Network Modeling Analysis in Health Informatics and Bioinformatics (2021) 10:14
https://doi.org/10.1007/s13721-020-00276-1

ORIGINAL ARTICLE

Estimation of drug-likeness properties of GC–MS separated bioactive compounds in rare medicinal *Pleione maculata* using molecular docking technique and SwissADME in silico tools

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Received: 6 August 2020 / Revised: 26 November 2020 / Accepted: 28 November 2020 / Published online: 24 February 2021

Abstract
The main aim of the paper was to determine bioactive compounds in *Pleione maculata* extracts using gas chromatographic technique and to investigate their drug-likeness potential using molecular docking algorithm and ADME studies on the recent intractable disease, for example, SARS-CoV-2. *Pleione maculata* sample was prepared for GC–MS analysis. The peak components were identified based on the NIST Library. Molecular docking was performed using PatchDock, and energy refinement was carried out using the FireDock algorithm followed by drug-likeness analysis using the SwissADME tool. The mass spectrum revealed various pharmacologically important compounds and novel compounds 8-oxatetracyclo{5.2.1.1(2,6).1(4,10)}dodecane, 7-tert-butyl-1,9,9-trimeth, docosane, 2,4-dimethyl, kryptogenin 2,4-dinitrophenyl hydrazine, and *N*-decyl-alpha,*D*-2-deoxyglycoside which are reported for the first time. Molecular docking using PatchDock illustrates GC–MS compounds Nor-diazepam,3-{*N*-hydroxymethyl}aminocarbonyloxy a good docking and high binding affinity with atomic contact energy -10.95 kcal/mol against SARS-CoV-2 spike protein S2 subunit. ADME analysis predicts Nor-diazepam,3-{N-hydroxymethyl}aminocarbonyloxy and andrographolide showed very high drug-likeness parameters with no metabolism disturbances. The random control antiviral drug arabidiol revealed a lower binding affinity and lower solubility compared to bioactive compounds of *P. maculata*. The study depicts the first and novel report on various pharmaceutical important GC–MS bioactive compounds and molecular docking study on *Pleione maculata* having potential against various intractable diseases.

Keywords Gas chromatography · SARS-CoV-2 · *Pleione maculata* · Molecular docking · Drug-likeness

1 Introduction

A worldwide viral outbreak of dreadful disease COVID-19 arose during December 2019 in Wuhan, China (Yang and Wang 2020; Yang et al. 2020). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) as named by the International Committee on Taxonomy of Viruses (ICTV) and diseases cause was coronavirus disease 2019 (COVID-19). COVID-19 is no new viruses but a possible mutation of the long-known SARS-CoV-1. A genome variation analysis was analyzed using a detective genome computational tool, and it revealed SARS-CoV-2 shares 80% similarities with the gene pool of SARS-CoV-1 (Zhang et al. 2017) with nearly 17% variation which was a mutation occurring in spike protein and envelope protein (Sardar et al. 2020). The viral genome analysis of the SARS-CoV-1 open reading frame (orf) was observed to have a potential mutation to adapt to a new environment (Groneberg et al. 2005) and recombination (Li Fang 2016) which might cause severe virulence of the virus. The severe acute respiratory syndrome (SARS) is a crown-like virus which was spread widely in late 2000 over 25 countries causing thousands of cases and death (Wen et al. 2011). Since 2003, antiviral research has been evaluated for an anti-SARS-COV-1 activity to prevent re-emergence of the disease. The genome of SARS-CoV-1 encodes various vital target proteins: spike protein (S), 3CL protease, NTPase/helicase, RNA-dependent RNA polymerase, membrane protein (M), an envelope protein (E), and nucleocapsid phosphoprotein (N) which takes part in virus replication, transcription,

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and translation (Yang and Wang 2020). The main molecule that mediates coronavirus entry into a host cell is their spike protein (S) which is multi-functional (Fang 2016), where the attachment is initiated by the S1 subunit and conformation changes took place from pre-fusion to post-fusion or membrane fusion form. The virus incorporation is initiated by the S2 subunit of spike glycoprotein through membrane fusion with the host receptor (Rane et al. 2020). The viral 3-chymotrypsin-like protease responsible for replication complex (Anand et al. 2003) is considered highly conserved between SARS-CoV-1 and SARS-CoV-2 (Zhang et al. 2017; Donald and Hai-Feng 2020). The SARS-CoV-1 spike protein has a strong binding affinity towards human receptor angiotensin-converting enzyme 2 (ACE2) based on structure and interaction (Zhang et al. 2020a, b). The main agent for transmission is through respiratory droplets and can be transmitted from human to human through contact with droplets (Yang and Wang 2020). For early diagnosis of SARS-CoV-1, improved RT-PCR assays were carried out which is used worldwide for virus identification and its high specificity (Shen et al. 2020). The symptoms of SARS-CoV-1 were persistent fever, chills, dry cough, dizziness, headache, sore throat, sputum production, vomiting, and nausea; special attention was given for watery diarrhea, but the primary target for infection was respiratory epithelial cells. The viral effect immune-mediated mechanism and molecular studies showed epithelial cells of the gastrointestinal tract to be major target cells (Groneberg et al. 2020). In 2019, various health authorities of Hubei Province, China, reported novel COVID-19 disease as pneumonia (Wu et al. 2020) or COVID-19 pneumonia (Tian et al. 2020). Pneumonia is a type of fatal respiratory tract infection that is caused by either bacteria (Streptococcus pneumonia) or viruses, and symptoms are no different from the deadly virus SARS-CoV-2 such as high fever, shortness of breath, rapid breathing, and cough (Zafar 2016). Earlier, SARS-CoV-1 patients were treated with anti-inflammatory steroidal compounds such as methylprednisolone (Groneberg et al. 2005; Wu et al. 2017), and metabolite profiling for SARS-CoV-1 survivors was carried out after 12 years of recovery using ultra-high-performance liquid chromatography–mass spectrometry (UPLC-MS) and gas chromatography–mass spectrometry (GC–MS); a significant portion (64%) of recovered patients were prone to lung infections and various serum metabolic disorders associated with lipid metabolism including hyperlipidemia (HL), cardiovascular abnormality (CVA), and an abnormality in glucose metabolism (AGM). Single-stranded antisense as an antiviral compound has been a vital therapeutic area for emerging viruses (Gulam et al. 2016). Antisense therapy (antisense antivirals) treats diseases using single-stranded antisense oligonucleotides to target specific mRNA sequences and block translation of viral protein (Gulam et al. 2016) or modifies protein expression (Sharad 2019). To date, there are a lot of controversies regarding vaccine and drug development against SARS-CoV-2 pneumonia, though various antiviral drugs are being used for treatment there appeared to be many disadvantages and side effects caused. The transmission from person to person is highly contagious due to inadequate global healthcare facilities (Panda et al. 2020). Plants are the main source of natural medicines as they produce various biologically active secondary metabolites. Secondary metabolites provide nutritional and beneficial effects on human health (Lakshmi and Rajalakshmi 2011). According to World Health Organization (WHO), about 80–90% population relies on traditionally prepared medicinal plants for regular health care as it is safe and ready to use (Rizvi and Misra 2013; Ekor 2014). Orchids are one large kingdom of plants that are overexploited and also climatic changes; their illegal trading led to extinction and biodiversity loss (Pant 2003). About 50% of orchids are being used in traditional medicines apart from being sources of ornaments (Tsering et al. 2017). Epiphytic orchid growing on other living or non-living materials for physical supports tends to release bioactive secondary metabolites when they are exposed to disturbance (Lindley and Paxton 1851). *Pleione maculata* commonly known as peacock orchid is a rare unexplored epiphyte on the verge of extinction (Chauhan and Sharma 2017) growing on trees at a high elevations of about 600–1600 m (Lindley and Pacton 1851). The epiphyte is a well-known medicinal plant in the northeastern region of India, where local people use pseudobulbs or rhizomes to treat liver problems, stomach ailments, and headaches (Pant 2003; Teoh 2016).

Today, in silico studies are more favored for drug identification to find the interaction of the pharmaceutically important compounds with their targets. The most commonly known computational tool for drug target is molecular docking using various algorithms. PatchDock is highly efficient (Prabhu and Rajeswari 2016) accurate (Doss et al. 2014), fast transformational search, and free-online server in comparison to other computational molecular docking servers. PatchDock is a molecular docking algorithm based on the principle of shape complementarity. A complementarity molecular shape is a yield forming a conformational transformation of each docking complex known as induced fit. The transformed molecules can be further evaluated based on the scoring function which involves geometric-fit and binding affinity based on atomic contact energy (ACE). PatchDock calculates the amount of atomic contact energy (ACE) which is an atomic desolvation free energy required to replace ligand molecule from water contact to protein contact (Guo et al. 2012; Maiti and Banerjee 2020). PatchDock algorithms contain three stages, (a) molecular shape representation based on geometric patches (concave, convex, and flat surface pieces), (b) surface patch matching, and (c) filtering and scoring (Duhovny et al. 2002). There are various parameters involved for running a docking

interaction between molecules such as root mean square deviation (RMSD) and a complex type. The RMSD is applied to prevent redundancy of molecule and is exact (Duhovny et al. 2002). PatchDock uses techniques such as geometry hashing and pose clustering which detects advance data structures and spatial pattern. In docking, energy refinement is required for further development of drug compounds for example FireDock (Andrusier et al. 2007; Surana et al. 2018). FireDock (fast iteration refinement in molecular docking) refinement of energy uses Monte Carlo binding score minimization, is highly efficient and easy to understand, and requires no prior knowledge in docking (Lipinski et al. 1997). The scores are atomic contact energy (ACE), softened van der Waals interaction, partial electrostatics, and additional estimation of binding energy. FireDock algorithm includes three refinement steps: (1) side-chain optimization, (2) rigid-body minimization, and (3) scoring and ranking (Lipinski et al. 1997). The docking analysis can be predicted base on higher binding affinity and lowest docked energy (Iyamah et al. 2017). Before clinical studies, the drug-likeness of compounds can be analyzed using computational tools that are cost-effective and less tedious. SwissADME is a free web tool available to evaluate pharmacokinetics based on different drug-likeness parameters such as physicochemical properties, solubility, and pharmacokinetics of molecule (Daina et al. 2003).

A compound separation technique gas chromatography–mass spectrophotometry will provide ideas on different bioactive compounds present in plants. Gas chromatography is an instrumental technique coupled with mass spectrometry applied for separation, identification, and quantification of organic compounds and chemical mixtures study. An inert gas such as helium is used as a mobile phase (carrier gas). The samples to be analyzed will be injected and interacted with glass or metal columns coated with the stationary phase and elute different compounds at the different times called retention time (Ghosal and Srivastava 2013). The GC–MS method is highly sensitive, reproducible, and high-speed resolution (Dua and Garg 2013). The study aimed to exploit safe, medicinal, nutraceutical effective natural compounds from *Pleione maculata* using GC–MS analysis as there seems to be an unreached target globally requiring active research against SARS-COV-2. The selected GC–MS compounds for docking were based on their bioactivity against symptoms related to SARS-CoV-2 pneumonia such as anti-inflammatory activity, preventing cardiac insufficiency, preventing fatigue, preventing shortness of breath, preventing gastrointestinal diseases, heartbeat improvement, antiviral activities, and a compound having repellent activity, larvicidal activity, based on earlier knowledge in using an antimalarial drug for reducing a viral load (Rane et al. 2020). In earlier years, steroidal compound and antisense target were also used for the treatment of viral diseases (Chidambaram et al. 1996; Kim et al 2009; Chen et al. 2014); therefore, with this prior knowledge, GC–MS analysis of *Pleione maculata* identified steroidal antiviral and an antisense target compound as a key compound to perform docking. The paper also evaluates the drug-likeness potential of compounds possessing multi-target bioactivity using a molecular docking algorithm to observe high binding affinity and conformational fit between bioactive compounds of *P. maculata* against target proteins of SARS-CoV-2. A random control antiviral drug arabidiol was used in severe cases of COVID-19 as it was observed to reduce the viral disease (Wang et al. 2020).

2 Materials and methods

2.1 Collection and extract preparation of plant material

Pleione maculata sample was collected from dense forest of Khliehriat, East Jaintia Hills regions of Meghalaya, and was processed. The parts of *P. maculata* were washed under running tap water, surface-sterilized with distilled water, 1% sodium hypochlorite, and re-washed with distilled water. The samples were shade-dried and crushed, and each plant part was soaked in three different solvents (ethanol, methanol, acetone) followed by 24–48-h incubation. The crude extract was filtered using Whatman filter paper Grade No-1 with circle size of 125 mm diameter (Cat No 1001125) (Vijisaral and Arumugam 2014). The solvent extracts are then evaporated using open-air evaporation in a laminar airflow hood for 24 h and centrifuged at 12,000 rpm for about 15 min at 4 °C. The concentrated extracts were transferred into a micro-centrifuge tube for GC–MS analysis.

2.2 GC–MS analysis

Gas chromatography–mass spectrometry of samples was analyzed in IIT Guwahati Biotech Park, Assam, using PerkinElmer (USA). The GC–MS system model was Clarus 680 GC & Clarus 600 C MS comprising a liquid autosampler with aid of Turbo mass ver. 5.4.2 software. The chromatography was performed on a capillary column Elite of 5MS 60.0 m × 250 µm, ID of 0.25 mm, and film thickness of 0.25 µm, and stationary phase was 5% diphenyl 95% dimethylpolysiloxane. The injection volume of the sample was 1 µl with a 0:1 split ratio. Helium (99.999%) was used as carrier gas throughout the column. The solvent delay was by 9.00 min, and transfer temperature was 200 °C. The injector and ion source temperature were 280 °C and

180 °C, respectively. The initial temperature in the oven was programmed from 110 °C for 3 min (Thomas et al. 2013), ramp 5 °C/min to 200 °C and hold for 3 min and was again increased for 5 °C/min to 300 °C and hold for 10 min (Darmasiwi et al. 2015). The sample was scanned from 40 to 600 Da.

2.3 Identification of components using NIST

The peaks were analyzed using the data analysis software NIST-2008. The National Institute of Standards and Technology (NIST) is a mass spectral search database for comparisons of the acquired and unknown spectrum with NIST/EPA (Environmental protection Agency)/NIH (National Institute of Health) databases. The components were identified based on standards employed by the National Institute Standards and Technology (NIST) Library (Darmasiwi et al. 2015). The detection was employed by comparing peaks with that of mass spectral standard reference data NIST having more than 62,000 patterns. A detailed chemical structure of the GC–MS graph of a molecule was presented using ChemDraw Ultra 8.0.3 by CambridgeSoft (www.cambridgesoft.com) (CS ChemOffice—Drawing, Modelling, and Information).

2.4 Molecular docking using PatchDock

2.4.1 Input

Protein structure retrieval: Protein receptor target was retrieved from RCSB (Research Collaboratory for Structural Bioinformatics) Protein Data Bank (PDB) (https://www.rcsb.org/) in 3D structure as shown in Fig. 1. The following three target receptors were (1) SARS-CoV-2-3CL protease (PDB ID: 6M2Q), (2) SARS-CoV-2 RNA-dependent RNA-polymerase (PDB ID: 6M71), and (3) SARS-CoV-2 spike glycoprotein receptor S2 subunit (PDB ID: 6LXT).

2.4.2 Ligand retrieval

A total of 19 ligand molecules as shown in Fig. 2 were retrieved from PubChem (http://pubchem.ncbi.nlm.nih.gov/) database in SDF file format. The small ligand in SDF format was converted into PDB format using PyMOL a molecular modeling package (The PyMOL Molecular Graphics System, Version System, version 1.7.4 Schrödinger, LLC) (Prabhu and Rajeswari 2016; Yadav et al. 2017). The compound ID of the 3D structures of ligands was CID: 6211 (2,4,6-pyrimidinetrione), CID: 248,856 (21-acetoxypregenelone), CID: 543,946 (*P*-menth-8(10)-en-9-ol), CID: 541,761 (Nor-diazepam, 3-*N*-hydroxymethyl,aminocarbonyloxy), CID: 441,207 (digitoxin), CID: 19,089,489 (DI-*N*-decylsulfone), CID: 3893 (14-dodecanoic acid), CID: 13,948 (estra,13,5 (10)-trien-17-beta-ol), CID: 5,283,405 (arachidonic amide, *N*-5-hydroxy-*N*-pentyl), CID: 572,031 (1-methylsulfanyl-9,10-dioxo-9,10-dihydro-anthracene-2-carboxylic acid), CID: 14,077,841 (cholesterol margarate), CID: 8215 (docosanoic acid), CID: 99,470 (26-hydroxy cholesterol), CID: 5,318,517 (andrographolide), CID: 135,426,867 (6H-purin-6-one-,1,7-dihydro-2-methylamino), CID: 261,799 (pseduosarsasapogenin), CID: 71,360,559 (oxiraneundecanoic acid, 3-pentyl, methyl ester, cis), CID: 5,486,971 (pregabalin), and CID: 131,411(arabidol).

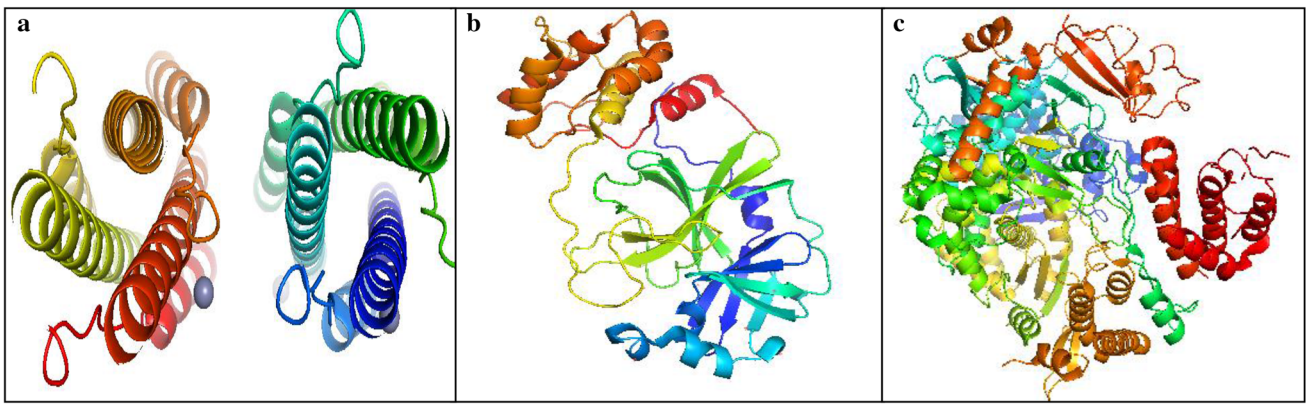


Fig. 1 The 3D ribbon structures representation of SARS-CoV-2 target proteins **a** spike glycoprotein S2 subunit post-fusion core, **b** 3CL protease and **c** RNA-dependent RNA polymerase visualized using PyMOL

2.4.3 Molecular Docking analysis

Protein–small ligand molecule docking was performed using the PatchDock algorithm (Prabhu and Rajeswari 2016; Yadav et al. 2017; Surana et al. 2018). The parameters were set, the complex type was selected, and clustering root mean square deviation (RMSD) was set to 1.5 Å for protein–ligand interaction. The protein receptor and small ligand molecule were uploaded in PDB format followed by form submission. The following output will be further sent by PatchDock to the given email ID. A 1000 transformed docking candidate generated from PatchDock was refined and re-scored using

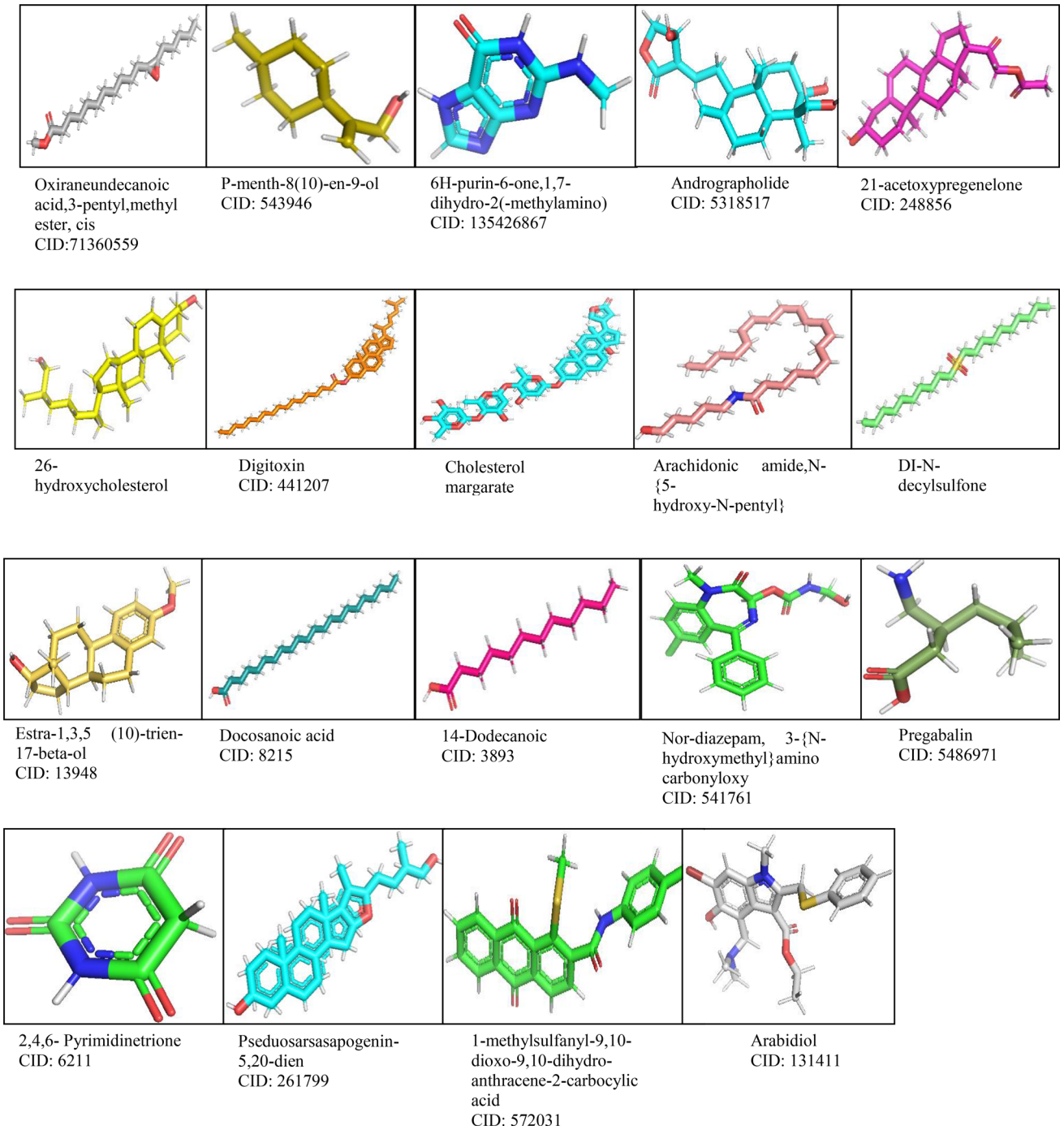


Fig. 2 GC–MS compounds and positive control arabidol ligands downloaded from PubChem data bank with compound ID and visualized using PyMOL for molecular docking

FireDock. The result was visualized using PyMOL a molecular visualization graphics system tool.

2.4.4 Drug-likeness analysis of bioactive compounds using SwissADME tool (Daina et al. 2003)

Chemical structure of compounds was downloaded from PubChem data bank (http://pubchem.ncbi.nlm.nih.gov/) in SDF (structure data format), SwissADME web page was opened, and files were imported from the external file option and were converted into molecular sketcher based on ChemAxon's Marvin JS followed by ADME calculation using default parameters.

3 Results

GC–MS analysis reported more than 146 hits and lead compounds from different parts of *P. maculata* (Fig. 3). The compounds identified from acetone leave extracts were more when compared to other solvent extracts. The following hit and lead compounds of *P. maculata* with their bioactivity are listed in Tables 1, 2, and 3.

A molecular docking study performed for nineteen GC–MS compounds using PatchDock with energy minimization and structure refinement using FireDock was analyzed. The targets were docked properly as the binding affinity was shown to be negative and the docked ligand RMSD value was < 2.0 Å (Singh et al. 2017). The binding residues and atomic contact energy of ligands against the target proteins are listed in Table 4. The highest ACE of a docked molecule was considered below 6.00 kcal/mol (higher negative value); the higher the binding affinity value, the higher the binding potential between molecules. The different GC–MS compounds were interacted with numbers of residues on both side chain and backbone of the target protein as shown in Figs. 4, 5, and 6. A non-covalent (polar) interaction was observed between the docking molecules at a closer distance of 1.5 Å. The docking complex showed zero or one-to-three hydrogen bonding between them but formed a specific

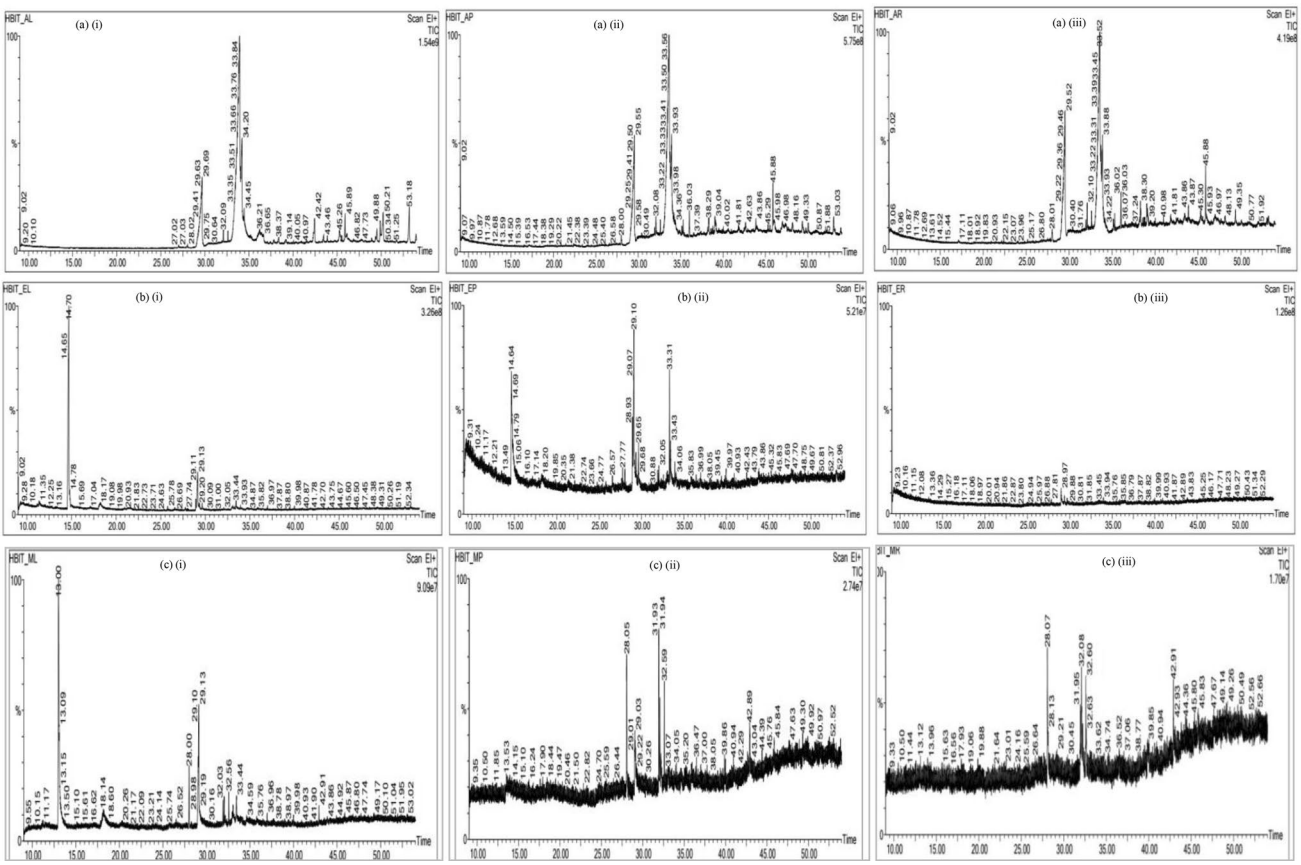


Fig. 3 GC–MS spectrograms showing peaks of compounds of *Pleione maculata* extracts **(a)** acetone, **(b)** ethanol **(c)** methanol extracts of (i) leave (ii) stem and (iii) root

Table 1 GC–MS analysis of acetone extracts of *Pleione maculata*

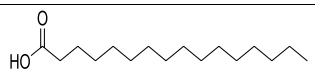
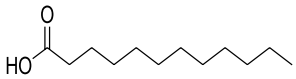
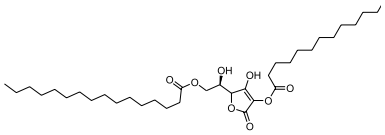
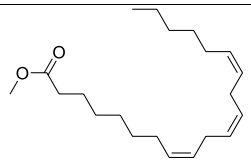
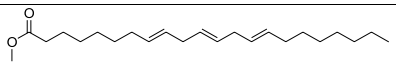
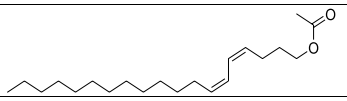
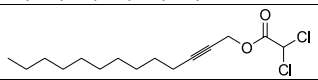
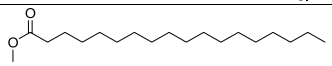
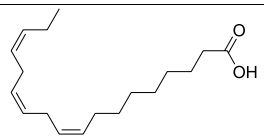
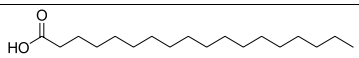
Parts of *P. maculata*	Peak name	Chemical structure	Molecular name	Molecular formula	Molecular weight	Activity
Leave	N-hexadecanoic acid		Palmitic acid	$C_{16}H_{32}O_2$	256	Anti-inflammatory, Antioxidant, hypocholesterolemic nematicide, pesticide, anti-androgenic flavor, hemolytic, 5-alpha reductase inhibitor Anti-carcinogenic (Aparna et al. 2012; Kumar et al. 2010; Shree 2012)
	Dodecanoic acid			$C_{12}H_{24}O_2$	200	Antibacterial, anti-viral, antioxidant, hypercholesterolemic (Gideon 2015)
	3-L- (+) Ascorbic acid 2, 6-dihexadecanoate			$C_{38}H_{68}O_8$	652	Anti-tumour and antibacterial activity (Babar et al. 2016)
	8,11,14 Eicosatrienoic acid, Methyl ester		Methyl dihomo-γ-linoleic acid	$C_{21}H_{36}O_2$	320	Tumoricidal (Das and Madhavi 2011)
	8, 11, 14-Docosatreienoic acid, Methyl ester			$C_{23}H_{20}O_2$		Anti-diabetic activity (George et al. 2018)
	Z,Z,-4,6-Nonadecadien-1-ol-acetate		Esters	$C_{21}H_{38}O_2$	322	Insecticidal activity (Hamada et. 2018)
	Dichloroacetic acid, Tridec-2-YNYL ester			$C_{15}H_{24}C_{12}O_2$	306	Anti-mastitis (Dinesh et al. 2016)
	Octadecanoic acid, Methyl ester		Methyl stearate	$C_{19}H_{38}O_2$	298	Antifungal and antioxidant (Pinto et al. 2017)
	Nonanoic acid, 9(3-hexemyldenecycyclop ropylidene)-,2-hydroxy-1-1(HYD)		Nonanoic acid derivative			Not reported usually nonanoic acid have nematicidal activity components of biodegradable polyesters (Sahin et al. 2006)
	9,12,15-Octadecatrienoic acid, (Z,Z,Z)-		Linoleic acid	$C_{18}H_{30}O_2$	278	Anti-inflammatory, antihistaminic, cancer preventive, anti-acne, anti-coronory (Kumar et al. 2010)
	Octadecanoic acid		Stearic acid	$C_{18}H_{36}O_2$	284	Hypocholesterolemic, surfactant and softening agent, perfumery, flavor and in cosmetic Antibacterial activity (Rajashyamala and Elango 2015; Da Silva et al. 2003)

Table 1 (continued)

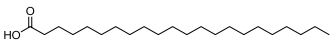
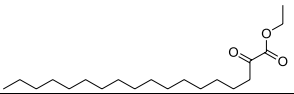
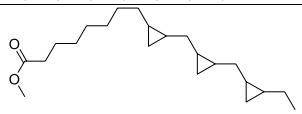
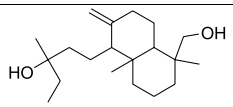
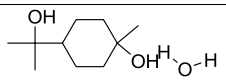
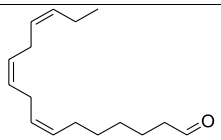
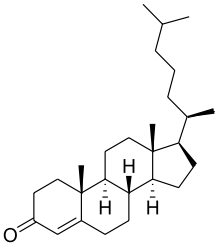
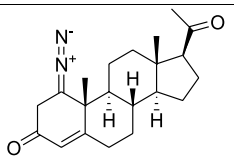
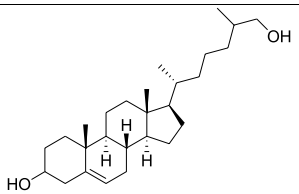
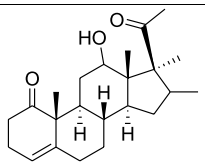
Docosanoic acid/ Behenic acid		Fatty acid	$C_{23}SH_{44}O_2$	340	Anti-cancer potential against MCF7 and HeLa cell lines, Hair moisturizer (Lawal et al. 2015; Eswaraiah et al. 2020)
Alpha-Ketostearic acid, ethyl ester			$C_{20}H_{38}O_3$	326	No activity reported
Cyclopropaneoctanoic acid, 2-[[2-Ethylcyclopropyl)Methyl]cyclo			$C_{22}H_{38}O_2$	334	Anti-carcinogenic (Shree 2012)
1-naphthaleneproponal, alpha-ethyl Decahydro-5-(hydroxymethyl)-			$C_{20}H_{36}O_2$	308	No activity reported
Terpin hydrate			$C_{10}H_{22}O_3$	172	Expectorant commonly used to loosen mucus in patients presenting with acute or chronic bronchitis and related conditions (Jahan et al. 2015)
Cis, Cis, Cis-7,10,13-Hexadecatrienal		aldehyde	$C_{16}H_{26}O$	234	No activity reported (Prabhadevi et al. 2012; Abulaziz et al. 2019)
Cholest-4-en-3-one		Cholestenone	$C_{27}H_{44}O$	384	Anti-obesity, suppress body weight and body fat accumulation (Suzuki 1993, 1998)
Diazoprogesterone		Steroid, Nitrogen compound	$C_{21}H_{30}N_4$	338	Antimicrobial anti-inflammatory, Hepatoprotective, Duiretic, Anti-cancer Anti-HIV (Gopinath et al. 2013; Jothi et al. 2015)
26-hydroxy cholesterol		steroid compound	$C_{27}H_{46}O_2$	402	Biomarkers in diagnosis of Alzheimers disease (AD) and other neurodegenerative disorders (De Knock 2016)
pregn-4-ene-1,20-Dione, 12-hydroxy-16,17-dimethyl-		Steroid compound	$C_{23}H_{34}O_3$	358	Sexual disorders, baldness, anti-psioriatic, anti-pyretic, anti-allergic (Ansarali et al. 2018)

Table 1 (continued)

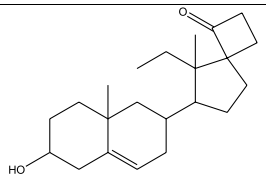
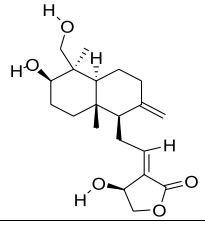
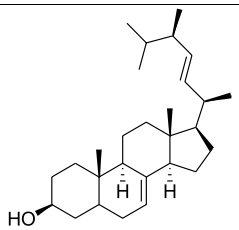
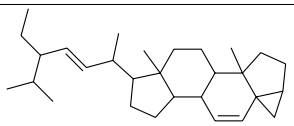
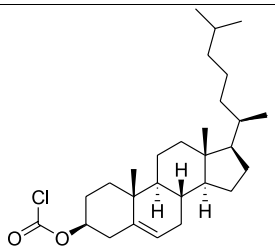
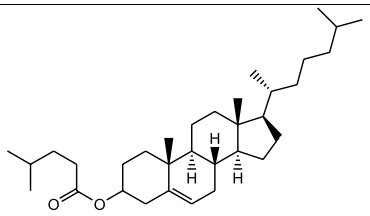
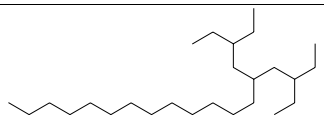
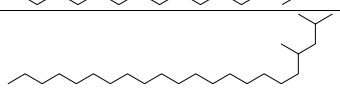
Spiro[Androst-5-ene-17,1′-cyclobutan]-2′-one,3-hydroxy-,(3,beta,17,beta)			$C_{22}H_{32}O_2$	328	Anti-inflammatory and anti-microbial Antiarthritic, anticancer, antiasthma, Hepatoprotective (Sathibalan et al. 2014; Okereke 2017)
Andrographolide		Diterpenoid	$C_{20}H_{30}O_5$	350	cell signaling, Immunomodulator, used in stroke (Selvan and Velavan 2015)
8-oxatetracyclo {5.2.1.1(2,6). 1(4,10)}Dodecane, 7-tert-Butyl-1, 9,9-Trimeth				262	compound not reported
Ergosta-7,22-dien-3-ol,(3.Beta, 22E)			$C_{28}H_{46}O$	398	Anti-inflammatory effect (Pereira et al. 2014)
Stigmastan-6,22-dien,3,5-dedihydro			$C_{29}H_{46}$	394	Antimicrobial Antiasthma, Anti-inflammatory Diuretic, Anticancer, Antiarthritic Antioxidant, insecticidal activity (Sujatha and Vijayalakshmi 2013; Rajeswari et al. 2013; Asara and Sahayaraj 2013)
Cholest-5-en-3-ol(3,beta)-,carbonochloridate			$C_{28}H_{45}ClO_2$	448	Antibacterial (Agboke and Attama 2016)
Cholesterol Isocaproate			$C_{33}H_{56}O_2$	484	No activity reported
Octadecane,3-ethyl-5-(2-ethylbutyl)-			$C_{26}H_{54}$	366	Antimicrobial, antioxidant (Chandrasekar et al. 2015)
Docosane, 2,4-Dimethyl					compound not reported

Table 1 (continued)

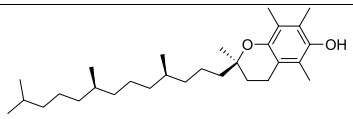
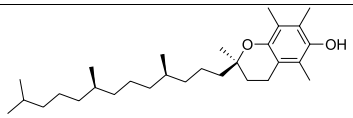
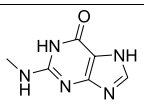
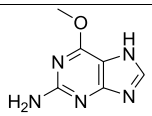
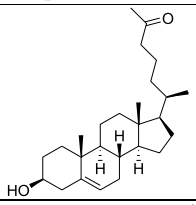
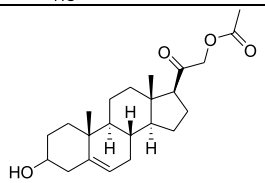
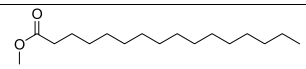
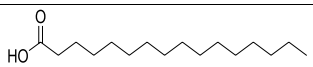
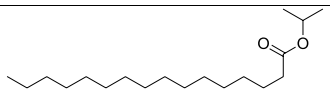
	DL-alpha-tocopherol		Vitamin E	$C_{29}H_{50}O_2$	430	Anti-oxidation effects, protects human skin against cytotoxic effect of UVB and dietary supplement (Kondo et al. 1990; Jialal and Grundy 1992)
	Vitamin E		Vitamin E	$C_{29}H_{50}O_2$	430	Analgesic, anti-cataract, anti-coronary, anti-diabetic, antioxidant, Hepatoprotective, Vasodilator, protein-kinase-c-inhibitor, anticancer, Lipoxygenase inhibitor, Anti-bronchitic, anti-coronary (Jothi et al. 2015; Rajalakshmi and Mohan 2016)
	6h-Purin-6-one,1,7-dihydro-2(methylamino)		imidazole derivatives	$C_7H_8N_4O$	164	Acts as anti-viral (active against HSV-1 and HSV-2) (Kumar et al 2017)
	1H-Purin-2-amine-6-methoxy			$C_6H_7N_5O$	165	No activity reported
	26-nor-5-cholesten-3,beta,-ol-25-one			$C_{26}H_{42}O_2$	386	Anti-tumor, anti-inflammatory, anti-oxidant and anti-bacterial (Yuvaraj and Arul 2014)
	21-Acetoxypregnenolone			$C_{25}H_{36}O_5$	416	Anti-microbial, antioxidant, targets antisense strands (targets single stranded RNA complimentary to protein coding mRNA which hybridizes and block translation of protein) mainly use in gene knockdown Antiproliferative activity against melanoma cells (Chidambaram et al. 1996; Kim et al. 2009; Chen et al. 2014)
Stem	Hexadecanoic acid, methyl ester			$C_{17}H_{34}O_2$	270	Antioxidant, hypocholesterolenic, flavor, hemolytic 5-alpha reductase inhibitor, nematicide, antiandrogenic (Easwaran and Ramani 2014)
	N-hexadecanoic acid		Palmitic acid	$C_{16}H_{32}O_2$	256	Anti-inflammatory, Antioxidant, hypocholesterolemic nematicide, pesticide, anti-androgenic flavor, hemolytic, 5-alpha reductase inhibitor (Kumar et al. 2010; Aparna et al. 2012)
	Isopropyl palmitate			$C_{19}H_{38}O_2$	298	Anti-proliferative activity (Saxena et al. 2007)

Table 1 (continued)

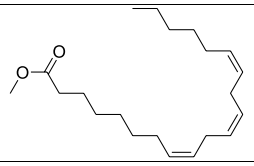
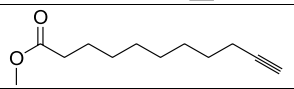
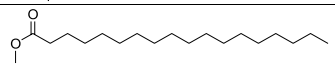
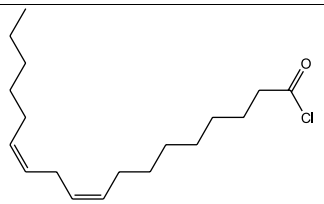
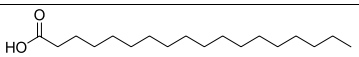
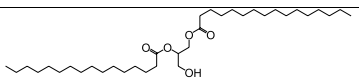
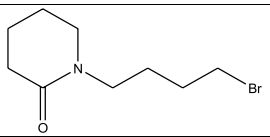
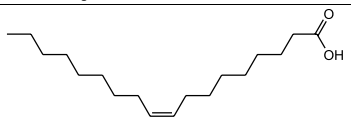
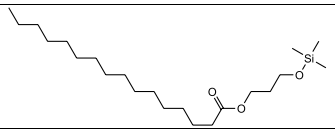
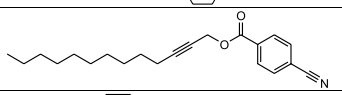
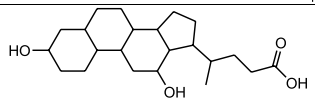
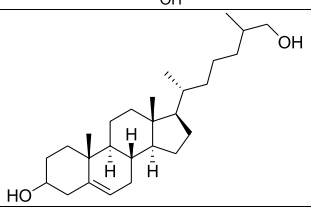
8,11,14 Eicosatrienoic acid, methyl ester		Methyl dihomo-γ-linoleic acid	$C_{21}H_{36}O_2$	320	Tumoricidal (Das and Madhavi 2011)
10-undecynoic acid, methyl ester			$C_{12}H_{20}O_2$	196	Anti-oxidant (Palakkal et al. 2017)
Octadecanoic acid, methyl ester		Methyl stearate	$C_{19}H_{38}O_2$	298	Antifungal and antioxidant (Pinto et al. 2017)
9,12-octadecadienoyl chloride, (Z,Z)-		Linoleoyl chloride	$C_{18}H_{31}ClO$	298	Anticancer, Anticoronary, Antieczemic, Antihistamic (Kumar et al. 2015)
Octadecanoic acid		Stearic acid	$C_{18}H_{36}O_2$	284	Hypocholesterolemic, surfactant and softening agent, perfumery, flavor and in cosmetic Antibacterial activity (Da Silva et al. 2003; Rajashyamala and Elango 2015)
Hexadecanoic acid, 1-(hydroxymethyl)-1,2-ethanediyl ester		Glyceryl 1,2-dipalmitate	$C_{35}H_{68}O_5$	568	Antimicrobial, Antioxidant (Kumar et al 2013)
2-piperidinone,N-(4-Bromo-N-butyl)-		Alkaloid	$C_9H_{34}O_7S$	370	Anti-inflammatory, anti-microbial, anti-cancer (Jothi et al. 2015)
oleic acid		Carboxylic acid	$C_{18}H_{34}O_2$	282.468	Anti-inflammatory, cancer preventive, antimicrobial, anti-tumour activity (Padma et al. 2018; Karunanithi and Venkatachalam 2019)
Hexadecanoic acid, 3-[(trimethylsilyl)oxy]propyl ester		3-Trimethylsilyl oxypropyl hexadecanoate	$C_{22}H_{46}O_3Si$	386	Antimicrobial, Antioxidant (Chandrasekar et al. 2015)
4-cyanobenzoic acid, Tridec-2-YNYL,ester			$C_{21}H_{27}NO_2$	325	No activity reported
Bisnor-7-desoxycholic acid			$C_{22}H_{36}O_4$	364	Antimicrobial, Antioxidant, Anticancer (Wei et al. 2011)
26-hydroxycholesterol		LDL	$C_{27}H_{46}O_2$	402	Inhibition of cholesterol synthesis (Javitt 1990)

Table 1 (continued)

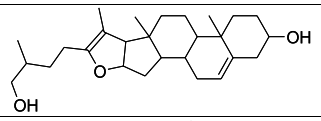
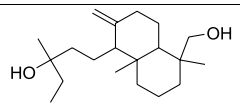
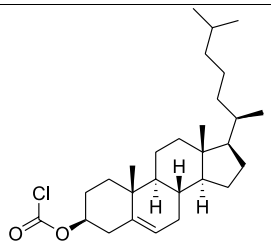
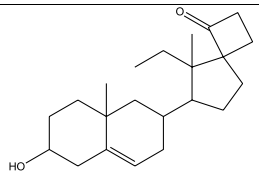
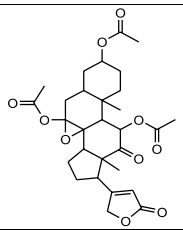
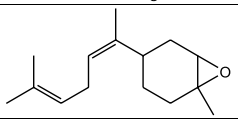
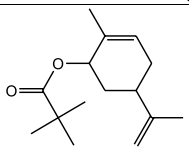
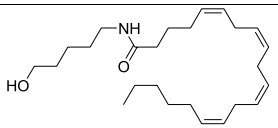
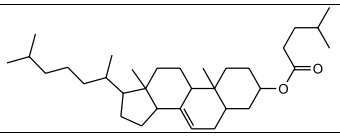
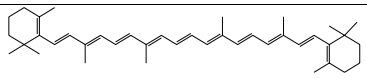
pseudosarsasapogenin-5,20-dien		$C_{27}H_{42}O_3$	414	Treatment of Amyotrophic lateral sclerosis (Suthanabegam et al. 2019)
1-napthalenepropanol, Alpha-ethyl decahydro-5(hydroxymethyl)		$C_{20}H_{36}O_2$	308	No activity reported
Cholest-5-en-3-ol (3.beta)., carbonochloridate		$C_{28}H_{45}ClO_2$	448	Antibacterial (Agboke and Attama 2016)
Spiro[Androst-5-ene-17,1'-cyclobutan]-2'-one, 3-hydroxy-, (3.beta.,17.bet		$C_{22}H_{32}O_2$	328	Anti-inflammatory and anti-microbial Antiarthritic, anticancer, antiasthma, Hepatoprotective (Sathiyabalan et al. 2014; Okereke et al. 2017)
Serverogenin acetate		$C_{29}H_{36}O_{10}$	544	Anti-insect, anti-microbial, anti-oxidant, anti-cancer, and anti-ulcerogenic activity (Karunanithi and Venkatachalam 2019)
Trans-Z-Alpha-Bisabolene epoxide		$C_{15}H_{24}O$	220	Anti-bacterial activity Anti-inflammatory effects (Hameed et al. 2016)
Limonene-6-ol,Pivalate		$C_{15}H_{24}O_2$	236	Anti-inflammatory and antioxidant anti-stress activity (Hadi et al. 2015; Hussein 2016)
Arachidonic amide,N-(5-Hydroxy-N-pentyl)		$C_{25}H_{43}NO_2$	389	COX enzyme expression for catalysis of prostalglandins (plays a significant role in health and disease in the gastrointestinal tract (GI), in renal, skeletal and ocular system (Barry et al. 1997; Autore et al. 2010)
7.dehydrocholesterol isocaproate		$C_{33}H_{56}O_2$	484	No activity reported
Kryptogenin 2,4-dinitrophenyl hydrazine				compound not reported
Beta-Carotene		Vitamin A precursor	$C_{40}H_{56}$ 536	used in leukaemia therapies, cardiovascular disease protective (Dreosti 1996; Zaini et al. 2012)

Table 1 (continued)

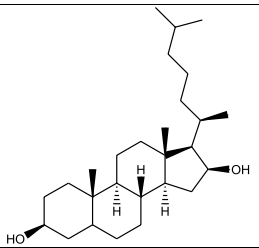
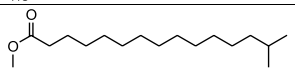
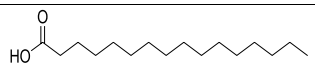
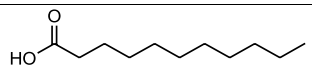
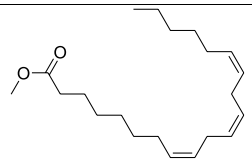
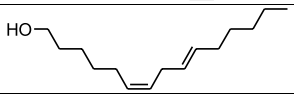
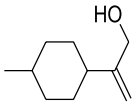
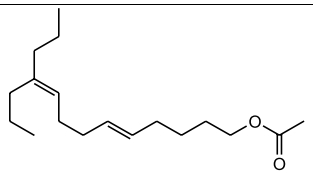
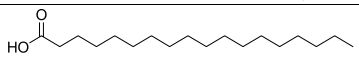
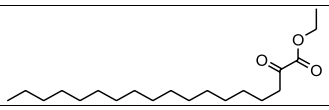
	Coprostan-3. Beta, 16. Beta-Diol			$C_{41}H_{56}O_4$	612	No activity reported
Roots	Pentadecanoic acid, 14 methyl ester-, methyl ester		Palmitic acid methyl ester	$C_{19}H_{34}O_2$	270	Antioxidant, antifungal and antimicrobial (Vijisaral and Arumugam 2014; Elaiyaraja and Chandramohan 2016)
	N-hexadecanoic acid		Palmitic acid	$C_{16}H_{32}O_2$	256	Anti-inflammatory, Antioxidant, hypocholestero lemic nematicide, pesticide, anti-androgenic flavor, hemolytic, 5-alpha reductase inhibitor (Kumar et al. 2012; Aparna et al. 2012)
	Undecanoic acid		carboxylic acid	$C_{11}H_{22}O_2$	186.295	Anti-mycotic activity (Padma et al. 2018)
	8,11,14-Eicosatrienoic acid, methyl ester		Methyl dihomo-γ-linoleic acid	$C_{21}H_{36}O_2$	320	Tumoricidal (Das and Madhavi 2011)
	(Z)6,(Z)9-Pentadecadien-1-ol			$C_{15}H_{28}O$	224	Antifungal (Umaiyambigai et al. 2017)
	P-menth-8(10)-en-0-ol, cis			$C_{10}H_{18}O$	154	Sedative effect, depressant effect in the CNS, such as anti-convulsants and anxiolytics, increase the time of sleep, larvicidal and repellant activity against dengue fever (De Sousa et al. 2007; Balasubramani et al. 2018)
	Propylure			$C_{18}H_{32}O_2$	280	Sex pheromone (Jacobson 1969)
	Octadecanoic acid		Stearic acid	$C_{18}H_{36}O_2$	284	Hypocholesterolemic, surfactant and softening agent, perfumery, flavor and in cosmetic Antibacterial activity (Da Silva et al. 2003; Rajashyamala and Elango 2015)
	Alpha-Ketostearic acid, ethyl ester			$C_{20}H_{38}O_3$	326	No activity reported

Table 1 (continued)

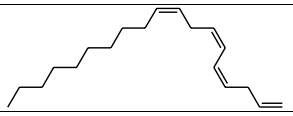
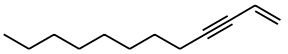
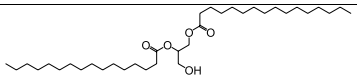
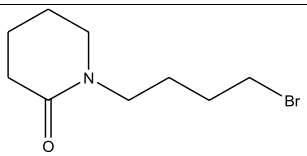
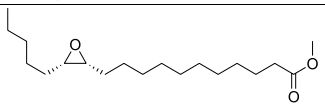
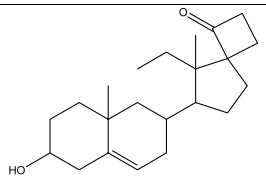
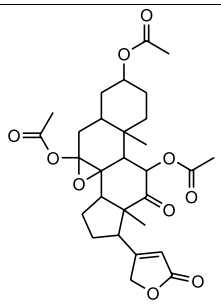
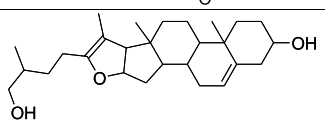
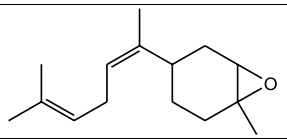
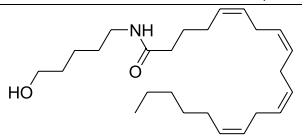
Z,Z,Z-1,4,6,9-Nonadecatetraene			$C_{19}H_{32}$	260	Antioxidant (Naidu et al. 2012; Suffo et al. 2016)
1-Dodecen-3-yne					Anti- skin pathogen, Anti-oxidant (Kim et al. 2011)
Hexadecanoic acid, 1-(hydroxymethyl)-1,2-ethanediyl ester		Glyceryl 1,2-dipalmitate	$C_{35}H_{68}O_5$	568	Antimicrobial, Antioxidant (Kumar et al. 2013)
2-piperidinone,N-(4-Bromo-N-Butyl)-		Alkaloid	$C_9H_{16}BrNO$	233	Anti-inflammatory Anti-microbial Anti-cancer (Jothi et al 2015)
Oxiraneundecanoic acid, 3-pentyl, methyl ester, cis			$C_{19}H_{36}O_3$	312	Larvicidal activity Antioxidant activity (Elumalai et al. 2015; Al-Marzoqi et al. 2016)
9-octadecanoic acid (Z)-, 2-Hydroxy-1-(hydroxymethyl)ethyl ester		Fatty acid ethyl ester, Oleic acid compound	$C_{21}H_{40}O_4$	356	No activity reported (Vijisaral and Arumugam 2014; Rajalakshmi and Mohan 2016)
Spiro[Androst-5-ene-17, 1'-cyclobutan]-2'-one, 3-hydroxy-,(3.beta.,17.bet			$C_{22}H_{32}O_2$	328	Anti-inflammatory and anti-microbial Antiarthritic, anticancer, antiasthma, Hepatoprotective (Sathiyabalan et al. 2014; Okereke et al. 2017)
Serverogenin acetate			$C_{29}H_{36}O_{10}$	544	Anti-insect, anti-microbial, anti-oxidant, anti-cancer, and anti-ulcerogenic activity (Karunanithi and Venkatachalam 2019)
pseduosarsasapogenin-5,20-dien			$C_{27}H_{42}O_3$	414	Treatment of Amyotrophic lateral sclerosis (Sulthanagebam et al. 2019)
Trans-Z-Alpha-bisabolene epoxide			$C_{15}H_{24}O$	220	Anti-bacterial activity Anti-inflammatory effects (Hameed et al. 2016)
Arachidonic amide, N-(5-hydroxy-N-pentyl)			$C_{25}H_{43}NO_2$	389	COX enzyme expression for catalysis of prostalglandins (plays a significant role in health and disease in the gastrointestinal tract (GI), in renal, skeletal and ocular system (Barry et al. 1997; Autore et al. 2010)

Table 1 (continued)

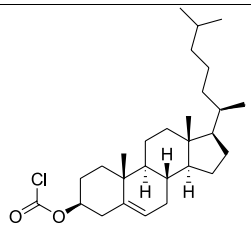
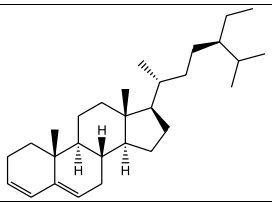
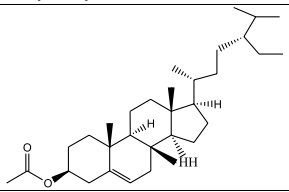
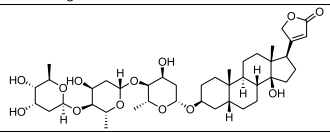
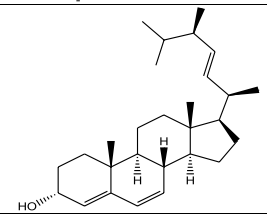
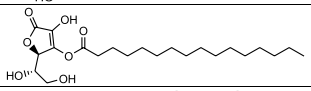
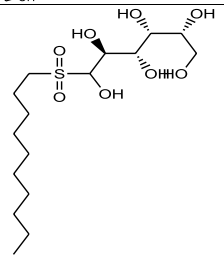
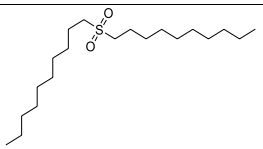
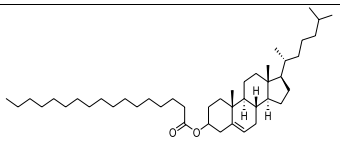
Cholest-5-en-3-ol (3.beta)- ,carbonochloridate			$C_{28}H_{45}ClO_2$	448	Antibacterial (Agboke and Attama 2016)
Stigmastan-3,5-diene			$C_{29}H_{48}$	396	Antimicrobial and Antioxidant (Khan et al. 2016)
Beta-Sitosterol acetate			$C_{31}H_{52}O_2$	456	Anti-inflammatory, inducing apoptosis, chemoprotective or chemoprotective effects, angiogenic effect, prostatic cancer treatment (Saeidmia et al. 2014)
Digitoxin		cardiac glycoside	$C_{41}H_{64}O_{13}$	764	used for chronic cardiac insufficiency (fatigue, shortness of breath and edema) (Vardanyan and Hruby 2006)
Ergosta-4,6,22-Trien-3, alpha-ol		steroid	$C_{28}H_{44}O$	396	Anti-microbial, anti-inflammatory, anti-cancer, anti-arthritic, anti-asthma, diuretic (Lalithi et al. 2015)
Ascorbyl palmitate		Ascorbic acid ester	$C_{22}H_{38}O_7$	414	Food additive and cosmetic ingredient (Tuffino et al. 2019)
D-mannitol, 1-Decylsulfonyl		Sulfur compound	$C_{16}H_{34}O_7S$	370	antimicrobial antidiabetic (Muthukrishnan and Thinakaran 2012; Alagammal et al. 2012; Jothi et al. 2015; Ezekiel et al. 2018)
DI-N-Decylsulfone			$C_{20}H_{42}O_2S$	346	Anti-microbial and anti-cancer Larvicidal activity (Vijayakumari and Raj 2019; Karthi et al. 2020)
Alpha-L-Fucopyranose 1,2.3,4-Bis (Benzeneboonate)			$C_{18}H_{18}B_2O_5$	336	No activity reported
cholesterol margarate			$C_{44}H_{78}O_2$	639	No activity reported
N-decyl-Alpha,D-2-Deoxyglycoside					Compound not reported

Table 2 GC–MS analysis of ethanol extracts of *Pleione maculata*

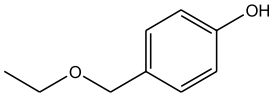
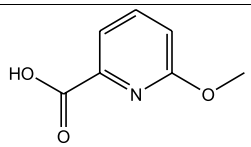
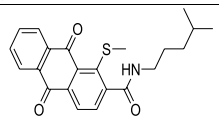
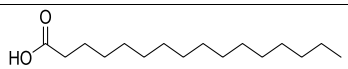
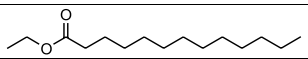
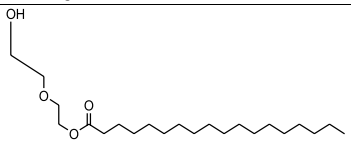
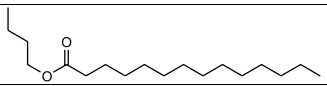
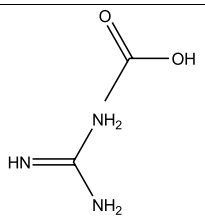
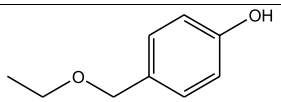
Parts of *P. maculata*	Peak name	Chemical structure	Molecular name	Molecular formula	Molecular weight	Activity
Leaves	Phenol, 4-(ethoxymethyl)		4-(Ethoxymethyl) Phenol	$C_9H_{12}O_2$	152	No activity reported
	2.pyridinecarboxylic acid, 6-methoxy			$C_8H_9NO_3$	153	No activity reported
	1-methyl sulfanyl -9-10-Dioxo-9,10-dihydro-anthracene-2-carbxylic acid			$C_{23}H_{17}NO_3S$	387	No activity reported
	N-hexadecanoic acid		Palmitic acid	$C_{16}H_{32}O_2$	256	Anti-inflammatory, Antioxidant, hypocholesterolemic nematicide, pesticide, anti-androgenic flavor, hemolytic, 5-alpha reductase inhibitor (Kumar et al. 2010; Aparna et al. 2012)
	Ethyl tridecanoate			$C_{15}H_{30}O_2$	242	Antioxidant (Qurzeddine et al. 2017)
	Octadecanoic acid, 2-(2-hydroxyethoxy) ethyl ester		Diethylene glycol stearate	$C_{22}H_{44}O_4$	372	Used in cosmetic, textile, serve as plasticizer, lubricant, binding and thickening agent (Oduje et al. 2015)
	N-butyl myristate			$C_{18}H_{36}O_2$	284	used as plasticizers anti-microbial activity (Sujatha et al. 2014)
	Guanidine acetic acid		Glycocyamine	$C_3H_7N_3O_2$	117	Antibacterial activity Biosynthesis of creatine as a suitable food and feed supplement Beneficial effect on the stamina (US 8, 501, 810 B2) (Gastner and Krimmer 2013)
Stem	Phenol, 4-(ethoxymethyl)		4-(Ethoxymethyl) Phenol	$C_9H_{12}O_2$	152	No activity reported

Table 2 (continued)

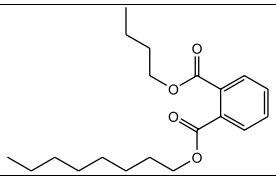
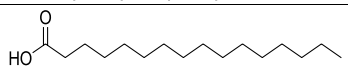
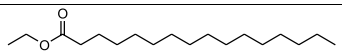
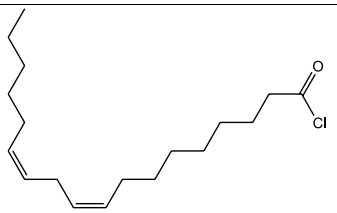
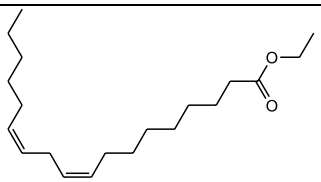
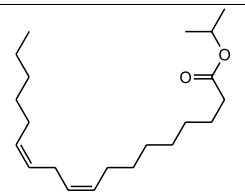
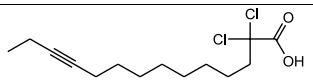
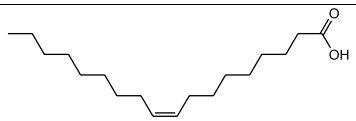
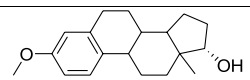
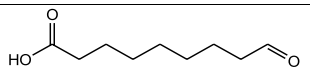
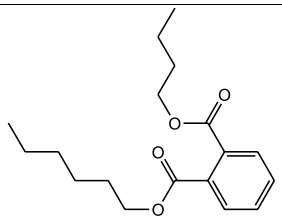
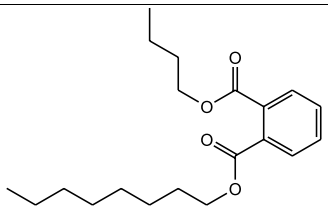
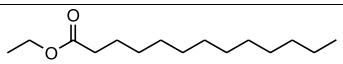
1,2-benzenedicarboxylic acid, butyl octyl ester		Phthalic acid, butyl octyl ester, Plasticizer BOP	$C_{20}H_{30}O_4$	334	Antimicrobial, Antifouling (Lakshmi and Rajalakshmi 2011; Khalil et al. 2014)
N-hexadecanoic acid		Palmitic acid	$C_{16}H_{32}O_2$	256	Anti-inflammatory, Antioxidant, hypocholesterolemic nematicide, pesticide, anti-androgenic flavor, hemolytic, 5-alpha reductase inhibitor (Kumar et al. 2010; Aparna et al. 2012)
Hexadecanoic acid, ethyl ester		Palmitic acid ester	$C_{18}H_{36}O_2$	284	Antioxidant, Hemolytic, hypocholesterone, Flavor, Nematicide, Anti-androgenic (Tyagi and Agarwal 2016)
9,12-octadecadienoic acid (Z,Z)-		Conjugated Linoleic acid	$C_{18}H_{32}O_2$	280	Anti-Inflammatory, hypocholesterolic, cancer preventive, Hepatoprotective, nematicide, antihistaminic, antieczemic, antiacne, 5-α reductase inhibitor, anti-coronary, antimicrobial (Adeoye-Isijola et al. 2018)
Linoleic acid ethyl ester			$C_{20}H_{34}O_2$	308	Hypocholesterolemic, nematicide, anti-arthritic, hepatoproctective, anti-androgenic, hypycholesterolemic, 5-alpha reductase inhibitor, anti-histaminic, anti-coronary, insectifuge, anti-eczemic, anti-acne (Chidambarampillai and Mohan 2013; Tyagi and Agarwal 2016)
Isopropyl linoleate			$C_{21}H_{38}O_2$	322	Antioxidant, antidiabetic, anti-inflammatory Formulation of skin and hair care products, facial makeup (Rajendra et al. 2017; Rautela et al. 2018)
Dichloroacetic acid, dodec-9-YNYL			$C_{14}H_{23}ClO_2$	292	Acidifier, arachidonic acid inhibitor, increase aromatic amino acid decarboxylase activity, inhibit production of uric acid (Mohammad et al. 2019)
Oleic acid			$C_{18}H_{34}O_2$	282	Antibacterial activity (Abubakar and Majinda 2016)
Estra-1,3,5 (10)-Trien-17-Beta-ol			$C_{18}H_{24}O$	256	Anti-arrhythmic activity (Al-Gara'wi 2019)

Table 2 (continued)

	9-Oxononanoic acid (9-ONA)			$C_9H_{16}O_3$	172	Lipid peroxidation (treats disorder such as inflammation, atherosclerosis and other degenerative diseases) induces phospholipase A2 activity and thromboxane A2 production in human blood (Ren et al. 2013)
Roots	Phthalic acid, butyl hexyl ester		Butyl hexyl phthalate	$C_{18}H_{26}O_4$	306	Antimicrobial (Ingole 2016)
	1,2-benzenedicarboxylic acid, butyl octyl ester		Phthalic acid, butyl octyl ester, Plasticizer BOP	$C_{20}H_{30}O_4$	334	Antimicrobial, Antifouling (Lakshmi and Rajalakshmi 2011; Khalil et al. 2014)
	Ethyl tridecanoate			$C_{15}H_{30}O_2$	242	Antioxidant (Qurzeddine et al. 2017)

electrostatic, van der Waals interaction, and some interacted with positively charged functional groups of an amino acid (lysine, arginine, and histidine), while some interacted with hydroxyl groups of amino acid serine, threonine, and tyrosine. Amino acid residues such as serine, threonine, and tyrosine contribute to rotating hydroxyl groups in the docking complex are considered rigid (Pantsar and Poso 2018).

3.1 Docking analysis of ligand against SARS-CoV-2 RNA-dependent RNA-polymerase (PDB ID—6M71) target

A high binding affinity was observed between GC–MS compounds digitoxin, cholesterol margarate, docosanoic acid, pseudosarsasapogenin-5,20-dien, arachidonic amide,*N*-{5-hydroxy-*N*-pentyl), DI-*N*-decylsulfone, oxiraneundecanoic acid, 3-pentyl, methyl ester, cis, andrographolide, 21-acetoxypregenelone, p-menth-8(10)-en-9-ol, 26-hydroxycholesterol, and pregabalin against target protein RNA-dependent RNA-polymerase with high atomic contact energies of − 22.96, − 21.60, − 13.13, − 12.54, − 12.04, − 11.57, − 11.38, − 8.43, 8.38, − 7.18, − 7.11, and − 6.85 kcal/mol. The most prominent and common amino acid residues binding to the target proteins were Asn 414, Lys 411, Tyr 141, Val 12, Tyr 546, and Asn 781.

3.2 Docking analysis of ligands against target SARS-CoV-2 3CL protease (3CL pro) (PDB ID—6M2Q)

GC–MS compounds of *P. maculata* digitoxin, 26-hydroxycholesterol, 1-methylsulfanyl-9,10-dioxo-dihydro-anthracene-2-carboxylic acid, arachidonic amide,*N*-{5-hydroxy-*N*-pentyl), cholesterol margarate, 21-acetoxypregenelone, pseduosarsasapogenin-5,20-dien, DI-*N*-decylsulfone, Nor-diazepam,3-{*N*-hydroxymethyl}aminocarbonyl, andrographolide, *p*-menth-8(10)-en-9-ol, and pregabalin exhibited high binding affinity − 13,27, − 12.61, − 12.22, − 10.86, − 9.91, − 9.22, − 8.41, − 7.39, 7.19, − 7.17, 6.75, and − 6.33 kcal/mol against target SARS-CoV-2 3CL protease. The most commonly found amino acid residues binding to the target pocket were Gln 110, Phe 294, and Thr 111.

3.3 Docking analysis of ligands against target SARS-CoV-2 post-fusion core structure of spike glycoprotein S2 subunit (PDB ID- 6LXT)

The target spike glycoprotein-S2 subunit amino acid residues interacted with compounds, 1-methylsulfanyl-9,10-dioxo-9,10-dihydro-anthracene-2-carboxylic, Nor-diazepam, 3-{*N*-hydroxymethyl} aminocarbonyloxy, andrographolide,

Table 3 GC–MS analysis of methanol extracts of *Pleione maculata*

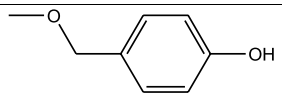
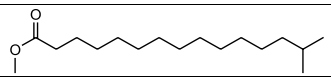
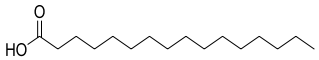
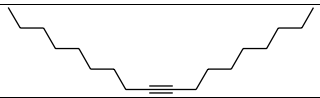
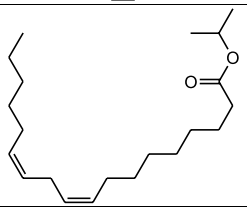
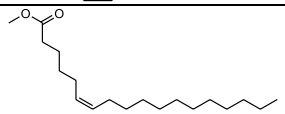
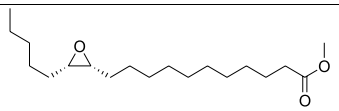
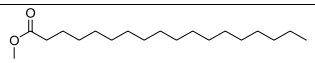
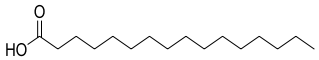
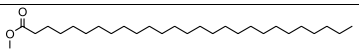
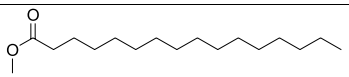
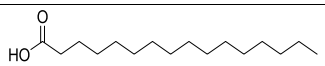
Parts of *P. maculata*	Peak name	Chemical structure	Molecular name	Molecular formula	Molecular weight	Activity
leaves	Phenol, 4-(methoxymethyl)-			$C_8H_{10}O_2$	138	Anti-diabetic (Balamurugan et al. 2017)
	Pentadecanoic acid, 14-methyl-, methyl ester		Palmitic acid methyl ester	$C_{19}H_{34}O_2$	270	Antioxidant (Vijisaral and Arumugam 2014)
	N-hexadecanoic acid		Palmitic acid	$C_{16}H_{32}O_2$	256	Anti-inflammatory, Antioxidant, hypocholesterolemic nematicide, pesticide, anti-androgenic flavor, hemolytic, 5-alpha reductase inhibitor (Kumar et al. 2010; Aparna et al. 2012)
	9-octadecyne		Alkene compound	$C_{18}H_{34}$	250	Antioxidant, Antimicrobial (Upgade and Bhaskar 2013)
	Isopropyl linoleate			$C_{21}H_{38}O_2$	322	Antioxidant, antidiabetic, anti-inflammatory Formulation of skin and hair care products, facial makeup (Rajendra et al. 2017; Rautela et al. 2018)
	6-octadecenoic acid, methyl ester, (Z)-		*Trans*-13-octadecanoic acid, methyl ester 7	$C_{19}H_{36}O_2$	296	Anti-inflammatory, antiandrogenic, cancer preventive, dermatitigenic irritant, antiluekotriene-D4, Hypocholesterolemic, 5-alpha reductase inhibitor, anemiagenic, insectifuge, flavor (Abubakar and Majinda 2016)
	Oxiraneundecanoic acid, 3-pentyl, methyl ester, cis			$C_{19}H_{36}O_3$	312	Larvicidal activity Antioxidant activity (Elumalai et al. 2015; Al-Marzoqi 2016)
	Octadecanoic acid, methyl ester		Methyl stearate	$C_{19}H_{38}O_2$	298	Antifungal and antioxidant (Pinto et al. 2017)
	N-hexadecanoic acid		Palmitic acid	$C_{16}H_{32}O_2$	256	Anti-inflammatory, Antioxidant, hypocholesterolemic nematicide, pesticide, anti-androgenic flavor, hemolytic, 5-alpha reductase inhibitor (Kumar et al. 2010; Aparna et al. 2012)
	Heptacosanoic acid, methyl ester		Methyl heptacosanoate	$C_{28}H_{56}O_2$	424	No activity reported
Stem	Hexadecanoic acid, methyl ester			$C_{17}H_{34}O_2$	270	Antibacterial and antifungal (Abubakar and Majinda 2016)
	N-hexadecanoic acid		Palmitic acid	$C_{16}H_{32}O_2$	256	Anti-inflammatory, Antioxidant, hypocholesterolemic nematicide, pesticide, anti-androgenic flavor, hemolytic, 5-alpha reductase inhibitor (Kumar et al. 2010; Aparna et al. 2012)

Table 3 (continued)

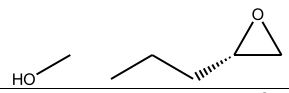
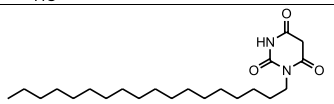
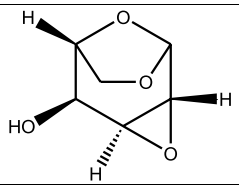
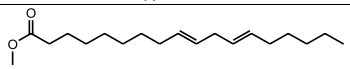
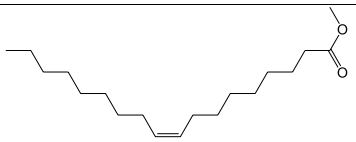
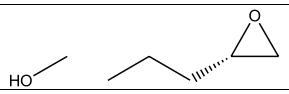
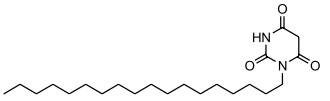
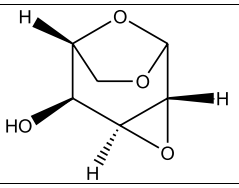
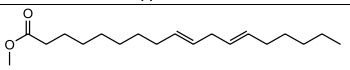
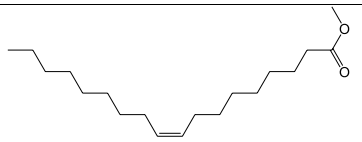
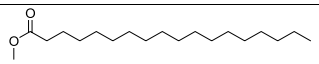
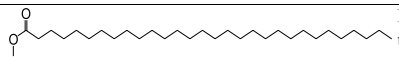
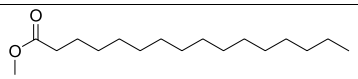
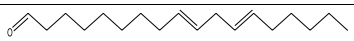
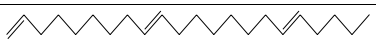
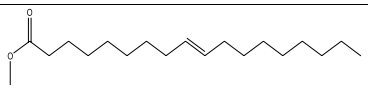
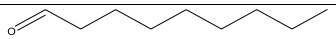
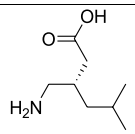
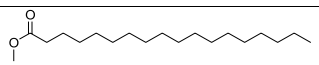
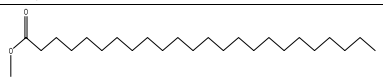
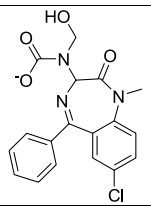
(2s,3s)-(-)-3-propyloxirane methanol			$C_6H_{12}O_2$	116	Anti-oxidant (Yusufzai et al. 2019)
pyrimidine-2,4,6(1H,3H,5H)-Trione-1-octadecyl)			$C_{22}H_{40}N_2O_3$	380	compound not reported 2,4,6-trisubstituted pyrimidine were evaluated as anti-malaria drug (Agrawal et al. 2005)
2,3-anhydro-D-galactosan		Sugar moeity	$C_6H_8O_4$	144	preservative (Paulpriya et al. 2014)
9,12-octadecadienoic acid, methyl ester			$C_{19}H_{34}O_2$	294	Anticancer, anti-inflammatory, antileukotriene, flavor (Abubakar and Majinda 2016)
9-octadecenoic acid (Z)-, methyl ester		*Trans*-13-octadecanoic acid, methyl ester 7	$C_{19}H_{36}O_2$	296	Anti-inflammatory, antiandrogenic, cancer preventive, dermatitigenic irritant, antiluekotriene-D4, Hypocholesterolemic, 5-alpha reductase inhibitor, anemiagenic, insectifuge, nematicide, pesticide, anti-androgenic flavor, hemolytic, 5-alpha reductase inhibitor (Kumar et al. 2010; Aparna et al. 2012)
(2s,3s)-(-)-3-propyloxirane methanol			$C_6H_{12}O_2$	116	Anti-oxidant (Yusufzai et al. 2019)
pyrimidine-2,4,6(1H,3H,5H)-Trione-1-octadecyl)			$C_{22}H_{40}N_2O_3$	380	compound not reported 2,4,6-trisubstituted pyrimidine were evaluated as anti-malaria drug (Agrawal et al. 2005)
2,3-anhydro-D-galactosan		Sugar moeity	$C_6H_8O_4$	144	preservative (Paulpriya et al. 2014)
9,12-octadecadienoic acid, methyl ester			$C_{19}H_{34}O_2$	294	Anticancer, anti-inflammatory, antileukotriene, flavor (Abubakar and Majinda 2016)

Table 3 (continued)

	9-octadecenoic acid (Z)-, methyl ester		*Trans*-13-octadecanoic acid, methyl ester 7	$C_{19}H_{36}O_2$	296	Anti-inflammatory, antiandrogenic, cancer preventive, dermatitigenic irritant, antiluekotriene-D4, Hypocholesterolemic, 5-alpha reductase inhibitor, anemiagenic, insectifuge, flavor (Abubakar and Majinda 2016)
	Octadecanoic acid, methyl ester		Methyl stearate	$C_{19}H_{38}O_2$	298	Antifungal and antioxidant (Pinto et al. 2017)
	Triacontanoic acid, methyl ester		Methyl triacontanate	$C_{31}H_{62}O_2$	466	Antimicrobial (Kumar et al. 2015)
Roots	Hexadecanoic acid, methyl ester			$C_{17}H_{34}O_2$	270	Antibacterial and antifungal activity (Abubakar and Majinda 2016)
	9,12-octadecadienal			$C_{18}H_{32}O$	264	Antimicrobial and antioxidant (Gurnani et al 2015)
	E,E-1,9,17-Docasatriene		alkene compound	$C_{22}H_{40}$	304	No activity reported (Subavathy and Thilaga 2016; Kumaravel et al. 2016, 2019)
	9-octadecenoic acid, methyl ester		*Trans*-13-octadecanoic acid, methyl ester 7	$C_{19}H_{36}O_2$	296	Anti-inflammatory, antiandrogenic, cancer preventive, dermatitigenic irritant, antiluekotriene-D4, Hypocholesterolemic, 5-alpha reductase inhibitor, anemiagenic, insectifuge, flavor (Abubakar and Majinda 2016)
	Nonanal		aldehyde	$C_9H_{18}O$	142	Anti-aging use in cosmetics Fungicides (Plainfosse et al. 2017; Zhang et al. 2017)
	pregabalin			$C_8H_{17}NO_2$	159	Adjunctive treatment of partial seizures, use in neuropathic pain, neuralgia, use in alcohol withdrawal syndrome, restless leg syndromes, migraine and vasomotor symptoms of menopause (World Health Organization 2018)
	Octadecanoic acid, methyl ester		Methyl stearate	$C_{19}H_{38}O_2$	298	Antifungal and antioxidant (Pinto et al. 2017)
	Tetracosanoic acid, methyl ester		Methyl lignocerate	$C_{25}H_{50}O_2$	382	Antibacterial, Antimicrobial (Valiei et al. 2011; Ukil et al. 2015)
	Nor-Diazepam,3-{(N-hydroxymethyl)aminocarbonyl oxy}			$C_{18}H_{16}ClN_3O_4$	373	No activity reported

digitoxin, cholesterol margarate, 26-hydroxycholesterol, *p*-menth-8(10)-en-9-ol, and pregabalin with high binding affinity (ACE) of − 10.95, − 9.23, − 8.93, − 8.23, − 8.23, 6.68, and 6.29 kcal/mol. The most common residues binding to target proteins were Ser 943, Ser 940, Glu 1188, Ser 939, Asp 1184, Asp 936, Lys 1191, Gln 935, and Asn 1187.

3.4 Drug-likeness analysis of bioactive compound

Drug-likeness was analyzed to check whether bioactive compounds possess favorable ADME (absorption, distribution, metabolism, and excretion) properties. Drug-likeness compounds should have a good aqueous solubility which is predicted by three methods ESOL, (ALI) logS, and (SILICOS-IT) logS (Shweta and Rashmi 2019). Orally active drug should obey Lipinski five rule in Table 5, molecular weight (MW) not more than 500 g/mol, hydrogen bond acceptors not more than 10, hydrogen bond donors not more than 5, LogP value less than 5, and number of rotatable bonds not less than 10 (Lipinski et al. 1997), and a violation of two or more rule depicts a molecule as not orally active. Drug-likeness analysis of bioactive compounds listed in Table 6 with their different parameters is shown in SwissADME bioavailability radar in Fig. 7. Nor-diazepam,3-{*N*-hydroxymethyl}aminocarbonyloxy bioactive compound showed good binding affinity against SARS-CoV-2 with high drug-likeness parameters such as good solubility and no excretion problems as there is no pharmacokinetics P-gp (permeability glycoprotein) interference and non-inhibitor of CYP enzymes and compound is specific in nature (zero alerts for PAINS (pan assay interference compounds)). 1-Methylsulfanyl-9,10-dioxo-9,10-dihydro-anthracene-2-carboxylic acid drug-likeness parameters is also good, since it follows Lipinski RO5, Ghose, Veber, Egan, Muegge rule, and Bioavailability score 0.55 but the PAINS (Pan assay interference compounds) exhibited some interference with Quinone A compound which indicates compound is not specific and is moderately soluble in nature. Digitoxin might have shown good binding affinity but does not obey any of the drug-likeness parameters. Pregabalin and *p*-menth-8(10)-en-9-ol bioactive compounds are highly soluble in nature but depict one or two violations as drug-likeness due to lower molecular weight (< 160). 21-Acetoxypregenolone an antisense target compound showing good binding affinity against SARS-CoV-2 shows moderate drug-likeness parameters, specific in nature, and no excretion problems but is an inhibitor of CYP2C9 enzyme. Pseudosarsasapogenin-5, 20-dien, and andrographolide drug-likeness activity are moderate with good solubility property. Compounds such as DI-*N*-decylsulfone, arachidonic amide, *N*-{5-hydroxy-*N*-pentyl}, 26-hydroxycholesterol, cholesterol margarate, and docosanoic acid showed poor solubility with various violations as a drug molecule. Arabidiol an already marketed antiviral drug does follow Lipinski RO5 but does not obey drug-likeness parameters and is poorly soluble compared to bioactive compounds of *Pleione maculata* with high solubility in nature.

4 Discussion

The GC–MS analysis of other orchids mostly focuses on flower scent profile rather than a therapeutic profile, for example, Vanda species (Darmasiwi et al. 2015), *Rhynchostylis gigantean Ridl, Rhynchostylis gigantean var. harrisonianum Holtt., Vanda coerulea and Dendrobium parishii Rchb*. F., (Julsrigival et al. 2013) and *Dendrophylax lindenii* (Sadler et al. 2011). In this paper, the GC–MS report of *Pleione maculata* mainly focused on total medicinal important compounds present in different parts. Compounds such as phenol 4-(ethoxymethyl), heptacosanoic acid methyl ester, 9-octadecanoic acid (Z)- 2-hydroxy-1-(hydroxymethyl) ethyl ester (Vijisaral and Arumugan 2014; Rajalakhsmi and Mohan 2016), nonanoic acid 9(3-hexemyldenecyclopropylidene-2-hydroxy-1–1 (HYD) (Sahin et al. 2006), alpha-ketostearic acid ethyl ester, 1-naphthaleneproponal alpha-ethyl decahydro-5-(hydroxymethyl), cis, cis, cis-7,10,13-hexadecatrienal (Prabhadevi et al. 2012; Abdulaziz et al. 2019), 1H-purin-2-amine-6-methoxy, 4-cyanobenzoic acid Tridec-2-YNYL ester, alpha-*L*-fucopyranose 1,2.3,4-bis (benzeneboonate), cholesterol margarate, 2.pyridinecarboxylic acid 6-methoxy, 1-methyl sulfanyl -9–10-dioxo-9,10-dihydro-anthracene-2-carboxylic acid, pyrimidine-2,4,6(1H,3H,5H)-trione-1-octadecyl), E,E-1,9,17-docasatriene (Subavathy and Thilaga 2016; Kumaravel et al. 2019), *N*-decyl-alpha *D*-2-deoxyglycoside, cholesterol isocaproate, 7.dehydrocholesterol isocaproate, and pyrimidine-2,4,6(1H,3H,5H)-trione-1-octadecyl) are a few of the compounds which were identified but have no bioactivity reported so far. Compounds such as 8-oxatetracyclo{5.2.1.1(2,6). 1(4,10)}dodecane, 7-tert-butyl-1,9,9-trimeth, docosane, 2,4-dimethyl, kryptogenin 2,4-dinitrophenyl hydrazine, *N*-decyl-alpha,*D*-2-deoxyglycoside are some novel compounds which have not been reported earlier. Phytochemical studies and antimicrobial activity of *Pleione maculata* were also reported which depicts the presence of various phytochemical compounds in different parts of epiphyte and antibacterial activity showed a distinct zone of inhibition against *Streptococcus pneumonia* (Sympli et al. 2019).

Docking involves the interaction of various polar and non-polar groups, and both play a significant role in the stability of protein–ligand interactions. In docking, water solvent is removed by most programs as they tend to form hydrogen bonds with molecules either as donor or acceptor (Pantsar and Poso 2018). Protein–ligand interactions are strong on the removal of H-bond but in association

Table 4 Docking analysis depicting the binding residues and their binding energy

Protein Name	Drug-likeness ligands	Polar contact binding residues	Other intermolecular contact binding residues	Global energy (kcal/mol)	Attractive Vdw (kcal/mol)	Repulsive Vdw (kcal/mol)	ACE (kcal/mol)
RNA-dependent RNA-pol (6M71)	2,4,6-Pyrimidinetrione	Cys 780, Arg 467, Leu 470, Arg 305	All side bonded by polar contacts	− 23.59	− 10.00	0.72	− 5.79
	21-Acetoxypregenelone	Ala 706, Leu 707, Asn 705	Gly 774, Asp 135, Ala 130, Ser 709	− 34.15	− 20.12	10.12	− 8.38
	P-menth-8(10)-en-9-ol	Thr 141, Leu 142	Ala 130, Asp 126	− 31.56	− 12.13	0.87	− 7.18
	Nor-diazepam, 3{n-hydroxymethyl}aminocarbonyloxy	Thr 556, Arg 555, Arg 624	All side bonded by polar contact	− 35.35	− 23.08	4.90	− 3.16
	Digitoxin	Lys 267, Ser 255, Thr 252	Ser 255, Tyr 265, Thr 319	− 79.90	− 36.74	12.20	− 22.96
	DI-*N*-decylsulfone	Tyr 546, Val 410, Lys 141	Lys 411, Asn 414, Gln 408	− 44.31	− 19.74	2.12	− 11.57
	14-dodecanoic acid	Lys 411, Val 410	Tyr 546, Ser 15, Asn 414	− 29.99	− 14.73	2.24	− 6.96
	Estra-1,3,5(10)-trien-17-beta-ol	Gln 18, Gln 19	Ser 15, Asn 414	− 36.68	− 20.43	4.20	− 6.57
	Arachidonic amide,N-{5-hydroxy-N-Pentyl}	Tyr 268	Lys 267	− 46.08	− 21.29	4.04	− 12.04
	1-methylsulfanyl-9–10-dioxo-9,10-dihydro-Anthracene-2-carboxylic acid	Asp 218, Thr 206	Tyr 217, Ile 37, Tyr 38	− 37.97	− 20.97	3.26	− 6.72
	Cholesterol margarate	Lys 391	Thr 393, Lys 395, Asn 136	− 70.69	− 31.28	9.37	− 21.60
	Docosanoic acid	No polar contact	Ser 15, Asn 414, Tyr 546, Lys 411	− 47.59	− 23.22	8.71	− 13.13
	26-hydroxycholesterol	Asn 781, Asp 126	Ser 784, Lys 47, Thr 141, Lys 780	− 42.36	− 21.98	1.38	− 7.11
	Andrographolide	Leu 142, Asp 140, Tyr 129, Asn 781, Ser 709, Leu 708	Cys 139, Asp 140, Thr 141, Lys 47	− 37.42	− 19.40	4.39	− 8.43
	6H-purin-6-one,1,7-dihydro-2-(methylamino)	Tyr 530, Asn 534	Asn 360, Val 342	− 29.00	− 12.14	0.14	− 6.92
	Pseduosarsasapogenin-5,20-dien	Ser 15	Val 12, Asp 846, Asn 414, Val 12	− 56.41	− 29.45	6.51	− 12.54
	Oxiraneundecanoic acid,3-pentyl, methyl ester, cis	No polar contact	Lys 411, Ser 15, Asn 414, Val 12	− 46.14	− 22.77	5.77	− 11.38
	Pregabalin	Asn 356, Tyr 530, Asp 377	Thr 344, Ser 343	− 30.35	− 13.26	0.32	− 6.85
	Arabidol	Asn 781, Tyr 129	Lys 780, Ser 709, Thr 710, Ser 784	− 41.54	− 20.55	5.40	− 9.95
3CL Protease (6M2Q)	2,4,6-Pyrimidinetrione	Met 6, Asp 295, Gln 127, Val 296, Arg 298	All side bonded by Polar contacts	− 16.68	− 7.33	0.09	− 4.42
	21-Acetoxypregenelone	Arg 188, Gln 184, Thr 190, Met 165, Glu 166, Leu 167, Ser 46, Thr 45	Thr 25, Thr 24, Thr 26	− 28.57	− 14.64	8.41	− 9.22
	P-menth-8(10)-en-9-ol	Asn 142	Gly 143, Cys 145, His 163, Asn 143	− 24.19	− 11.51	2.27	− .6.75
	Nor-diazepam, 3{n-hydroxymethyl}aminocarbonyloxy	Met 165, Glu 166, Asn 142	Ser 46, Met 49	− 25.73	− 11.42	0.80	− 7.19
	Digitoxin	Gly 116, Tyr 154	Asn 151, Asp 153, Tyr 154, Phe 305, Phe 294	− 54.15	− 27.23	6.90	− 13.27
	DI-*N*-decylsulfone	Phe 294, Gln 110, Thr 111, Thr 292	Asp 295, Pro 293	− 28.23	− 14.86	5.07	− 7.39

Table 4 (continued)

Protein Name	Drug-likeness ligands	Polar contact binding residues	Other intermolecular contact binding residues	Global energy (kcal/mol)	Attractive Vdw (kcal/mol)	Repulsive Vdw (kcal/mol)	ACE (kcal/mol)
	14-dodecanoic acid	Leu 253, Leu 250, Ile 249, Pro 252	Phe 294, Val 297, Asp 248, Asp 245	− 18.11	− 9.92	4.01	− 5.98
	Estra-1,3,5(10)-trien-17-beta-ol	Phe 294, Pro 293, Thr 111, Gln 110, His 246	All side bonded by polar contacts	− 19.00	− 10.41	3.39	− 5.43
	Arachidonic amide,*N*-{5-hydroxy-*N*-Pentyl}	Asn 142, Gly 143	Ser 144, Glu 166, Leu 167	− 38.03	− 17.95	5.31	− 10.86
	1-methylsulfanyl-9–10-dioxo-9,10-dihydro-anthracene-2-carboxylic acid	Glu 166, Met 165	Ser 46, Thr 25, Glu 47	− 39.16	− 16.63	4.12	− 12.29
	Cholesterol margarate	Gln 110, Gln 109	Pro 108, Gln 240	− 40.95	− 23.94	9.46	− 9.91
	Docosanoic acid	no polar contacts	Phe 294, Gln 110, Thr 111, Asp 153	− 28.31	− 14.82	1.65	− 6.51
	26-hydroxycholesterol	His 163, Met 165, Glu 166	Asn 142, Cys 145, Ser 46, Thr 45	− 40.85	− 17.40	4.98	− 12.61
	Andrographolide	Thr 25, Ser 46, Glu 166, Met 165	Asn 142, His 41	− 24.51	− 13.53	7.31	− 7.17
	6H-purin-6-one,1,7-dihydro-2-(methylamino)	Glu 166, Met 165, Leu 167, Cys 145	His 163, Asn 142, Gly 143	− 21.58	− 8.97	2.01	− 6.60
	Pseduosarsasapogenin-5,20-dien	Thr 243, Phe 294, Thr 111, Gln 110	Thr 242, Asp 245	− 34.40	− 18.57	6.71	− 8.41
	Oxiraneundecanoic acid,3-pentyl, methyl ester, cis	Gln 110, Gly 109	Phe 294, Pro 293, His 246, Asr 153	− 24.73	− 12.67	1.46	− 5.53
	Pregabalin	Arg 298, Met 6	Val 303, Thr 304, Arg 298, Gln 299	− 20.69	− 10.29	3.12	− 6.33
	Arabidol	Glu 166, Met 165, His 164	Thr 26, Thr 25, Thr 24, Thr 45	− 37.06	− 16.29	10.23	− 14.02

Table 4 (continued)

Protein Name	Drug-likeness ligands	Polar contact binding residues	Other intermolecular contact binding residues	Global energy (kcal/mol)	Attractive Vdw (kcal/mol)	Repulsive Vdw (kcal/mol)	ACE (kcal/mol)
Spike glycoprotein (6LXT)	2,4,6-Pyrimidinetrione	Val 952, Asn 955, Asn 956, Asn 953	All side bonded by polar contact	− 26.44	− 10.31	0.16	− 6.94
	21-Acetoxypregenelone	Ala 942, Ser 940, Arg 1185	Asn 1187, Ser 943, Lys 1181, Ile 183	− 28.10	− 19.75	5.74	− 2.22
	P- menth-8(10)-en-9-ol	Leu 922	Ile 923, Ala 924, Asn 919, Gln 920	− 24.89	− 11.41	1.94	− 6.68
	Nor-diazepam, 3{n-hydroxymethyl}aminocarbonyloxy	Ile 1198, Asn 928, Leu 1197	Asp 1199, Asn 925	− 36.22	− 17.30	4.48	− 10.95
	Digitoxin	Ser 940, Arg 1185	Glu 1182, Ser 943, Asp 936, Lys 1191, Gln 935	− 63.54	− 42.37	17.15	− 8.93
	DI-*N*-decylsulfone	Ser 940	Ser 943, Ser 939, Lys 1181, Lys 947	− 41.11	− 26.75	5.32	− 4.29
	14-dodecanoic acid	Ser 939	Asn 1194, Asn 1187, Glu 1188, Glu 1195, Gln 935	− 23.19	− 13.50	1.46	− 3.08
	Estra-1,3,5(10)-trien-17-beta-ol	Ala 1190, Lys 1191	Arg 1185, Asn 1187, Gln 935	− 32.36	− 19.07	3.90	− 4.34
	Arachidonic amide,*N*-{5-hydroxy-*N*-Pentyl}	Lys 947	Asp 1184, Glu 1188, Asn 1187, Asp 936, Lys 1191, Ser 939	− 42.54	− 27.63	3.87	− 2.74
	1-methylsulfanyl-9–10-dioxo-9,10-dihydro-anthracene-2-carboxylic acid	Asp 184, Ser 940, Arg 1185, Lys 947	Ser 943, Ser 949	− 31.67	− 21.43	1.25	− 0.52
	Cholesterol margarate	no polar contact	Asn 1184, Asn 1187, Asp 936, Gln 935	− 54.12	− 32.79	9.27	− 8.23
	Docosanoic acid	Asn 1178, Lys 1181	Ser 943, Ser 939, Lys 947, Gln 935	− 37.20	− 26.13	3.97	− 2.01
	26-hydroxycholesterol	Asn 925, Gln 926, Lys 1191	Gln 1195, Asp 936, Gly 932, Asn 928	− 41.67	− 20.53	2.58	− 8.23
	Andrographolide	Gln 920, Lys 921, Tyr 917	Glu 1202, Val 915	− 29.04	− 21.14	20.25	− 9.23
	6H-purin-6-one,1,7-dihydro-2-(methylamino)	Tyr 917	Leu 1200, Asp 1199, Tyr 917	− 19.45	− 8.27	0.66	− 5.86
	Pseduosarsasapogenin-5,20-dien	Ser 939	Ser 940, Glu 1182, Lys 1181	− 41.80	− 28.41	2.51	− 2.20
	Oxiraneundecanoic acid,3-pentyl, methyl ester, cis	Lys 1181	Arg 1181, Asp 936, Ser 943, Ser 939	− 34.65	− 25.21	6.80	− 2.26
	Pregabalin	no polar contacts	Leu 1200, Ile 923, Ala 924	− 27.07	− 13.01	2.00	− 6.29
	Arabidiol	Arg 1185, Leu 1186, Asp 1184	Lys 1181, Asn 1187, Ser 943	− 29.82	− 22.67	4.74	0.13

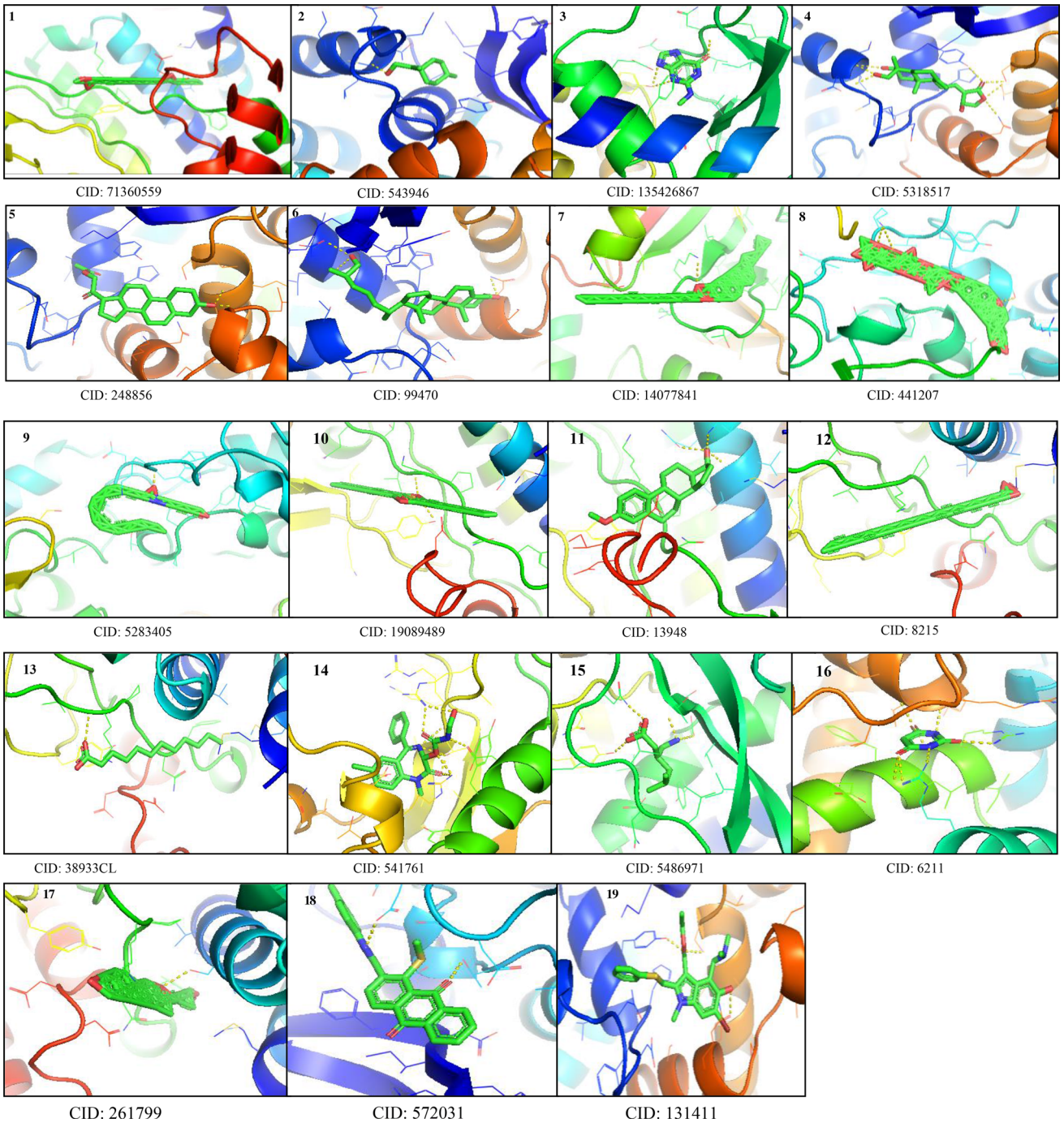


Fig. 4 Molecular docking of target SARS-CoV-2 RNA-dependent RNA-polymerase (PDB ID- 6M71) with the S-CoV-2 RNA-dependent RNA polymerase (PDB ID-6M71) with the GC–MS bioactive compounds of *Pleione maculata* (1) oxiraneundecanoic acid,3-pentyl, methyl ester, cis (2) p-menth-8(10)-en-9-ol (3) 6H-purin-6-one,1,7-dihydro-(2-methylamino) (4) andrographolide (5) 21-acetoxypregenelone (6) 26-hydroxycholesterol (7) cholesterol margarate (8) digitoxin (9) arachidonic amide, *N*-{5-hydroxy-*N*-pentyl} (10) DI-*N*-decylsulfone (11) estra-1,3,5(10)-trien-beta-ol (12) docosanoic acid (13) 14-dodecanoic acid (14) Nor-diazepam,3-{*N*-hydroxymethyl} aminocarbonyloxy (15) pregabalin (16) 2,4,6-pyrimidinetrione (17) pseudosarsasapogenin acid, 3-pentyl, methyl ester, cis, (18) 1-methyl-sulfanyl-9,10-dioxo-9, 10-dihydro-anthracene-2-carboxylic acid and positive control (19) arabidiol

with other non-covalent interactions (electromagnetic interactions, ionic interactions, van der Waals interaction, and hydrophobic interactions) play an important role in protein–ligand stability (Yadav et al. 2017). van der Waals interactions are non-covalent repulsive or attractive intermolecular interactions, bonding energy decreases from zero to

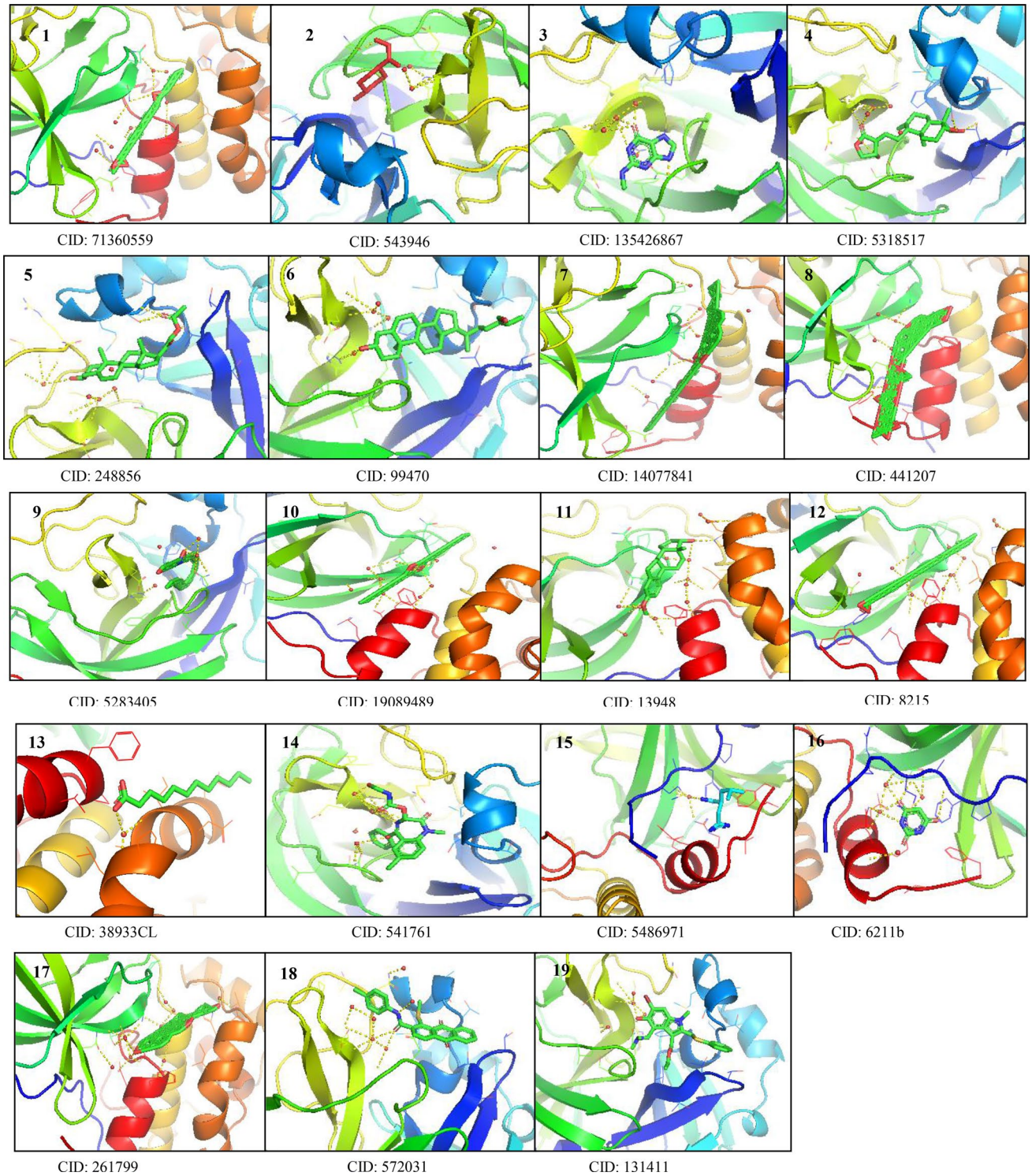


Fig. 5 Molecular docking of target SARS-CoV-2 3CL protease (PDB ID- 6M2Q) with the GC–MS bioactive compounds of *Pleione maculata* (1) oxiraneundecanoic acid,3-pentyl, methyl ester, cis (2) p-menth-8(10)-en-9-ol (3) 6H-purin-6-one,1,7-dihydro-(2-methylamino) (4) andrographolide (5) 21-acetoxypregenelone (6) 26-hydroxycholesterol (7) cholesterol margarate (8) digitoxin (9) arachidonic amide, *N*-{5-hydroxy-*N*-pentyl} (10) DI-*N*-decyl-sulfone (11) estra-1,3,5(10)-trien-beta-ol (12) docosanoic acid (13) 14-dodecanoic acid (14) Nor-diazepam,3-{N-hydroxymethyl}aminocarbonyloxy (15) pregabalin (16) 2,4,6-pyrimidinetrione (17) pseduosarsasapogenin acid, 3-pentyl, methyl ester, cis, (18) 1-methyl-sulfanyl-9,10-dioxo-9, 10-dihydro-anthracene-2-carboxylic acid and positive control (19) arabidiol

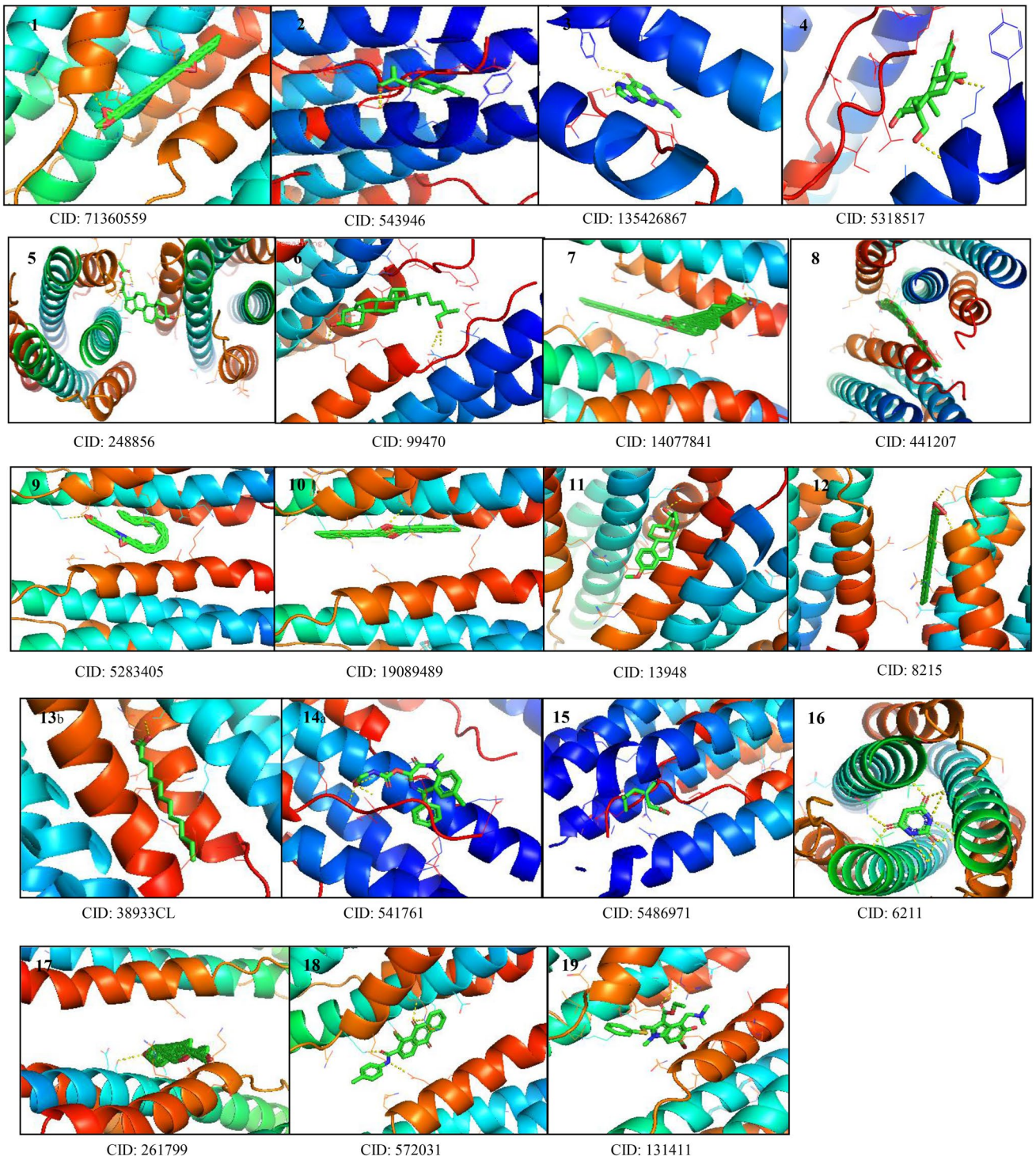


Fig. 6 Molecular docking of target SARS-CoV-2 spike glycoprotein S2 subunit (PDB ID- 6LXT) with the GC–MS bioactive compounds of *Pleione maculata* (1) oxiraneundecanoic acid,3-pentyl, methyl ester, cis (2) p-menth-8(10)-en-9-ol (3) 6H-purin-6-one,1,7-dihydro-(2-methylamino) (4) andrographolide (5) 21-acetoxypregenelone (6) 26-hydroxycholesterol (7) cholesterol margarate (8) digitoxin (9) arachidonic amide, N-{5-hydroxy-*N*-pentyl} (10) DI-*N*-decyl-sulfone (11) estra-1,3,5(10)-trien-beta-ol (12) docosanoic acid (13) 14-dodecanoic acid (14) Nor-diazepam,3-{N-hydroxymethyl}aminocarbonyloxy (15) pregabalin (16) 2,4,6-pyrimidinetrione (17) pseduosarsasapogenin acid, 3-pentyl, methyl ester cis, (18) 1-methyl-sulfanyl-9,10-dioxo-9, 10-dihydro-anthracene-2-carboxylic acid and positive control (19) arabidiol

Table 5 Lipinski rule of five (RO5) violation

Molecular weight	< 500 Daltons
Hydrogen bond donors	No > 5
Hydrogen bond acceptors	No > 10
Octanol–water partition coefficient (logP)	< 5
Number of rotatable bonds	No < 10

its negative value when the distance of attraction between two molecules is close, and repulsive forces occurs when the distance of separation decreases and bonding energy increases (Singh 2016). van der Waals interaction may be considered weak, but they play a vital role in structure and biomolecules interaction. Hydrogen bonds are also weak non-covalent bond which induces thermal fluctuation in energies and tend to form or break rapidly causing conformational changes during binding (Bronowska 2011). GC–MS bioactive compound Nor-diazepam,3-{*N*-hydroxymethyl} aminocarbonyloxy, andrographolide, depicts a high binding affinity of − 10.95 and − 9.23Kcal/mol and very good drug-likeness properties when compared to the binding affinity of fisetin, quercetin, isorhamnetin, genistein, luteolin, resveratrol, and apigenin with − 8.5, − 8.5, − 8.3, − 8.2, − 8.2, − 7.9, − 7.7 kcal/mol, respectively, against S2 subunit spike glycoprotein (Rane et al. 2020). The atomic contact energy (ACE) was also reported higher in tea flavonoid catechin products epigallocatechin and theaflavin gallate without re-docking refinement used (Maiti and Banerjee 2020). A docking complex of epitope-based peptide vaccine component and toll-like receptor-5 (TLR-5) of SARS-COV-2 spike glycoprotein exhibits good binding affinity which might have the potential to activate immune cascades for destroying viral antigens (Bhattacharya et al. 2020). Molecular docking between structure-based drug design PC786 bearing ChEMBL ID 4291143 against SARS-COV-2 S protein and M^{pro} revealed a good binding affinity ranging from − 1.5 to 11.5 kcal/mol (Panda et al. 2020). *Pleione maculata* compounds Nor-diazepam,3-{*N*-hydroxymethyl}aminocarbonyloxy, andrographolide, pregabalin, *P*-menth-8(10)-en-9-ol, 21-acetoxypregenolone, and 1-methylsulfanyl-9,10-dioxo-9,10-dihydro-anthracene-2-carboxylic acid are few drug-likeness compounds obeying the Lipinski RO5 properties such as solubility, lipophilicity (Log P) less than 5, hydrogen bond not more than 5, good solubility, and absorption. The drug-likeness parameters described are the main criteria in primary drug development. The bioactive compounds of *P. maculata* screened using GC–MS have more potential as drug-likeness against various intractable diseases, for example, here SARS-CoV-2 pneumonia (COVID-19) because of its stronger binding affinity, closer interaction, and abide by ADME characteristics.

5 Conclusions

GC–MS analysis in methanol, ethanol, and acetone extracts of different parts (leaves, stem, and roots) of *P. maculata* identified major peaks indicating the presence of phytochemical constituents such as palmitic acid, vitamin E, vitamin A precursor, cardiac glycoside, ascorbic acid, linoleic acid, oleic acid, stearic acid, alkaloid, di-terpenoid, flavonoid, and phenolic and steroidal compound. Cholestenone compound which has the capability to suppress fat accumulation and antiobesity activity is not commonly found in other medicinal plants but reported in GC–MS study of *P. maculata*. The identified compounds were known to have various activities commonly antimicrobial, anti-inflammatory, antioxidant, cancer preventive, hypocholesterolemic, nematicide, anti-asthma, antiarrhythmic activity (improve heartbeat), antiviral activity, larvicidal activity, anticonvulsants, and antiobesity activities. Molecular docking analysis is a structure-based design of drugs. The compounds of *P. maculata* showed a highly effective binding affinity (atomic contact energy). The spike glycoprotein S2 subunit of SARS-CoV-2 was one rigid target as it initiates membrane fusion with host receptor but bioactive compound Nor-diazepam,3-{*N*-hydroxymethyl} aminocarbonyloxy exhibits good docking and high binding affinity with atomic contact energy − 10.95 kcal/mol and very high drug-likeness properties. For centuries, plants are the main source of medicinally important natural products. The paper represents the first report on GC–MS analysis, molecular docking, and drug-likeness study on *P. maculata*. The findings are expected to contribute a significant and major therapeutic impact in the pharmaceutical and nutraceutical companies. An in vitro and in vivo analysis has to be implemented to understand the mechanism of action, cytotoxicity studies on the above effective bioactive compounds. In conclusion, a study on rare *Pleione maculata* highlights their prospective therapeutic potentialities against various intractable diseases and their bioactive components will enhance a sustainable rural livelihood in both primary and secondary health care and also to save them from extinction and over-exploitation. The effective drug-likeness compound does not have to be separated or isolated directly from the source plant, but the study will provide a basic idea on a synthetic production of effective bioactive compounds.

Table 6 Drug-likeness analysis of bioactive compounds showing good binding energy against SARS-CoV-2 proteins

Drug-likeness compounds	Physicochemical properties (Lipinski rule of five)					Solubility			Pharmacokinetics	
	MW	HB donors	HB acceptors	No of rotatable bond	Consensus log P	Log S (ESOL)	Log S (Ali)	Log S (SILICOS-IT)	GI absorption	CYP enzymes inhibitors
Digitoxin	764	5	13	7	2.61	Moderately soluble	Moderately soluble	Moderately soluble	Low	No
26-hydroxycholesterol	402	2	2	6	5.86	Poorly soluble	Poorly soluble	Moderately soluble	High	No
1-methylsulfanyl-9,10-dioxo-9,10-dihydro-anthracene-2-carboxylic acid	387	1	3	4	4.10	Moderately soluble	Poorly soluble	Poorly soluble	High	Yes
Arachidonic amide,*N*-{5-hydroxy-*N*-pentyl}	389	2	2	20	6.27	Moderately soluble	Poorly soluble	Poorly soluble	High	No
Cholesterol margarate	639	0	2	22	12.43	Insoluble	Insoluble	Insoluble	Low	No
21-acetoxypregenolone	374	1	4	4	3.77	Moderately soluble	Soluble	Soluble	High	Only CYP2C9 inhibitor
DI-*N*-decylsulfone	346	0	2	18	6.68	Poorly soluble	Poorly soluble	Poorly soluble	Low	CYP2C9, CYP1A2 inhibitor
Pseduosarsasapogenin-5,20-dien	414	2	3	4	4.86	Moderately soluble	Moderately soluble	Moderately soluble	High	No
Nor-diazepam,3-{*N*-hydroxymethyl} aminocarbonyloxy	373	2	5	5	2.16	Soluble	Soluble	solUble	High	No
Andrographolide	350	3	5	3	2.33	Soluble	Soluble	Soluble	High	No
Pregabalin	159	2	3	5	0.56	Highly soluble	Highly soluble	Soluble	High	No
P-menth-8(10)-en-9-ol	154	1	1	2	2.55	Soluble	Soluble	Soluble	High	No
Docosanoic acid	340	1	2	20	7.40	Poorly soluble	Insoluble	Poorly soluble	Low	CYP1A2 inhibitor
Arabidol	444	2	2	7	6.97	Poorly soluble	Poorly soluble	Poorly soluble	Low	No

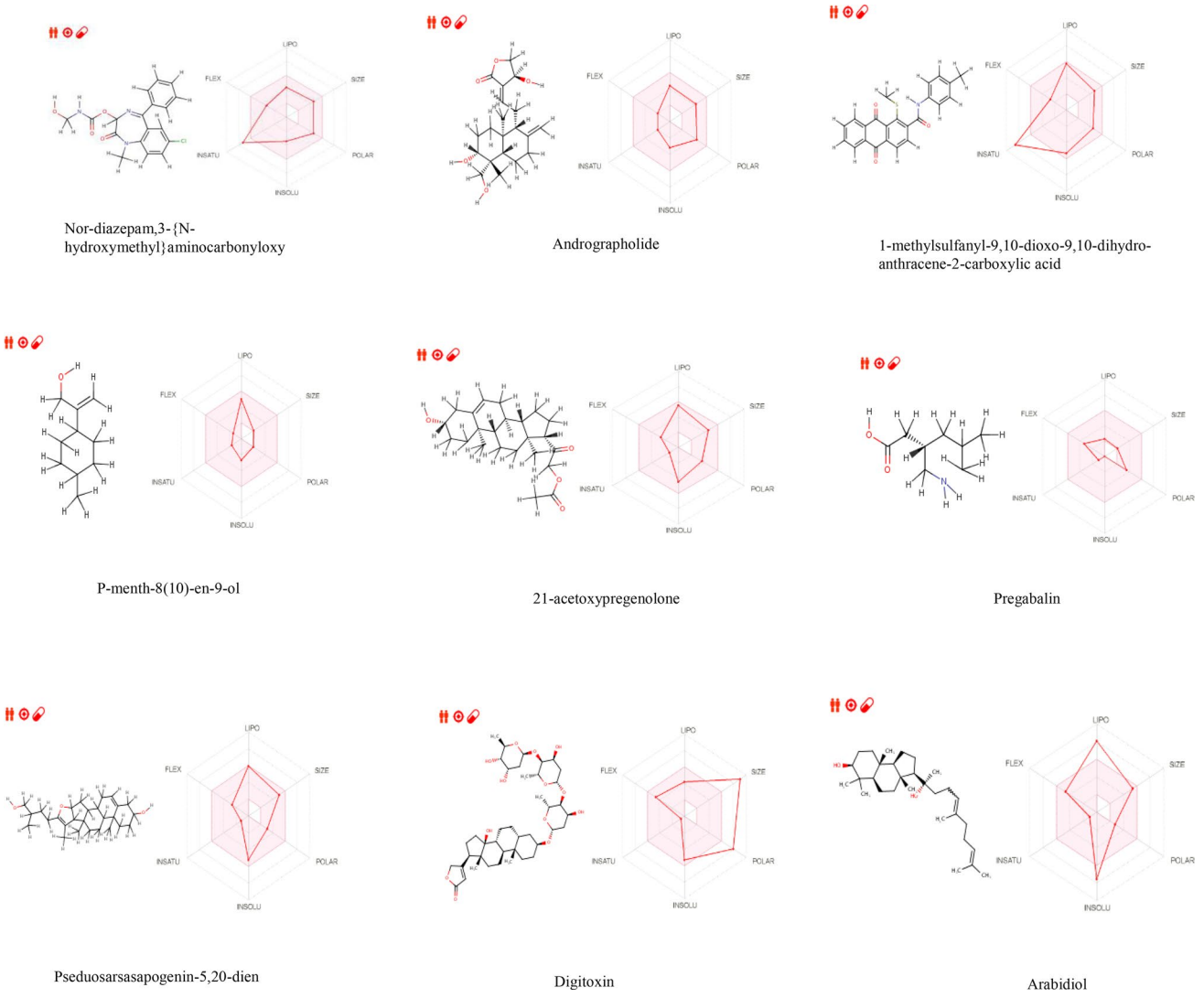


Fig. 7 SwissADME bioavailability radar of different bioactive drug-likeness molecules, where the pink areas represent each property (lipophilicity, molecular weight, solubility, and flexibility)

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13721-020-00276-1.

Acknowledgements I thank Dr. Mahua Gupta Choudhury, MSc. dissertation guide, and Dr. Vedant V. Borah, doctoral research guide, for their support. I would also like to thank Dr. Supriyo Sen for introducing me to Indian Institute of Technology (IIT), Biotech Park Guwahati, Assam, for GC-MS analysis. I sincerely acknowledge the School of Biosciences, Assam Don Bosco University, for permitting and providing me with basic requirements for the methodology part. Lastly, I acknowledge Dr. Rajiv Chandra Dev Goswami, IIT, Guwahati, for the guidance and information on GC-MS analysis. The work is financially supported by Ministry of tribal affair, Govt. of India (Ref: 201819-NFST-MEG-00850).

Compliance with ethical standards

Conflict of interest The author declares no conflict of interest. The research work is original.

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