RESEARCH ARTICLE

In-silico Study of Phytochemicals of Ethnobotanical Plant *Cannabis sativa* for Anti-Diabetic Potential

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Abstract

Ethnobotany is an applied multidisciplinary science in which we not only systemically study inter-relations between human and plant kingdom but also has applications in many fields, including food industry, climate change, biodiversity conservation, and human health. Ethnobotanical plants form an integral part of human life. Many medicinal and aromatic plants are used by locals and nomadic people, which come from a wild source. According to Atharva-Veda, *Cannabis* is one of the most sacred plants.

Perfect development provides insurance for health and healthy life and maintains stability in the ecosystem. If we deeply observe our different traditions, we will find that every ritual shows the close relationship of humans with nature. There are a number of natural ingredients used for performing different rituals. *Cannabis* is the plant that is commonly known as "Bhang". *Cannabis* has been traditionally associated with lord "Shiva" worship. There are various stories behind these rituals mentioned in various mythology books. In this research, we focus on this plant's ethnomedicinal value and assessed the antidiabetic potential of *Cannabis sativa*, an ethnobotanical plant of Ranikhet tehsil, by *in-silico* method. Hence, we conducted molecular docking of phytochemicals with molecular antidiabetic targets, alpha-amylase. The aim of this paper is an *in-silico* study of the *C. sativa's* phytochemicals on the glucose metabolism related to alpha-amylase. From our study, we hope to find potential phytochemicals which could be useful in treating diabetes problems.

Keywords: Ethnobotany, Biodiversity Conservation, Ecosystem, Phytochemicals, Development, Rituals, *Cannabis sativa*.

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Introduction

Type 2 diabetes is the commonest type of diabetes, accounting for around 90% of all diabetic sufferers. it is a metabolic disorder characterized by chronic hyperglycemia together with the interference in the metabolism of carbohydrates, proteins, and lipids Porth (2010), Nogueira *et al.*(2011), Stout *et al.*(2011), Vieira *et al*. (2019) due to inadequate or ineffective insulin. Its complications are increasing due to the current modern lifestyle Carbone *et al.*(2019). The combination of three main factors- genetic disposition, large food intake, and less physical activity- obesity leads to an imbalance between the energy supply and energy expenditure, increasing free fatty acids in the blood and turn, reducing glucose utilization in muscle and fatty tissues, finally contributing to insulin resistance and an increase of insulin release, further raised by the resulting down-regulation of the insulin receptors. International Diabetes Federation (IDF) reported approximately 537 million adults (20–79) are affected with diabetes in 2021 worldwide and foretold that it would rise to 783 million by 2045:IDF, 2017**.** Diabetes is responsible for 6.7 million death in 2021, one every five seconds: IDF, 2021.

The eventual aim behind diabetes treatment is to lower and maintain the glycosylated hemoglobin level below 7% to avert micro-and macro-vascular complications associated with the disease Stein *et al*., (2013). For reducing blood glucose levels and the risks associated with T2D, insulin sensitizers, insulin secretagogues, and external insulin delivery (insulin analogs) are primarily used. Mostly, combinations of different therapeutic drugs are used to control diabetes. However, the adverse side effects associated with various synthetic antidiabetic medicines have rejuvenated interest in traditional ayurvedic systems of medicine Sharma *et al*. (2021). Many medicinal plants as well as herbal formulations, have been used in the treatment of diabetes. One such medicinal plant is *Cannabis sativa,* commonly known as bhang in India and belongs to the family Cannabaceae.This annual flowering herb originates from central Asia Christelle *et al.* (2016) but now shows worldwide distribution (Fig. 1).

This fast-growing plant has multi-purpose applications: it is a treasure trove of phytochemicals and a rich source of cellulosic fibers. It is a popular medicinal plant in Ayurvedic and folk medicines. *Cannabis* is being developed as a key ingredient in a variety of food items, including bakery, confectionery, beverages, dairy, fruits, vegetables, and meat. Hemp seeds are high in readily digestible proteins, lipids, polyunsaturated fatty acids (PUFA), insoluble fiber, and carbohydrates and have high nutritional value. The antioxidants of *Cannabis*, such as polyphenols, help with anxiety, oxidative stress, and the risk

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Fig. 1: *Cannabis sativa*(Bhang)

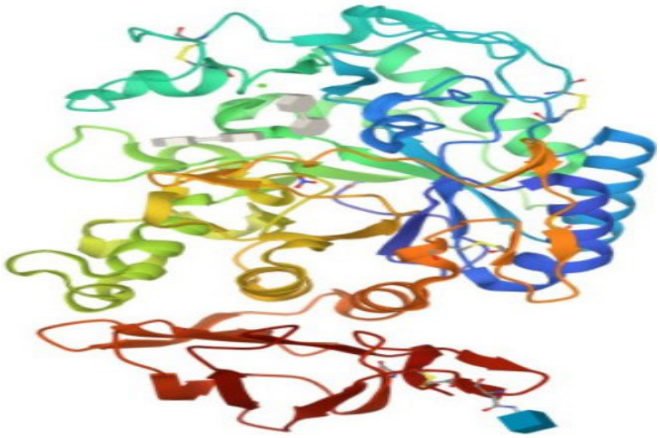


Fig. 2 : 3BAJ PROTEIN (PDB DOI: 10.2210/pdb3BAJ/pdb)

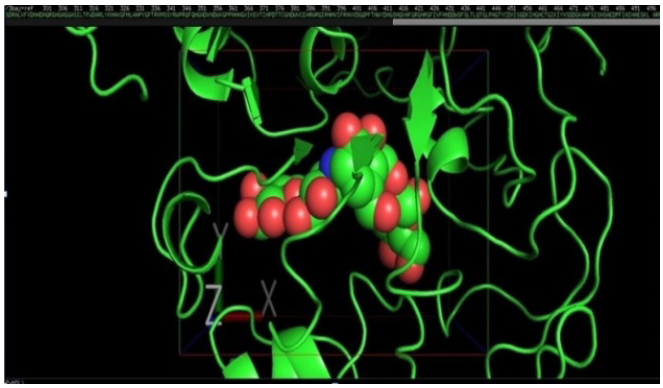


Fig. 3: Binding Pocket of Reference Molecule

of chronic illnesses, including cancer, neurological disorders, digestive problems, rheumatic arthritis, and skin diseases Amna *et al.* (2021).

In Africa and Asia many rural communities rely heavily on the use of numerous medicinal plants to manage diabetes mellitus. However, few have received scientific scrutiny Ojewole (2002) since *C. sativa* is used in indigenous medicines as a treatment for diabetes.

Present day, computational approaches are a constitutive part of drug discovery. This computational technique reduces the cost and time of drug discovery Yang (2010), Yan *et al.* (2014), Mukesh (2011). The target-based drug discovery approach has been widely used due to its accurate action and specific nature. Many molecular targets have been reported to develop new drugs against T2D. Currently, glucagon-like peptide-1 (GLP-1) agonists, sodium-dependent glucose transporter 2(SGLT2) inhibitors, aldose reductase (AR), peroxisome proliferator-activated receptor gamma (PPAR-c), free fatty acid receptor 1, also known as GPR40, and dipeptidyl peptidase-4 (DPP4), etc. are being clinically tested. Although *C. sativa* is a potential antidiabetic plant the specific phytochemicals of *C. sativa* and their molecular targets are not been explicitly discovered. Hence, to find out the specific targets and phytochemicals involved in exerting the antidiabetic effect of *C. sativa*, virtual screening was carried out by molecular docking using the receptors; alpha-amylase against 155 phytochemicals (Table 1). Virtual Screening (VS) results revealed that 3BAJ might be the most prominent target on which phytochemicals of *C. sativa* exert their action to reduce glucose levels in the blood. Human pancreatic alpha-amylase (BAJ) is a 496 amino acid single polypeptide chain that binds to essential calcium, chloride, and nitrate ions. This enzyme is responsible for the hydrolysis of small oligosaccharides or partially digested disaccharides in the small intestine into glucose. Inhibition of HPA provides an effective target for the treatment of type 2 diabetes.

Materials And Methods

Data Source

The IMPPAT database (https://cb.imsc.res.in/imppat/home) and PubChem were used to download phytochemicals of *C. sativa* and standard drug compounds (3D PDB). Phytochemicals' names with canonical smiles and CID no. is shown in Table 1.

PubChem and IMPPTdata base were used to find the 3D-SDF structures of phytochemicals of *C. sativa*. Open Babel GUI software was used to convert the 3D structure of the ligand file format from SDF to PDB file.

Preparation of Target Protein

Human pancreatic alpha-amylase 3BAJ was selected from RCSB PDB online site which has a co-crystallized inhibitor (ARE) (Fig. 2). Molecular docking could not be performed on the raw PDB protein structure because 3D proteins have different unwanted molecules like metal ions, water molecules, etc. The target protein was refined and energy-optimized before moving on to the docking analysis.

Using PyMOL software, we obtained coordinates of the binding pocket of an already bound inhibitor to the protein alpha-amylase (BAJ) and prepared 3D PDBs of protein with the inhibitor. A binding pocket is a 3D configuration in which an inhibitor binds tightly with protein and inhibits its function (Fig. 3).

Molecular Docking

InstaDock v1.1was used for docking to dock clean 3baj with reference molecules and 155 phytochemicals of *C. sativa*.

Molecular docking-based virtual screening of a library of 154 compounds with 3bajcln was performed to predict their binding affinity and detailed interactions. The docking was performed using InstaDock, a single-click molecular docking tool that automizes the entire process of molecular docking-based virtual screening Mohammad *et al.* (2020). The binding energies of molecules with 3BAJ were calculated using molecular docking.

For docking first, we made a folder and put the instadock exe file, PDB of clean protein, 3D PDB of reference molecule, and 154 phytochemicals of *C. sativa* (Table 1). Opened instadock file, clicked on the tool, and clicked on prepare receptor.

Table 1: Phytochemicals of cannabis sativa(source: IMPPAT and Pubchem)Preparation of ligands

S.No	*Phyto Chemical*	*Sm*	*CID.No*
1.	Cannabinol	CCCCCc1cc(O)c2-c3cc©ccc3C(Oc2c1)©C	2543
2.	Cannabidiol	CCCCCc1cc(O)c(c(c1)O)[C@@H]1C=C©CC[C@H]1C(=C)C	644019
3.	Dronabinol	CCCCCc1cc(O)c2c(c1)OC([C@H]1[C@H]2C=C©CC1)©C	16078
4.	beta-Bisabolene	CC(=CCCC(=C)[C@H]1CCC(=CC1)C)C	10104370
5.	6,10,14 Trimethylpentadecan-2-one	CC(CCCC©C)CCCC(CCCC(=O)C)C	10408
6.	Sativene	CC([C@H]1CC[C@@]2([C@@H]3[C@H]1[C@@H](CC3)C2=C)C)C	11830550
7.	2-(4-Methylphenyl)propan-2-ol	Cc1ccc(cc1)C(O)©C	14529
8.	Myrcene	C=CC(=C)CCC=C©C	31253
9.	7-Epi-sesquithujene	CC(=CCC[C@H]([C@]12CC=C([C@@H]2C1)C)C)C	56927990
10.	Gamma-Terpinene	CC1=CCC(=CC1)C©C	7461
11.	Selina-4(15),7(11)-diene	C=C1CCC[C@]2([C@H]1CC(=C©C)CC2)C	10655819
12.	Germacrene B	C/C/1=CCC/C(=C/CC(=C©C)CC1)/C	5281519
13.	p-Cymene	Cc1ccc(cc1)C©C	7463
14.	Tricyclene	CC12C3C1CC(C2©C)C3	79035
15.	3,7(11)-Eudesmadiene	CC1=CCCC2(C1CC(=C©C)CC2)C	522296
16.	gamma-Curcumene	CC(=CCC[C@H](C1=CC=C(CC1)C)C)C	12304273
17.	(-)-beta-Chamigrene	CC1=CC[C@@]2(CC1)C(=C)CCCC2©C	442353
18.	3-Carene	CC1=CCC2C(C1)C2©C	26049
19.	4-Carvomenthenol	CC1=CCC(CC1)(O)C©C	11230
20.	(1R)-2-methyl-5-propan-2-ylbicyclo[3.1.0]hex-2-ene	CC1=CCC2([C@@H]1C2)C©C	6451618
21.	Alpha-Selinene	CC1=CCC[C@]2([C@H]1C[C@@H](CC2)C(=C)C)C	10856614
22.	Terpinolene	CC1=CCC(=C©C)CC1	11463
23.	Alpha-Terpinene	CC1=CC=C(CC1)C©C	7462
24.	Beta-Farnesene	C=CC(=C)CC/C=C(/CCC=C©C)C	5281517
25.	alpha-Gurjunene	C[C@@H]1CC[C@@H]2[C@H](C3=C(CC[C@H]13)C)C2©C	15560276
26.	Humulene epoxide II	C/C/1=CCC©©/C=C/C[C@@]2([C@@H](CC1)O2)C	10704181
27.	Humulene	C/C/1=CCC©©/C=C/C/C(=C/CC1)/C	5281520
28.	(Z)-Gamma-bisabolene	CC(=CCC/C(=C1/CCC(=CC1)C)/C)C	3033866
29.	(+)-Beta-Phellandrene	CC([C@@H]1CCC(=C)C=C1)C	442484
30.	Alpha-Pinene	CC1=CCC2CC1C2©C	6654
31.	Beta-Pinene	C=C1CCC2CC1C2©C	14896
32.	Sabinene	C=C1CCC2(C1C2)C©C	18818
33.	3-(1,5-Dimethyl-4-hexenyl)-6-methylene-1-cyclohexene	CC(C1CCC(=C)C=C1)CCC=C©C	519764
34.	Levomenol	CC(=CCC[C@@]([C@H]1CCC(=CC1)C)(O)C)C	442343
35.	Caryophyllene oxide	C=C1CC[C@H]2O[C@@]2(CC[C@@H]2[C@@H]1CC2©C)C	1742210
36.	Isocaryophyllene	C/C/1=C/CCC(=C)[C@@H]2[C@@H](CC1)C(C2)©C	5281522
37.	(Z)-Beta-Ocimene	C=C/C(=CCC=C©C)/C	5320250
38.	Gamma-Elemene	C=C[C@]1©CCC(=C©C)C[C@H]1C(=C)C	6432312
39.	Beta-Selinene	C=C1CCC[C@]2([C@H]1C[C@@H](CC2)C(=C)C)C	442393
40.	Alpha-Phellandrene	CC1=CCC(C=C1)C©C	7460
41.	beta-Caryophyllene	C/C/1=CCCC(=C)[C@@H]2[C@@H](CC1)C(C2)©C	5281515
42.	(E)-beta-ocimene	C=C/C(=C/CC=C©C)/C	5281553
43.	Bornyl acetate	CC(=O)OC1CC2C(C1©CC2)©C	6448
44.	Camphene	C=C1C2CCC(C1©C)C2	6616
45.	cis-alpha-Bergamotene	CC(=CCCC1©[C@@H]2CC=C([C@H]1C2)C)C	91753502

46.	Limonene	CC1=CCC(CC1)C(=C)C	22311
47.	Nerolidol	C=CC(CC/C=C(/CCC=C©C)C)(O)C	5284507
48.	Alpha-Copaene	CC([C@@H]1CC[C@]2([C@@H]3[C@H]1C2C(=CC3)C)C)C	70678558
49.	Gamma-Camphorene	CC(=CCCC1=CCCC(C1)C(=C)CCC=C©C)C	5315649
50.	trans-alpha-Bergamotene	CC(=CCC[C@]1©[C@H]2CC=C([C@@H]1C2)C)C	6429302
51.	Selina-4,7-diene	CC1=C2CC(=CC[C@]2(CCC1)C)C©C	91748132
52.	Cannabisin D	Coc1cc2C=C(C(=O)NCCc3ccc(cc3)O)[C@H]([C@@H](c2cc1O)c1ccc(c(c1)OC)O)C(=O)NCCc1ccc(cc1)O	44584134
53.	1-(3,4-dihydroxyphenyl)-6,7-dihydroxy-2-N,3-N-bis[2-(4-hydroxyphenyl)ethyl]naphthalene-2,3-dicarboxamide	Oc1ccc(cc1)CCNC(=O)c1cc2cc(O)c(cc2c(c1C(=O)NCCc1ccc(cc1)O)c1ccc(c(c1)O)O)O	15086398
54.	(1R,2S)-1-(3,4-dihydroxyphenyl)-6,7-dihydroxy-2-N,3-N-bis[2-(4-hydroxyphenyl)ethyl]-1,2-dihydronaphthalene-2,3-dicarboxamide	Oc1ccc(cc1)CCNC(=O)C1=Cc2cc(O)c(cc2[C@H]([C@@H]1C(=O)NCCc1ccc(cc1)O)c1ccc(c(c1)O)O)O	101631692
55.	(1R,2S)-1-(3,4-dihydroxyphenyl)-7-hydroxy-2-N,3-N-bis[2-(4-hydroxyphenyl)ethyl]-6-methoxy-1,2-dihydronaphthalene-2,3-dicarboxamide	Coc1cc2C=C(C(=O)NCCc3ccc(cc3)O)[C@H]([C@@H](c2cc1O)c1ccc(c(c1)O)O)C(=O)NCCc1ccc(cc1)O	101631693
56.	Trans-Zeatin	OC/C(=C/CNc1ncnc2c1[nH]cn2)/C	449093
57.	p-Coumaroyltyramine	O=C(/C=C/c1ccc(cc1)O)NCCc1ccc(cc1)O	5372945
58.	3-Benzofurancarboxamide, 2,3-dihydro-2-(4-hydroxy-3-methoxyphenyl)-N-(2-(4-hydroxyphenyl)ethyl)-5-((1E)-3-((2-(4-hydroxyphenyl)ethyl)amino)-3-oxo-1-propenyl)-7-methoxy-, (2R,3R)-rel-	Coc1cc(/C=C/C(=O)NCCc2ccc(cc2)O)cc2c1O[C@@H]([C@H]2C(=O)NCCc1ccc(cc1)O)c1ccc(c(c1)OC)O	101262727
59.	Moupinamide	Coc1cc(/C=C/C(=O)NCCc2ccc(cc2)O)ccc1O	5280537
60.	Cannabispirenone B	Coc1cc(O)cc2c1[C@@]1(CCC(=O)C=C1)CC2	101176447
61.	(-)-Beta-Curcumene	CC(=CCC[C@H](C1=CCC(=CC1)C)C)C	14014430
62.	Cannabicyclol	CCCCCc1cc(O)c2c(c1)OC1(C3C2C(C3CC1)©C)C	30607
63.	Nonanal	CCCCCCCCC=O	31289
64.	2-Acetamido-2-deoxy-beta-D-glucopyranose	OC[C@H]1O[C@@H](O)[C@@H]([C@H]([C@@H]1O)O)NC(=O)C	24139
65.	Choline	OCC[N+]©©C	305
66.	Cannabichromene	CCCCCc1cc2OC©(CCC=C©C)C=Cc2c(c1)O	30219
67.	Kaempferol	Oc1ccc(cc1)c1oc2cc(O)cc(c2c(=O)c1O)O	5280863
68.	Canniprene	Coc1cc(CCc2ccc(c(c2CC=C©C)O)OC)cc(c1)O	53439651
69.	Quercetin	Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O	5280343
70	Cannabisativine	CCCCC[C@H]([C@H]([C@@H]1C=CC[C@@H]2N1CCCNCCCCNC(=O)C2)O)O	442846
71.	Cannabigerol	CCCCCc1cc(O)c(c(c1)O)C/C=C(/CCC=C©C)C	5315659
72.	(1R,4R,13S)-1,5,5-Trimethyl-9-pentyl-6,15-dioxatetracyclo[9.3.1.04,13.07,12]pentadeca-7(12),8,10-triene	CCCCCc1cc2O[C@]3©CC[C@@H]4[C@@H](c2c(c1)OC4©C)C3	186149
73.	Cannabispiran	Coc1cc(O)c2c(c1)CCC12CCC(=O)CC1	162936
74.	Orientin	OC[C@H]1O[C@H]([C@@H]([C@H]([C@@H]1O)O)O)c1c(O)cc(c2c1oc(cc2=O)c1ccc(c(c1)O)O)O	5281675
75.	6-Methyl-3-pentyl-9-(prop-1-en-2-yl)dibenzo[b,d]furan-1-ol	CCCCCc1cc(O)c2c(c1)oc1c2c(ccc1C)C(=C)C	59444381
76.	Beta-Panasinsene	C=C1CCCC2(C31CC(C3CC2)©C)C	595133
77.	Estragole	Coc1ccc(cc1)CC=C	8815
78.	Hordenine	CN(CCc1ccc(cc1)O)C	68313
79.	Cannabispiradienone	Coc1cc(O)c2c(c1)CCC12C=CC(=O)C=C1	90475437
80.	Isovitexin	OC[C@H]1O[C@H]([C@@H]([C@H]([C@@H]1O)O)O)c1c(O)cc2c(c1O)c(=O)cc(o2)c1ccc(cc1)O	162350

81.	Delta-Guaiene	CC(=C)[C@@H]1CCC(=C2[C@@H](C1)[C@@H]©CC2)C	94275
82.	Cannabiglendol	CCCc1cc(O)c2c(c1)OC1(CC2C(CC1)C(O)©C)C	156998
83.	Cannabinodiol	CCCCCc1cc(O)c(c(c1)O)c1cc©ccc1C(=C)C	11551346
84.	Eucalyptol	CC12CCC(CC1)C(O2)©C	2758
85.	Cannabispirol	Coc1cc(O)c2c(c1)CCC12CCC(CC1)O	194174
86.	Gamma-Muurolene	CC1=C[C@@H]2[C@H](CC1)C(=C)CC[C@H]2C©C	12313020
87.	Valencene	CC(=C)[C@@H]1CCC2=CCC[C@H]([C@@]2(C1)C)C	9855795
88.	Camphor	O=C1CC2C(C1©CC2)©C	2537
89.	Linalool	C=CC(CCC=C©C)(O)C	6549
90.	Carvone	CC(=C)C1CC=C(C(=O)C1)C	7439
91.	alpha-Bergamotene	CC(=CCCC1©C2CC=C(C1C2)C)C	86608
92.	alpha-Curcumene	CC(=CCCC(c1ccc(cc1)C)C)C	92139
93.	Vitexin	OC[C@H]1O[C@H]([C@@H]([C@H]([C@@H]1O)O)O)c1c(O)cc(c2c1oc(cc2=O)c1ccc(cc1)O)O	5280441
94.	Vitexin 2′-O-beta-D-glucoside	OC[C@H]1O[C@H]([C@@H]([C@H]([C@@H]1O)O)O[C@@H]1O[C@H](CO)[C@H]([C@@H]([C@H]1O)O)O)c1c(O)cc(c2c1oc(cc2=O)c1ccc(cc1)O)O	5280641
95.	Menthol	CC1CCC(C(C1)O)C©C	1254
96.	Allo-Aromadendrene	C[C@@H]1CC[C@H]2[C@@H]1C1C(C1©C)CCC2=C	42608158
97.	Cannabidiolic acid	CCCCCc1cc(O)c(c(c1C(=O)O)O)[C@@H]1C=C©CC[C@H]1C(=C)C	160570
98.	Friedelin	O=C1CC[C@@H]2[C@]([C@H]1C)©CC[C@H]1[C@@]2©CC[C@@]2([C@]1©CC[C@@]1([C@H]2CC©©CC1)C)C	91472
99.	Epifriedelanol	O[C@H]1CC[C@@H]2[C@]([C@H]1C)©CC[C@H]1[C@@]2©CC[C@@]2([C@]1©CC[C@@]1([C@H]2CC©©CC1)C)C	119242
100.	(+)-Dihydrocarvone	CC(=C)[C@@H]1CC[C@H](C(=O)C1)C	22227
101.	Nabiximols	CCCCCc1cc(O)c2c(c1)OC([C@H]1[C@H]2C=C©CC1)©C. CCCCCc1cc(O)c(c(c1)O)[C@@H]1C=C©CC[C@H]1C(=C)C	9852188
102.	Beta-Sitosterol	CC[C@@H](C©C)CC[C@H]([C@H]1CC[C@@H]2[C@]1©CC[C@H]1[C@H]2CC=C2[C@]1©CC[C@@H](C2)O)C	222284
103.	Cannabitriol	CCCCCc1cc(O)c2c(c1)OC(C1=C2C(O)C(CC1)©O)©C	11551959
104.	Campest-4-en-3-one	CC([C@@H](CC[C@H]([C@H]1CC[C@@H]2[C@]1©CC[C@H]1[C@H]2CCC2=CC(=O)CC[C@]12C)C)C)C	11988279
105.	IsoCannabispiran	Coc1cc(O)cc2c1C1(CCC(=O)CC1)CC2	154496776
106.	AcetylCannabispirol	Coc1cc(O)c2c(c1)CCC12CCC(CC1)OC(=O)C	25141336
107.	Eugenol	C=CCc1ccc(c(c1)OC)O	3314
108.	Betaine	[O-]C(=O)C[N+]©©C	247
109.	beta-Sitostenone	CC[C@@H](C©C)CC[C@H](C1CCC2[C@]1©CCC1C2CCC2=CC(=O)CC[C@]12C)C	60123241
110.	Tricyclo(6.3.1.02,5)dodecan-1-ol, 4,4,8-trimethyl-, (1R,2S,5R,8S)-	C[C@]12CCC[C@](C2)(O)[C@@H]2[C@@H](CC1)C(C2)©C	11746218
111.	Longifolene	C=C1C2CCC3C1©CCCC(C23)©C	289151
112.	7-O-Allylapigenin	C=CCOc1cc(O)c2c(c1)oc(cc2=O)c1ccc(cc1)O	50992828
113.	4-(Hydroxymethyl)benzoic acid	Occ1ccc(cc1)C(=O)O	76360
114.	Cannabichromevarin	CCCc1cc2OC©(CCC=C©C)C=Cc2c(c1)O	6451726
115.	Cannabifuran	CCCCCc1cc(O)c2c(c1)oc1c2c(ccc1C)C©C	9966466
116.	Cannabicoumaronone	CCCCCc1cc2OC©©C(c3c2c(c1)oc3)CCC(=O)C	625303
117.	Nonacosane	CCCCCCCCCCCCCCCCCCCCCCCCCCCCC	12409

118.	Vitexin 7-O-glucoside	OCC1O[C@H](C([C@H]([C@@H]1O)O)O)c1c(O[C@@H]2OC(CO)[C@H]([C@@H](C2O)O)O)cc(c2c1oc(cc2=O)c1ccc(cc1)O)O	44257744
119.	Guaiacol	Coc1ccccc1O	460
120.	Humuleneepoxyde	C/C/1=CCC©©/C=CCC2(C(CC1)O2)C	5463721
121.	Cinnamic acid	OC(=O)/C=C/c1ccccc1	444539
122.	Benzoic acid	OC(=O)c1ccccc1	243
123.	Ferulic acid	Coc1cc(/C=C/C(=O)O)ccc1O	445858
124.	Caffeic acid	OC(=O)/C=C/c1ccc(c(c1)O)O	689043
125.	Muscarine	O[C@@H]1C[C@H](O[C@H]1C)C[N+]©©C	9308
126.	Trigonelline	C[n+]1cccc(c1)C(=O)[O-]	5570
127.	Cannabichromevarinic acid	CCCc1cc2OC©(CCC=C©C)C=Cc2c(c1C(=O)O)O	11110322
128.	Cannabispirenone	Coc1cc(O)c2c(c1)CC[C@@]12CCC(=O)C=C1	10105874
129.	2-[(1S,6S)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-propylbenzene-1,3-diol	CCCc1cc(O)c(c(c1)O)[C@H]1C=C©CC[C@@H]1C(=C)C	45783233
130.	(4S)-4-hydroxy-4-[(E,3R)-3-hydroxybut-1-enyl]-3,3,5-trimethylcyclohexan-1-one	O=C1CC©[C@](C(C1)©C)(O)/C=C/[C@H](O)C	15847407
131.	Cannabistilbene I	Coc1cc(CCc2ccc(c(c2)CC=C©C)O)cc(c1)O	146349
132.	Pyrrolidine	C1CCCN1	31268
133.	Caryophyllenol I	C=C1CC[C@H](O)/C(=CC[C@@H]2[C@@H]1CC2©C)/C	12312991
134.	Stearic acid	CCCCCCCCCCCCCCCCCC(=O)O	5281
135.	Vomifoliol	C[C@H](/C=C/[C@@]1(O)C(=CC(=O)CC1©C)C)O	5280462
136.	Cytisoside	OCC1O[C@H](C([C@H]([C@@H]1O)O)O)c1c(O)cc(c2c1oc(cc2=O)c1ccc(cc1)OC)O	44257872
137.	FlavoCannabiside	OCC1O[C@H](C([C@H]([C@@H]1O)O)O)O[C@@H]1OC(CO)[C@H]([C@@H](C1O)O)O)c1c(O)cc(c2c1oc(cc2=O)c1ccc(c(c1)O)O)O	44257930
138.	Cannabichromanone	CCCCCc1cc(O)c2c(c1)OC(C(C2=O)CCC(=O)C)©C	186690
139.	Cannabielsoin	CCCCCc1cc(O)c2c(c1)O[C@H]1[C@@H]2[C@@H](CC[C@]1©O)C(=C)C	162113
140.	Methylparaben	COC(=O)c1ccc(cc1)O	7456
141.	Cannabistilbene II	COC1=CC(/C=C/c2ccc(c(c2OC)O)OC)CC(=C1)O	6439895
142.	Cannabigerovarinic acid	CCCc1cc(O)c(c(c1C(=O)O)O)C/C=C(/CCC=C©C)C	59444383
143.	Cannabidivarinic acid	CCCc1cc(O)c(c(c1C(=O)O)O)[C@@H]1C=C©CC[C@H]1C(=C)C	59444387
144.	Hexadecanamide	CCCCCCCCCCCCCCCC(=O)N	69421
145.	Piperidine	C1CCCNC1	8082
146.	Nicotine	CN1CCC[C@H]1c1cccnc1	89594
147.	delta(9)-Tetrahydrocannabinolic acid	CCCCCc1cc2OC©©[C@H]3[C@H](c2c(c1C(=O)O)O)C=C(CC3)C	98523
148.	1-Methyl-4-(prop-1-en-2-yl)benzene	Cc1ccc(cc1)C(=C)C	62385
149.	Cannflavin A	Coc1cc(ccc1O)c1cc(=O)c2c(o1)cc(c(c2O)C/C=C(/CCC=C©C)C)O	10071695
150.	Cannflavin B	Coc1cc(ccc1O)c1cc(=O)c2c(o1)cc(c(c2O)CC=C©C)O	403815
151.	4-Hydroxybenzoic acid	Oc1ccc(cc1)C(=O)O	135
152.	DL-Borneol	O[C@@H]1C[C@@H]2C([C@]1©CC2)©C	10049
153.	Sophoraflavonoloside	OC[C@H]1O[C@@H](Oc2c(oc3c(c2=O)c(O)cc(c3)O)c2ccc(cc2)O)[C@@H]([C@H]([C@@H]1O)O)O[C@@H]1O[C@H](CO)[C@H]([C@@H]([C@H]1O)O)O	5282155
154.	alpha-Farnesene	C=C/C(=C/C/C=C(/CCC=C©C)C)/C	5281516

Table 2: List of phytochemicals of *Cannabis sativa* showed the best binding affinity(Affinity result file)

S. No.	*Name of the ligand*	*Binding energy(kcal/mol)*	*pKi*	*Ligand Efficiency(kcal/mol/non-Hatom)*
1.	Friedelin 91472	-10.9	7.99	.3516
2.	1-(3,4-dihydroxyphenyl)-6,7-dihydroxy-2-N,3-N-bis[2-(4-hydroxyphenyl) ethyl]naphthalene-2,3-dicarboxamide 15086398	-9.8	7.19	.2227
3.	Campest-4-en-3-one 11988279	-9.4	6.89	.3241
4.	*Cannabis*inC 101631693	-9.3	6.83	.2067
5.	Cannflavin A 10071695	-9.2	6.75	.2875
6.	*Cannabis*inB 101631692	-9.2	6.75	.2091
7.	3bajref(ARE)	-8.9	6.53	.1618
8.	Cannabicyclol 30607	-8.6	6.31	.3739
9.	Cannabichromene 30219	-8.5	6.23	.3696
10.	Kaempferol 5280863	-8.4	6.16	.4
11.	Delta(9)-Tetrahydrocannabinolic acid 98523	-8.4	6.16	.3231

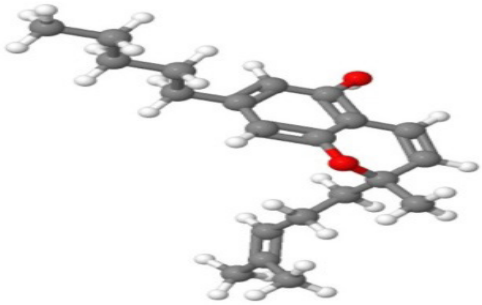
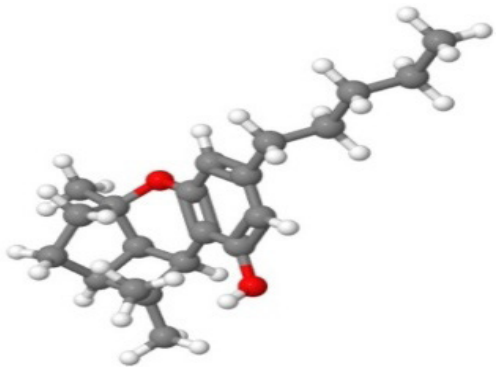
InstaDock change receptor PDB into PDBQT. After preparing the receptor configuration file generated. The coordinates of this configuration file were set according to PyMOLbinding pocket coordinates and saved. Now clicked on prepare ligand(s), InstaDock changed all phytochemicals PDB into PDBQT and started docking. After the docking folder had auto-generated the result folder, conf file, and PDBs and PDBQTs of protein, references, and ligands, the resulting folder had log and out files of reference and ligands, affinity result file, and InstaDock result summary. 10 phytochemicals showed the best binding affinity with protein after the result analysis (Table 2).

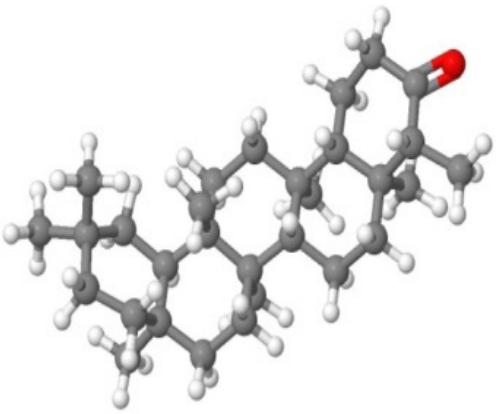
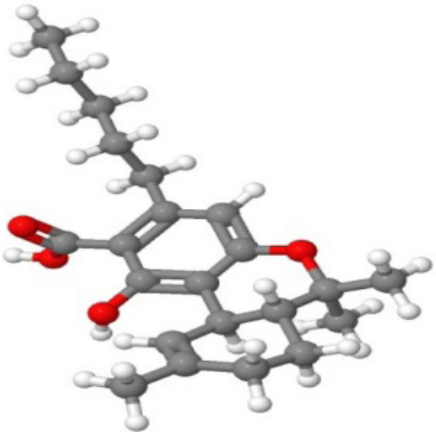
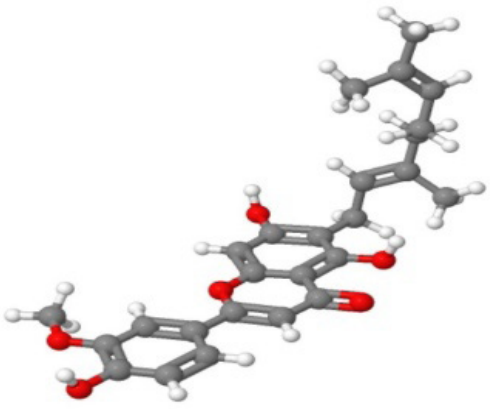
Out file contains 9 models of each ligand. Took that model which showed the maximum affinity with reference. We made PDB of clean protein and selected a model of the ligand with the help of PyMOL. With the help of this PDB form ligPLOT. Checked drug-likeness and ADMET properties of selected phytochemicals.

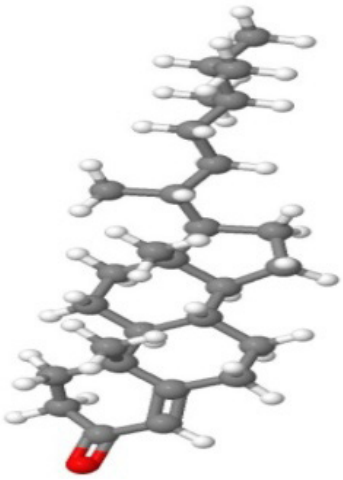
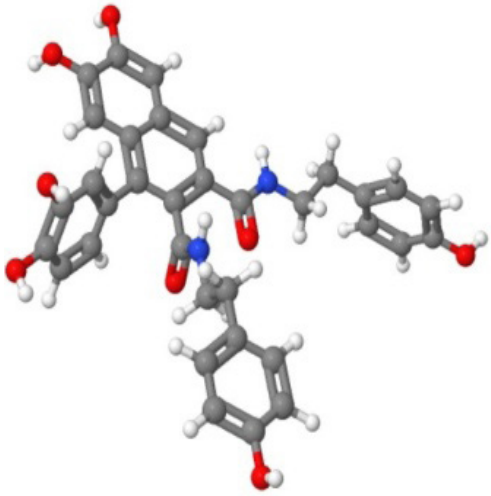
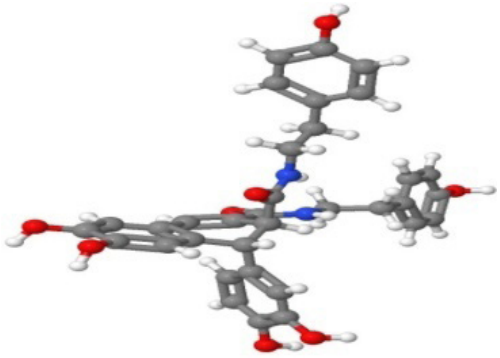
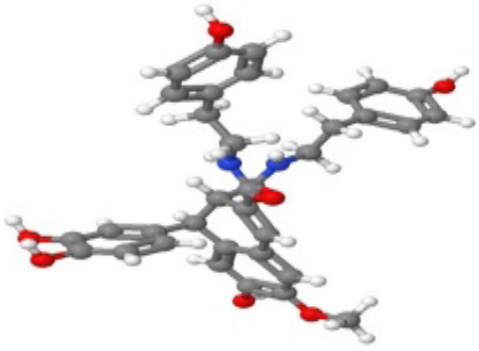
Evaluation of Drug Likeliness

There are two main rules for checking drug-likeness- Lipinski's rule of five and Muegge *et al.* rule. Lipinski's rule of five (RO5) is used to assess the drug-likeliness of a chemical or biochemical molecule. It possesses qualities that would make it a likely or potential drug in humans Davella and Mamidala (2019). Calculating molecular properties such as log P (partition coefficient), number of hydrogen bond donors, number of hydrogen bond acceptors, and molecular weight might help forecast a pharmacological compound's oral action. Muegge *et al.* rule Calculating molecular properties such as A log P, molecular weight, no. of atoms, and molar refractivity. Table 3 shows the results of a drug likeliness evaluation based on

Table 3: The molecular and drug likeness properties

S.No.	*Name of phytochemical*	*Molecular formula And Weight*	*Structure*	*AlogP*	*HBA*	*HBD*	*Lipinski's rule of 5*
1.	Cannabichromene 30219	C21H30O2 314.5		6.04	2	1	passed
2.	Cannabicyclol 30607	C21H30O2 314.47		5.43	2	1	passed

3.	Friedelin 91472	C30H50O 426.7		8.46	1	0	passed
4.	delta(9)-Tetrahydrocannabinolic acid 98523	C22H30O4 358.5		5.43	3	3	passed
5.	Kaempferol 5280863	C15H10O6 286.24		2.28	6	4	passed
6.	Cannflavin A 10071695	C26H28O6 436.5		5.82	6	3	passed

7.	Campest-4-en-3-one 11988279	C28H46O 398.7		7.84	1	0	passed
8..	1-(3,4-dihydroxyphenyl)-6,7-dihydroxy-2-N,3-N-bis[2-(4-hydroxyphenyl) ethyl]naphthalene-2,3-dicarboxamide 15086398	C34H30N2O8 594.6		4.69	8	8	failed
9.	*Cannabis*in b 101631692	C34H32N2O8 596.6		3.78	8	8	failed
10.	*Cannabis*in c 101631693	C35H34N2O8 610.7		4.09	8	7	failed

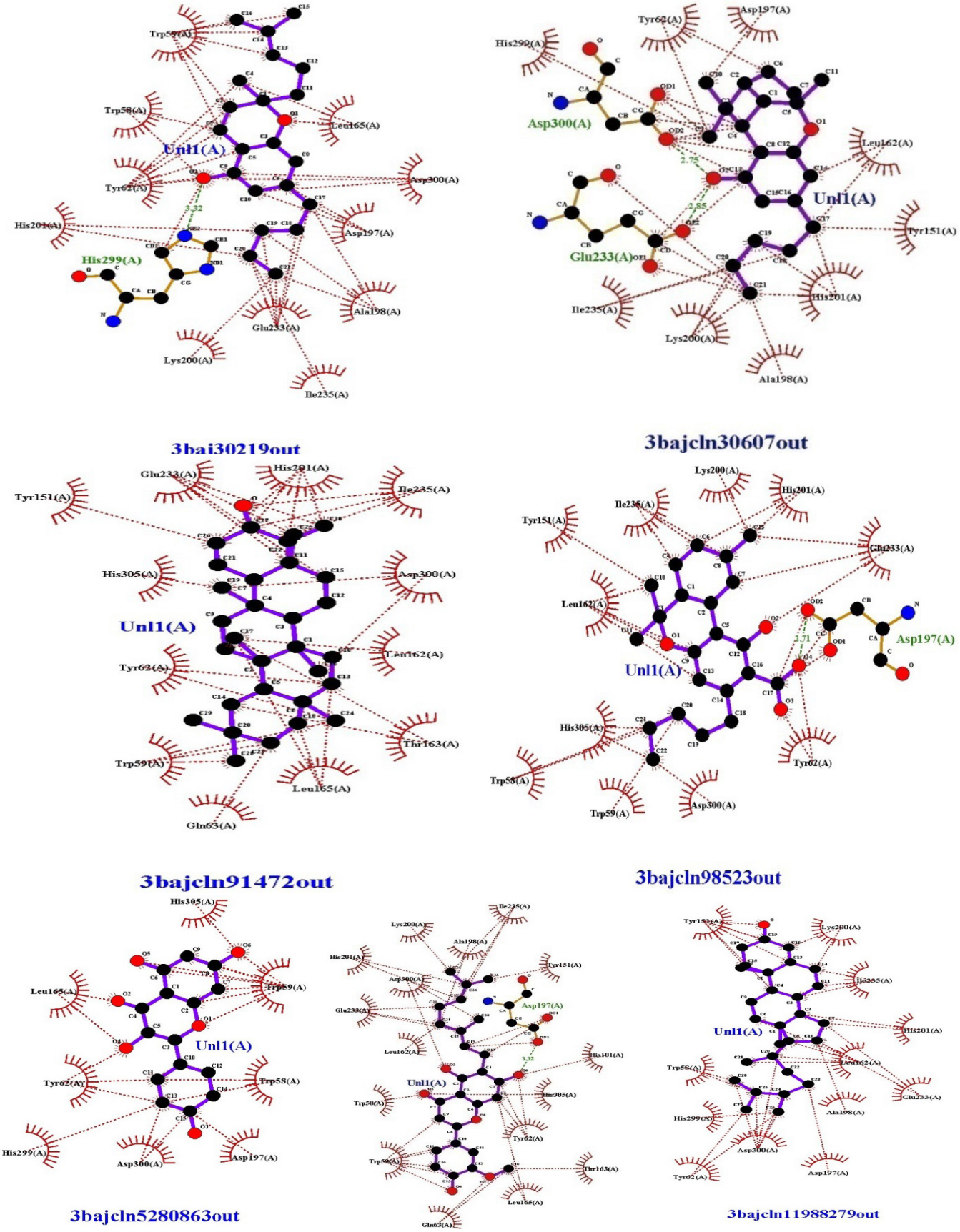


Fig. 4: Hydrogen and Hydrophobic Bonds with Selective A.A. Residue of Protein by LIGPLOT+ **Version v.2.2.7**

Table 4: ADME properties of selected Phytochemicals

S. No.	*Phytochemical name*	*Bioavailability score*	*Solubility class*	*BBB*	*Glabsorption*	*Water solubility*	*Carcinogenicity (binary)*	*P- glycoprotein Inhibitor*	*Biodegradation*
1.	Cannabichromene 30219	.55	Moderately soluble	+	+	-4.471	-	-	-
2.	Cannabicyclol 30607	.55	Moderately soluble	+	+	-4.233	-	-	-
3.	Friedelin 91472	.55	Poorly soluble	+	+	-3.997	-	-	-
4.	delta(9)-Tetrahydrocannabinolic acid 98523	.85	Poorly soluble	+	+	-4.135	-	-	-
5.	Kaempferol 5280863	.55	soluble	-	+	-3.142	-	-	-
6.	Cannflavin A 10071695	.55	Poorly soluble	-	+	-4.489	-	+	-
7.	Campest-4-en-3-one 11988279	.55	Poorly soluble	+	+	-4.28	-	+	-

Lipinski's rule of five of 10 ligands. Lipinski's rule of five is maintained for the majority of ligands based on drug likeliness evaluation. An orally active medication has no more than one criterion violation. The compound that follows the criteria in this investigation indicates that they have good oral bioavailability. Both rules are useful for characterizing the molecular features of medicinal compounds that are needed to estimate critical pharmacokinetic parameters like absorption, distribution, metabolism, excretion, and toxicity (ADMET). These processs are helpful in medication development and design Stein *et al.* (2013) (Table 4). The IMPPAT and admet SAR server was used to estimate drug similarity and molecular properties

Ligplot v.2.2.7 is used to show various hydrogen and hydrophobic interaction between selected phytochemicals and different amino acids (AA) residues of the target protein (Fig. 4).

Results

Computational docking is a powerful method for learning about manufactured compounds and their interactions with biological therapeutic targets, which is crucial in drug development. The amino acids in the active site region of the target protein were predicted using the Molecular Docking program. The phytochemicals and target protein interaction screening were scored using a knowledge-based approach. During docking, there are 10 phytochemicals that showed the best affinity with ARE protein. When drug-likeness and ADME properties of these phytochemicals were checked by different software and online tools, we got 7 eligible phytochemicals that follow the Lipinski and 3 phytochemicals that follow both the Lipinski and Muegge rules.

Conclusion

Understanding the interaction between protein and phytochemicals(ligands) is important for the pharmaceutical and food industries. Bioinformatics has offered a platform to explore disease at the molecular level using computational tools. According to the docking interpretation, chosen phytochemicals may establish conventional hydrogen bonds and hydrophobic bonds with various residues to interact effectively with a selected target protein. This docking procedure shows that 7 phytochemicals-Cannabichromene (30219), Cannabicyclol (30607), Friedelin (91472), delta(9)-Tetrahydrocannabinolic acid (98523), Kaempferol 5280863, Cannflavin A(10071695), Campest-4-en-3-one(11988279) have a great affinity with DM target protein BAJ. However, the mechanisms associated with these effects need further investigation, but computer-based drug designing plays a significant role in structural-based drug designing. The results of molecular docking are an important and potential tool for the pharmacophore model which is used catalytic activity of the enzyme because docking had a high affinity and nearby to the active site pocket of alpha-amylase.

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Auther Contributions

Arti chauhan and Priyanka Sharma both wrote the paper and prepared result after using different software. Anjala Durgapal and Subhash Chandra both made correction in the paper writing, style and checked the results.

Conflict of Interest

None

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