In silico identification of potent inhibitors of Piper betle and Laurus nobilis phytoconstituents on Mycobacterium tuberculosis via molecular docking.

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ABSTRACT

Objective: Mycobacterium tuberculosis is the bacterium that causes tuberculosis, an infectious disease that primarily affects the lungs. There are some noticeable side effects from first-line medications like Isoniazid, rifampicin, etc. and second-line medications like amikacin, capreomycin, etc. To combat synthetic medications' adverse effects, we used the medicinal plants Laurus nobilis (Family: Lauraceae) and Piper betel (Family: Piperaceae). Molecular docking studies are a time-consuming and inexpensive computer technique that is a critical component of drug discovery. **Methodology:** In silico used for virtual screening, binding affinity and free energy calculations, tracing and visualizing different bonded and non-bonded interactions between ligands and protein amino acid residues. The body's accessibility to a molecule is demonstrated by its Absorption, Distribution, Metabolism, and Elimination (ADME) properties, which are based on Lipinski's rule of five. Before using time-consuming experimental approaches, accurately estimate (ADME) characteristics. The ADME descriptors and earlier methods were compared using the Qikprop module of Schrodinger. Maestro software is used for the determination of docking study **Results:** We learned through this investigation that the conventional medicine Isoniazid (-3.727 kcal/mol) has a lower docking score than gallic acid (-7.09 kcal/mol) from Laurus nobilis and eugenol (-5.19 kcal/mol) from Piper betle. **Conclusion:** Therefore, we conclude that these plant phytoconstituents may work as more effective anti-tubercular medicines by preventing the dihydrofolate reductase pathway on the target protein 4KL9 of Mycobacterium TB.

INTRODUCTION

The Piperaceae family includes the evergreen perennial creeping plant known as Piper betle (also known as betle leaf)[1]. Over 2500 years have passed since Malaysia and tropical Asia began cultivating the Piper betle, a plant native to central and eastern Malaysia[2]. In Tamil Nadu, it is frequently referred to as vetrilai[3]. However, it is also grown in Sri Lanka, Bangladesh, Burma, and Nepal, and Malaysia is the plant's most likely place of origin[1]. It's also known as "green gold"[4]. The leaf has a lustrous upper surface ranging from yellowish to dark green. It smells distinctive and pleasantly. The flavour is spicy, sweet, and aromatic. The leaves have varied sizes and a heart in shape. In Asia, betle is a well-liked medicinal plant. Traditional medicine uses plant leaves to treat a variety of illnesses. Numerous diseases and ailments have been treated with betel leaf [2&5]. A bluish-green grape can be grown as a tiny climber or ground cover. The branching betle leaf plant can reach 10 to 15 feet[6]. Moreover, India has 45 different varieties of betle leaves. Phenol, flavonoids[7], alkaloids, tannins, glycosides, phenolic compounds, terpenes, and oligosaccharides[3] are the phytoconstituents studied in this plant. It has pharmacological properties like anti-allergic, anti-filarial, anti-halitosis, antibacterial, insecticidal, anti larvicidal, antioxidant, gastroprotective, anti-cancer, anti-nociceptive, anti-fertility, anti-ulcer, anti-dermatophytic, anti-hypercholesterolemic, anti-diabetic, immunomodulatory, antiasthmatic effect, wound healing[8], antimalarial, Antiproliferative, analgesic, anti-inflammatory, anti-anxiety, anti-stress, anticholinesterase, Alzheimer disease, nootropic effect, hepatoprotective, antihyperlipidemic, anti-atherogenic, cardioprotective, antiplatelet, anti-hematolytic, and radioprotective activity are just a few of the compounds that have been studied.

Laurus nobilis [Bay Leaf] is an evergreen perennial plant[9]. Laurel or bay leaves are commonly referred to as Laurus

nobilis. It belongs to the Lauraceae family and is among the most well-known plants. It is a native of the southern Mediterranean region and can be found in areas with mild climates. Commercial growers include Algeria, Morocco, Portugal, Spain, Italy, France, Turkey, and Mexico. It is one of the most often used cooking spices10 for soup, fish, and meat preparations. Additionally, the leaf is utilized as an aromatic component in fragrances and a flavouring in fresh or dried cookery[11]. In the food business, it serves as a food preservative[12]. A single-trunked tree and a multi-trunked shrub can be grown from it, and it responds well to shaping and pruning. Topiary can also be made with it[13]. The leaves are 10 cm long and 3 to 5 cm broad. In the wild, laurel can reach heights up to 12 meters. The bay leaf contains alkaloids, flavanol, flavones, glycosylated flavonoids, sesquiterpenes, lactones, monoterpenes, germacrene alcohol, and Eugenol[14]. Other activities like wound healing activity, antioxidant, anticonvulsant, analgesic, anti-inflammatory, antimutagenic, immunostimulant, antiviral, anticholinergic, insect repellent, antimicrobial, acarcidal[9], nematicidal, antibacterial, antifungal, cytotoxic[15], anti-diabetic, antihyperlipidemic, hepatoprotective[11], neuroprotective, anti-ulcerogenics[16].

Despite being preventable and curable, tuberculosis remains a global hazard and the 13th most significant cause of mortality after Coronavirus (2019) Covid-19[17]. Mycobacterium tuberculosis was identified as the primary cause of tuberculosis's potentially fatal disease in 1882[18]. Mycobacterium tuberculosis is an acid-resistant rod-shaped bacteria that causes tuberculosis[19]. It is still a primary infectious disease all over the world. The World Health Organization (WHO) has agreed to bring the epidemic under control by 2035. The WHO has established the "End TB strategy," which seeks to reduce tuberculosis by 90% by enhancing efforts to diagnose persons with active TB. A Mycobacterium tuberculosis genomic analysis revealed several co-infections with the pathogen Mycobacterium TB that were not discovered by culture-based diagnostics. Mycobacterium TB has a 4.4 million base pair genome that encodes around 4000 genes[18&20]. Chronic cough, sputum production, appetite loss, weight loss, fever, night sweats, hemoptysis, and other classic tuberculosis symptoms [21]. Clinical examination, sputum smear microscopy, culture method, radiography, serological method, Tuberculin skin test, conventional culture method, LED fluorescence microscopy, Loop-mediated isothermal amplification (LAMP), Interferon-gamma release assay (IGRA), chest x-rays are the commonly used diagnostic tests for the detection of the disease-causing pathogen Mycobacterium tuberculosis. Various approaches are gradually improving their accuracy in detecting Mycobacterium tuberculosis. However, there are still many problems with diagnostic methods [22]. Isoniazid, rifampicin, ethambutol, pyrazinamide, amikacin, kanamycin, ofloxacin, cycloserine, capreomycin, ethionamide, gatifloxacin, moxifloxacin, clofazimine, and para-aminosalicylic acid are antituberculosis medications. Bedaquiline and Delamanid have just been approved for marketing [23]. Anti-tubercular drugs may have significant, detrimental adverse effects if taken regularly. The most undesirable effects caused by anti-tubercular drugs are mild side effects (65.8%) and severe side effects (34.2%). Some mild side effects include loss of appetite, nausea, stomach ache, joint pain, tingling, burning in the legs, and a crimson tinge to the urine. Serious side effects include purpura, blurred vision, hearing loss, shock, itchiness and redness[24].

Molecular docking studies provide a framework for comprehending the interactions between substances and biological systems, and they incorporate computational and experimental approaches that have proven to be more valuable for finding and creating novel, promising compounds. Additionally, in-silico screening of medication candidates helps to cut costs and time [25]. Databases for macromolecular structure, molecular docking, molecular dynamic simulation, tiny molecular databases, and de novo drug designs are used in in-silico experiments[26]. The distribution of drugs can be predicted.

METHODOLOGY

Protein preparation:

The protein data bank (PDB ID-4KL9) was used to get the crystal structure of dihydrofolate reductase[27&28] from Mycobacterium tuberculosis in space group C2 with a resolution of 1.39. Before docking the ligands into the Protein active site, the protein was created using the protein preparation wizard of Schrodinger's molecular docking software[29]. The following steps were carried out: bond order assignment and complete removal of all water molecules and heteroatoms from this protein preparation. Hydrogen atoms were added to the protein to define the proper ionization and tautomeric states and to optimize the hydrogen bond using the PROPKA tool. The optimization and minimization gears in the preparation process were ended, and they provided the finished form of the produced protein to pinpoint the grid position (Drug binding site)[30&31]. In the middle of the workspace, a grid box was generated. The grid box is on the corresponding axes, 20Å=X, 23Å= Y, and 19Å= Z.

Ligand Preparation: 175 phytoconstituents were chosen from the plant's Piper betle (63) and Laurus nobilis (112). From the PubChem database at https://pubchem.ncbi.nlm.nih.gov, the chosen plant phytoconstituents or ligand structures were obtained. Structured Data File (SDF) format is used to store the obtained ligand structures. Then, the ligand structures

were reduced using the Schrodinger Suite's ligprep tool, the geometry of the ligand was improved using the OPLS-3e force field, and the forms were ionized using Epic[32]. Total 175 phytoconstituents listed in supplementary(S1&S2).

ADME analysis: The body's accessibility to a molecule is demonstrated by its Absorption, Distribution, Metabolism, and Elimination (ADME) properties, which are based on Lipinski's rule of five[33]. Before using time-consuming experimental approaches, accurate calculation of Absorption, Distribution, Metabolism, and Elimination (ADME) qualities[34]. ADME descriptors and earlier methods were compared using the Qikprop module of Schrodinger[35].

Molecular Docking: The Maestro V.12.7 program used either the grid glide docking module or the Schrodinger program suite to dock the produced phytochemical compounds with the tuberculosis protein. Then, a single docking was done after the processed ligand structure was anchored to a grid-based docking system in the gliding module. The maximum negative value of the Glide docking score (G-Score) was used to determine the best-docked ligand, and the protein-ligand complex can be viewed using the Maestro suite's 2D and 3D structure module[36].

RESULTS

To investigate the ability of the phytochemicals that can be used alternatively as a medicine against tuberculosis, we collected about 175 plant phytoconstituents from the medicinal plants Laurus nobilis and Piper betle. Then, ADME analysis is performed on the chosen phytochemicals. Only 20 phytoconstituents passed out of the total number of phytoconstituents selected because they exceeded "Lipinski's rule of five" and the "Rule of three" thresholds. Table 1 provides a list of the 20 phytoconstituents that were chosen.

Table 1: ADME analysis results of selected phytochemicals

Plants name	Phytoconstituents name	MW	Donor HB	Acceptor HB	CNS	QP logPo/w	QP logHERG	Rule of five	Rule of three
Laurus nobilis	3,4-dihydroxybenzoic acid	154.122	1	2.25	-1	-0.453	-2.085	0	0
	p-Hydroxybenzoic acid	138.123	1	2.5	-1	-0.358	-2.004	0	0
	Gallic acid	170.121	1	2	-2	-0.545	-2.168	0	0
	Homovanillic acid	182.176	1	2.5	-1	0.675	-3.972	0	0
	Alpha-Pinene	136.236	0	0	2	5.278	-4.995	1	0
	m-Hydroxybenzoic acid	138.123	1	2.5	-1	-0.358	-2.004	0	0
	Vanillic acid	168.149	1	2.5	-1	0.271	-2.946	0	0
	(+)-Catechin	290.272	2	2	-2	1.393	-5.223	1	0
	Syringic acid	198.175	2	3.5	0	0.453	-3.946	1	0
	p-Anisaldehyde	136.15	1	3	1	0.195	-1.91	0	0
	Myrcene	136.236	0	0	2	4.232	-3.007	0	0
	(−)-Epicatechin	290.272	2	2	-2	1.393	-5.223	1	0
	Hesperetin	302.283	2	4.25	-1	0.497	-3.37	1	0
	Pinocarvone	150.22	0	1.7	1	2.424	-4.473	0	0
	Eugenol	164.204	1	0.75	1	1.523	-2.633	0	0

Piper betle	Allylpyro catechin	162.188	0	2	0	0.959	-2.486	0	0
	Alpha pinene	136.236	0	0	2	5.278	-4.995	1	0
	Chavibetol methyl ether	178.23	2	2	0	1.281	-2.662	0	0
	Estragol	148.204	1	1	1	1.426	-2.232	0	0
	Beta pinene	136.236	0	0	2	4.578	-4.656	0	0

MW- Molecular Weight, CNS- Central Nervous System

Table 2: Docking results of selected phytoconstituents

Plants	Phytoconstituents name	Docking score (kcal/mol)	Glide energy (kcal/mol)	$Glide_{evdw}$(kcal/mol)	Interaction residues	Pi-Pi stacking
Laurus nobilis	Gallic acid	-7.097	-19.236	-35.786	HIS 733 GLY 734 ASN 803 and 2-ASN 9	-
	(−)-Epicatechin	-6.921	-28.603	-32.013	GLN 676 GLU 672	-
	Hesperetin	-6.356	-27.173	-38.605	PHE 728 LEU 727 LYS 679 TYR 678	-
	(+)-Catechin	-5.684	-27.761	-40.472	PHE 728 ASN 732 HIS 733	-
	3,4 dihydroxybenzoic acid	-5.525	-18.17	-32.488	GLY 734 CYS 805 ASN 803 2-GLU 675	-
	Syringic acid	-5.404	-22.159	-31.634	LEU 727 TYR 678	-
Piper betle	Eugenol	-5.19	-17.838	-12.364	ASN 590	TYR670
	Allylpyro catechin	-4.267	-13.809	-13.89	-	TYR670
	Chavibetol methyl ether	-3.753	-15.23	-14.22	-	-
	Alpha pinene	-3.56	-12.276	-12.132	-	-
	Beta pinene	-3.152	-10.498	-10.514	-	-
	Estragol	-3.055	-9.526	-9.515	-	-
Std.drug	**Isoniazid**	**-3.727**	**-25.376**	**-19.713**	**ASN 803, HIS 733**	

The tuberculosis protein was then obtained from the protein data bank (PDB-4KL9) and docked with the chosen phytochemicals, after which the glide docking score for the produced phytochemicals was determined. Table 2 lists the docking outcomes of the chosen phytoconstituents with the TB protein and their interactions with the amino acids and pi-pi stacking.

According to the docking data, the top hit phytoconstituents of the plants include gallic acid from Laurus nobilis and Eugenol from Piper betle, which have a more affinity for the tuberculosis protein. Gallic acid produced an H-bond with the amino acids HIS 733, GLY 734, ASN 803, and 2-ASN 9, as shown in Figure 1, and it has the highest docking score of -7.097 kcal/mol, glide energy reached -19.236 kcal/mol, and $glide_{evdw}$ (-35.786 kcal/mol). With a docking score of -5.19 kcal/mol, a glide energy of about -17.838 kcal/mol, and a $glide_{evdw}$ of about -12.364 kcal/mol, the Eugenol from Piper betle formed an H-bond with the amino acid ASN590 and interacted with TYR670 via a pi-pi stacking, as illustrated in Figure 2. In comparison to the standard medication we used in the study, Isoniazid, which has a docking score of -3.727 kcal/mol, glide energy of -25.376 kcal/mol, and a $glide_{evdw}$

of -19.713 kcal/mol and interacts with amino acids like ASN 803 and HIS 733, see Figure 3, both phytoconstituents exhibit low binding energy with the tuberculosis protein.

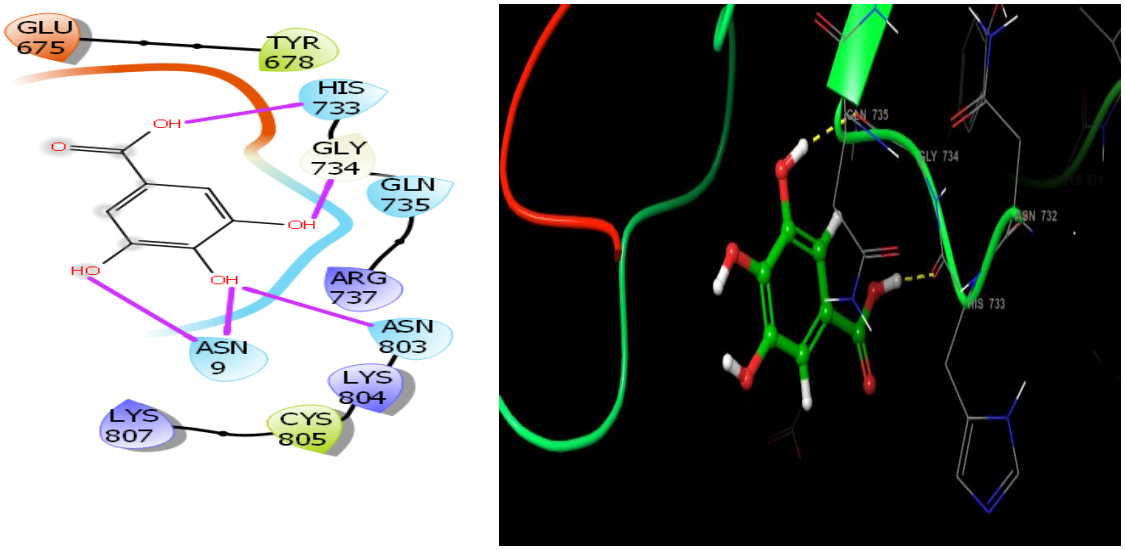

Figure 1: 2D and 3D structure of Gallic acid docking interaction with the dihydrofolate reductase from Mycobacterium tuberculosis 4KL9.

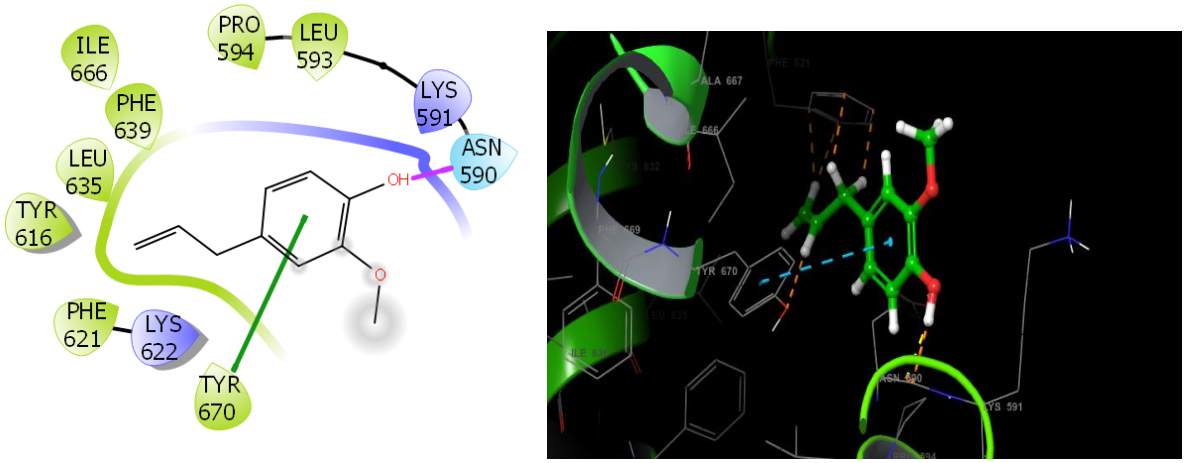

Figure 2: 2D and 3D structure of Eugenol docking interaction with the dihydrofolate reductase from Mycobacterium tuberculosis 4KL9.

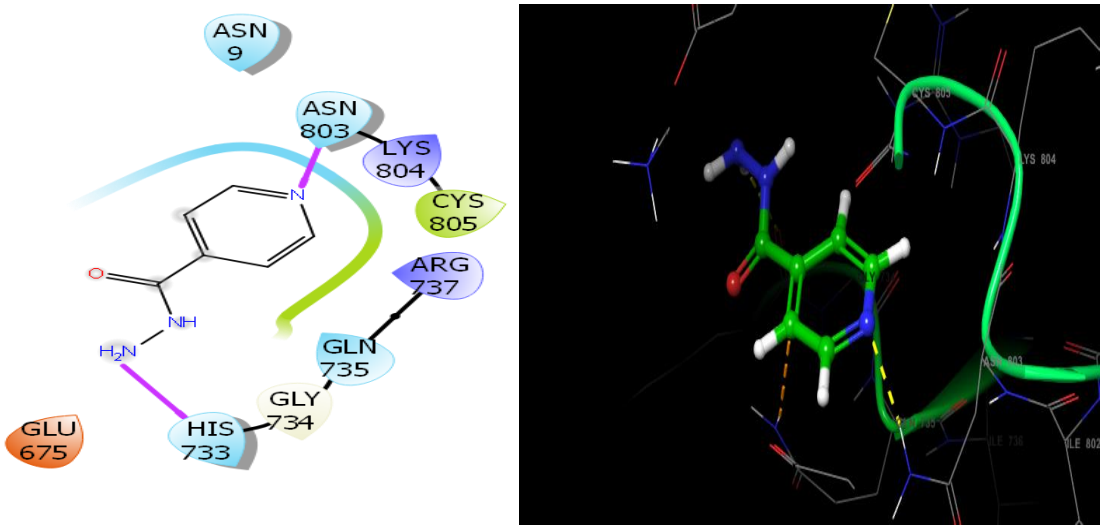

Figure 3: 2D and 3D structure of Isoniazid docking interaction with the dihydrofolate reductase from Mycobacterium tuberculosis 4KL9.

DISCUSSION:

The infectious disease tuberculosis mainly affects the lung parenchyma and is brought on by the bacterium Mycobacterium tuberculosis. Drugs used to treat tuberculosis include Isoniazid, rifampin, pyrazinamide, kanamycin, cycloserine, etc. These medications have several potential adverse effects, including hepatotoxicity, acute gout, reduced appetite, tingling, and tendinopathy. As we prefer a natural approach to treating these adverse effects, we instead selected some phytoconstituents from the curative herbs Laurus nobilis (Bay leaf) and Piper betle (Betle pepper), which have strong antibacterial properties. We have gathered 63 phytoconstituents from Piper betle and 112 phytoconstituents from Laurus nobilis (Bay leaf). The molecular docking of Piper betle phytoconstituents such as phytol, chavibetol, and hydroxychavicol on protein dihydrofolate reductase of Mycobacterium tuberculosis was described by Nur Cholis Endriyatno et al. in the year 2022. The chosen phytoconstituents have the following binding affinities: hydroxychavicol (-5.26 kcal/mol), chavibetol (-5.17 kcal/mol), and phytol (-5.07 kcal/mol). He concluded that the chosen phytoconstituents have potential as antituberculosis medications. In this investigation, ligands were selected and used in a silico method instead of those phytoconstituents. The results determined the Eugenol docking score (-5.19 kcal/mol). Additionally, this phytoconstituent's drug-like qualities were limited. It might be an essential medication candidate for treating TB.

CONCLUSION:

Lung disease tuberculosis is a dangerous condition. Mycobacterium tuberculosis is the organism responsible for tuberculosis. It is an infectious disease that spreads by saliva and airborne respiratory droplets. Due to their antibacterial properties, Piper betle and Laurus nobilis are used to cure tuberculosis. We selected 112 phytoconstituents from Laurus nobilis and 63 phytoconstituents from Piper betle. Only 20 phytoconstituents were chosen from 175 because they adhere to the "Lipinski rule of five" and "Rule of three" criteria. Through this analysis, we discovered that eugenol (-5.19 kcal/mol) from Piper betle and gallic acid (-7.09 kcal/mol) from Laurus nobilis have higher docking scores than the traditional drug isoniazid (-3.727 kcal/mol). We consequently conclude that these plant phytoconstituents may function as more effective anti-tubercular medications by blocking the dihydrofolate reductase pathway on the target protein 4KL9 of Mycobacterium TB.

AUTHORS' CONTRIBUTION

SD, SA, SS, SB, SS: Concept and design, interpretation, drafting, and agree to be accountable for all aspects of the work. GJ, JS, SKS, and SG: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

Conflict of interest:

The authors declared no conflict of interest.

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S1: List of phytoconstituents of Laurus nobilis

S.NO	PHYTOCONSTITUENTS OF Laurus nobilis	PUBCHEM ID
1	a-Thujene	17868
2	a-Pinene	6654
3	Sabinene	18818
4	L-b-Pinene	44096
5	Myrcene	31253
6	p-Cymene	7463
7	L-Limonene	439250
8	a-Fenchene	28930
9	a-Terpinene	7462
10	Linalool	6549
11	Orange/Rose oil	637566
12	cis-Limonene oxide	6857487
13	Pinocarvone	121719
14	Citronellal	7794
15	1,8-Cineole	2758
16	L-(-)-Menthol	16666
17	Terpinen-4-ol	11230
18	(R)-(+)-beta-Citronellol	8842
19	D(+)-Carvone	16724
20	Geraniol	637566
21	p-Anisaldehyde	31244
22	Cinnamic aldehyde	637511
23	(+)Reticuline	439653
24	(+)-Criptodorine	11438278
25	(+)-Neolitsine	10064778
26	(+)-Actinodaphnine	160502
27	(+)-N-Methylactinodaphnine	442194
28	(+)-Isodomesticine	69523059
29	(+)-Launobine	177134
30	(+)-Nandigerine	422682
31	(+)-Boldine	10154
32	Deacetyllaurenobiolide	44602442
33	Costunolide	5281437

34	Artemorin	5281428
35	Verlotorin	13895607
36	Lucentolide	101708806
37	Dehydrocostus lactone	73174
38	Zaluzanin C	72646
39	Zaluzanin D	12445012
40	Eremanthin	100572
41	Santamarine	188297
42	(3aS,5aR,6R,7R,9aS,9bS)-6,7-Dihydroxy-5a,9-dimethyl-3-methylidene-4,5,6,7,9a,9b-hexahydro-3aH-benzo[g][1]benzofuran-2-one	60202040
43	Reynosin	482788
44	Magnolialide	636954
45	3a-Peroxyarmefolin	71473708
46	(3aS,5aR,6R,9S,9aS,9bS)-6,9-Dihydroxy-5a,9-dimethyl-3-methylidene-3a,4,5,6,7,8,9a,9b-octahydrobenzo[g][1]benzofuran-2-one	60199554
47	(3aS,5aR,6R,9R,9aS,9bS)-6-Hydroxy-9-methoxy-5a,9-dimethyl-3-methylidene-3a,4,5,6,7,8,9a,9 boctahydrobenzo[g][1]benzofuran-2-one	60199555
48	Romarinic acid	5281792
49	11,13-Dehydrosantonin	181840
50	Tubiferin	325139
51	Gazaniolide	14467712
52	10-Epigazaniolide	14467711
53	Spirafolide	14757922
54	Germacra-4(15)5,10(14)-trien-1 alpha-ol	51543750
55	Alpha-Eudesmol	92762
56	Beta-Eudesmol	91457
57	Gamma-Eudesmol	6432005
58	Baynol C	51136468
59	Baynol B 12-acetate	101095971
60	Spathulenol	92231
61	Oplopanone	10466745
62	Beta-Caryophyllene	5281515
63	Caryophyllene oxide	1742210
64	Baynol A	101095970
65	Lauroside A	101367899
66	Lauroside C	11223421
67	Ampelopsisionoside	11269249
68	4,5-Dihydroblumenol A	21630916
69	Dendranthemoside A	11760952
70	Lauroside E	101367898
71	Blumenol C	118284
72	Icariside B1	15628136
73	Citroside A	14312562
74	2-Hydroxycinnamic acid	637540
75	3,4-Dihydroxybenzoic acid	72
76	Caffeic acid	689043
77	Ferulic acid	445858
78	Gallic acid	370
79	Homovanillic acid	1738
80	m-Hydroxybenzoic acid	7420
81	p-Hydroxybenzoic acid	135

82	Protocatechuic acid	72
83	Syringic acid	10742
84	Vanillic acid	8468
85	(−)-Epicatechin	72276
86	(+)-Catechin	9064
87	Apigenin	5280443
88	Apigenin 8-C-glucoside	5280441
89	Apigenin-6-C-glucoside	162350
90	Hesperetin	72281
91	Kaempferol	5280863
92	Kaempferol-3-O-arabinopyranoside	5481882
93	Kaempferol-3-O-glucopyranoside	5282102
94	Kaempferol-3-O-pentoside	14749097
95	Kaempferol-3-O-rhamnopyranosil	102333896
96	Kaempferol-3-O-rutinoside	5318767
97	Luteolin	5280445
98	Luteolin-6-C-glucoside	114776
99	Naringenin	439246
100	Nobiletin	72344
101	Quercetin-3-O-glucopyranoside-5280804 Quercetin-3-O-rhamnopyranoside	5280459
102	Quercetin-3-O-rutinoside	5280805
103	Tangeretin	68077
104	Procyanidin B-2	122738
105	Procyanidin B-4	147299
106	Procyanidin B-5	124017
107	Procyanidin B-7	13990893
108	4-O-p-Coumaroylquinic acid	5281766
109	Chlorogenic acid	1794427
110	Cryptochlorogenic acid	9798666
111	Lyoniside	14521039
112	Neochlorogenic acid	5280633

S2: List of phytoconstituents of Piper betel

S.NO	PHYTOCONSTITUENTS OF Piper betel	PUB CHEM ID
1	Terpene	6651
2	Eugeno	3314
3	Chavibetol	596375
4	Hydroxychavicol	70775
5	Chavibetol methyl ether	7127
6	a-pinene	11240513
7	1,8-cineol	2758
8	Allylpyrocatechol monoacetate	10219771
9	Piperol-A	102586046
10	Piperol-B	101715614
11	Terpinen-4-ol	11230
12	Estragol	8815
13	Alpha pinene	6654
14	Beta pinene	14896
15	a-limonene	91496
16	Alpha selinene	10856614
17	Alpha farnesene	5281516
18	Phytosterol	222284
19	Allylpyro catechin	5144

20	Beta carotin	15788327
21	Linalool	6549
22	Cubene	57178215
23	Trans-propenyl-guaiacol	1781947
24	Isoeugenol	853433
25	Alpha -gurjunene	521243
26	Spathulenol	92231
27	Caryophyllene	5281515
28	Globulol	12304985
29	Cubenol	11770062
30	Alpha-cadinol	10398656
31	Methyl chavicol	8815
32	Chavicol	68148
33	Anethole	637563
34	Safrole	5144
35	Eugenol acetate	23698978
36	Methyl eugenol	7127
37	Dotriacontanoic acid	19255
38	Stearic acid	5281
39	Piperlonguminine	5320621
40	Hentriacontane	12410
41	n-Triacontane	68972
42	Pentatriacontane	12413
43	Beta-sitosterylpalmitate	9852570
44	Ursolic acid	64945
45	Stigmasterol	5280794
46	Cadinene	3032853
47	Limene	3033866
48	Beta-Caryophyllene	5281515
49	Alpha-pinene	6654
50	Carvacrol	10364
51	Allylpyrocatechol	292101
52	P-cymene	7463
53	Allylpyrocatechol diacetate	46700759
54	Sabinene	18818
55	Myrcene	31253
56	Beta-phyllendrene	11142
57	Gamma-terpinene	7461
58	Beta-ocimen	5281553
49	Alpha-terpineol	17100
60	Gamma-elemene	6432312
61	Alpha-copaene	19725
62	Beta-copaene	57339298
63	Beta-elemene	6918391