OPEN ACCESS
Scholars International Journal of Traditional and Complementary Medicine
Abbreviated Key Title: Sch Int J Tradit Complement Med
ISSN 2616-8634 (Print) |ISSN 2617-3891 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

Molecular Screening, Docking and DFT Study of Phytochemicals from *Sesbania grandiflora* against HER 2 Protein of Oral Cancer

Chandra Sekhar Tripathy[1], Dr. Santosh Kumar Behera[2*]

[1]M.Sc., Regional Institute of Education, NCERT, Bhubaneswar, Odisha, India
[2]Ph.D., Scientist Grade II, National Institute of Pharmaceutical Education and Research, Ahmedabad, Gujarat, India

DOI: 10.36348/sijtcm.2022.v05i10.003 | **Received:** 14.10.2022 | **Accepted:** 21.11.2022 | **Published:** 25.11.2022

***Corresponding author:** Dr. Santosh Kumar Behera
Ph.D., Scientist Grade II, National Institute of Pharmaceutical Education and Research, Ahmedabad, Gujarat, India

Abstract

The most frequent type of head and neck cancer is oral cancer (mouth cancer). It usually affects adults over the age of 60. Oral cancer affects your lips, the tip of your tongue, and the roof and floor of your mouth. It also affects the oropharynx, which includes the last section of your tongue and the roof of your mouth, as well as your tonsils and the sides and back of your throat. It is getting a global threat. Excess consumption of Tobacco and alcohol are the key factors of Oral cancer. *Sesbania grandiflora* is a medicinal plant found in most of the regions of Asia including India. It is full of medicinal properties. Here, in this investigation 33 reported phyto compounds are taken from *Sesbania grandiflora* and undergone various *in silico* study. Here, the highly expressed HER 2 protein in oral cancer is targeted. The compounds which pass in computation investigation were docked against the HER 2 protein of Oral cancer. The Sativan was found to be the highest binding affinity scoring molecule among phyto selected from this plant and expected to stop the over expression of HER 2 protein and future drug candidate .

Keywords: HER 2 protein, Oral cancer, *Sesbania grandiflora* , future drug candidate, HOMO and LUMO.

INTRODUCTION

Oral cancer is a major public health issue that dental surgeons must deal with. It is among the top ten cancers in terms of incidence, and despite advances in research and therapy, survival has remained stagnant in recent years, posing a constant challenge for biomedical science. Oral cancer is a type of malignant neoplasia that develops on the lips or in the mouth. Because 90% of malignancies in the dental area are histologically generated in squamous cells, it is traditionally characterized as a squamous cell carcinoma (OSCC) [1]. In most ethnic groups, men are two to three times more likely than women to get oral cancer. Cancers of the oral cavity and pharynx are lumped together in global reports and collectively represent the world's sixth most prevalent malignancy. According to the latest reports from the International Agency for Research on Cancer (IARC), annual incidence of oral cancer (ICD-10 code C00-08: Lip, Oral Cavity), which includes the lips, tongue, gingiva, mouth floor, parotid, and salival glands, is higher around the world, with over 300.000 cases diagnosed and 145,000 deaths per year. The most oral cancer occurring areas of the world are South-East Asia and Europe region [2]. Oral cancer is prevalent in South and Southeast Asia (Sri Lanka, India, Pakistan, and Taiwan), Western (France) and Eastern Europe (Hungary, Slovakia, and Slovenia), Latin America and the Caribbean (Brazil, Uruguay, and Puerto Rico), and the Pacific (Brazil, Uruguay, and Puerto Rico) (Papua New Guinea and Melanesia).

Oral cancer is a preventable disease in which significant risk factors such as smoking and alcohol are present in 90% of cases, creating a synergistic impact [3]. "There is enough evidence to prove that snuff smoke is carcinogenic, and that it causes cancer of the oral cavity and pancreas, for example," the IARC found in 2007 [4]. When compared to nonsmokers, smokers have a threefold increased chance of acquiring mouth cancer [5]. When compared to people who have never smoked, the risk of oral cancer is 35 percent lower in people who quit smoking four years ago vs those who continue smoking, and it is not higher in people who have no smoking antecedents for more than 20 years [6]. Those who have never smoked but have been exposed to cigarette smoke (involuntary smoking) have an 87 percent higher risk of oral cancer than those who have never smoked but have not been exposed to cigarette smoke [7]. Cigarette smoke impairs oral immunity by encouraging, periodontitis, and oral cancer

[8]. This smoke contains various cancer-promoting components that can be divided into three categories: nitrosamines, benzopyrenes, and aromatic amines. These compounds are known as pre-carcinogens, and they must be subjected to coordinated oxidative enzymatic changes such that the final product loses electrons and becomes a covalently bonded agent to DNA, resulting in an adduct altered area [9]. Alcohol (ethanol) can be a local as well as a systemic danger factor: increased permeability of the oral mucosa, causing epithelial atrophy and interference with DNA synthesis and repair by dissolving lipid components of the epithelium. It also has genotoxic and mutagenic effects, producing decreased salivary flow, impairing the liver's ability to cope with toxic or potentially carcinogenic substances, and chronic usage is linked to a reduction in innate and acquired immunity, increasing susceptibility to infections and neoplasms [10].

Now a day no satisfactory drug candidate has been identified to cure this disease. In the current study we have used various computational drug discovery techniques to predict out expected drug compounds from natural sources.

One of the proteins involved in the formation and over expressed in oral cancer is HER2 (human epidermal growth factor 2) [11]. The human epidermal growth factor receptor (HER) family of receptors is involved in the development of numerous malignancies in humans. They participate in cellular proliferation and differentiation and govern cell growth, survival, and differentiation via numerous signal transduction pathways. HER-1, HER-2, HER-3, and HER-4, also known as ErbB1, ErbB2, ErbB3, and ErbB4, are the four main members of the family [12]. A cysteine-rich extracellular ligand binding region, a Tran's membrane lipophilic segment, and an intracellular domain with tyrosine kinase catalytic activity are found in all four HER receptors [13]. The HER2 receptor is a 1255-amino-acid, 185-kD Tran's membrane glycoprotein found on human chromosome 17's long arm (17q12) (14). HER2 is expressed in a variety of organs, and its main function in these tissues is to promote uncontrolled cell proliferation and cancer [15]. So, in the current investigation this highly expressed HER2 protein in oral cancer is targeted.

Here for predicting out the drug candidate for the oral cancer therapeutic a plant namely *Sesbania glandiflora* is taken into account. Agathi, also known as *Sesbania grandiflora* L. (Agast), is a tiny, loosely branched legume plant native to India, Indonesia, Malaysia, Myanmar, and the Philippines. It is a member of the *Leguminosae* family. It is closely related to the Australian species *S. formosa*. Agathi is not a commercial crop, and the leaves and blooms are not sold in the same way as other important crops. Agathi is widely grown in India, particularly in Tamil Nadu, Andhra Pradesh, Kerala, Assam, Gujarat, and Bengal. It thrives in hot, humid environments and can quickly spread like weeds. In English, agati sesbania is also known as August flower, Australian corkwood tree, flamingo bill, grandiflora, sesban, swamp pea, tiger tongue, scarlet wisteria tree, vegetable hummingbird, West Indian pea, and white dragon tree.It is also called So dua in Vietnamese, agasti, agati, anari in Sanskrit, agasti, bak, basma, basna, chogache, hatiya in Hindi, agati, agusta, bagphal, bak, bake in Bengali, kacang turi, petai belalang, sesban, sesban getih in Malayalam, agasti in Nepali. In other names in Telugu, Avisi is used; in Oriya, Agastee is used; in Marathi, Heta is used; in Kannada, Agase is used; and in Tamil, agathi, agati, peragathi is used [16]. Antioxidant, antiuroithiatic, anticonvulsive, ant ligament, anti-inflammatory, anthelminthic, antibacterial, and anxiolytic properties are all present in *S. grandiflora*. For rheumatic swelling, powdered roots of this plant are combined with water and used externally as a poultice or massage. Nasal catarrah, nyctalopia, and cephalagia have all been treated with the leaves in the past. *Sesbania grandiflora* leaves may be used as a treatment for thrombosis, diarrhoea, and inflammatory illnesses, as well as a few major bacterial pathogens. Bronchitis, cough, vomiting, sores ulcers, diarrhoea, and dysentery have all been said to be treated using the juice of *S. grandiflora* leaves. Antimicrobial activity has been discovered in the flowers [17]. Looking into such medicinal properties the plant, in this in silico investigation the natural compounds present in this plant collected from various research papers and under gone a computation approach to find out the expected drugs to treat out the Oral cancer.

MATERIAL METHOD

Gene Target Selection of Oral cancer

In Oral cancer cell lines the HER 2(human epidermal growth factor 2) protein is frequently found. The best human derived protein X-ray crystallographic structure is obtained from PDB database [18] with PDB Id 3PP0 having a resolution of 2.25 Å combined with nucleic acids, according to a search in the UniProt database [19] with the entry id P04626, of 1255 base pairs length, mass 137,910 Da. This is the protein that is chosen for this in silico study. The HER2 protein's 3D structure was viewed using Discovery studio visualizer version 2019 [20]. The structure's chain A was chosen for the research.

Prediction of Binding Sites of the HER 2 Protein of Oral Cancer

The binding sites of a protein determine the active sites of molecules where tiny molecules will attach. As a result, the CastP website [21] was utilized to predict the HER 2 protein binding sites that were employed in the study.

Reported Phytocompounds from *Sesbania Grandiflora*

A number of compounds found in *Sesbania grandiflora* have medicinal properties. The phytocompounds' detailed information was retrieved using the PubChem database [22].

Lipinski Rule of Five, ADME Profiling, Toxicity Studies and Probable Side Effects of Phytocompounds

Lipinski Rule of Five

According to Lipinski's Rule of Five (Lipinski CA, 2004), an orally active medicine/drug must match the following criteria: molecular mass (<=500 D), logP (<=5), hydrogen bond donor (<=5), hydrogen bond acceptors (<=10), and molar refractivity (40-130). Any rule violation disqualifies a molecule from being classified as a drug. Lipinski Rule of Five – SCFBio (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) was employed to predict the Lipinski's Rule of Five.

ADME Profiling

The pharmacokinetic properties of the ligands were checked using pkCSM (http://biosig.unimelb.edu.au/pkcsm/) (23), which was used to shortlist the compounds based on the consensus results. Similar modules were utilized in all of the web servers to examine relevant medicinal features, such as BBB (Blood Brain Barrier) penetration, Caco2 cell permeability, and HIA (Human intestinal absorption). The compounds that met the criteria were then tested for drug potential and toxicity.

Toxicity

The ligands/compounds were processed using Lipinski's Rule of Five, and ADME was then tested for toxicity using Protox-II (https://tox-new.charite.de/protox II/) [24] and Toxicity Checker (https://mcule.com/apps/toxicity-checker/) [25]. The default settings were used in all of the tools.

Probable Side Effects of Phytocompounds

The drugs which completely satisfy the Lipinski's Rule of 5, ADME profiling and found to be non-toxic in nature are finally studied through ADVERpred Webserver (http://www.way2drug.com/adverpred/) (26) to predict out probable side effects of the Drugs along with commercially used drug Fluorouracil [27].

Molecular Docking Using Auto Dock 4.2 Tool

In this investigation, the AutoDock 4.2 tool [28] was used to conduct a molecular docking analysis of four screened compounds and one commercially available medicine (fluorouracil) against the HER2 protein in oral cancer as a test and benchmark comparison. Using ADT v.1.5, Kollman charges were assigned to the protein, followed by Gasteiger partial charges to the above-mentioned inhibitors. The grid's dimensions and spacing are as follows: x- centering: 16.403, y-centering: 17.491, and z-centering: 30.11. For further investigation, protein-ligand complexes with higher binding energy values, intermolecular hydrogen (H)-bonds, and ligand efficiency were chosen. The Discovery studio tool was used to show the presence of intermolecular interactions between protein–ligand complexes.

DFT Analysis

A quantum computational analysis was conducted using the notion of Density Functional Theory (DFT) to determine the reactivity and efficacy of the possible ligands used in this investigation. The Becke, 3-parameter, LeeYang- Parr (B3LYP) correlation function of density functional theory was used to study reactivity and efficiency (DFT) [29]. DFT analysis was used to assess the maximum occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies of the ligand molecules that showed improved binding affinity coupled with fluorouracil (standard) with inhibitory activity against the HER2 protein. The energy was calculated using the ORCA Program version 4.0 [30]. Potential medicines' electronic energy, HOMOs, LUMOs, gap energy, and dipole moment were all measured.

RESULT

Selected Gene of Oral Cancer Study

In the current study, a highly expressed oral cancer protein namely HER 2 protein selected. From PDB database its structure was downloaded with pdb id 3PP0. The structure was then visualized under the Discovery studio tool. Here, the unwanted present molecules like water molecules and drug attached with it were removed first. Then the Chain A was selected for the study.

Predicted Binding Sites of the HER 2 Protein of Oral Cancer

The CastP web server was used to predict out the binding sites of the HER 2protein of oral cancer. Here, Chain A of the HER 2 protein selected for the study was uploaded in the server and it depicted out the binding sites of the HER2 protein. Here , the binding sites are LYS724, LEU726,GLY727, SER728,GLY729, ALA730,PHE731, VAL734,ALA751, LYS753, LEU755, ARG756, THR759, ALA763,GLU766, ILE767, GLU770, ALA771, MET774, SER783, ARG784, LEU785, VAL797, THR798, GLN799, LEU800, MET801, PRO802, TYR803, GLY804,CYS805,ASP808,HIS809,GLU812,ASP845,ARG849,ASN850,LEU852,THR862,ASP863,PHE864,GLY865, LEU866 and ARG868.

Retrieval of Phytocompounds of *Sesbania Grandiflora*

Here, in this study, 33 phytoconstituents of *Sesbania grandiflora* were selected based on the information from various literatures [31-35]. The

structural information for these phytochemical compounds was obtained in Structure Data Format from the PubChem database. In addition, a commercially available drug, fluorouracil (a standard), was retrieved from the PubChem database. The 3D-structures were converted to PDB format using Biovia Discovery Studio 2019 (https://www.3ds.com/products-services/biovia/products/molecular-modeling-simulation/biovia-discovery-studio/). The details of the molecules were listed in the Table 1.

Table 1: Description of Phytochemical compounds present in *Sesbania grandiflora*

SL. No.	Chemical name	Molecular formula	PMID	SMILE ID
1.	Leuco-cyanidin	$C_{15}H_{14}O_7$	71629	C1=CC(=C(C=C1C2C(C(C3=C(C=C(C=C3O2)O)O)O)O)O)O
2.	Cyanidin	$C_{15}H_{11}O_6^+$	128861	C1=CC(=C(C=C1C2=[O+]C3=CC(=CC(=C3C=C2O)O)O)O)O
3.	Oleanolic acid	$C_{30}H_{48}O_3$	10494	CC1(CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)O)C)C)C2C1)C)C(=O)O)C
4.	Kaempferol-3-rutinoside	$C_{27}H_{30}O_{15}$	5318767	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC=C(C=C5)O)O)O)O)O)O)O
5.	3,4,5-Trimethoxyphenol	$C_9H_{12}O_4$	69505	COC1=CC(=CC(=C1OC)OC)O
6.	Erucic acid	$C_{22}H_{42}O_2$	5281116	CCCCCCCCC=CCCCCCCCCCCCC(=O)O
7.	Phytofluene	$C_{40}H_{62}$	6436722	CC(=CCCC(=CCCC(=CCCC(=CC=CC=C(C)C=CC=C(C)CCC=C(C)CCC=C(C)C)C)C)C
8.	2-Furancarboxaldehyde	$C_5H_4O_2$	7362	C1=COC(=C1)C=O
9.	Acrylonitrile	C_3H_3N	7855	C=CC#N
10.	4-methyloxazole	C_4H_5NO	69663	CC1=COC=N1
11.	1-Propanol, 2-methyl-	$C_{10}H_{14}O$	5325937	CC(C)C(C1=CC=CC=C1)O
12.	3-Hexen-2-one, 3,4-dimethyl-	$C_8H_{14}O$	30227	CCC(=C(C)C(=O)C)C
13.	6-Octadecenoic acid,	$C_{19}H_{36}O_2$	5366845	CCCCCCCCCCCC=CCCCCC(=O)OC
14.	3,5-di-t-butyl phenol	$C_{22}H_{27}BrClNO_3$	15521189	CC(C)(C)C1=CC(=CC(=C1O)C(C)(C)C)CC(=O)NC2=C(C(=CC(=C2)Cl)Br)O
15.	Urea	CH_4N_2O	1176	C(=O)(N)N
16.	Hexadecanoicacid	$C_{18}H_{36}O_2$	520159	CCC(C)CCCCCCCCCCCCC(=O)OC
17.	9-hexadecenol	$C_{16}H_{32}O$	5283282	CCCCCCC=CCCCCCCCCO
18.	Dioctyl ester	$C_{24}H_{42}O_6$	6441470	CCCCCCCCOC(=O)C=CC(=O)OCCCCCCCC.CC(=O)OC=C
19.	Vitamin E acetate	$C_{31}H_{52}O_3$	86472	CC1=C(C(=C(C2=C1OC(CC2)(C)CCCC(C)CCCC(C)CCCC(C)C)C)OC(=O)C)C
20.	Malonic acid	$C_3H_4O_4$	867	C(C(=O)O)C(=O)O
21.	kaurenoic acid	$C_{20}H_{30}O_2$	73062	CC12CCCC(C1CCC34C2CCC(C3)C(=C)C4)(C)C(=O)O
22.	lupeol	$C_{30}H_{50}O$	259846	CC(=C)C1CCC2(C1C3CCC4C5(CCC(C(C5CCC4(C3(CC2)C)C)(C)C)O)C)C
23.	stigmast-4-en-3-one	$C_{29}H_{48}O$	5484202	CCC(CCC(C)C1CCC2C1(CCC3C2CCC4=CC(=O)CCC34C)C)C(C)C
24.	stigmasterol	$C_{29}H_{48}O$	5280794	CCC(C=CC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
25..	linoleic acid	$C_{18}H_{32}O_2$	5280450	CCCCCC=CCC=CCCCCCCCC(=O)O
26.	acarbose	$C_{25}H_{43}NO_{18}$	41774	CC1C(C(C(C(O1)OC2C(OC(C(C2O)O)OC3C(OC(C(C3O)O)O)CO)CO)O)O)NC4C=C(C(C(C4O)O)O)CO
27.	catechin	$C_{15}H_{14}O_6$	9064	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O
28.	chlorogenic acid	$C_{16}H_{18}O_9$	1794427	C1C(C(C(CC1(C(=O)O)O)OC(=O)C=CC2=CC(=C(C=C2)O)O)O)O
29.	neochlorogenic acid	$C_{16}H_{18}O_9$	5280633	C1C(C(C(CC1(C(=O)O)O)OC(=O)C=CC2=CC(=C(C=C2)O)O)O)O
30.	isovestitol	$C_{16}H_{16}O_4$	591830	COC1=C(C=CC(=C1)O)C2CC3=C(C=C(C=C3)O)OC2
31.	medicarpin	$C_{16}H_{14}O_4$	336327	COC1=CC2=C(C=C1)C3COC4=C(C3O2)C=CC(=C4)O
32.	sativan	$C_{17}H_{18}O_4$	596401	COC1=CC(=C(C=C1)C2CC3=C(C=C(C=C3)O)OC2)OC
33.	betulinic acid	$C_{30}H_{48}O_3$	64971	CC(=C)C1CCC2(C1C3CCC4C5(CCC(C(C5CCC4(C3(CC2)C)C)(C)C)O)C)C(=O)O

Lipinski Rule of five, ADME Profiling, Toxicity Studies and Probable Side Effects Study

While checking through Lipinski's filter, only 7 phytomolecules pass out of 33 molecules taken for the study. Table 2 represents the results. These 7 molecules further gone for ADME profiling checking to study the pharmacokinetic properties using pkCSM server. The Table 3 represents the results. Then these 7 phyto compounds gone for toxicity checking using the Protox-II server and toxicity checker tool. The compounds which pass through the both the servers gone for further analysis. Table 4 reflects the results. Only molecules like 1-Propanol, 2-methyl, isovestitol, medicarpin and Sativan found to be satisfying all the parameters like the Lipinski's rule of 5, ADME profiling, and non- toxic in nature. Then these compounds were checked through

ADVERpred Webserver to study their probable side effects along with the reported drug fluorouracil. The Table 5 represents the results obtained.

Table 2: Results obtained from Lipinski's Filter

SL. NO	Phytochemical compound	tool	molecular mass(<=500 D)	logP(<=5)	Hydrogen bond donor(<=5)	Hydrogen bond acceptors(<=10)	Molar refractivity(40-130)
1.	Leuco-cyanidin	lipinski filter	306.000000	1.037000	6	7	73.878769
2.	Cyanidin	lipinski filter	287.000000	2.718889	5	6	73.719978
3.	Oleanolic acid	lipinski filter	456.000000	7.233602	2	3	132.681549
4.	Kaempferol-3-rutinoside	lipinski filter	594.000000	-1.584400	9	15	135.830673
5.	3,4,5-Trimethoxyphenol	lipinski filter	184.000000	1.418000	1	4	47.762791
6.	Erucic acid	lipinski filter	338.000000	7.668902	1	2	105.555756
7.	Phytofluene	lipinski filter	542.000000	13.610011	0	0	185.854355
8.	2-Furancarboxaldehyde	lipinski filter	96.000000	1.092100	0	2	24.095499
9.	Acrylonitrile	lipinski filter	53.000000	0.695980	0	1	15.810000
10.	4-methyloxazole	lipinski filter	83.000000	0.983020	0	2	21.239996
11.	1-Propanol, 2-methyl	lipinski filter	150.000000	2.376000	1	1	46.239792
12.	3-Hexen-2-one, 3,4-dimethyl-	lipinski filter	126.000000	2.321800	0	1	39.345989
13.	6-Octadecenoic acid	lipinski filter	282.000000	6.108500	1	2	87.087769
14.	3,5-di-t-butyl phenol	lipinski filter	467.500000	6.289902	3	4	118.657265
15.	Urea	lipinski filter	60.000000	-0.976200	4	3	13.770800
16.	Hexadecanoicacid	lipinski filter	284.000000	5.886701	0	2	86.874969
17.	9-hexadecenol	lipinski filter	240.000000	5.236000	1	1	77.303772
18.	Dioctyl ester	lipinski filter	426.000000	6.043001	0	6	119.772949
19.	Vitamin E acetate	lipinski filter	472.000000	9.059964	0	3	144.035049
20.	Malonic acid	lipinski filter	104.000000	-0.454300	2	4	19.888601
21.	kaurenoic acid	lipinski filter	302.000000	5.040099	1	2	87.445778
22.	lupeol	lipinski filter	426.000000	8.024803	1	1	130.649750
23.	stigmast-4-en-3-one	lipinski filter	412.000000	8.233003	0	1	127.216942
24.	stigmasterol	lipinski filter	412.000000	7.800803	1	1	128.122742
25..	linoleic acid	lipinski filter	280.000000	5.884500	1	2	86.993774
26.	acarbose	lipinski filter	645.000000	-8.564498	14	19	137.735062
27.	catechin	lipinski filter	290.000000	1.546100	5	6	72.622978
28.	chlorogenic acid	lipinski filter	354.000000	-0.645900	6	9	82.518768
29.	neochlorogenic acid	lipinski filter	354.000000	-0.645900	6	9	82.518768
30.	isovestitol	lipinski filter	272.000000	2.825099	2	4	74.705574
31.	medicarpin	lipinski filter	270.000000	3.010499	1	4	72.705780
32.	sativan	lipinski filter	286.000000	3.128099	1	4	79.592773
33.	betulinic acid	lipinski filter	456.000000	7.089501	2	3	132.611557

Table 3: ADMET property of phytochemical compounds using various pkCSM servers

S.N.	Phytocompound	Tool	Caco2 cell permeability	HIA (Human intestinal absorption)	BBB* (Blood Brain Barrier penetration)	Domain
1.	Cyanidin	pkCSM	-0.35 (low Caco2 cell permeability)	87.303 (Highly absorbed)	-1.234 (poorly distributed to the brain)	
		admetSAR 2.0				IN
2.	3,4,5-Trimethoxyphenol	pkCSM	1.249 (High Caco2 cell permeability)	93.738 (Highly absorbed)	-0.198 (poorly distributed to the brain)	
		admetSAR 2.0				IN
3.	1-Propanol, 2-methyl	pkCSM	1.619 (High Caco2 cell permeability)	93.365 (Highly absorbed)	0.474 (readily cross BBB)	
		admetSAR 2.0				IN
4.	catechin	pkCSM	-0.283 (low Caco2 cell permeability)	68.829 (Highly absorbed)	-1.054 (poorly distributed to the brain)	
		admetSAR 2.0				IN
5.	isovestitol	pkCSM	1.199 (High Caco2 cell permeability)	93.564 (Highly absorbed)	0.128 (readily cross BBB)	
		admetSAR 2.0				IN
6.	medicarpin	pkCSM	1.246 (High Caco2 cell permeability)	95.188 (Highly absorbed)	0.324 (readily cross BBB)	
		admetSAR 2.0				IN
7.	sativan	pkCSM	1.28(High Caco2 cell permeability)	93.206 (Highly absorbed)	-0.052 (poorly distributed to the brain)	
		admetSAR 2.0				IN

Table 4: Toxicity Checking the Phtocompounds

S.N.	Phytocompound	Tools	Toxic/Non-Toxic
1.	Cyanidin	Protox-II	Non-Toxic
		Toxicitychecker	Toxic
2.	3,4,5-Trimethoxyphenol	Protox-II	Non-Toxic
		Toxicitychecker	Toxic
3.	1-Propanol, 2-methyl	Protox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
4.	catechin	Protox-II	Non-Toxic
		Toxicitychecker	Toxic
5.	isovestitol	Protox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
6.	medicarpin	Protox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
7.	sativan	Protox-II	Non-Toxic
		Toxicitychecker	Non-Toxic

Table 5: Analysis of probable side effects of selected phytocompounds and Fluorouracil through ADVERpred Webserver

Compound/drug	Probable activity (Pa)	Probable inactivity (Pi)	Side Effect
1-Propanol, 2-methyl	0.463	0.074	Cardiac failure
	0.394	0.189	Arrhythmia
	0.358	0.292	Hepatotoxicity
	0.347	0.119	Myocardial Infarction
isovestitol	0.435	0.234	Hepatotoxicity
	0.302	0.170	Cardiac failure
medicarpin	0.362	0.220	Arrhythmia
	0.337	0.313	Hepatotoxicity
Sativan	0.452	0.223	Hepatotoxicity
	0.335	0.140	Cardiac failure
Fluorouracil	0.688	0.105	Hepatotoxicity

Molecular Docking

The compounds like 1-Propanol, 2-methyl, isovestitol, medicarpin and Sativan found to be satisfying the pharmaco properties and get docked with the HER2 protein of Oral cancer along with the standard drug fluorouracil. The molecular docking study was performed by using the AutoDock 4.2 tool. The Table 6 represents the results. In the docking study, it was found that, the PCs namely Sativan shows the highest binding affinity of -7.54 kcal/mol, with a ligand efficiency of-0.36, inhibition constant 2.98 µm and forms conventional hydrogen bond with MET801 and ASP863 with average distance of 2.461905Å vis-à-vis the HER2 protein of oral cancer. Isovestitol shows the second highest binding affinity of -7.24 kcal/mol, with an ligand efficiency of -0.36, inhibition constant 4.9 µm and forms an conventional hydrogen bond with MET801 and ASP863 with an Average Distance of 1.8515Å and other 3 (of the 5) follow. Figure 1 (A) represents the 2D-interaction of Sativan with HER2 protein (B) represents the 3D-interaction of Sativan with HER2 protein of Oral Cancer. Figure 2 (A) represents the 2D-interaction of Isovestitol with HER2 protein (B) represents the 3D-interaction of Isovestitol with HER2 protein of Oral Cancer.

Quantum Chemical Calculation

Quantum chemistry was used to investigate the frontier molecular descriptors of Sativan and Fluorouracil (reported drug), such as HOMO and LUMO, gap energy, and dipole moment, due to the relevance of quantum computation (Table 7). The effective reactivity for each compound with a band energy gap (E), i.e. the difference between LUMO and HOMO, was 11.483 eV and 12.51 eV, respectively. Sativan has a higher reactivity than Fluorouracil based on its lowest band energy gap. HOMO energy values were -8.193 eV for Sativan, and -10.146 eV for Fluorouracil. LUMO energy values were 3.290eV for Sativan, and 2.364 eV for Fluorouracil. Figure 3 (A, B) represents the HOMO and LUMO of Sativan. Figure 4(A, B) represents the HOMO and LUMO of Fluorouracil (for comparison).

DFT, HUMO, LUMO, and other parameters are all ion-mediated. Ions have now been identified as being responsible for therapeutic potency, reactivity, and the efficacy spectrum of any compounds [36]. And, in the kinetic pathways of treatments, ions are completely dependent on paramagnetism, including (super-para magnetism) [37]. The smaller the eV value, the smaller the equivalent distance between the anti-body and the antigen, which is clinically observable as more medication delivery in less time and (perhaps) a shorter copulation period. At the clinical level, the ultimate results are critical, especially for a conservative practitioner.

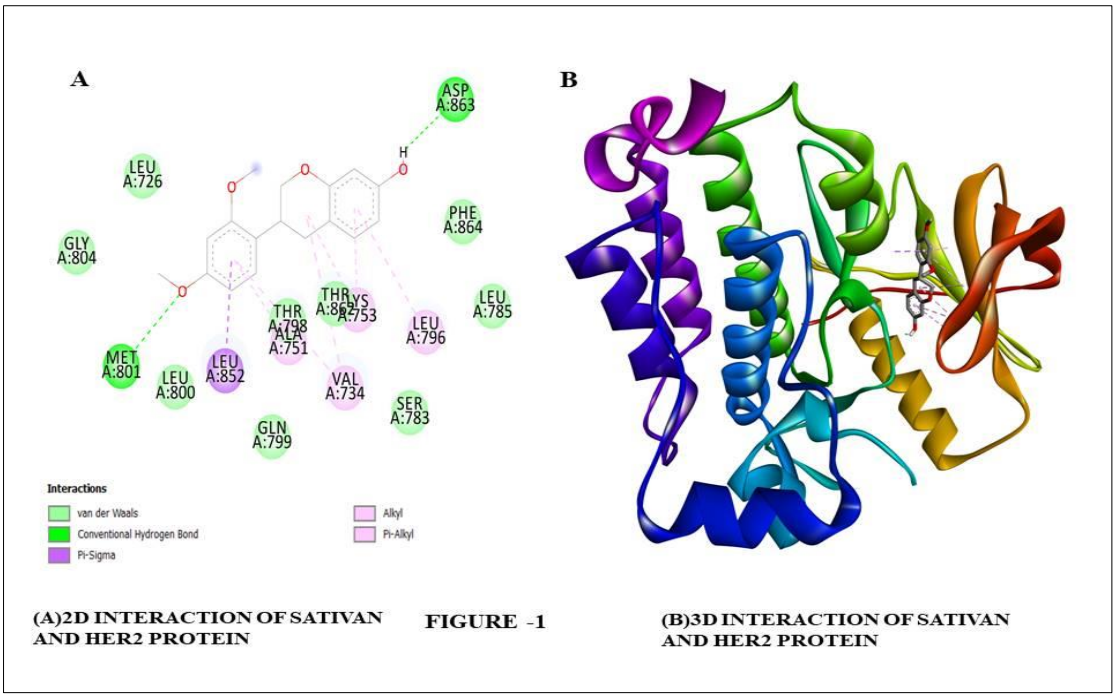

Figure 1: (A) 2d Interaction of Sativan and Her2 Protein (B) 3d Interaction of Sativan and Her2 Protein

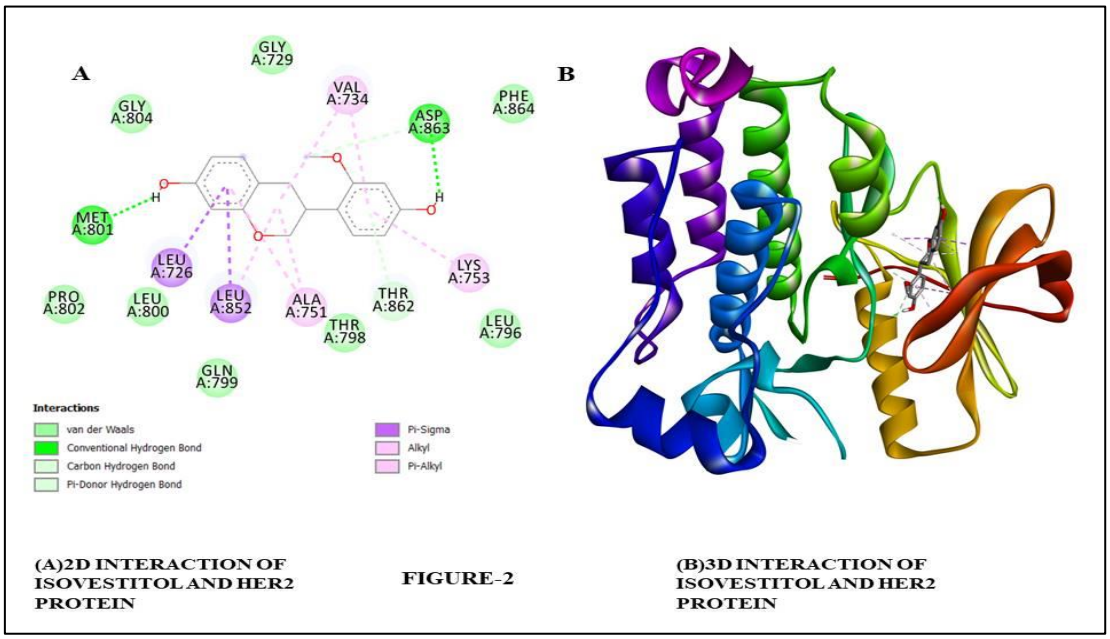

Figure 2: (A) 2d Interaction of Isovestitol and Her2 Protein (B) 3d Interaction of Isovestitol and Her2 Protein

Table 6: Docking of selected Compounds from *Sesbania grandiflora and* Fluorouracil against HER 2 protein over expressed in oral Cancer

Sl. No.	Phytocompound	Binding Energy(kcal/Mol)	Ligand Efficiency	Inhibition Constant (µm)	No. of H Bonds	H-Bond Forming Residues	Average Distance of H-Bonds (Å)
1.	Sativan	-7.54	-0.36	2.98	2	MET801,ASP863	2.461905
2.	isovestitol	-7.24	-0.36	4.9	2	ASP863,MET801	1.8515
3.	medicarpin	-7.13	-0.36	5.96	3	CYS805,THR862,ASP808	2.49203
4.	1-Propanol, 2-methyl	-5.5	-0.5	93.07	1	ASP863	1.80182
5.	Fluorouracil (reported drug in use of Oral cancer)	-3.68	-0.41	2.01	3	THR862,ASP863, SER783	2.4364525

Table 7: HOMO LUMO of selected phytochemical compounds from *Sesbania grandiflora* and Fluorouracil

SL.NO.	Phytochemical name	Electronic Energy(eV)	LUMO(eV)	HOMO(eV)	GAP Energy(eV)	Dipole Moment(Debye)
1.	Sativan	-69928.83870	3.290	-8.193	11.483	2.98754
2.	Fluorouracil	-25854.57652	2.364	-10.146	12.51	4.43516

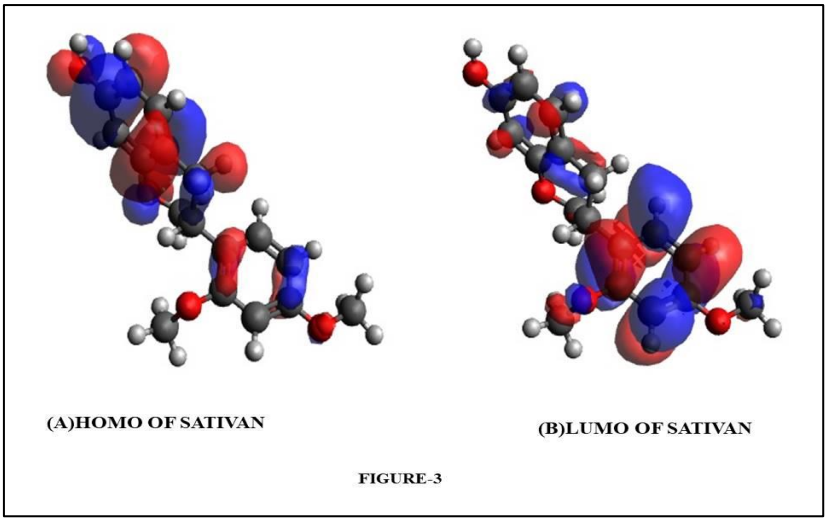

Figure 3: (A) Homo of Sativan (B) Lumo of Sativan

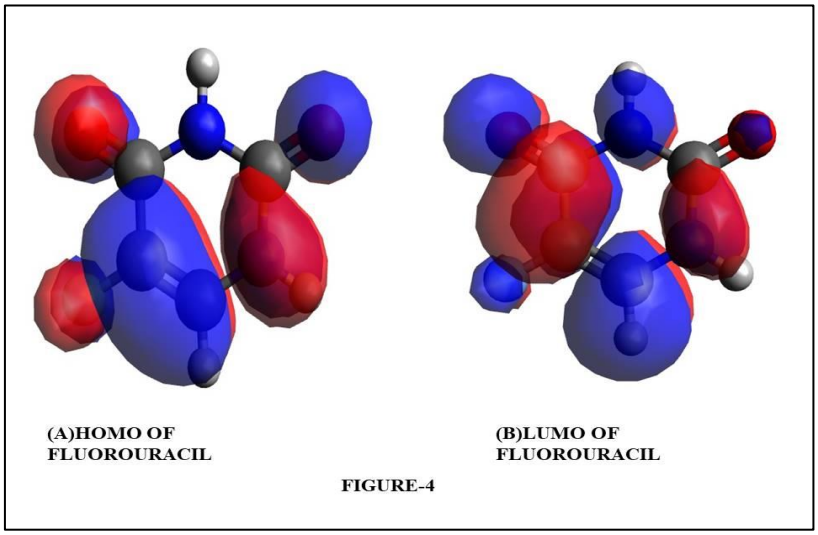

Figure 4: (A) Homo of Fluorouracil (B) Lumo of Fluorouracil

DISCUSSION

In attempt to uncover natural chemicals as lead molecules against various diseases, a vast number of *in silico* studies have lately been conducted. *Sesbania grandiflora* is a medicinal plant bearing number of bioactive constituents having number of clinical importance. Nasal catarrah, nyctalopia, and cephalagia have all been treated with the leaves in the past. S. grandiflora has antioxidant, antiuroithiatic, anticonvulsive, anti-ligament, antiinfammatory, anti-helminthic, antibacterial, and anxiolytic properties, according to studies [38, 39]. Looking into activity of the phytoconstiuents of the plant, in current, around 33 phytochemicals reported of this plant were collected and under gone various in silico investigations. First the reported phyto names were collected. The Table 1 represents it. Here its details are given. Then these phytochemicals studied through Lipinski's rule server to check and find out the phytochemicals which follows the rule of 5 given by Lipinski. Here, only 7 compounds found to be successfully passing the rule of 5 .Table 2 gives the results. Then these 7 molecules under gone pkCSM server to check their pharmacokinetic properties. The Table 3 shows the results. Then the toxicity of the 7 compounds was checked through the Protox-II server and Toxicity checker tool. Here, only 4 compounds found to be non-toxic in nature and gone for further study. Table 4 reviles the results. ADVERpred Webserver was used to predict out the adverse effects of the phytocompounds along with reported drug namely Fluorouracil. The Table 5 depicts out the results. These 4 phyto-compounds and the

reported drug got docked against the HER 2 protein of Oral cancer. In the molecular docking results it was found that, the phyto compound namely Sativan with highest binding affinity of -7.54 kcal/mol, in the other hand reported drug Fluorouracil has only -3.68 kcal/mol binding energy, which is very low in comparison to the Sativan binding affinity against HER 2 protein of oral cancer. Table 6 represents the docking results.

In DFT analysis was carried out to monitor the reactivity of Sativan and Fluorouracil towards KLK12 protein. In this analysis, Sativan showed higher reactivity due to the lowest band energy gap (11.483eV) than Fluorouracil with band energy gap 12.51 eV. In addition, the HOMO and LUMO values of these 2 molecules signified Sativan to be most reactive molecule towards the protein HER2 protein of Oral cancer [40]. Table 7 reflects the DFT results.

CONCLUSION

The current study may be able to reveal the optimal inhibitory affinity of the compounds Sativan against the major protein HER 2 involved in Oral Cancer by taking into account these combinatorial approaches of various *in-silico* analyses. On the basis of drug ability, molecular docking, and DFT studies, these screened compounds were praised. According to the findings, these chemicals could give new routes and methodologies for the development of therapeutic medication candidates for oral cancer. As a result of the findings, it is recommended that candidate compounds be isolated and the lead molecule be synthesised from *Sesbania grandiflora.* Furthermore, these lead compounds can be processed for in-vitro and in-vivo studies to confirm their efficacy and evaluate their anti-cancer potency before moving forward with clinical trials.

DECLARATIONS

Acknowledgement: None

Conflict of Interest: The authors declare no conflict of interest

Source of Funding: This study is non-commercial; not funded; non donor driven.

Ethical issues: None

Author Contribution: C.S. Tripathy designed the work, data collection, writing and bioinformatics analysis and manuscript correction, S. K. Behera, did the writing and bioinformatics analysis work.

REFERENCES

1. Lingen, M. W., Kalmar, J. R., Karrison, T., & Speight, P. M. (2008). Critical evaluation of diagnostic aids for the detection of oral cancer. *Oral oncology*, 44(1), 10-22.
2. Warnakulasuriya, S. (2009). Global epidemiology of oral and oropharyngeal cancer. *Oral oncology*, 45(4-5), 309-316.
3. Dissanayaka, W. L., Pitiyage, G., Kumarasiri, P. V. R., Liyanage, R. L. P. R., Dias, K. D., & Tilakaratne, W. M. (2012). Clinical and histopathologic parameters in survival of oral squamous cell carcinoma. *Oral surgery, oral medicine, oral pathology and oral radiology*, 113(4), 518-525.
4. World Health Organization. (2007). Cancer IAfRo. Smokeless tobacco and some tobacco-specific N-nitrosamines. World Health Organization.
5. Gandini, S., Botteri, E., Iodice, S., Boniol, M., Lowenfels, A. B., Maisonneuve, P., & Boyle, P. (2008). Tobacco smoking and cancer: a meta-analysis. *International journal of cancer*, 122(1), 155-164.
6. Marron, M., Boffetta, P., Zhang, Z. F., Zaridze, D., Wünsch-Filho, V., Winn, D. M., ... & Hashibe, M. (2010). Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. *International journal of epidemiology*, 39(1), 182-196.
7. Lee, Y. C. A., Marron, M., Benhamou, S., Bouchardy, C., Ahrens, W., Pohlabeln, H., ... & Hashibe, M. (2009). Active and involuntary tobacco smoking and upper aerodigestive tract cancer risks in a multicenter case-control study. *Cancer Epidemiology and Prevention Biomarkers*, 18(12), 3353-3361.
8. Lee, J., Taneja, V., & Vassallo, R. (2012). Cigarette smoking and inflammation: cellular and molecular mechanisms. *Journal of dental research*, 91(2), 142-149.
9. Parise Junior, O. (2000). Câncer de boca: aspectos básicos e terapêuticos. In Câncer de boca: aspectos básicos e terapêuticos (pp. 256-256).
10. Reidy, J., McHugh, E., & Stassen, L. F. A. (2011). A review of the relationship between alcohol and oral cancer. *The surgeon*, 9(5), 278-283.
11. Arun, K., Sharmila, R., Akila, K., & Jaikumar, B. (2016). In-silico approach for the assessment of oral cancer property on Limonia acidissima. *International Journal of Pharmaceutical Sciences and Research (IJPSR)*, 7(3), 1271-1275.
12. Riese, D. J., & Stern, D. F. (1998). Specificity within the EGF family/ErbB receptor family signaling network. *Bioessays*, 20(1), 41-48.
13. van der Geer, P., Hunter, T., & Lindberg, R. A. (1994). Receptor protein-tyrosine kinases and their signal transduction pathways. *Annual review of cell biology*, 10(1), 251-337.
14. Brandt-Rauf, P. W., Pincus, M. R., & Carney, W. P. (1994). The c-erbB-2 protein in oncogenesis: molecular structure to molecular epidemiology. *Critical Reviews™ in Oncogenesis*, 5(2-3).
15. Olayioye, M. A. (2001). Intracellular signaling pathways of ErbB2/HER-2 and family members. *Breast cancer research*, 3(6), 1-5.
16. Karmakar, P., Singh, V., Yadava, R. B., Singh, B., Singh, R., & Kushwaha, M. (2016, February). Agathi [Sesbania grandiflora L.(Agast)]: Current status of production, protection and genetic

improvement. In National symposium on vegetable legumes for soil and human health (pp. 153-161).
17. Mohiuddin, A. K. (2019). Medicinal and therapeutic values of Sesbania grandiflora. *J Pharm Sci Exp Pharmacol*, 2019, 81-86.
18. Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., ...& Bourne, P. E. (2000). The protein data bank. *Nucleic Acids Res*, 28(1), 235-242.
19. Bairoch, A., Apweiler, R., Wu, C. H., Barker, W. C., Boeckmann, B., Ferro, S., ... &Yeh, L. S. L. (2005). The universal protein resource (UniProt). *Nucleic acids research*, 33(suppl_1), D154-D159.
20. Kalathiya, U., Padariya, M., Faktor, J., Coyaud, E., Alfaro, J. A., Fahraeus, R., ...&Goodlett, D. R. (2021). Interfaces with structure dynamics of the workhorses from cells revealed through cross-linking mass spectrometry (CLMS). *Biomolecules*, 11(3), 382.
21. Binkowski, T. A., Naghibzadeh, S., & Liang, J. (2003). CASTp: computed atlas of surface topography of proteins. *Nucleic acids research*, 31(13), 3352-3355.
22. Kim, S., Thiessen, P. A., Bolton, E. E., Chen, J., Fu, G., Gindulyte, A., ... & Bryant, S. H. (2016). PubChem substance and compound databases. *Nucleic acids research*, 44(D1), D1202-D1213.
23. Pires, D. E., Blundell, T. L., & Ascher, D. B. (2015). pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *Journal of medicinal chemistry*, 58(9), 4066-4072.
24. Banerjee, P., Eckert, A. O., Schrey, A. K., & Preissner, R. (2018). ProTox-II: a webserver for the prediction of toxicity of chemicals. *Nucleic acids research*, 46(W1), W257-W263.
25. Kiss, R., Sandor, M., & Szalai, F. A. (2012). http://Mcule. com: a public web service for drug discovery. *Journal of cheminformatics*, 4(1), 1-1.
26. Ivanov, S. M., Lagunin, A. A., Rudik, A. V., Filimonov, D. A., & Poroikov, V. V. (2018). ADVERPred–Web service for prediction of adverse effects of drugs. *Journal of Chemical Information and Modeling*, 58(1), 8-11.
27. Italo Giannola, L., De Caro, V., Giandalia, G., Gabriella Siragusa, M., Paderni, C., Campisi, G., & Maria Florena, A. (2010). 5-Fluorouracil buccal tablets for locoregional chemotherapy of oral squamous cell carcinoma: formulation, drug release and histological effects on reconstituted human oral epithelium and porcine buccal mucosa. *Current drug delivery*, 7(2), 109-117.
28. Ravi, L., & Kannabiran, K. (2016). A Handbook on Protein-Ligand Docking Tool: Auto Dock 4. *Innovare Journal of Medical Sciences*, 28-33.
29. Gill, P. M., Johnson, B. G., Pople, J. A., & Frisch, M. J. (1992). The performance of the Becke—Lee—Yang—Parr (B—LYP) density functional theory with various basis sets. *Chemical Physics Letters*, *197*(4-5), 499-505.
30. Neese, F. (2012). The ORCA program system. Wiley Interdisciplinary Reviews: *Computational Molecular Science*, 2(1), 73-78.
31. Wagh, V. D., Wagh, K. V., Tandale, Y. N., & Salve, S. A. (2009). Phytochemical, pharmacological and phytopharmaceutics aspects of Sesbania grandiflora (Hadga): A review. *Journal of Pharmacy Research*, 2(5), 889-892.
32. Hussain, A. Z., & Kumaresan, S. (2014). GC-MS studies and phytochemical screening of Sesbania grandiflora L. *J. Chem. Pharm. Res*, 6(9), 43-47.
33. Afrin, S., Sohrab, M., & Ahmed, M. (2019). Terpenoids and steroids from the stem bark of Sesbania grandiflora and biological studies of the plant extracts. *Pharmacy & Pharmacology International Journal*, 7(6), 307-313.
34. Baessa, M., Rodrigues, M. J., Pereira, C., Santos, T., da Rosa Neng, N., Nogueira, J. M. F., ... & Custódio, L. (2019). A comparative study of the in vitro enzyme inhibitory and antioxidant activities of Butea monosperma (Lam.) Taub. and Sesbania grandiflora (L.) Poiret from Pakistan: New sources of natural products for public health problems. *South African Journal of Botany*, 120, 146-156.
35. Hasan, N., Osman, H., Mohamad, S., Chong, W. K., Awang, K., & Zahariluddin, A. S. M. (2012). The chemical components of Sesbania grandiflora root and their antituberculosis activity. *Pharmaceuticals*, 5(8), 882-889.
36. Bhattacharya Deepak, (2007). Tannins, Ions, Cations & Malariasis: Observations & Theory. *American Journal of Tropical Medicine and Hygiene*, 77(5), 27.
37. Inyushin, M., Kucheryavih, Y., Kucheryavih, L., Rojas, L., Khmelinskii, I., & Makarov, V. (2016). Superparamagnetic properties of hemozoin. *Scientific reports*, 6(1), 1-9.
38. Gomase, P. V. (2012). Sesbania sesban Linn: a review on its ethnobotany, phytochemical and pharmacological profile. *Asian journal of biomedical and pharmaceutical sciences*, 2(12), 11.
39. China, R., Mukherjee, S., Sen, S., Bose, S., Datta, S., Koley, H., ... & Dhar, P. (2012). Antimicrobial activity of Sesbania grandiflora flower polyphenol extracts on some pathogenic bacteria and growth stimulatory effect on the probiotic organism Lactobacillus acidophilus. *Microbiological Research*, 167(8), 500-506.
40. Kumar, C. C., Panicker, C. Y., Fun, H. K., Mary, Y. S., Harikumar, B., Chandraju, S., ... & Ooi, C. W. (2014). FT-IR, molecular structure, first order hyperpolarizability, HOMO and LUMO analysis, MEP and NBO analysis of 2-(4-chlorophenyl)-2-oxoethyl 3-nitrobenzoate. Spectrochimica Acta Part A: *Molecular and Biomolecular Spectroscopy*, 126, 208-219.