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IN-VITRO AND *IN-SILICO* STUDIES ON SELECTED PHYTOCONSTITUENTS OF *MITRAGYNA PARVIFOLIA* (ROXB.) STEM BARK FOR ANTI-CANCER ACTIVITY

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Keywords:

Mitragyna parvifolia, MTT assay, GC-MS, Molecular docking, *In-silico* study

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ABSTRACT: Cancer is a dreadful disease all over the world. The death rate had been increasing because of different types of cancers even though several drugs, treatment models and regimens are invented by scientists. Natural drugs have been showing remarkable results in the treatment of different cancers with less or no side effects. Advancements in screening methods using computer aided tools helping the researchers to discover new phytochemicals with prominent and specific activity against different diseases. The objective of the present study was to evaluate the anti-cancer potential of dichloromethane extract of *Mitragyna parvifolia* stem bark using MTT assay and molecular docking studies. MTT assay was performed on MCF7, A549 and HepG2 cell lines. IC_{50} values were found to be 402.8 µg/ml, 207.4µg/ml and 104.4µg/ml, respectively. The phytoconstituents of extract were determined by GC-MS GC-MS analysis, most probable structures were identified and named using NIST library. GC-MS study revealed 76 compounds in which acontanes, decenes, and decanoicacids are of maximum percentage. A molecular docking study was conducted on the selected compounds by choosing respective anti-cancer drug target proteins, VEGFR 2 kinase (lung cancer), (breast cancer) and EGFR kinase (liver cancer) using autodockvina. In the docking study, the binding energy and interactions of steroidal derivatives were comparable to those of standards (Sorafenib, SYR, and Erlotinib), indicating remarkable anti-cancer activity of the extract.

INTRODUCTION: Plants serving the human race from the start of life on the earth for food, shelter, and wellbeing. The treaties on medicinal uses of plants written by our ancestors had been revealing the innumerable applications of the plants to treat many diseases.

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The knowledge on medicinal plants transferred by tribes orally also had been paving the way to discover new lead molecules [1, 2]. Natural drugs are becoming alternatives to synthetic drugs for many chronic and life-threatening diseases all over the world [3, 4].

The emerging techniques in the field of identification, standardization, ADME evaluation providing assurance regarding the safety and efficacy of natural drugs and hence acceptance to natural source derived medicines had been increasing worldwide [5, 6]. Cancer is attacking any part of the body irrespective of age and gender. The

number of is rising globally and treatment is a panic financial burden to all classes of society [7]. Still, there is a necessity to discover or invent specific treatments to treat various cancers.

Mitragyna parvifolia leaves were used by folklore people to treat jaundice, fever, muscular pain, colic pain, wounds, ulcers, *etc*. Bark used in the treatment of rheumatic pain, burning sensation, poisoning cases, gynaecological disorders, cough and oedema. Roots were also used in similar disorders like barks. Fruit juice used to given to lactating mothers and reported to possess lactodepurant property. The tree is rich in bioactive phytoconstituents like alkaloids, glycosides, flavonoids, terpenoids *etc*. A wide spectrum of pharmacological activities, anti-oxidant, anti-proliferative, anti-microbial, anti-convulsant, anti-helmintic, anti-inflammatory, anti-nociceptive, anti-diabetic, anxiloytic, anti-arthritic, anti-pyretic, *etc*. have been carried out by the researchers [8, 9]. The Phytochemistry of the tree provides still many opportunities to study the medicinal potential of the phytoconstituents using latest pharmacokinetic and bioinformatics tools [10, 11]. So, the present research study aimed to prove the specific anti-cancer potential of *Mitragyna parvifolia* stem bark extract using molecular docking technique.

MATERIALS AND METHODS:

Collection and Identification of Plant: *Mitragyna parvifolia* stem bark was collected near boy's hostel 'B' in Osmania University campus and shade dried for two weeks. A voucher specimen containing leaves and flowers was prepared and preserved in the department of Pharmacognosy, G. Pulla Reddy College of Pharmacy. The plant was identified and authenticated by P. V. Prasanna, Scientist 'F' at Botanical Survey of India, regional, Attapur, Hyderabad, Telangana.

Reagents and Chemicals: Solvents, n-Hexane and Dichloromethane, precoated TLC plates purchased from Sri Venkateshwara Scientific Suppliers, Hyderabad. Alcohol (RS) procured through central excise department, Telangana state govt.

Extraction: The dried bark was powdered and stored in well-closed containers. Successive solvent extraction was carried out using n-Hexane, Dichloromethane, and 80% Alcohol in soxhlet apparatus *i.e.*, hot percolation method. Solvent recovered from extracts in the flash evaporator and was dried under vacuum. The weight, colour, and consistency of the extracts were noted and the extracts were stored in a dessicator.

Phytochemical Screening and TLC: All the extracts were subjected to phytochemical screening and observations were noted. TLC was performed for the three extracts in different solvent systems with increasing order of polarity and the spots were were observed under short UV and long UV light. Then, sprayed with vanillin sulphuric acid reagent, over hot plate and the observed spots were interpreted as per literature.

MTT Assay: The cytotoxic potential of MPDME (*Mitragyna parvifolia* Dichloromethane Extract) was evaluated on MCF7, HepG2, and A549 cell lines. It is a colorimetric assay that measures the reduction of yellow 3-(4, 5-dimethythiazol- 2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase.

The MTT Assay was performed with five concentrations of extract in triplicates on HepG2 and A549 cells whereas 4 on MCF-7 cells. Cells were trypsinized and performed the tryphan blue assay to know viable cells in cell suspension. Cells were counted by haemocytometer and seeded at a density of 5.0 X 10^3 cells/well in 100 µl media in 96 well plate culture medium and incubated overnight at 37 ºC.

After incubation, old media was removed, and 100 µl of fresh media was added with different concentrations of the test compound in represented wells in 96 plates. After 48 h, the drug solution was discarded. Fresh medium and MTT solution (0.5 mg / mL^{-1}) was added to each well and plates were incubated at 37 ºC for 3 h. At the end of incubation time, precipitates were formed as a result of the reduction of the MTT salt to chromophore formazan crystals by the cells with metabolically active mitochondria. The optical density of solubilized crystals in DMSO was measured at 570 nm on a microplate reader. The percentage growth inhibition was calculated using the following formula.

% Inhibition = 100 (Control – Treatment) / Control

The IC_{50} values were determined by using linear regression equation *i.e.*

$$Y = mx + C,$$

Here, Y = 50, m and C values are derived from the %viability graph [12].

Characterization of MPDME by GC-MS Analysis: GC-MS analysis of the extract was performed at Skanda Life Sciences, Bangalore, Karnataka. 10 mg of MPDME was reconstituted in 1000 µL methanol. 1.0 µl of this extract was injected into Agilent DB 5MS (30 meter X 0.25 mm) column fitted to thermo scientific GC trace 1310 instrument equipped with thermo scientific MS TSQ 8000.The temperature of ion source maintained at 230 °C and that of transfer line at 300 °C. EI mode of ionization method used to generate ions.

Helium was used as carrier gas at flow rate of 1 ml/min. An initial temperature of 60 °C maintained for 5min and then raised to 240 °C at a rate of 10 °C/min and held at the same temperature for 5 min. Then, raised to 300 °C at a rate of 10 °C/min and held for 5 min. The mass of the compounds and fragments recorded and chromatograms were obtained. The mass spectrum of the unknown component was compared with that of the known components stored in the NIST library, then names and structures were assigned [13, 14].

***In-silico* Studies:** Total nine molecular structures have been selected from the GC MS data and their 3d structures were drawn using Marvin sketch 3d tool and the energies were minimized. These 3D structures were used for the *in-silico* studies on three anti-cancer drug targets, VEGFR 2 kinase (lung cancer), ErbB2 Kinase (breast cancer) and EGFR kinase (liver cancer). Auto dock was employed to dock the 3D molecules into the active site of three target proteins.

The docking methodology followed according to the earlier published procedure. The protein structure of VEGFR-2 PDBID: 4asd was downloaded from the protein data bank along with co-crystal ligand Sorafenib BAY 43-9006. From the ligand water molecules were removed, charges were added to the refined protein and its PDBQT file was created.

The docking procedure was performed in the active site by defining the 3D grid coordinates in X, Y and Z axes with grid dimensions -25.93, -1.63 and -10.66, respectively with grid points 50-50-50. The docking was performed for all the molecules using the Lamarckian Genetic Algorithm for upto 10 successful runs, and the final docking scores in terms of binding energies (kcal/mole) were noted.

The binding energies of molecules were compared with the standard Sorafenib to identify potential anti-cancer molecules against lung cancer. Similarly, the protein structures of Human HER2 erbB2)-PDBID: 3PP0; EGFR tyrosine kinase domain-PDBID: 4hjo and their co-crystal ligand, SYR and Erlotinib were downloaded from protein databank.

The active site of the Human protein HER2 (erb2)-PDBID3PP0 was defined by X, Y and Z axes with grid dimensions-16.387, 17.394 and 26.218 respectively and with grid points 50-50-50. After docking, binding energies, binding poses of best-docked confirmations, and docking interactions were recorded for test compounds and compared with that of standard. Molecular docking studies also performed on EGFR2 Kinase (4jho).

Erlotinib has taken as standard and all the selected compounds docked into the active site of EGFR2 using the same procedure described above. The grid dimensions selected were 25.53, 10.5, -0.75 for X, Y, Z axes, respectively to define the active site on the target [15, 16, 17].

RESULTS AND DISCUSSION: Phytochemical screening of the n-Hexane extract (MPNHE) shown positive test results for the presence of alkaloids, glycosides, carbohydrates, steroids and tannins. The dichloromethane extract (MPDME) and hydro alcoholic extract (MPHAE) revealed the presence of alkaloids, glycosides, carbohydrates, terpenoids, steroids and tannins. MPHAE also had shown positive result for flavonoids.

TLC profile of MPDME with vanillin sulphuric acid reagent has shown yellow, pink purple and blue spots. 5spots observed in 90:10, 80:20, whereas 3 spots observed in 50:50 20:80 ratios of dichloromethane and ethyl acetate solvent system as shown in **Fig. 1**.

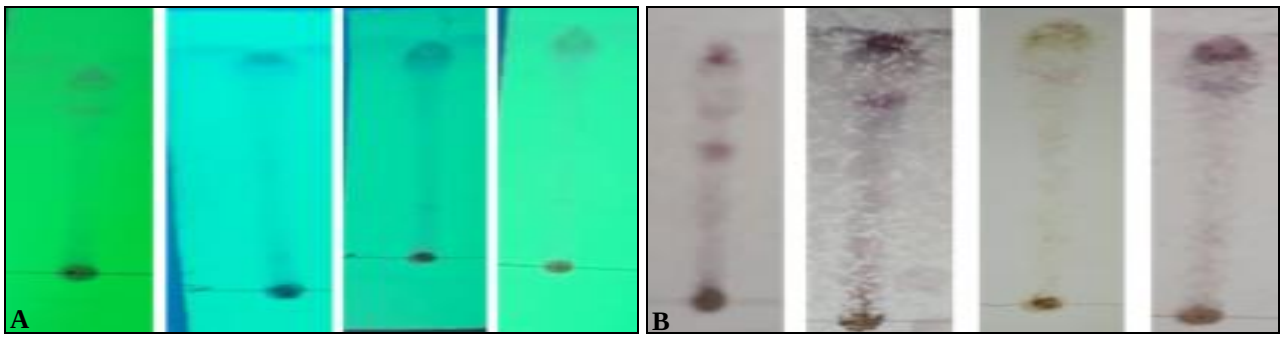


FIG. 1: TLC PROFILE OF MPDME IN DICHLOROMETHANE AND ETHY ACETATE SOLVENT SYSYTEM, A: Under short UV light, B: derivatization with vanillin sulphuric acid

TLC revealed the presence of a considerable number of steroidal and terpenoid compounds in the extract. Hence, it was assumed to possess good cytotoxic potential according to literature and hence MTT assay was carried out on MPDME.

TABLE 1: MTT ASSAY OF MPDME ON MCF-7 CELL LINE

MPDME Conc.(µg/ml)	Absorbance at 570 nm*	% Inhibition	% Viability	IC_{50} Value (µg/ml)
50	3.02	0.658	99.392	402.877
100	2.785	8.388	91.612	
150	2.588	14.868	85.132	
200	2.378	21.776	78.224	
Untreated	3.040	0	100	
Blank	0	0	0	

*Average of 3 determinations

TABLE 2: MTT ASSAY OF MPDME ON A549 CELL LINE

MPDME Conc.(µg/ml)	Absorbance at 570 nm*	% Inhibition	% Viability	IC_{50} Value (µg/ml)
5	0.361	53.41	46.59	207.39
10	0.239	69.16	30.84	
25	0.187	75.87	24.13	
50	0.209	73.03	26.97	
100	0.365	52.9	47.1	
Untreated	0.775	0	100	
Blank	0	0	0	

*Average of 3 determinations

TABLE 3: MTT ASSAY ON HEPG2 CELL LINE

MPDME Conc.(µg/ml)	Absorbance at 570 nm*	% Inhibition	% Viability	IC_{50} Value (µg/ml)
5	0.526	29.67	70.33	104.26
10	0.291	61.09	38.91	
25	0.243	67.51	32.49	
50	0.248	66.84	33.16	
100	0.391	47.72	52.28	
Untreated	0.748	0	100	
Blank	0	0	0	

*Average of 3 determinations

The IC_{50} values of MPDME on MCF7, A549, and HepG2 cell lines are 402.87, 207.39, and 104.226 µg/ml, respectively, indicating excellent anti-cancer potential of the extract, which can be attributed to the phytoconstituents present in it. The % inhibition of the cells by the extract is also listed in **Tables 1**, **2** and **3**. The MTT assay led to GC-MS analysis of the extract. The GC-MS chromatogram **Fig. 2** has shown decenes, decanoic acids, Phytol, oleic acid, carboxylic acids, esters, acontanes, germanicol, lupenone, betulin, cholesterol, and its derivatives, stigmasterol, and its derivatives. The majority of the compounds are decanoic acids, decenes, and acontanes, as listed in **Table 4**. From the GC-MS analysis of MPDME nine compounds were selected to perform the *in-silico* studies. Molecular docking was carried out on selected anti-cancer targets, EGFR (4hjo), ErbB2 (3 ppo), and VEGFR2 (4asd) using autodockvina software.

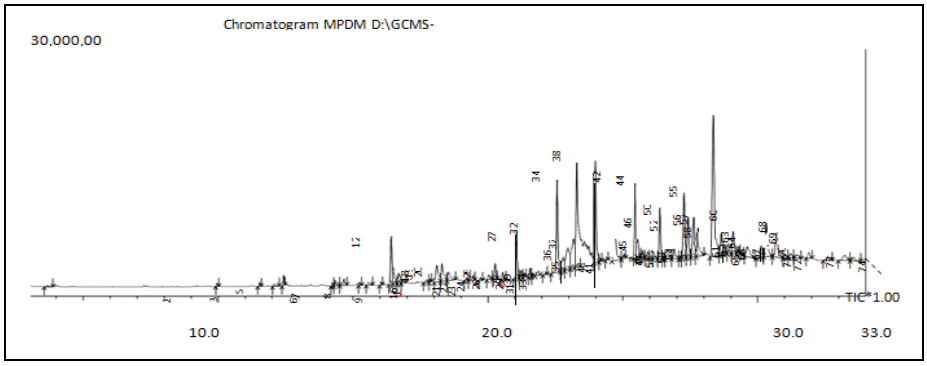


FIG. 2: GC-MS CHROMATOGRAM OF MPDME

TABLE 4: MAJOR COMPOUNDS OBTAINED FROM MPDME IN GC-MS ANALYSIS

S. No.	Name	Retention Time in Minutes	Area%
1	n-Hexadecanoic acid	16.426	2.8
2	Dibutyl phthalate	16.500	1.0
3	Oleic acid	18.105	1.54
4	Octadecanoic acid	18.300	1.65
5	Hexatricontane	21.067	2.17
6	Dotriacontane	22.578	5.15
7	Ergost-5-en-3-ol	27.275	4.23
8	Tetrapentacontane	27.421	2.43
10	Stigmasterol	27.623	2.93
11	2-Heptadecanone	27.792	2.06
12	Gamma sitosterol	28.368	11.21
13	Lupen-3-ol	29.63	1.18
14	Stigmast-4-en-3-one	30.313	2.66
15	2-Triacontanone	30.702	2.02

TABLE 5: MOLECULAR DOCKING STUDY ON SELECTED COMPOUNDS OF MPDME

S. no.	Ligand/Molecule	Binding Energy (Kcal/mole)		
		HER2 (erbB2):3ppo (MCF7 cells-Breast cancer)	**VEGFR2 kinase:4asd** (A-549Cells-lung cancer)	**EGFR kinase:4hjo** (HepG2Cells- liver cancer).
1	SYR (Standard)	-10.74	----------	------
2	Sorafenib	-------	-12.5	------
3	Erlotinib	------	---------	-8.2
4	Gamma sitosterol	-11.47	-14.3	-12.2
5	Stigmast-4-en-one	-12.28	-8.0	-8.7
6	Ergost-5-ene-3-ol	-10.79	-8.2	-7.6
7	2-Heptadecanone	-6.55	-6.3	-6.6
8	Hexadecanoic acid	-7.31	-8.4	-8.5
9	Tricosenoic acid	-7.05	-7.3	-6.3
10	Dotriacontane	-6.80	-7.2	-6.3
11	Tetrapentacontane	-6.54	-6.9	-5.8
12	Nonadecene	-6.56	-6.6	-5.8

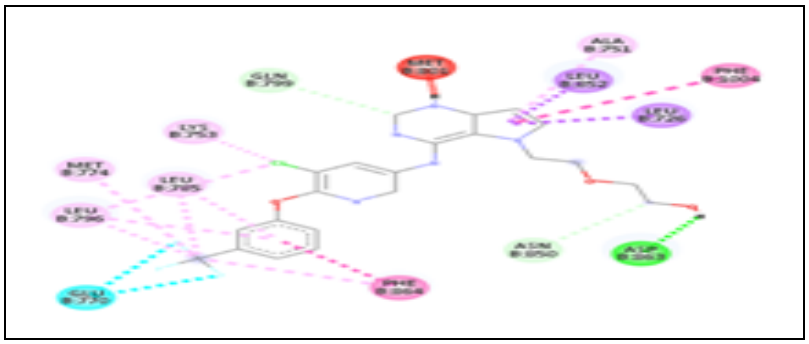
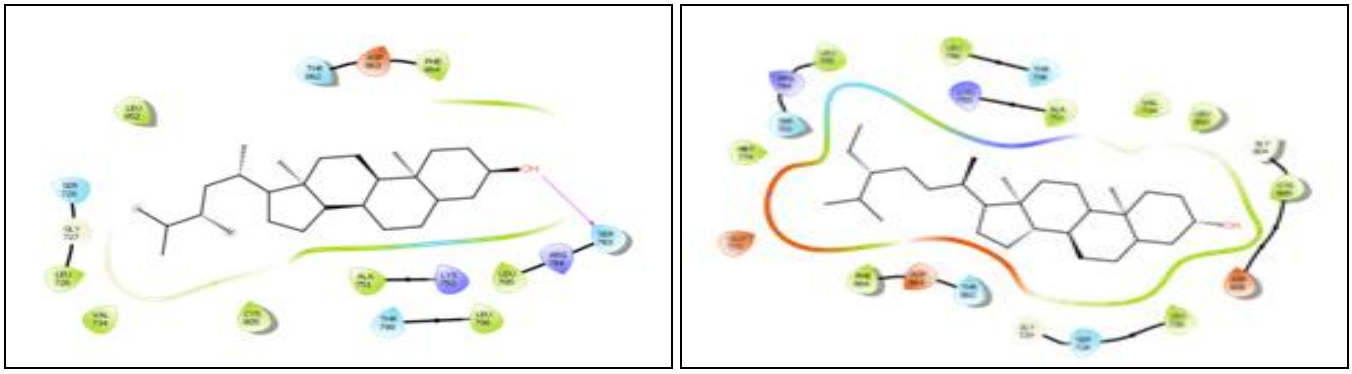
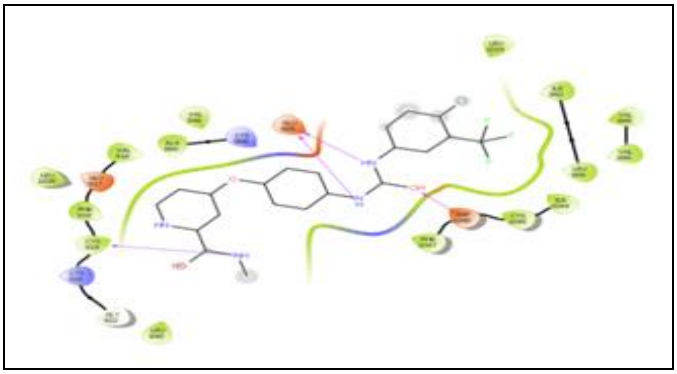


FIG. 3: 2D INTERACTIONS OF SYR ACTIVE CO-CRYSTAL LIGAND WITH THE ACTIVE SITE OF HUMAN HER2 (ERBB2)

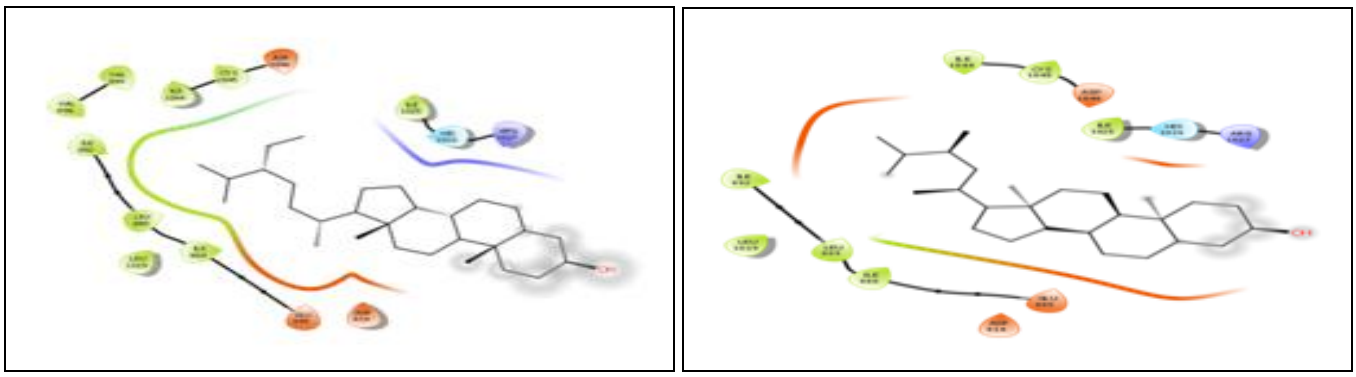


ERGOST -5-ENE-3-OL **STIGMAST-4-EN- ONE**

FIG. 4: INTERACTIONS WITH HER2 (erb2) KINASE

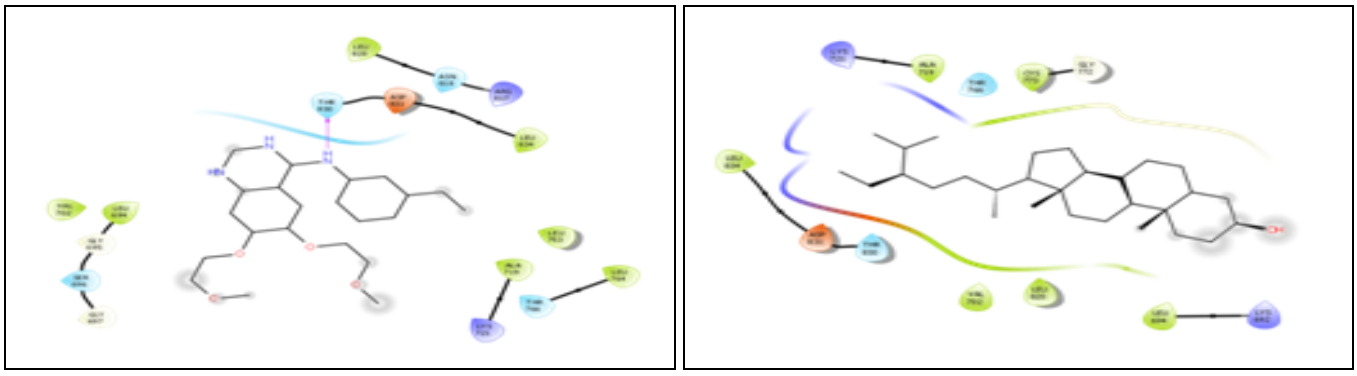


SORAFENIB (STANDARD DRUG



STIGMAST-4-EN-ONE **ERGOST-5-ENE-3-OL**

FIG. 5: INTERACTIONS WITH VEGFR2 KINASE



ERLOTINIB **STIGMAST-4-EN-ONE**

FIG. 6: INTERACTIONS WITH EGFR KINASE: 4HJO

The selection of anti-cancer targets for the *in-silico* studies was based on the cell lines used for the *in-vitro* anti-cancer testing i.e. MCF7 (breast cancer), A549 (lung cancer) and HepG2 (liver cancer) and

hence the anti-cancer targets expressed in these cases were selected as prime targets to correlate the data for the meaningful conclusions. In docking studies, bonding energies and bonding poses of compounds were considered. Among the tested compounds stigmast-4-enone, gammasitosterol and ergost-5-ene-3-ol were found to have excellent binding affinity -12.28, -11.47 and -10.79 kcal/mole respectively towards HER2 protein (3PP0), which is evident from their higher binding energies than that of the standard (SYR—10.74 kcal/mole) as shown in **Table 5**.

This indicates an excellent anti-cancer property of those compounds against breast cancer. The binding interactions of these compounds Fig 2 and 3 also compared with the standard which revealed the possible relevance in binding energies. The side chain of stigmast-4-enone has occupied the hydrophobic site within the target site formed hydrophobic interactions with MET774, SER783, ARG794, LEU785 and LEU796 which are comparable with those of standard indicating comparable with those of standard indicating the anti-cancer ability. Another compound, ergost-5-ene-3-ol shown hydrophobic interaction with ALA751 and LEU753. The hydroxyl group forms H- bond with SER783. Similar interactions were observed with gamma sitosterol another steroidal compound on HER2 protein [18, 19, 20].

Similarly, anti-cancer potency of the lung cancer target (VEGFR2) also studied. Most interestingly, gammasitosterol binding is excellent with the target (4asd) with binding energy -14.4kcal/mole and possesses more binding affinity than the standard Sorafenib. Although stigmast-4-ene and ergost-5-ene-3-ol devoid of polar functional group in their side chain, still interacts as good as the standard drug, particularly with CYS 1044 and ILE 1045 however the binding affinities were less than the standard drug and are shown in **Fig. 4**. This further supports the anti-cancer potency against lung cancer cell lines [21].

Moreover the compounds acting on liver cancer target EGFR (4hjo) gave more appreciable results. The gamma-sito-sterol has shown excellent binding with binding energy of-12.2 KCal/mole, indicating a stable interaction with the target compared with the standard drug Erlotinib. It shows polar interactions with THR830, ASP831, THR766 and some hydrophobic interactions with ALA719 and LEU721, which are shown in **Fig. 5** [22, 23].

CONCLUSISON: Different extracts of *Mitragyna parvifolia* stem bark screened for phytochemical nature, and TLC analysis was carried out. Among those extracts dichloromethane extract subjected to cytotoxic activity using MTT assay on MCF7, A549, and HepG2 cell lines. The IC_{50} values of the assay revealed the considerable cytotoxic potential of the extract against the selected cell lines. Hence, GC-MS analysis of the extract was performed to find the phytocompounds present in it, and the compounds were named using the NIST library.

GC-MS results had shown the presence of a wide spectrum of phytoconstituents of different functional groups and the cytotoxic potential may be because of those compounds. Molecular docking study on respective anti-cancer target proteins for selected compounds also revealed the significant, specific anti-cancer potential of the compounds. Some compounds exhibited greater binding affinities than the standard drugs. Thus, these studies emphasize the anti-cancer potency of the phytoconstituents of dichloromethane extract of *Mitragyna parvifolia* stem bark. Further studies on those phytocompounds will establish their druggability against proposed cancer cell lines.

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CONFLICTS OF INTEREST: Authors declare no conflicts of interest.

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