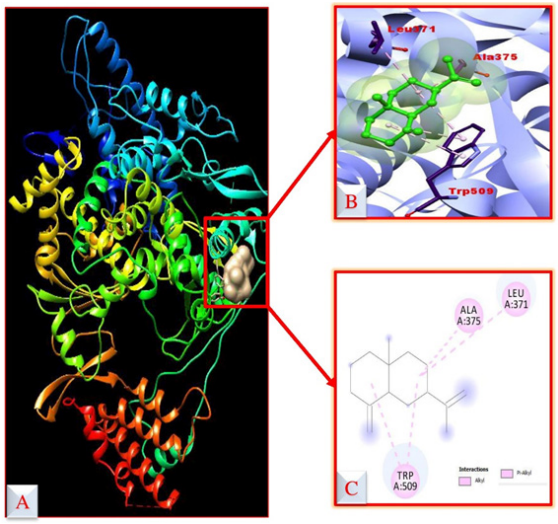

Figure 5 Interaction of β-eudesmene with RdRp.

A=solid ribbon model; B=active sites of amino acid residues; C= hydrophobic interactions

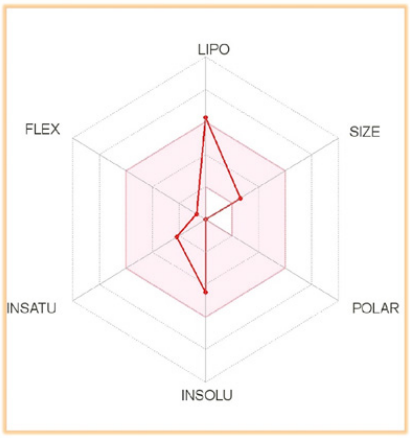

Figure 6 Bioavailability radar for the compound β-eudesmene.

Table 2 ADME and toxicity results of selected components presents in essential oils of *Ayush Kwath*

	1	2	3	4	5	6	7	8	9	10
ADME										
Blood-Brain Barrier	0.591	0.716	0.788	0.44	0.788	0.855	0.816	0.728	0.787	0.803
Human Intestinal Absorption	94.168	94.097	93.87	96.882	94.553	95.385	95.937	95.408	94.668	93.793
Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55
Caco-2 Permeability	1.561	1.414	1.414	1.654	1.419	1.396	1.428	1.402	1.408	1.411
Aqueous solubility (LogS)	-6.06	-5.513	-5.926	-2.113	-6.112	-5.594	-6.419	-3.543	-6.055	-6.363
Skin permeation (Log Kp)	-1.168	-1.594	-1.276	-2.345	-1.236	-1.901	-1.606	-1.744	-1.223	-1.213
CYP2C19 inhibitor	NO	YES	YES	NO	NO	YES	YES	NO	YES	YES
CYP2C9 inhibitor	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES
CYP2D6 inhibitor	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
CYP3A4 inhibitor	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Renal Organic Cation Transporter Inhibitor	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
TOXICITY										
AMES Toxicity	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO
Carcinogens	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Oral Rat Acute Toxicity (LD50) mol/kg	1.742	1.552	1.568	1.869	1.648	1.5	1.539	1.877	1.584	1.479
Rat Oral Chronic Toxicity (log mg/kg_bw/day)	1.426	1.425	1.322	1.98	1.348	1.389	1.489	2.352	1.314	1.317
Maximum tolerated dose (human) (log mg/kg_bw/day)	0.751	0.214	0.358	0.862	0.416	-0.241	-0.004	0.776	0.273	0.102

1= α-Curcumene; 2= β-Caryophyllene; 3= α-Zingiberene; 4= Cinnamaldehyde; 5=β-Bisabolene; 6= α-Copaene; 7= β-Eudesmene; 8= D-Limonene; 9= β-Sesquiphellandrene; 10= β-Elemene

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Table 2 provides an overview of the pharmacokinetic parameters. The bioavailability score for all substances was 55% and the human intestine absorption rate was higher than 93. All of the chosen compounds were moderately permeable, as indicated by the estimated Caco-2 cell absorption being larger than 1.4. With the exception of α-curcumene and cinnamaldehyde, computed metabolism revealed that inhibition of the enzyme CYP2C9 was prominent for all substances. Figure 6 depicts the bioavailability radar of β-eudesmene. The optimal zone for each property, including size (SIZE), polarity (POLAR), flexibility (FLEX), insolubility (INSOLU), unsaturation (INSATU), and lipophilicity (LIPO), was indicated by the pink area in Figure 6. The substances have demonstrated neither AMES toxicity nor carcinogenicity.

Discussion

Numerous plant essential oils have also been studied for a range of bioactivities, such as antimicrobial, antifungal, antioxidant, anticancer, and antiviral.[1] To the best of our knowledge, there is no report on EO of AK to combat Covid-19 infection. Major chemicals found in EO derived from *O. sanctum* include eugenol, caryophylline, β-elemene, and D-germacrene.[19] EO of *O. sanctum* exhibit strong antiviral activity against a number of viruses, including Herpes Simplex, HIV, and Adenovirus, and they may be a useful bioresource in the fight against Covid-19.[3] The major components of *Z. officinale* EO were α-zingiberene, β-bisabolene, β-sesquiphellandrene, α-curcumene.[20] In EO of *C. zeylanicum*, significant amounts of cinnamaldehyde stereoisomers were identified[21] and antiviral activity against influenza virus was noted.[22] According to reports, *P. nigrum* fruit's EO contains higher concentrations of D-limonene, β-caryophylline, β-bisabolene, α-copaene and has the potential to be antiviral.[6] In the current investigation, it was found that EO of AK exhibits the chemical characteristics of EO from each of its constituent parts. The primary constituents identified and quantified constituents were α-zingiberene > α-curcumene > cinnamaldehyde > β-caryophyllene > β-bisabolene > β-sesquiphellandrene > D-limonene > β-eudesmene > β-elemene > and -copane. Recent studies by Gautam et al.[23] and Rastogi et al.[24] describe the potential for Indian herbs to be employed in a variety of traditional formulations, including AK to treat Covid-19.

SARS-CoV-2 acute infection has been linked to several proteins. Numerous molecular docking studies on the macromolecular targets of Covid-19 have previously been conducted.[25] Hence, the interactions between the ten EO found in AK and the RdRp enzyme from SARS-CoV-2 were further studied using molecular docking simulations. In silico methods have also been used to assess medications that are readily available on the market.[26] The enzyme RNA-dependent RNA polymerase, or RdRp, is crucial for the replication of RNA from an RNA template. These enzymes are good candidates for antiviral chemotherapeutic targets because they are essential for viral replication.[27] With the highest binding energy, β-eudesmene showed the best docking outcomes. Silva and colleagues[11] reported docking of numerous EO and components against all potential SARS-CoV-2 protein targets, but only find a weak docking with the target RdRp enzyme. As a result, this study suggests that EO's minor components, including β-eudesmene, would have significant therapeutic potential in addition to its main constituents. Viral membranes are easily penetrated by EOs due to their hydrophobicity, which causes membrane rupture. Numerous EOs were examined by Vimalanathan and Hudson[28] for potential direct effects on the main influenza virus surface proteins, suggesting that contact is a potential mechanism for the antiviral activity. Furthermore, EOs have a variety of active phytochemicals that can work together to inhibit several viral replication stages. These phytochemicals can also have beneficial effects on the host respiratory system, including bronchodilator and mucolytic.

Conclusion

Potential essential oils were found in *Ayush Kwath* (AK), one of which, β-eudesmene, demonstrated a considerable reduction in binding energy with RdRp sites as evident from *in silico* studies and was consequently anticipated to inhibit the pathogenic process of SARS-CoV-2 in the respiratory tract. According to this viewpoint, the current work represents an important step in the creation of a pharmacological weapon to battle SARS-CoV-2 that is based on the herbal remedies in India.

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Conflicts of interest

Authors declared no conflicts of interest.

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