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DISCOVERY OF INTERLEUKIN-6 INHIBITORY PROPERTIES OF THE COMPOUNDS DETECTED FROM METHANOLIC LEAF EXTRACTS OF *PLECTRANTHUS AMBOINICUS* (LOUR) SPRENG. THROUGH MOLECULAR DOCKING

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Keywords:

Plectranthus amboinicus, Gas chromatography-mass spectrometry, *In-silico* analysis, Rheumatoid arthritis (RA), Anti-inflammatory, Interleukin-6

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ABSTRACT: *Plectranthus amboinicus*, locally called Karpooravalli in Tamil Nadu, India, is known for its various traditional therapeutic properties. Rheumatoid arthritis is a chronic autoimmune disease where uncontrolled inflammatory markers are released to induce bone damage and pain. In this study, the methanolic extract of *P. amboinicus* was characterized phytochemically and subjected to *in-silico* analysis to evaluate its anti-inflammatory properties. The methanolic extract of *P. amboinicus* was subjected to gas chromatography-mass spectrometry (GCMS) analysis. The detected compounds were subjected to *in-silico* analysis with biomarkers specific for rheumatoid arthritis (RA) that is interleukin 6. Of the 86 profiled compounds, three belonging to flavonoid, porphyrin, and heterocyclic triazoles classification had the highest affinities for interleukin-6 and was compared with common DMARs given during RA treatment which had significantly low affinities to above 3 highest affinities bioactive compounds. The ADMET profile, drug-likeness, and bioactivity score were also calculated for all the GCMS profiled compounds, revealing adequate drug-like properties. *In-silico* analysis of the leaf extract of *P. amboinicus* compounds showed a promising result for its anti-inflammatory activities and indicates the possible use of *P. ambionicus* extract in treatment of Rheumatoid arthritis.

INTRODUCTION: *Plectranthus amboinicus* (Lour.) Spreng is a perennial, shrubby herb also called *Coleus amboinicus* that belongs to the Lamiaceae family originates from tropical and warm regions of Asia, Africa, and Australia [1, 2]. Along with beneficial essential oils, this edible herb has an aromatic nature used in folk medicine to treat conditions such as cough, cold, sore throat, nasal congestion, breast milk stimulant [3], asthma, fever, and headache [4].

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The extract is also effective against other diseases, such as flu, bronchitis, epilepsy, and skin diseases. A total of 76 volatiles and 30 nonvolatiles of different classes were detected and these plants are also known to contain highly bioactive compounds such as monoterpenoids [1].

In recent years, plants have gained scientific importance in pharmaceutical research for evaluating phytochemicals and discovering potential compounds that can treat various diseases. One study revealed that carvacrol in the ethyl acetate extract of *P. amboinicus* modulates the expression of inducible nitric oxide synthase, cyclooxygenase 2, interleukin 1β, the histamine 1 receptor gene, and the nuclear factor kappa B protein thus exhibiting anti-inflammatory and

antinociception properties [5]. Another study demonstrated that high doses of *P. amboinicus* decrease the production of proinflammatory cytokines [6]. Hsu and colleagues also postulated that rosmarinic acid from *P. amboinicus* inhibits osteoclastogenesis by inhibiting the activity of RANKL, an apoptotic regulatory gene, thus preventing bone destruction [7].

Inflammation is an essential biological response and part of the body's healing process. One of the first responses of the immune system is inflammatory cells travel to the site of injury or infection [8]. When this response occurs for an extended period it leads to chronic inflammation, which is the primary response in most autoimmune diseases. Rheumatoid arthritis (RA) is a chronic autoimmune disease in which inflammation and bone destruction is the primary prognoses [9]. It has been presumed that genetically inclined individuals exposed to environmental stimuli acts as triggering factors for the progression of RA. RA is associated with systemic pathology, including (i) triggering stages, including the production of inflammatory cells. The environment also triggers the production of inflammatory cells. (ii) In the maturation stage the inflammatory class activates MHC class II-dependent T-cells in lymphoid tissue, which produce B cells and many additional inflammatory cells that, in turn, induce pain, bone loss, and inflammation. The next step is (iii) targeting, during which leukocytes and proinflammatory cells infiltrate the synovial compartment and interact with synovial fibroblasts to produce an inflammatory cascade. The final stage is called the (iv) fulminant stage and is characterized by a hyperplastic synovium caused by the dysfunction of synovial fibroblasts [10].

The hallmark immune components responsible for the pathogenesis of RA are macrophages, neutrophils, CD4+ and CD8+ T cells and their associated cytokines such as tumor necrosis factor-α (TNF-α), interleukin- IL-1, IL-6, IL-17, and IL-23 [11]. The administration of non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease-modifying anti-rheumatic medications (DMARDs) are frequently used treatment methods. Physical therapy is also recommended to sustain joint mobility [10]. *In-silico* analysis of phytochemicals tremendously helps rapid screening of the vast amounts of compounds in medicinal plants which could have potential in the pharmaceutical industry. With the ability to treatmany diseases, diverse plant kingdoms have gained significant attention from researchers seeking new drugs with the help of computational technologies. *In-silico* analysis has also provided insight in to the immune response and its interaction with ligands and possible outcomes as well as how to narrow down the target protein, thus helping to modify ligands to improve interactions with targeted proteins and increase disease inhibiting activity.

In this study, we targeted *P. amboinicus* methanolic leaf extract as an herbal medicine for treating RA. Phytochemical analysis was performed, and an evaluation of the antiarthritic properties *via in-silico* analysis was performed.

MATERIALS AND METHODS:

Sample Collection, Preparation and Extraction: *Plectranthus amboinicus* leaves were collected from Coimbatore, Tamil Nadu (Lat. 11.022053º, Long. 77.017328º). The plants were extracted using a modified protocol from Samad *et al.*, 2019. *P. amboinicus* leaves were cleaned, shade-dried for 48 hours, and ground using an electric grinder. Then, the dried leaf powder was soaked for 5 hours in 30% methanol, and the solvent to solid ratio was 30mL/g. Then, the samples were irradiated for 2 minutes via microwave-assisted extraction (IFB Solo microwave, 2450MHz) [12].

Gas Chromatography-mass Spectroscopy Analysis: The methanolic plant extract was subjected to GC-MS analysis on an Agilent 7000 D GC/TQ instrument by a DB 35-MS capillary standard nonpolar column using helium gas at a flow rate of 1.0 mL/min and an initial temperature of 70°C after which the temperature increased to 260°C at a rate of 6°C to identify the compounds present.

***In-silico* Analysis (Molecular Docking):**

Docking: Compounds identified by GC-MS analysis were downloaded from the PubChem database in SDF format. Similarly, protein-interleukin 6 (Protein ID: IL6) was downloaded from the RCSB Protein Data Bank in PDB format. The compounds were converted to PDBQT

formatted using Open Babel GUI software 2006 v3.1.1. In contrast, after docking parameters such as deleting the water molecule, adding Kollman charges, computing Gasteiger, and assigning the AD4 type were applied, the proteins were converted to the PDBQT format in the AutoDock tool.

Docking was performed using AutoDock vina 1.5.7 via the command prompt method. A dock file was created in which ligand and protein files in PDBQT format were saved with the configuration file. The configuration file consists of the protein and ligand file names with the grid box configuration, the log output file name, and the exhaustiveness of the number of docking runs. A grid box was generated and set at 80 × 80 × 80 with the coordinates X-0.166 Y-0.191 Z-0.438 for the protein IL6. Ligand efficiency [13] was calculated using the following formula:

$$\text{Ligand efficiency} = \Delta G / (\text{Heavy atoms})$$

Moreover, the inhibition constant (Ki) 14 was calculated using the following formula:

$$\text{Inhibiton constant Ki} = \text{Exp} \times (\Delta G / RT)$$

Where ΔG is the binding energy, R is the universal gas constant (1.985×10^{-3} kcal/mol/K), and T is the temperature (298.15 K).

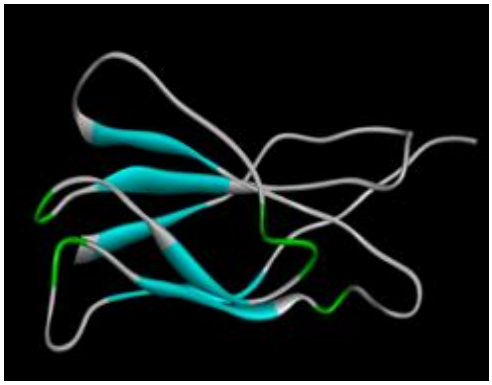


FIG. 1: BIOMARKER OF RA RETRIEVED FROM THE RCSB PDB; INTERLEUKIN 6 (IL6)

Receptor-ligand Interaction: Docking results and receptor-ligand interaction, such as the number of H-bonds formed with amino acid residue, were visualized using the BIOVIA Discovery Studio visualizer 2021V21.1.0.20298.

ADMET Profile: The parameters for ADMET (absorption, distribution, metabolism, excretion, and toxicity) were Human intestinal absorption (HIA) for absorption, blood-brain barrier (BBB), Plasma protein binding (PPB) for distribution, cytochrome P substrate/inhibition for metabolism, Time ½ (half-life) for excretion, and AMES, Carcinogenity, LD50 in rats for toxicity were profiled for the ligand derived from Pubchem using ADMETSAR 2.0 website(http://lmmd.ecust.edu.cn/admetsar2). The half-life was predicted using ADMETLab 2.0 (https://admet.scbdd.com/calcpre/index_sys/) and the LD_{50} toxicity in rats were determined using the Gusar-Way2Drug (http://way2drug.com/Gusar/acutoxpredict/).

Drug-likeness: SwissADME (http://www.swissadme.ch/index.php) was used to predict the drug-likeness of the ligands. The topological polar surface area (TPSA), solubility log S, C log P, molecular weight (MW), and Lipinski's rule for the drug-likeness of the given ligands was predicted.

Bioactivity Score: The molinspiration online predictor tool (https://www.molinspiration.com/cgi-bin/properties) was used to calculate the predicted values of various bioactivities such as G-protein-coupled receptor (GPCR), ion channel modulator, kinase inhibitor, nuclear receptor inhibitor, protease inhibitor, and enzyme inhibitor for the given ligands.

RESULTS:

GC-MS Analysis: The identified compounds were further functionally characterized to determine their pharmacological activity and were subjected to *in-silico* analysis. GC-MS profiling of the extracts revealed a total of 86chemical compounds. **Table 1** shows the compound list, retention time classification, and pharmacological characteristics.

Fig. 2 shows the chromatogram of methanolic *P. amboinicus* extract. The compounds are classified as terpenoids, alkaloids, phenols, and flavonoids. Pteridinone, thymol, diphenhydramine, α-farnesene, hydropapaveroline, and β-Bergamotene are some of the major compounds. A study revealed the presence of α-bergamotene, carvacrol, caryophyllene, ρ-cymene, and γ-terpinene as major constituents [15].

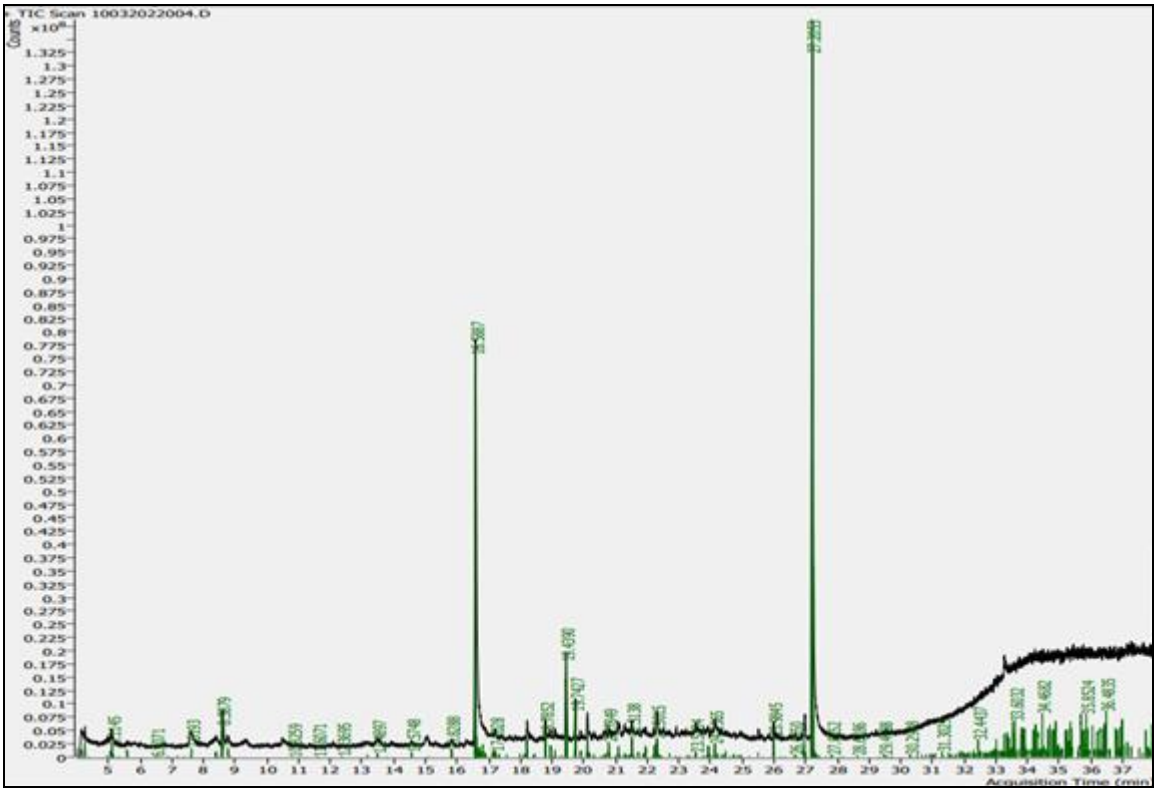
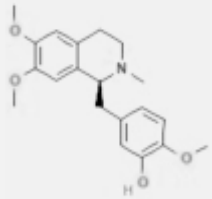
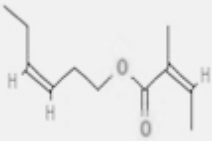
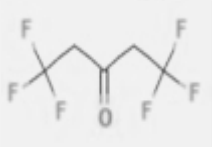
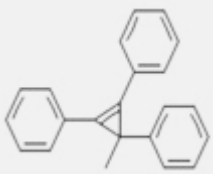
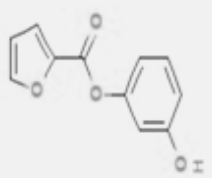
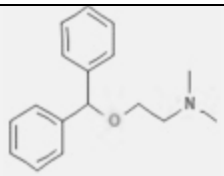
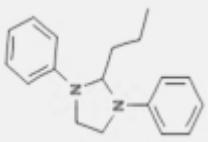
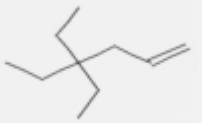
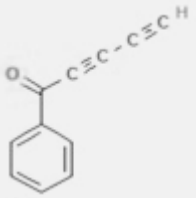
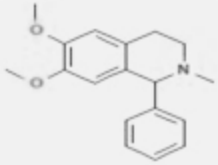
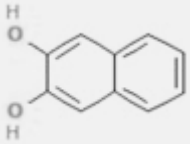
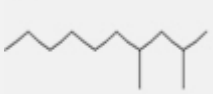
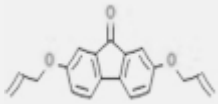
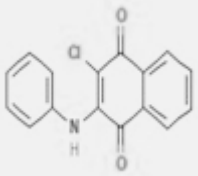
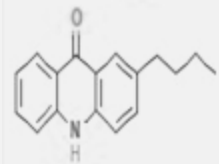
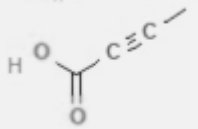
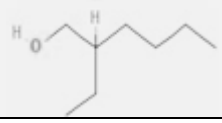
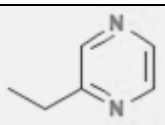
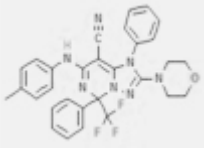
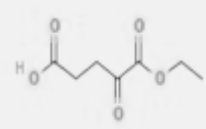
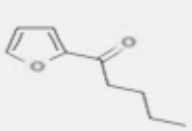
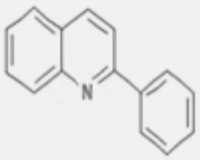
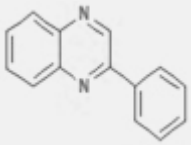
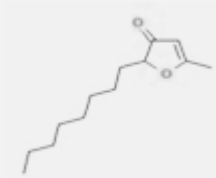
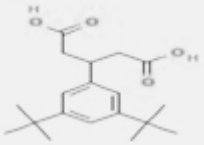
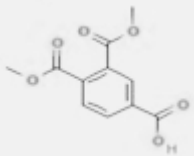
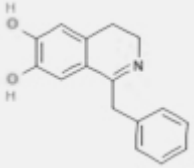


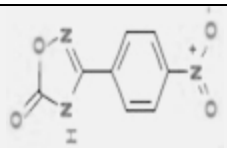
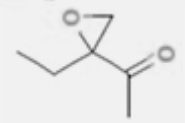
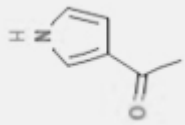
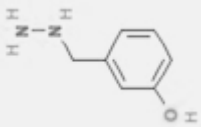
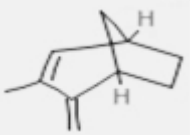
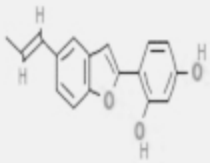
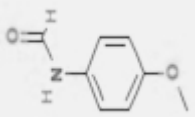
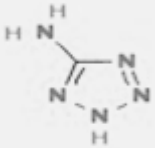
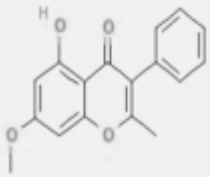
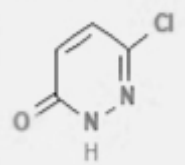
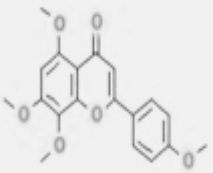
FIG. 2: MASS SPECTRA OF *P. AMBOINICUS* EXTRACTS

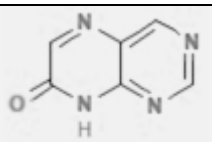
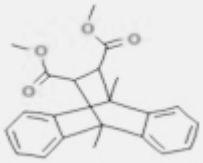
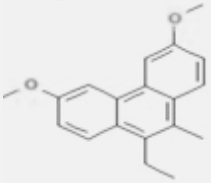
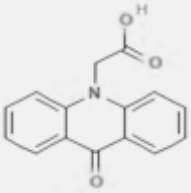
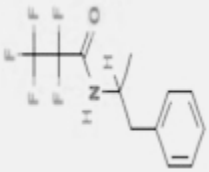
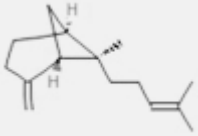
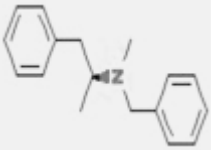
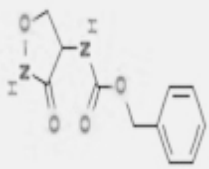
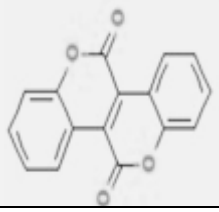
TABLE 1: *P. AMBOINICUS* COMPOUNDS IDENTIFIED BY GC-MS ANALYSIS

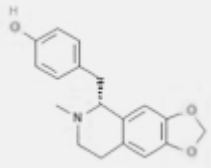
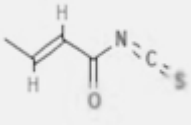
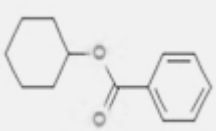
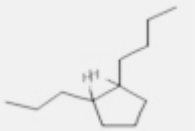
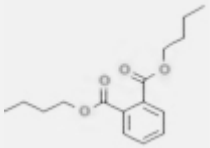
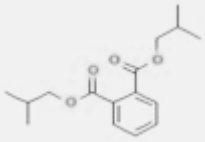
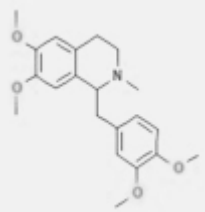
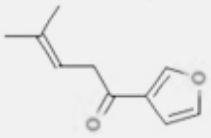
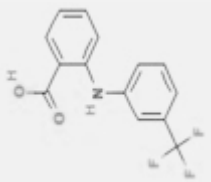
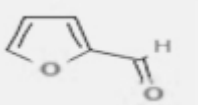
S. no.	Compound Name	RT	Structure	Formula	Classification	Pharmacological Property
1.	(S)-Laudanine	35.8524		$C_{20}H_{25}NO_4$	Phenols	Antioxidant anti-protozoal antimicrobial[16]
2.	(Z)-3-Hexenyl Angelate	14.5748		$C_{11}H_{18}O_2$	undetermined	unspecified
3.	1,1,1,5,5,5-Hexafluoropentan-3-one	21.9468		$C_5H_4F_6O$	Organofluorine	Unspecified
4.	1,2,3-Triphenyl-3-methyl-cyclopropene	35.3912		$C_{22}H_{18}$	undetermined	unspecified
5.	1,3-Benzenediol, o-(2-furoyl)	35.6205		$C_{11}H_8O_4$	esters	Unspecified

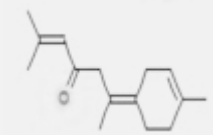
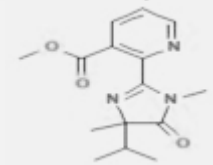
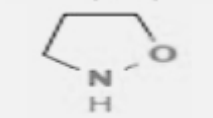
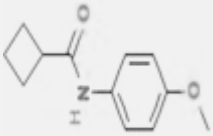
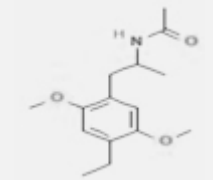
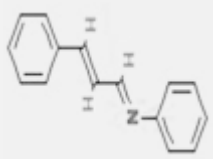
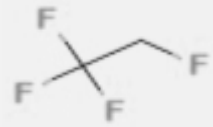
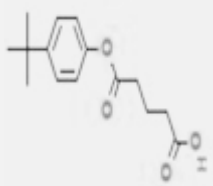
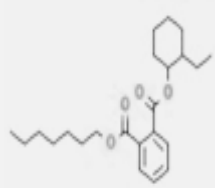
6.	diphenhydramine	19.4390		$C_{17}H_{21}NO$	Ethylamines	anti-allergic, antiparkinson , antipruritic, antidyskinesia [17], antitussive, oneirogen [18]
7.	1,3-Diphenyl-2-propyl imidazolidine	27.1891		$C_{18}H_{22}N_2$	Heterocyclic compounds	Antibacterial Anti-leishmanial[19]
8.	1-Hexene, 4,4-diethyl	13.4897		$C_{10}H_{20}$	Volatile hydrocarbans	unspecified
9.	1-Phenyl-2,4-pentadiyn-1-one(demethylcapillin)	19.1240		$C_{11}H_6O$	Flavonoids	Anti-proliferative [20]
10.	1-phenyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroxyquinoline	33.0116		$C_{18}H_{21}NO_2$	Alkaloids	Anti-angiogenic[21]
11.	2,3-Dihydroxynaphthalene	26.9708		$C_{10}H_8O_2$	Phenols	Anti-proliferative[22]
12.	2,4-Dimethyldecane	15.8288		$C_{12}H_{26}$	Alkanes	Antimicrobial Antioxidant[23]
13.	2,7-Bis-allyloxyfluoren-9-one	31.7128		$C_{19}H_{16}O_3$	undetermined	Antimicrobial[24]
14.	2-Anilino-3-chloro-1,4-naphthoquinone	34.0346		$C_{16}H_{10}CINO_2$	Phenols	Antitrypanosomal [25] Antitumor [26]
15.	2-butyl-10H-acridin-9-one	32.3700		$C_{17}H_{17}NO$	Aminoacridines	Antibacterial Antiprotozoal Anticancer Antiviral [27]
16.	2-Butynoic acid	24.9594		$C_4H_4O_2$	Unsaturated fatty acid	unspecified
17.	2-Ethylhexanol	8.5879		$C_8H_{18}O$	Hexanols	Food additives[28]

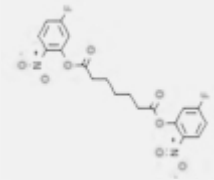
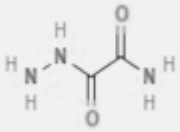
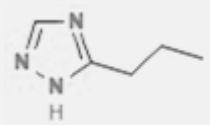
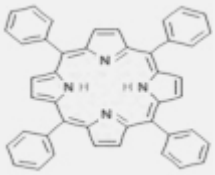
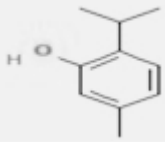
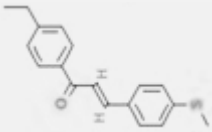
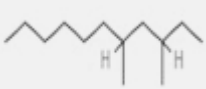
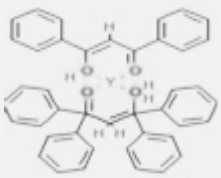
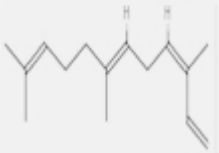
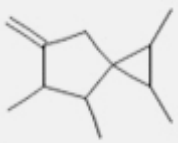
18.	2-Ethylpyrazine	16.6790		C_6H_8N2	Peptide alkaloids	Antioxidant[29]
19.	2-Morpholin-4-yl-1,5-diphenyl-7-p-tolylimino-5-trifluoromethyl-1,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-c]pyrimidine-8-carbonitrile	16.7173		$C_{30}H_{26}F_3N_7O$	Heterocyclic triazoles	unspecified
20.	2-Oxo-pentanedioic acid 1-ethyl ester	8.7695		$C_7H_{10}O_5$	Linear dicarboxylic acid	Antibacterial Antitumor Antioxidant[30]
21.	2-Pentanoylfuran	24.8601		$C_9H_{12}O_2$	Aromatic ketone	Antioxidant[29]
22.	2-Phenylethyl docosanoate	12.3695		$C_{30}H_{52}O_2$	Esters	Antioxidant[31]
23.	2-Phenylquinoline	27.3080		$C_{15}H_{11}N$	Organic heterocyclic compound	Antimicrobial[32] Antioxidant[33]
24.	2-Phenylquinoxaline	33.8430		$C_{14}H_{10}N_2$	N-heterocyclic compound	Antifungal, antibacterial[34],antiviral,[35]anticancer[36]
25.	3(2H)-Furanone, 5-methyl-2-octyl-(cepanone)	23.2901		$C_{13}H_{22}O_2$	oxolanes	Antioxidant[37]
26.	3-(3,5-di-tert-butylphenyl)pentanedioic acid	34.1681		$C_{19}H_{28}O_4$	linear dicarboxylic acid	Unspecified
27.	3,4-Bis(methoxycarbonyl)benzoic acid	32.2998		$C_{11}H_{10}O_6$	aromatic carboxylic acid	Unspecified
28.	3',4'-Desoxy-3,4-dihydropapaveroline	36.4835		$C_{16}H_{15}NO_2$	Alkaloids	Anticancer[38]

29.	3-(4-nitrophyenyl_-4,5-dihyro-1.2.4-oxadiazol-5-one	33.0011		$C_8H_5N_3O_4$	oxopyridine	Antimicrobial, anti-inflammatory, anticancer[39]
30.	3,4-Epoxy-3-ethyl-2-butanone	20.1784		$C_6H_{10}O_2$	Un-determined	unspecified
31.	3-Acetylpyrrole	27.2731		C_6H_7NO	Azoles alkaloids	Unspecified
32.	3-Ethyl-3-methylheptane	15.8421		$C_{10}H_{22}$	branched alkane	Antioxidant Antimicrobial[23]
33.	3-Hydroxybenzylhydrazine	4.2565		$C_7H_{10}N_2O$	Phenols	Central Nervous System Agents[40]
34.	3-Methyl-4-methylenebicyclo(3.2.1)oct-2-ene	19.7241		$C_{10}H_{14}$	Sesquiterpenoids	Antifungal[41] Anticancer[42]
35.	2-(2,4-dihydroxyphenyl)-5-(e)-propenylbenzofuran	35.0606		$C_{17}H_{14}O_3$	Heterocyclic compound	Anti-inflammatory Antioxidant[43]
36.	4-Methoxyformanilide	19.4691		$C_8H_9NO_2$	Undetermined	Unspecified
37.	5-Aminotetrazole	20.6271		CH_3N_5	Azoles	Anticancer[44]
38.	5-Hydroxy-7-methoxy-2-methyl-3-phenyl-4-chromenone	35.3794		$C_{17}H_{14}O_4$	flavonoids	Unspecified
39.	6-chloro-2H-pyridazin-3-one	16.5656		$C_4H_3CLN_2O$	Pyridazines derivative	Unspecified
40.	6-Demethoxytangeretin	35.7121		$C_{19}H_{18}O_6$	Flavonoids	Anti-inflammatory Anti-allergic[45]

41.	7(8H)-Pteridinone	27.2053		$C_6H_4N_4O$	Heterocyclic compound	Anti-proliferative[46]
42.	9,10-Dihydro-9,10-dimethyl-9,10-ethanoanthracene-11,12-dicarboxylic acid	36.3748		$C_{22}H_{22}O_4$	Polycyclic aromatic hydrocarbons	Unspecified
43.	9-Ethyl-3,6-dimethoxy-10-methylphenanthrene	34.9583		$C_{19}H_{20}O_2$	polycyclic aromatic hydrocarbon	Unspecified
44.	9-Oxo-10(9H)-acridineacetic acid	32.1181		$C_{15}H_{11}NO_3$	Heterocyclic Compounds	Anticancer Antimicrobial[47]
45.	Amphetamine, N-pentafluoropropionyl	32.3174		$C_{12}H_{12}F_5NO$	Organofluorines	Central nervous system stimulant[48] Antioxidant[49]
46.	beta-Bergamotene	19.4418		$C_{15}H_{24}$	sesquiterpene	Antioxidant Anti-inflammatory[50]
47.	Benzphetamine	19.7269		$C_{17}H_{21}N$	Ethylamines	Adrenergic Agents, Central Nervous System Stimulants51
48.	Bis[(2.3)paracyclophano][1,2-b:1',2'-i]anthraquinone	5.3099		$C_{44}H_{32}O_2$	Flavonoids	anticancer, anti-inflammatory, diuretic, anti-arthritic[52]
49.	Carbamic acid, N-(3-oxo-4-isoxazolidinyl)-, benzyl ester	5.1489		$C_{11}H_{12}N_2O_4$	undetermined	Unspecified
50.	Carbonic acid, octadecyl vinyl ester	21.5138		$C_{21}H_{40}O_3$	Fatty acid vinyl ester	Anti-diabetic[53],anti-inflammatory[54]
51.	Chromeno(4,3-c)chromene-5,11-dione	35.7456		$C_{16}H_8O_4$	Phenylpropanoids	anti-nociceptiveand anti-inflammatory[55]

52.	Cinnamolaurine	33.0264		$C_{18}H_{19}NO_3$	Alkaloids	Antioxidant, anti-inflammatory, anti-proliferative[56]
53.	Crotonyl isothiocyanate	13.1665		C_5H_5NOS	organosulfur compound	Anticancer[57] Anti-inflammatory, antioxidant,[58] Antimicrobial[59]
54.	Cyclohexyl benzoate	20.1184		$C_{17}H_{16}O_2$	aromatic carboxylic acid	Unspecified
55.	Cyclopentane, 1-butyl-2-propyl-	18.7852		$C_{12}H_{24}$	Fatty acid	Antioxidant[60], antimicrobial, Anti-inflammatory[38]
56.	Cyclotetracosene	6.8518		$C_{24}H_{46}$	Branched unsaturated hydrocarbon	Anti-inflammatory Antioxidant[61]
57.	dibutyl phthalate	27.2009		$C_{16}H_{22}O_4$	Phthalic acid	Antiparasitic[62]
58.	Diisobutyl phthalate	25.9845		$C_{16}H_{22}O_4$	Phthalic acid	Anti-inflammatory[63], antimicrobial[64],
59.	DL-Laudanosine	35.6852		$C_{21}H_{27}NO_4$	Isoquinolines	Central Nervous System Agents neuromuscular relaxant[65]
60.	Egomaketone	37.7898		$C_{10}H_{12}O_2$	Monoterpenoid	Antioxidant Anti-inflammatory Antibacterial Antiallergic[66]
61.	Eicosane, 10-methyl	20.7849		$C_{21}H_{44}$	Volatile hydrocarbon	Antimicrobial Antioxidant[67]
62.	Flufenamic acid	35.1844		$C_{14}H_{10}F_3NO_2$	Organofluorine	Analgesic Anti-inflammatory Antipyretic [68]
63.	Furfural	4.1476		$C_5H_4O_2$	heteroaromatic aldehyde	Anti- tyrosinase Antimicrobial[69]

64.	gamma atlantone	22.3299		$C_{15}H_{22}O$	Sesquiterpenoids	Antioxidant[70], anti-inflammatory[71]
65.	I-Leucine, N-(2-chloroethoxycarbonyl)-N-methyl-, tetradecyl ester	32.1576		$C_{24}H_{46}ClNO_4$	Ester	Anti-inflammatory[72]
66.	Imazapyr, N,O-dimethyl	32.0524		$C_{15}H_{19}N_3O_3$	Amine ester	Herbicide[73]
67.	Isoxazolidine	16.6046		C_3H_7NO	Saturated organic compound	Anti-inflammatory Anticancer Antiviral Antibacterial[74]
68.	N-(4-methoxyphenyl)cyclobutanecarboxamide	27.1719		$C_{12}H_{15}NO_2$	Phenols	Unspecified
69.	N-Acetyl-2,5-dimethoxy-4-ethylamphetamine	34.4682		$C_{15}H_{23}NO_3$	Alkaloids	Hallucinogenic[75]
70.	N-Cinnamylideneaniline	33.6032		$C_{15}H_{13}N$	Cyclopentanes	Antibacterial[76]
71.	Nonane, 2,2,4,4,6,8,8-heptamethyl	23.9368		$C_{16}H_{34}$	Acyclic hydrocarbons	Anticancer[77]
72.	Norflurane	18.2201		$C_2H_2F_4$	Fluorinated Organic Compound	Unspecified
73.	Pentandioic acid, (p-t-butylphenyl)	18.4623		$C_{15}H_{20}O_4$	linear dicarboxylic acid	Antimicrobial[78]
74.	Phthalic acid, 2-ethylcyclohexyl heptyl ester	32.9246		$C_{23}H_{34}O_4$	Aromatic carboxylic acid	anti-trypanosomal, anti-inflammatoryand antimicrobial agents[79]

75.	Pimelic acid, di(2-nitro-5-fluorophenyl) ester	32.1270		$C_{19}H_{16}F_2N_2O_8$	Aromatic Organofluorine	Unspecified
76.	Semioxamazide	8.6178		$C_2H_5N_3O_2$	Glyoxylates	Antimicrobial[80]
77.	s-Triazole, 3-propyl	22.2861		$C_5H_9N_3$	heterocyclic organic compound	Anti-inflammatory Anti-proliferative[81]
78.	Tetraphenylporphyrin	25.6537		$C_{44}H_{30}N_4$	porphyrins	Anti-inflammatory antinociceptive[82]
79.	Thiophene, 3-methyl-5-octadecyl-2-pentadecyl	19.0156		$C_{38}H_{72}S$	organosulfur heterocyclic compound	Unspecified
80.	Thymol	18.1194		$C_{10}H_{14}O$	Monoterpenes	antiseptic, antibacterial antifungal Anti-inflammatory [83]
81.	trans-4'-Ethyl-4-(methylthio)chalcone	35.4057		$C_{18}H_{18}OS$	unsaturated ketone	Anti-inflammatory,analgesic, antioxidant[84]
82.	Undecane, 3,5-dimethyl	8.9449		$C_{13}H_{28}$	Fatty Acyls	Anti-inflammatory Anti-allergic[59]
83.	Yttrium, tris(1,3-diphenyl-1,3-propanedionato	6.8518		$C_{45}H_{36}O_6Y$	Yttrium oxide	Antioxidant Anti-inflammatory[85]
84.	α-Farnesene	19.7427		$C_{15}H_{24}$	Sesquiterpene	antioxidant, antimicrobial, and antifungal[86]
85.	1,2,4,5-Tetramethyl-6-methylenespiro[2.4]heptan	20.1142		$C_{12}H_{20}$	Undetermined	Unspecified
86.	Hexacosane, 1,26-bis(4'-benzoylphenyl)	26.7183		$C_{52}H_{70}O_2$	Aliphatic saturated hydrocarbons	Unspecified

RT= Retention time

***In-silico* Analysis:**

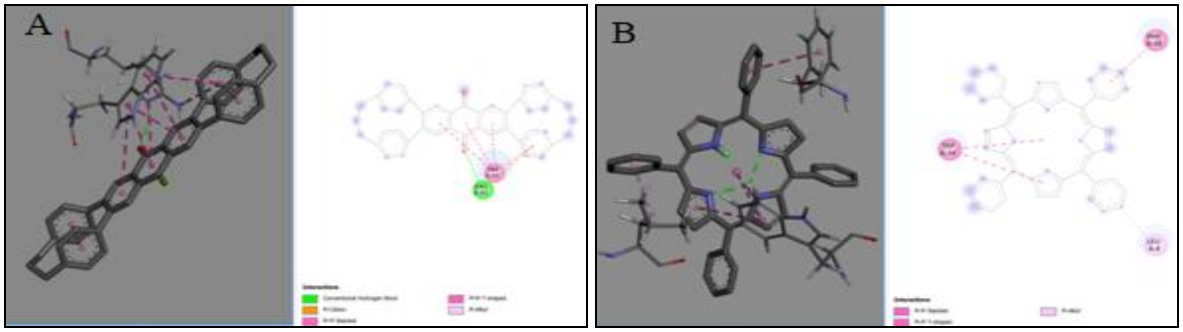
Docking: The compounds were subjected to molecular docking with the biomarker IL6 in AutoDock Vina *via* the command prompt method. The results show that the binding energies of the compounds ranged from -1.8 to -9.3. The compounds with the highest binding energy were Bis [(2.3) paracyclophano] [1,2-b:1',2'-i] anthraquinone, Tetraphenyl porphyrin, 2-Morpholin – 4 – yl - 1, 5 – diphenyl -7-p-tolylimino-5-trifluoromethyl-1, 5, 6, 7-tetrahydro-[1,2,4] triazolo[1,5-c]pyrimidine-8-carbonitrile which had affinities of -9.3, -7.9, and -7.0 respectively. The DMAR, hydroxychloroquine sulfate (HCQs) had a -5.3 affinity for IL6. The further binding energies of the other compounds and their ligand efficiencies and inhibition constants are summarized in **Table 2.** A study in 2014 targeted IL-6, as it has a profound role in treating RA, and performed docking with 5 compounds, out of which margaric acid exhibited good affinity [87]. Another study conducted in silico studies on the ability of the database-derived phytochemicals of *Murraya koenigii* to treat TNF-α of RA, revealed two compounds with high binding scores [88]. Maste and colleagues screened *P. ambionicus* against COVID-19 and showed two compounds in combination, i.e., plectranthol A and B had high viral anti-inflammatory activity [88]. (See supplementary data for the docking profiles of the remaining 76 compounds).

TABLE 2: LIGAND BINDING EFFICIENCY OF GC-MS PROFILED COMPOUNDS WITH INTERLEUKIN-6 DERIVED FROM AUTODOCK

S. no.	Compound Name	Pubchem Id	Kcal/Mol	Ligand Efficiency	Ki (µM)
1	Bis[(2.3)paracyclophano][1,2-b:1',2'-i]anthraquinone	636069	-9.3	-0.20	0.147
2	Tetraphenylporphyrin	86280046	-7.9	-0.16	1.576
3	2-Morpholin-4-yl-1,5-diphenyl-7-p-tolylimino-5-trifluoromethyl-1,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-c]pyrimidine-8-carbonitrile	6426583	-7.0	-0.17	7.210
4	1,2,3-Triphenyl-3-methyl-cyclopropene	624783	-6.6	-0.30	14.23
5	Flufenamic acid	3371	-6.5	-0.32	16.86
6	diphenhydramine	3100	-6.4	-0.33	19.99
7	Cyclotetracosene	5379442	-6.3	-0.24	23.70
8	3',4'-Desoxy-3,4-dihydropapaveroline	619942	-6.2	-0.32	27.81
9	2-(2,4-dihydroxyphenyl)-5-(e)-propenylbenzofuran	10355545	-6.2	-0.31	27.81
10	Chromeno(4,3-c)chromene-5,11-dione	622026	-6.1	-0.30	32.96
	DMARs				
11	Hydroxychloroquine sulphate	12947	-5.3	-0.18	128.4

Kcal/mol= Binding efficiency, Ki= Inhibition constant

Receptor-ligand Interaction: BIOVIA Discovery Studio helps to visualize the position of compounds interacting with the targeted protein. It also provides a 2D diagram of interactions at the amino acid level. *Van der Waal* formation was the primary bond found in the docking results. The amino acids found in most of the interactions were ARG, TRP, VAL, PHE, TYR, MET, GLN, ASN, and LYS. The significant bonds that formed were Pi-alkyl and conventional hydrogen bonds. (See supplementary data for the rest of the figures). A study was conducted on flavonoid compounds from *Glycyrrhiza glabra* as anti-inflammatory drugs against the inflammatory marker interleukin 1 in periodontitis using Autodock tools and the BIOVIA Discovery Studio Visualizer [90].



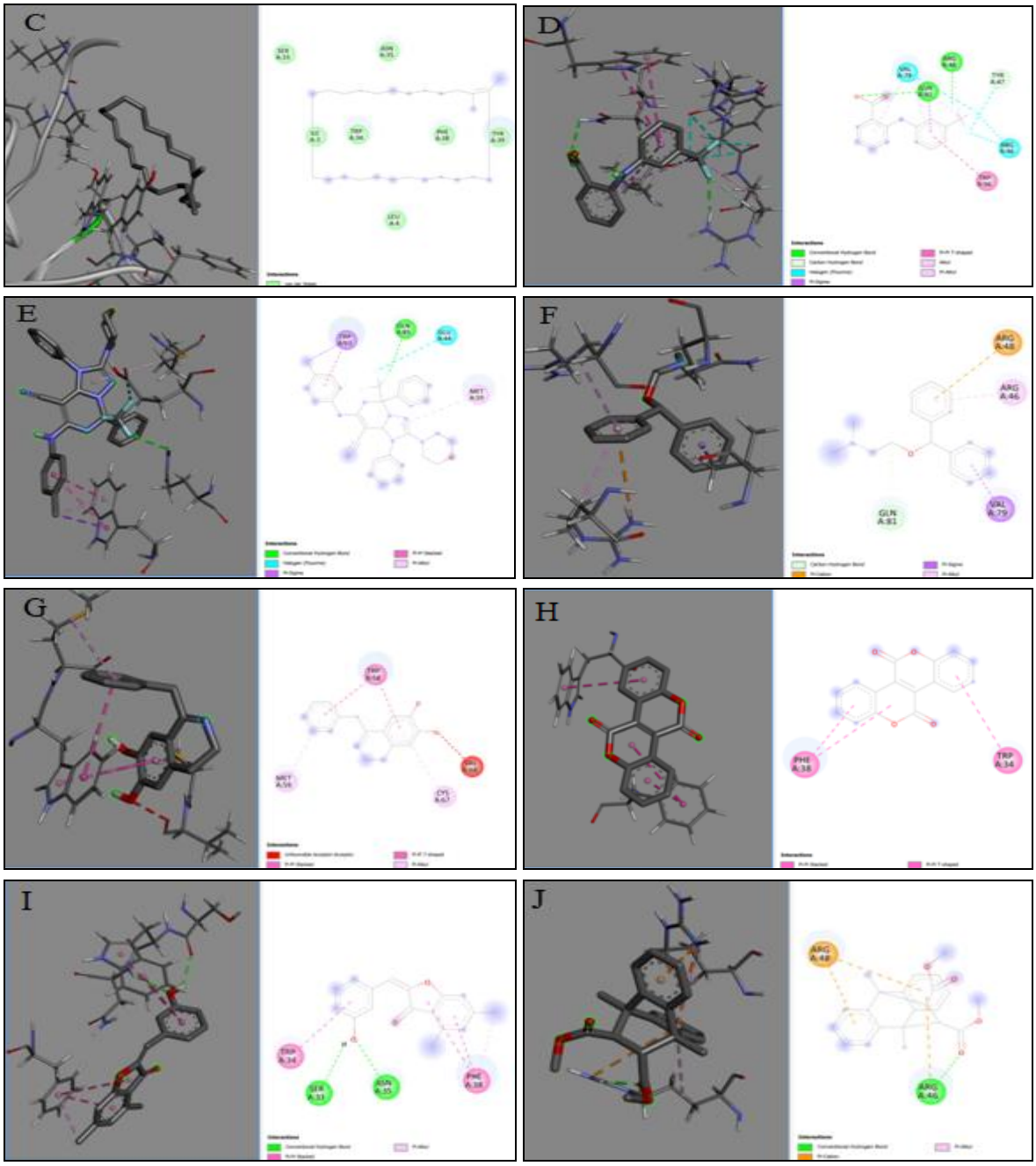


FIG. 3: A: BIS[(2.3)PARACYCLOPHANO][1,2-B:1',2'-I]ANTHRAQUINONE B: TETRAPHENYLPORPHYRIN, C: 2-MORPHOLIN-4-YL-1, 5-DIPHENYL-7-P-TOLYLIMINO-5-TRIFLUOROMETHYL - 1, 5, 6, 7 - TETRAHYDRO-[1,2,4]TRIAZOLO[1,5-C]PYRIMIDINE-8-CARBONITRILE, D: 1,2,3-TRIPHENYL-3-METHYL-CYCLOPROPENE, E: FLUFENAMIC ACID, F: DIPHENHYDRAMINE, G: CYCLOTETRACOSENE, H: 3',4'-DESOXY-3,4-DIHYDROPAPAVEROLINE, I: CHROMENO(4,3-C)CHROMENE-5,11-DIONE, J: 2-(2,4-DIHYDROXYPHENYL)-5-(E)-PROPENYLBENZOFURAN

ADMET Profile: ADMET was predicted using the ADMETSAR online tool, which is freely available. An HIA below 0.3 indicates low or no absorption, but the values of all the compounds are high; hence, the compounds have high intestinal adsorption. Compounds with a value greater than 0.1 are positive for the BBB. All the other compounds had a positive blood-brain barrier except for6-demethoxytangeretin, chromeno (4,3-c) chromene-5,11-dione, and flufenamic acid. Cytochrome P plays a role in drug metabolism. **Table 3** (the 10 compounds with the highest binding efficiency remaining available in supplementary data) shows whether the compounds are substrates or inhibitors. A positive value indicates a substrate and inhibitor, while a negative value indicates a non-substrate and non-inhibitor. Positive/negative indicates substrate/non-inhibitor,

whereas negative/positive indicates non-substrate/ inhibitor. The time ½ (ADMETLab) indicates the rate of elimination or excretion; all of the compounds have values less than 3hours and hence have a low elimination rate. PPB signifies that compounds with high protein-bound efficiency have a low therapeutic index; only 10 among the other compounds have low plasma-protein binding values. AMES predicts the mutagen city of the compound; 20 compounds are predicted to be mutagenic, and 33 are predicted to be carcinogenics. Acute toxicity prediction for the compounds was done using LD_{50} on Gusar- online way 2 drugs tool and subcutaneous administration of the compounds to rats was chosen because the hydrogel will be applied onto the skin. A recent study of the anti-inflammatory activity of lavender (*Lavandula officinalis*) essential oil bioactive compounds against COX-1 and COX-2, inflammatory markers, used the ADMETSAR tool to predict the drug-likeness and risk assessment of the compounds with high affinities for these compounds.[91]Another study used ADMETLab 2.0 for further analysis to evaluate potential candidates against SARS-CoV-2. This study designed 1389 protease inhibitors among which one compound was selected to be most favourable [92]. A study used GUSAR software to predict the toxicity of xenobiotic metabolites using quantitative structure–activity relationship (QSAR) models created for acute rat toxicity after the intravenous administration [93].

TABLE 3: ADMET PROFILE OF THE COMPOUNDS FROM *PLECTRANTHUS AMBOINICUS* EXTRACT

S. no.	Compound Name	HIA	BBB	CYP	T 1/2 (Half Life)	Plasma protein binding %	Ames	Carcin-genicity	LD50 in rats log10 (mmol/kg)
1	Bis[(2.3)paracyclophano][1,2-b:1',2'-i]anthraquinone	+	+	+	2.324	0.736	+	-	0.067
2	Tetraphenylporphyrin	+	+	-/+	2.541	0.901	-	-	0.09
3	2-Morpholin-4-yl-1,5-diphenyl-7-p-tolylimino-5-trifluoromethyl-1,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-c]pyrimidine-8-carbonitrile	+	+	+	1.951	0.934	-	+	0.261
4	1,2,3-Triphenyl-3-methyl-cyclopropene	+	+	-/+	2.529	0.898	-	+	0.526
5									
6	Flufenamic acid	+	-	-	1.259	0.939	-	-	0.198
7	diphenhydramine	+	+	-	1.843	0.716	-	+	0.115
8	Cyclotetracosene	+	+	+	1.859	0.775	-	-	0.673
9	3',4'-Desoxy-3,4-dihydropapaveroline	+	+	-/+	1.601	0.812	-	-	0.337
10	Chromeno(4,3-c)chromene-5,11-dione	+	-	-/+	2.268	0.854	-	+	0.943
11	2-(2,4-dihydroxyphenyl)-5-(e)-propenylbenzofuran	+	+	-/+	1.573	0.908	+	+	0.624

HIA: Human intestinal absorption; BBB: Blood brain barrier; CYP: Cytochrome P, + is substrate and inhibitor, - is non-substrate and non-inhibitor. +/- is substrate/non-inhibitor, and -/+ is non-substrate/inhibitor.

Druglikness: Drug-likeness refers to qualitative concepts such as the structure and physio-chemical properties of a compound and is used to assess its bioavailability as a drug. The TPSA represents the quality of the transport of compounds into the cell membrane; molecules with high TPSA are transported more easily than are those with low TPSA. Pimelic acid, di (2-nitro-5-fluorophenyl) ester, 3,4-Bis (methoxycarbonyl) benzoic acid, Semioxamazide, 3-(4-nitrophyenyl-4,5-dihyro-1.2.4-oxadiazol-5-onehad the highest TPSA value compared to the others. C Log P represents the hydrophilicity of the compound; high logP values indicate low hydrophillicity and poor absorption and permeation. 5-Aminotetrazole and semioxamazide are the compounds that were predicted to have low logP values. Solubility is an important parameter for the absorption of compounds and their subsequent distribution in the body, and is measured using solubility logS. The lower the value of logS is, the greater the solubility. Among the 86 compounds, hexacosane,

diphenhydramine highly soluble compounds and rest are moderately soluble. The molecular weight is directly related to the absorption rate; the lower the molecular weight is, the greater the absorption rate. The average molecular weight of the drug is between 160 and 480 g/mol and only seven compounds have molecular weights above the average. Lipinski's rule states that a compounds is drug-like if it has no more than one violation [94], and in **Table 4** (the 10 highest binding efficiency compounds remaining available in supplementary data), yes indicates that it passes the rule, whereas no means it does not, and the number indicates how many rules are not passed out of five; hence all the other six compounds pass this rule. A study conducted using the SwissADME tool for pharmacological and pharmacognostical profiling of *Butea momosperma* Lam. Taub [95].

TABLE 4: DRUGLIKENESS PREDICTION OF THE COMPOUNDS FROM *PLECTRANTHUS AMBOINICUS* EXTRACT

S. no.	Compound Name	TPSA	C Log P	Solubility Log S	Mw	Lipinski
1	Bis[(2.3)paracyclophano][1,2-b:1',2'-i]anthraquinone	34.14	8.76	-11.05	592.72	no;2
2	Tetraphenylporphyrin	56.3	7.23	-6.26	614.74	NO;2
3	2-Morpholin-4-yl-1,5-diphenyl-7-p-tolylimino-5-trifluoromethyl-1,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-c]pyrimidine-8-carbonitrile	83.4	4.6	-6.8	557.57	yes;1
4	1,2,3-Triphenyl-3-methyl-cyclopropene	0	5.44	-5.43	282.38	YES:1
5	Flufenamic acid	49.33	3.69	-5.07	281.23	yes
6	diphenhydramine	24.72	3.07	-3.27	204.72	yes
7	Cyclotetracosene	0	8.56	-9.67	362.68	yes;1
8	3',4'-Desoxy-3,4-dihydropapaveroline	52.82	2.61	-3.34	253.30	YES
9	Chromeno(4,3-c)chromene-5,11-dione	60.42	3.01	-3.88	264.23	yes
10	2-(2,4-dihydroxyphenyl)-5-(e)-propenylbenzofuran	46.53	3.34	-4.37	266.29	yes

Topological polar surface area (TPSA), molecular weight (MW), numbers in Lipinski= no. of violations

Bioactivity Score: The bioactivity score was calculated using the free tool from Molinspiration. **Table 5** (other 76 compounds; supplementary data) lists of the compounds with bioactivity scores for GPCRs, ion channel modulators, kinase inhibitors, nuclear receptor inhibitors, protease inhibitors, and enzyme inhibitors; yellow indicates a moderate score, whereas green indicates a high score. The compounds that had good bioactivity scores were Carbamic acid, N-(3-oxo-4-isoxazolidinyl)-, benzyl ester, β-Bergamotene, gamma atlantone, Carbonic acid, octadecyl vinyl ester, Amphetamine, N-pentafluoropropionyl, 9-Oxo-10(9H)-acridineacetic acid, 3-(3,5-di-tert-butylphenyl) pentanedioic acid. A study conducted in *Cassia auriculata* reported bioactivity scores for phytochemicals predicted via Molinspiration software, which resulted in high scores for to copherol compounds across all parameters [96]. In another study in which Molinspiration software was used to predict bioactivity scores of terpenoids and fatty acid esters extracted from the Tiliaceae shrub *Triumfetta pentandra* [97].

TABLE 5: BIOACTIVITY SCORE OF THE COMPOUNDS FROM *PLECTRANTHUS AMBOINICUS* EXTRACT

S. no.	Compound Name	GPCR	Ion Channel Modulator	Kinase Inhibitor	Nuclear Receptor Inhibitor	Protease Inhibitor	Enzyme Inhibitor
1	Bis[(2.3)paracyclophano][1,2-b:1',2'-i]anthraquinone	-0.13	-0.84	-0.39	-0.39	-0.04	-0.34
2	Tetraphenylporphyrin	-0.36	-0.99	-0.58	-0.77	-0.21	-0.55
3	2-Morpholin-4-yl-1,5-diphenyl-7-p-tolylimino-5-trifluoromethyl-1,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-c]pyrimidine-8-carbonitrile	-0.28	-0.6	-0.25	-0.62	-0.26	-0.44
4	1,2,3-Triphenyl-3-methyl-cyclopropene	0.11	-0.02	-0.05	-0.02	-0.06	-0.02

5	Flufenamic acid	-0.02	0.6	0.18	0.16	-0.21	0.06
6	diphenhydramine	-0.18	-0.06	-0.67	-0.4	-0.45	-0.02
7	Cyclotetracosene	-0.08	0.02	-0.11	0.14	-0.01	0.06
8	3',4'-Desoxy-3,4-dihydropapaveroline	-0.03	0.10	-0.48	-0.16	-0.14	0.22
9	Chromeno(4,3-c)chromene-5,11-dione	-0.37	-0.32	-0.25	0.06	-0.35	-0.03
10	2-(2,4-dihydroxyphenyl)-5-(e)-propenylbenzofuran	-1.22	-1.37	-0.61	-0.62	-1.25	-0.26

Yellow= Moderate activity, GREEN= High activity

DISCUSSION: *P. amboinicus* has potential therapeutic phytocompounds which is supported by published research. In a recent study on the anti-inflammatory potential of a Coleus amboinicus-based gel formulation, a good inhibitory effect was detected *via* an albumin denaturation assay [98]. A study conducted in 2019 investigates the anti-inflammation effects of *Plectranthus amboinicus* extract (PA-F4) on THP-1 monocytic leukemia cells. PA-F4 inhibited ATP-induced caspase-1, IL-1β, and IL-18 release from LPS-primed cells, blocking p65 NF-κB activation and ATP-induced signaling pathways. The constituents rosmarinic acid, cirsimaritin, salvinorin, and carvacrol may explain PA-F4's inhibitory activity [99]. Another study evaluates the antioxidant in a murine macrophage model, showing that PaE reduces nitric oxide production and inhibits DPPH free radicals and anti-inflammatory using the *in-silico* method of Indian borage (*Plectranthus amboinicus*) ethanol extract [100].

The hallmark inflammatory markers involved in RA are interleukins (IL-1, IL-6, IL-17, and IL-23) [11]. These inflammatory markers are also responsible for inflammation and detrimental activities in fibroblast-like synoviocytes (FLSs) among which IL-6 is involved, and other cells regulate fibroblast activated protein-α (FAP-α) in FLSs during RA [101]. IL-6 also plays a critical role in B cell differentiation into plasma cells and is a potent growth factor for plasmacytoma and myeloma [102], and it induces excess production of VEGF, leading to enhanced angiogenesis and increased vascular permeability [103]. Another critical role of IL-6is to cause bone resorption by inducing osteoclast formation via the induction of RANKL in synovial cells, and cartilage degeneration [104]. Hence IL-6 was targeted for this study to evaluate anti-inflammatory effects of phytocompounds from *P. amboinicus* extract on IL-6 via an *in-silico* method. In this investigation, the constituents of *P. amboinicus* methanolic extract were profiled using GC-MS analysis and the anti-inflammatory effects of the compounds were analyzed via molecular docking with the IL-6 of RA. The analysis revealed that the extract had significant anti-inflammatory effects on IL-6 and had a greater binding energy than the prescription medication for RA. Thus these compounds are potential agents for treating RA.

CONCLUSION: We subjected methanolic leaf extracts of *P. amboinicus* to microwave-assisted extraction and used analyzed phytochemical compounds *via* GC-MS, revealing many bioactive compounds belonging to terpenoids, alkaloids, and phenols classification. Furthermore, the 87 chemical compounds identified were analyzed via the *in-silico* method.

Molecular docking revealed that three compounds namely Bis[(2.3) paracyclophano] [1,2-b:1’,2’-i] anthraquinone, Tetraphenylporphyrin, 2 – Morpholin – 4 -yl-1,5-diphenyl-7-p-tolylimino-5-trifluoromethyl-1, 5, 6,7-tetrahydro-[1,2,4] triazolo [1,5-c] pyrimidine-8-carbonitrile, had high binding affinities, with affinities of -9.3, -7.9, and -7.0, respectively. Hydroxychloroquine sulphate, a common DMAR, was also docked for comparative purposes with IL6, resulting in a lower binding score (-5.3) than that of the above mentioned compounds. The ADMET profile and drug-likeness scores showed that in addition to Bis[(2.3) paracyclophano] [1,2-b:1’,2’-i] anthraquinone, Hexacosane, 1,26-bis(4'-benzoylphenyl), Tetraphenylporphyrin, Thiophene, 3-methyl-5-octadecyl-2-pentadecyl, α-Farnesene, all the other compounds had adequate drug-like properties. Finally, it can be concluded that phytochemicals from *P. amboinicus* have potent anti-inflammatory effects on rheumatoid arthritis.

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