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Original article

Pharmakinetics studies, molecular docking and discovery of anti- proliferative agents and its targeting EGFR inhibitors

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ABSTRACT

Objective: *Abutilon indicum* is a medicinal plant belonging to the Malvaceae family. The current study has been developed to detect *Abutilon indicum* bio-activity to produce an adequate drug design for cancer.
Methods: The objective of this work is to perform molecular docking and dynamics as well as inhibitors and cancer cell line studies of *Abutilon indicum* would be essentially effective to use current strong medicines from oncology therapies.
Results: By Docking best finding binding energy −12.02 kcal/mol (ARG310, ASP323, SER291, THR358, GLU293) amino acid has been found to be immersed in the formation of the hydrogen interaction. This finding also indicates that a range of compounds are ADMET positive drug molecules in cancer studies. Network pharmacology showed that the signal rule ERG, PTEN, NKX31, AR, ETV4, STAT3, PTPN11, CBL, KRAS, EREG, STAT3, GRB2, HRAS, and SHC1, and the axis of DRD2. Molecular simulation trajectories show that RMS deviation profiles were relatively stable during the simulation and it indicated the orientations were created by the docking studies. In cell lines MCF-7, the active compound R-N-1′-methoxycarbonyl-2′-phenylethyl-4-hydroxy benzamide has anticancer inhibitory 76.56% at 100 μg/mL. The ASP323 interaction of EGFR inhibitors interaction molecules were derived that can be successfully used to explain the cancer activities.
Conclusion: The results of pharmacodynamic and toxicity for natural organic derived compound and its active results epidermal growth factor receptor for identifying novel drugs for the treatment confirms compound moderate to a good cancer drug.

1. Introduction

Phytomedicine is herbal medicine with therapeutic and curative properties. It began with the dawn of human civilisation, and recently researchers have developed therapeutic plants with anti-cancer properties (Balachandran and Govindarajan, 2005, Abubakar., 2020). Since the plant treatment, has been proven to prevent or treat many cancers (Lauby-Secretan et al., 2015). According to the WHO, non-communicable diseases like cancer

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account for 63 % of all deaths globally (Singh et al., 2012). In detailed, age and adverse dietary habits, as well as ecological factors such as UV wave's diffusion, are all extremely subjective. In 2013 cancer patients were 12.7 million and are expected to increase to 21.4 million in 2030 (Travis et al., 2015). Breast cancer is the second leading cause of mortality worldwide, accounting for 9.6 million deaths in 2018. (Ferlay et al., 2013). Oncogenesis is the process of transforming a cell into a tumour cells. This a typical cell accumulates inside normal cells, producing genetic malfunction and changes. (Ameh et al., 2010). There are many types of cancer in humans; the most prevalent type is lung cancer in males, followed by breast cancer in women (Newman and Cragg, 2016).

Many beneficial properties of herbal medicines have been reported in clinical research, such as cancer patient survival rates and resistance properties. (Liu et al., 2005). Although natural products from plants have less structural variety than conventional combinatorial chemistry, they nevertheless enable the discovery of new low molecular weight lead compounds (Lu and Chong, 2012). Plants have been report naturally derived chemicals for therapeutic purposes. The study reported below illustrates the ambiguity surrounding the use of AI leaf as a source of active compounds with dose-dependent significant action (Gupta et al., 2001). In spite of numerous studies and clinical trials, experts are still searching for an indigenous plant to cure breast cancer (Cohen and Opal, 2016). Breast cancer is related to external and endogenous endocrine factors, including gender. However, its function in breast cancer aetiology is unknown. (Kumar et al.,2015). Plant chemicals have also been recognized as possible anticancer agents.(Liu et al., 2019). The current study sought to identify and isolate insilico docking, ADMET, Network pharmacology, Molecular Dynamics, and MCF-7 cell line experiments.

2. Material and methods

2.1. Preparation and extraction

The *Abutilon indicum* leaf was collected plant materials were washed and air-dried under laboratory environments. Plant has been authenticated and the voucher specimen number AU/SRC/1/18/2014/PP/234 has been collected. 100gm of plant leaf were crushed and extracted for 8 h in soxhlet apparatus with MeoH solvent. Later the extracts have been filtered; later the pooled solvent was evaporated at lower pressures at 40 °C in rotating evaporator (Heidolph, Germany). For further examination, the crude extracts have been stored in refrigerator at 4 °C.

2.2. Chemical profiling of Abutilon indicum

The AI MeoH extract was GC–MS analysed (JEOL GCMATE II GC–MS-Agilent 6890 N Network GC system for gas chromatography). Secondary electron multiplier GC–MS were used to analyse the active fraction of two microliters in chloroform. The samples were then compared to the spectrum library's known compounds to determine their molecular weight, empirical formula, component structure, and maximum area of test fraction (NIST 05).

2.3. Molecular docking studies

Auto Dock 4.2 was used to dock a flexible ligand to a stiff protein using the Lamarckian genetic algorithm. After identifying potential binding sites, compound 15 was docked to these sites to determine the most probable and energetically favorable binding conformations. e' completeness was 20 per protein-compound pair. An active site encloses a 32 A3 docking array with 0.375A grid spacing. The DS Visualizer 2.5 (http://3dsbiovia.com/products/) and PyMOL Molecular Graphics Framework 2.0 tools were used to verify the associations (Lachenmayer et al., 2010).

2.4. ADMEt

In Lipinski's rule of five, ADME/T, drug-like properties using compounds with biological and/or pharmacological activity were evaluated, which was used to evaluate if these compounds have the properties that would allow them to be a possibly orally active drug for humans. (Grosdidier et al., 2011).

2.5. Network construction

Multichannel regulation of signalling pathways is the core element for network pharmacology. It is often used to find natural product targets (Yun mao et al., 2020). Using simple software, we built a network analysis of pharmacological targets (string-db.org).

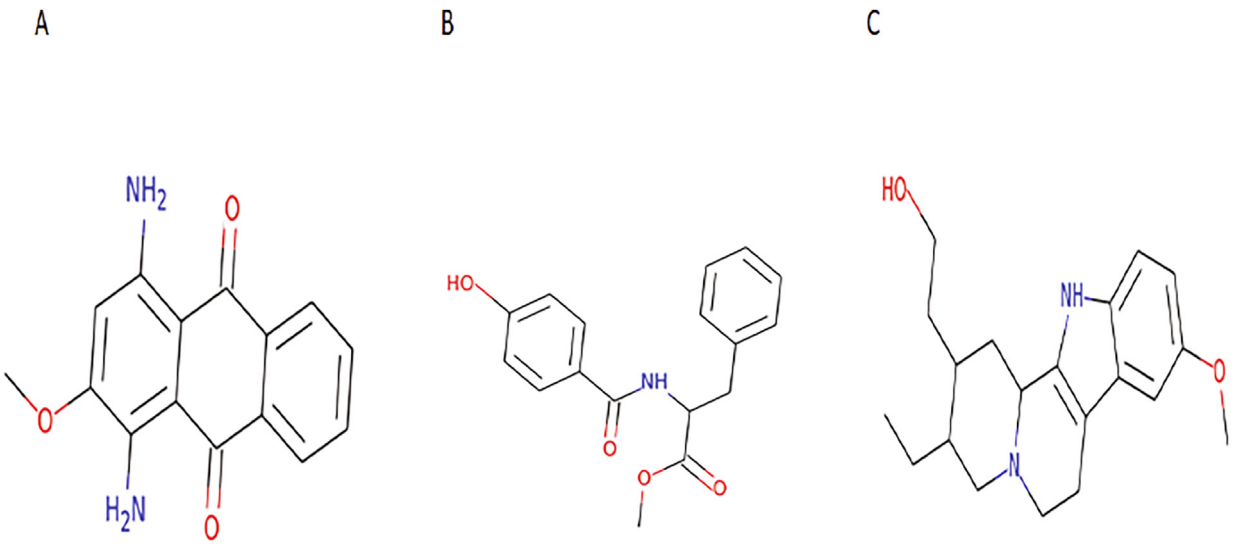

Fig. 1. Chemical structure A. Cancer-cell line (Compound 5), B. R)-N-(1′-methoxycarbonyl-2′-phenylethyl)-4- hydroxybenzamid of *Abutilon indicum* (Compound 2), C. Ergostanol (Compound 1).

2.6. Molecular dynamics

The OPLS-3e force field was used in MD simulations (Wu et al., 2006). Both systems were neutralised with Na + and Cl- ions, and the salt concentration was adjusted to 0.15 M Na + and Cl- ions to mimic physiological conditions. The systems were energy-efficient for 50,000 steps using steepest decline. The systems were heated to 310 K using 100 ps NVT steps with protein backbone constraint at 100 kcal/mol force. The systems were then equilibrated for 500 ps NPT steps with 100 kcal/mol protein backbone constraint. The Nose-Hoover chain thermostat and Martyna-Tobias-Klein barostat maintained the temperature and isotropic pressure coupling (Release and Desmond, 2014) . The coulombic and Van der Waals interactions are terminated at 10.0. At 310 K and 1.63 bar pressure, NPT MD simulations were run for 100 ns with a 2 fs time step. Desmond simulation interaction diagram tool was used for analysis and plotting.

2.7. Cell viability assay by enzyme-linked immunosorbent

MCF-7 cells were grown in 96-well plates for 24 h in 5 percent CO2 at 37 °C using the 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay (Mosmann, 1983). Compound 5 was added to the cells at various concentrations (6.25, 12.5, 25, 50, and 100 g/mL) during the incubation. The control group received 0.1 percent dimethyl sulfoxide (DMSO, Sigma-Aldrich, Bangalore, India). After 24 h, each well received 10 μL of 5 mg/mL MTT and also was incubated for another 4 h. The supernatant was removed, and each well received 100 mL DMSO, which was vortexed for 10 min. The optical density (OD, Sky technology India) was measured at 570 nm using an ELISA reader.

3. Results

3.1. Physiochemical properties

The molecular weight is determined by dockage, ADME and network and molecular dynamic and cancer-cell line (compound 5) and the active R-N—1′-methoxycarbonyl-2′-phenylethyl-4-hydroxy-benzamide (compound 2) and Ergostanol (compound 1) molecular weight, indicated some selectivity of these molecules respectively. (Fig. 1), all three molecules, which meets Lipinski's criterion, with molecular weight of < 500 g/mol. The molecules validating the rule of five Lipinski were demonstrated by the measurements of hydrogen bonding and molar refractivity. These molecules also follow Veber's policy, denoting drug molecules' oral bioavailability. Compound 5 and compound 1 molecules were found to have SA score of 2.84 and 5.88, respectively. It is easy for synthesizing molecules with score of one according to SA process. All three molecules score less than ten, so they're easy to synthesize.

3.2. Scrutiny of pharmacokinetic

The Lipinski rule is that all the compounds are based upon number of hydrogen bond donor 2, bond acceptor 7, and log P value 5. The molecule's Log-P value is linked to toxicity, metabolism, membrane transition, and intestinal absorption. As its log P value has been more than 5, Compound 5 were suppose to have maximum lipophilicity, whereas methane was expected for having highest hydrophilicity since its log P value has been −2.52. This means that aqueous dissolution and solubility will be low, whereas permeation through bio-membranes will be the compound's limiting factor. The TPSA value specifically indicates that Compound 5 one's hydrogen-bonding potential is optimum and is possible for having

Table 1
ADME/T predicted physiochemical properties for five compounds Plant derivate.

S. No	Name	Formula	MW	Heavy atoms	Aromatic heavy atoms	Fraction Csp3	Rotatable bonds	H-bond acceptors	H-bond donors	TPSA	iLoP	Logs	Ali logs	BBB
1	9,10-Anthracenedione,1,4 diamino-2-methoxy	$C_{15}H_{12}N_2O_3$	268.32	20	20	0.07	1	3	2	95.14	1.90	Moderate soluble	−11.66	No
2	Triamcinolone acetonide	$C_{24}H_{31}FO_6$	434	31	31	0.75	2	7	2	93.06	2.74	Soluble	−4.3	No
3	Ergostanol	$C28H50_O$	402.70	24	24	1.00	5	1	1	203.3	5.10	Moderate soluble	−10.15	No
4	10Methoxydihydrocorynantheol; 10-methoxycorynan-17-ol	$C_{11}H_{12}N_4OS$	248.3	22	9	0.60	4	3	2	48.2	2.96	Un soluble	−3.86	No
5.	(R)-N-(1′-methoxycarbonyl-2′-phenylethyl)-4-hydroxybenzamide	$C_{17}H_{17}NO_4$	299	22	11	0.18	7	4	2	75.63	2.52	Moderate soluble	−3.45	Yes

Table 2
ADME/T predicted physiochemical properties for five compounds Plant derivate.

S. No	Name compound	Formula	MW	Absorption	Cyp1a2	Cyp2c19	Cyp2c9	Cyp2d6	Cyp3A4	Bioavailability	Synthetic
1	9,10-Anthracenedione,1,4 diamino-2-methoxy	$C_{15}H_{12}N_2O_3$	268.32	High	Yes	Yes	Yes	Yes	Yes	0.11	2.52
2.	Triamcinolone acetonide	$C_{24}H_{31}FO_6$	434	Low	No	No	No	No	No	0.55	5.88
3	Ergostanol	$C28H50_O$	402.70	Low	No	No	No	Yes	No	0.55	5.25
4	10Methoxydihydrocorynantheol; 10 methoxycorynan-17-ol	$C_{11}H_{12}N_4OS$	248.3	High	No	No	No	Yes	No	0.55	3.95
5	(R)-N-(1′ methoxycarbonyl-2′-phenylethyl)-4- hydroxybenzamide	$C_{17}H_{17}NO_4$	299	High	No	No	No	Yes	No	0.55	2.37

MV = 150–500 g m/mol, TPSA (Total polar surface area) = 20 A^2 –130 A^2, H-A = no. Of H-bond acceptors ≤ 10, H-D = no of H- bond donor ≤ 5, Rotatable bonds = 0–9, Log S = 0–6, Insaturation + 0.25–1, NA toms (Number of atoms) = 20–70.

stronger bio-availability as well as membrane transition properties.

The ADME model screening results for five compounds shows trusted standard for human intestinal absorption and penetration of the blood-brainbarrier. Likewise, another predicate also has a 95% "confidence level for intestinal absorption for BBB penetration using cancer trials of compound 5 (S.Figure.S1). The compound shows very active and most quoted inhibition for cancer and will act as a potential pharmacotherapeutic agent for cancer (Table 1 - 2).

3.3. Molecular docking

These natural active molecules can be screened to pave the way for improving drugs against cancer. Bioactive molecules 5, along with docked ligand molecules structures with auto dock score, were listed based on auto dock obligatory likeness (Table.1). Dock binding energy −12.02 kcal/mol, the amino acid (ARG310, ASP323, GLU293, THR358, SER291) was involved in hydrogen bonding formation with (Fig. 2). From this opinion, it is evident that is one bioactive molecule have a better binding affinity with the target molecule, "the human estrogen receptor" which leads to the minor obligation for the inhibition.

3.4. Network analysis for identification of targets of active components

The PPI (45 edges and 11 nodes) structure has been built in (Fig. 3) that may play a significant role producing antiproliferative properties, and therapeutic agents. A score of 0.907 or above is considered to be highly reliable. The two diverse nodes with high trust scores have been DRD2, ERG, PTEN, NKX31, AR, ETV4, STAT3, PTPN11, CBL, KRAS, EREG, STAT3, GRB2, HRAS, and SHC1, and

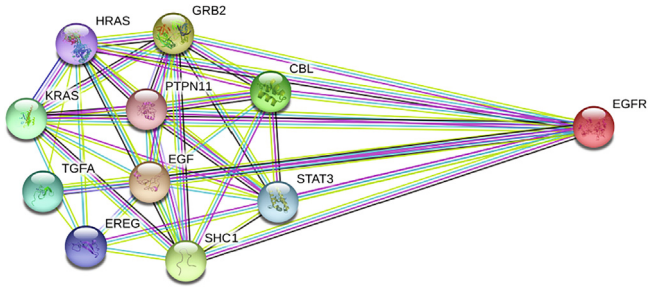

Fig. 3. EFGR interaction The cellular processes represented by each node in the network are coded by color, using the process categories

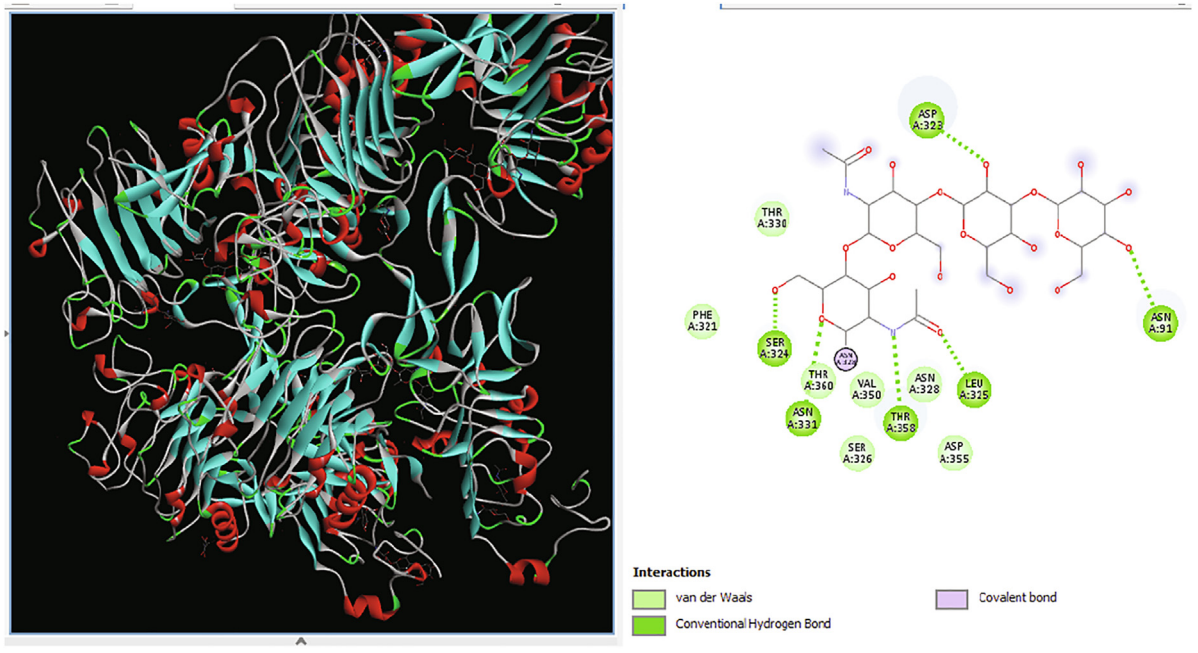

Fig. 2. Schematic representation of the main interaction of 3D and 2D structures for amino acid regions for(R)-N-(1'-methoxycarbonyl-2'-phenylethyl)-4 hydroxy benzamide" acid Interact with targeted protein

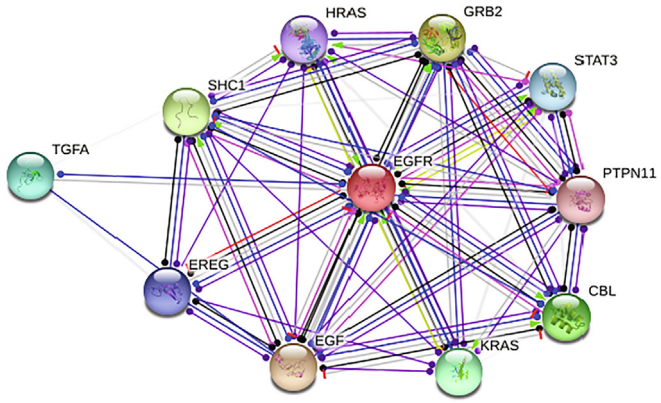

Fig. 4. Protein-protein interaction network of targets related to cancer. The colored nodes represent candidate proteins, and colored lines represent protein interactions. Light green - represents text mining; Black - represents co-expression; Light blue- represents known interactions from curated databases; State blue - represents protein homology; Magenta- represents experimentally determined known interactions; Green - represents predicted interactions between neighborhood genes; Red - represents predicted interactions of gene fusion; and Blue - represents predicted interactions between co-occurred genes

effects and complex drug action were considered by the network of science and ancient medicine and the multi-target drug approach

3.5. Molecular investigation and KEGG pathways enhancement studies

The 45 hub targets, protein ontology enhancement study, along with major functions were used. 1370 GO enhancement outcomes have been gotten, involving (biological processes, as shown in the enrichment results 5159 molecular functions 1513). By controlling four main molecular functions, such as same protein binding, protein homodimerization activity, the biological process, Compound 5 reveal better anticancer agent. The number of target mapping pathways has been greater than cancer pathways EBR signal pathway (hsa04012 number = 9 EFGR Tyrosine, kinase inhibitor resistance (hsa01521, number = 8), non-lung cancer (hsa05223, number = 7), Galima (hsa05214, number = 7) and colorectal cancer (has05120 terms 7; (Fig. 4). REACTOME analysis of active compounds objectives has been mapped to 21 respite pathways (P-value < 0.05) The pathways of the mapping target were higher than those of disease pathways signal PTK (HSA 8848021, number = 7 (HSA5637810, number = 6), EFGR HSA177929 = 6, ERB signaling HSA 1250196 = 6, respectively.

3.6. Compound-target-pathway relations network

45 hub targets were linked with investigating the cancer protein's metabolic activities. 1370 GO findings were improved, including biological processes (5159 and molecular functions 1513 terms). As a result of the gene-set enhancement study, 122 genes were discovered by the gene-set enhancement analysis. Oncogenic protein homodimerization is controlled by four major molecular activities, including protein binding.

3.7. Molecular dynamics simulation

MD simulations have been conducted in this work to understand the construction of the confirmative stability of the receptors.

3.8. Stability of protein

We have determined root mean square fluctuation of Ca to conform to local level stability, which calculates the fluctuation of amino acid residues at the time of MD simulation (Fig. 5). No major difference was observed for the apo and complex type, which indicates ligand binding, does not affect protein stability, and supports our RMSD outcomes.

3.9. Intermolecular interactions

The ligand molecule interactions of hydrogen with GLU293 in molecular docking generate SER340, GLU293 and SER291 connections with active site amino acid residues. It also forms hydrogen bonds with GLU293(1.1) in molecular docking, which is essential for inhibiting cancer enzymes. In molecular docking (5.06), the C (20) atom forms hydrogen bonds with GLU293; this bond remains intact in MD simulation (6.4). Residues produce numerous ligand interactions (values over 1.0). An MD simulation of 100 ns identifies up to 4 connections (Fig. 6). This implies that for 0.7, the connection is maintained for 70% of the simulation period. H-bonds are important in ligand binding. Hydrogen-bonding characteristics are important in drug design because they affect drug selectivity, adsorption, and metabolism. There is a 2.5 distance between

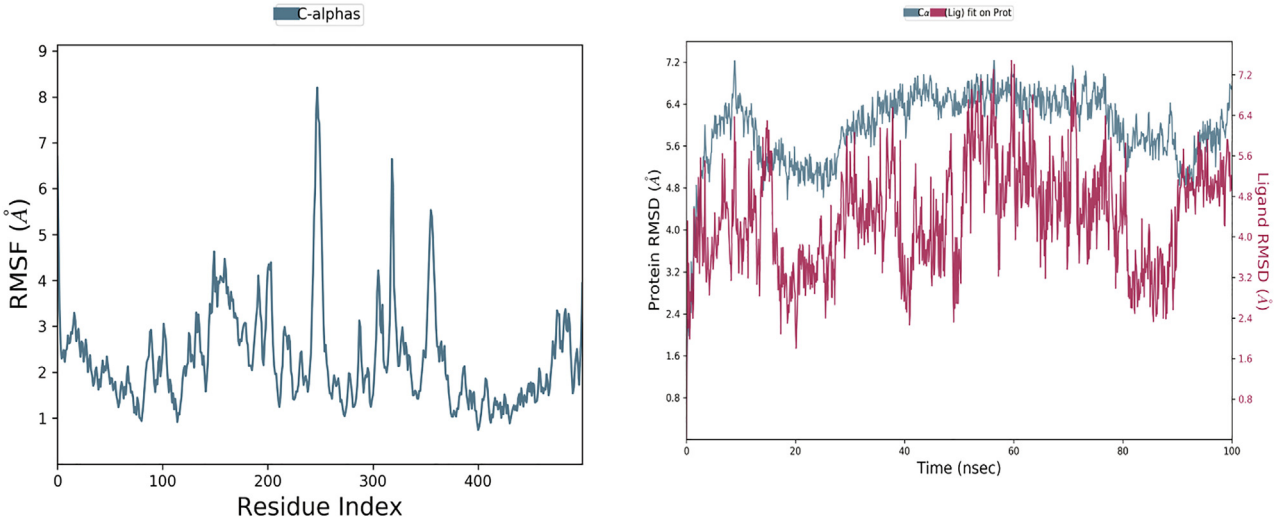

Fig. 5. RMSD plot RMSF atomic position protein Cα aphals atoms and cα (Lig) time dependent plot over the 100 ns trajectory during the MD simulation.

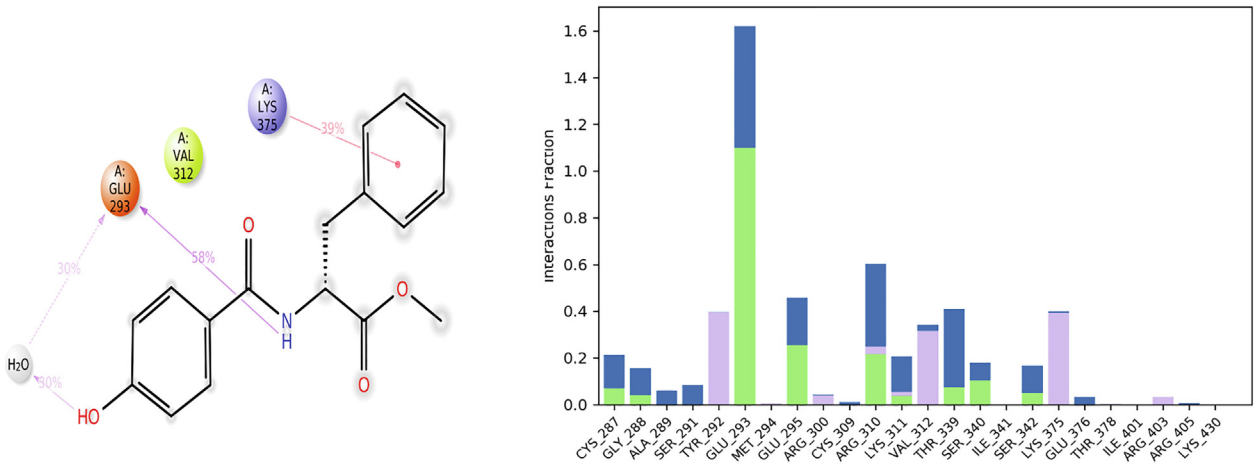

Fig. 6. MD calculated protein–ligand contacts at the allosteric site, region receptors

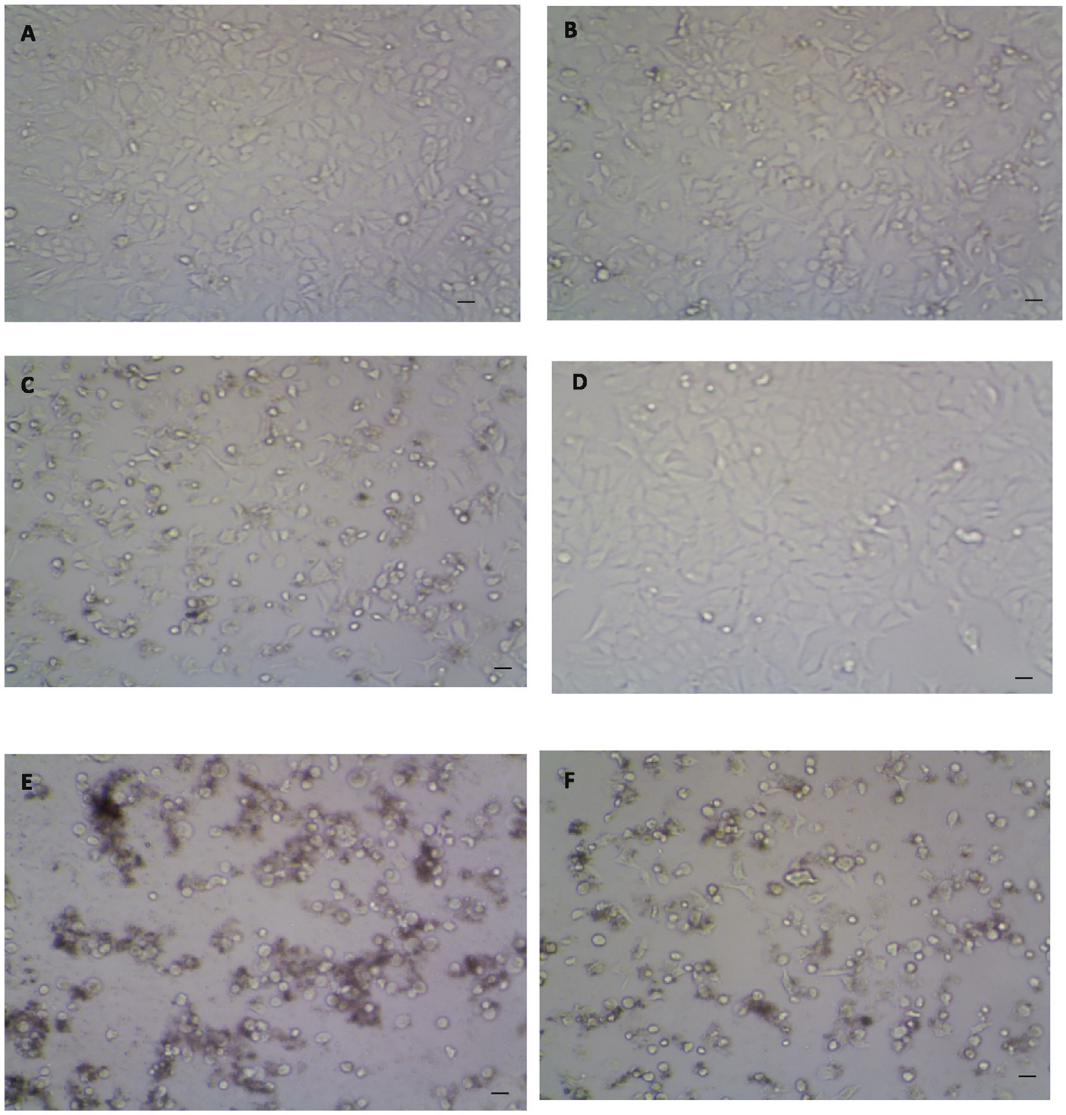

Fig. 7. The Cytotoxicity assay of compound 5 Human Breast Cancer (MCF-7) cell line Control (DMSO treatment) showed dense of cells; 18.75 μg/ml (A);12.5 μg/ml (B) treatment also showed dense of cells; 25μg/mL (C); 50μg/mL (D); 100/mL (E) treatment showed gradual cell toxicity compared to control (F) and low dose treatment.(scale bars.10μm)

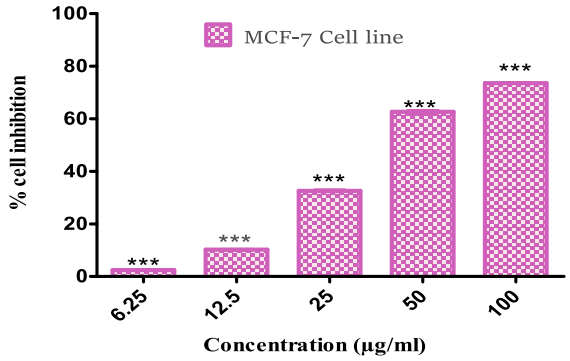

Fig. 8. Cellular metabolic activity indicated by cell viability of compound 5 on the cell viability and proliferation of breast cancer cells.

acceptor and donor atoms and a 3120° donor angle between donor-hydrogen-acceptor atoms. The Insilico and MD research concluded that the best compound 5 from herbal plants inhibit cancer cell activity.

3.10. Compound induce an anti-proliferative effect MCF-7 cancer cells

The vitality of MCF-7 cancer cells was significantly reduced when the concentration was increased from 2.46 percent to 76.56 percent (6.25, 12.5, 25, 50, and 100 g/mL) (Fig. 7–8). *Abutilon indicum* could serve as a new source of cancer-fighting benefits. Compounds may destroy MCF-7 cancer cells, halting cell cycle development. Our results show that compound 5 has 76.56 activity rate at 100 g/mL at lower dose and inhibition. (S.Figure.S2).

4. Discussion

Natural products offer a significant contribution towards the treatment of several human diseases, such as cancer the second leading cause of death worldwide diseases. Increasingly, natural sources utilize discovery of novel bioactive compounds using in therapeutic reasons (Mushtaq et al., 2018). Docking is a key approach in the design of computerized medicines for specific ailments (Mohapatra et al., 2021). The plant *Abutilon indicum* produces a range of medicinal secondary metabolites (Meng et al., 2011), which are used as chemotherapeutic drugs. Indigenous plant species have long been used in medicine, and many have been studied for medicinal chemicals (Desai et al., 2008). H bonds are essential in determining specificity and affinity towards protein–ligand complexes (Wang and Laszlo, 2004). The co-crystallized ligand selected compounds have low TPSA values (Wang et al.,2016).This ADME prediction was used to assess the compound's assets. These surfaces are important in medication absorption via the human gut layer and drug penetration across the blood–brain barrier (Ertl et al., 2000; Stary et al., 2021). Previous research has shown that the cardiotonic effect of SNDD is exerted by regulating the TNF signaling pathway (Bing et al.,2018). The EGFR signal pathway has a key role to play in various HCC processes, like metastasis, invasion, angiogenesis, and cell proliferation (Whittaker et al., 2010; Pawara et al., 2021). The amino acids were shown to be important in the systematic review, that means bicarbonate transport modulators will make serve as great medicines in cancer therapy. (Yin et al., 2013). Moreover C1 metabolic enzymes have recently shown novel therapeutic targets for cancer (Fares et al.,2020). Reasonable natural drug design has significantly reduced drug costs and the resources required over the years (Abdulkareem, 2013) This research, therefore, has important consequences for the design of drugs from natural products (Toh et al., 2004). Molecular docking presents a stable compound in the binding pocket of a protein (Reddy et al.,2015). There are several proteins and other variables that are involved in cell cycle regulation and cell proliferation of tumour growth. (Xiao et al.,2012). The extract is also high in antioxidants, further limiting cancer cell development (Sasikala and Meena, 2018). An previous research showed the significance of the AKT/mTOR pathway in reducing BC cell survival and proliferation by using another naturally occurring route (Memmott and Dennis, 2010). The finding reported here serve as an useful information to develop effective drug for EGFR-related cancer treatments.

5. Conclusion

The study that suggested bioactive compounds in Dynamics and molecular docking results demonstrated that the intermolecular hydrogen bonding along with hydrophobic interactions among receptor protein and ligands study suggested the calculated procurement of "(R)-N-(1'-methoxycarbonyl-2'-phenylethyl)-4-hydro xybenzamide" of bioactive molecules with high-level MCF-7 cancer cell resistance computational properties. Network pharmacology was then specifically extended to the action process of herbal formula science, encouraged its modernization, and evolved into a new drug research and development approach. In conclusion that (R)-N-(1'-methoxycarbonyl-2'-phenylethyl)-4-hydroxybenza mide has been further refined to devise the most optimal dose for the anti-cancer drug. These lead compounds also had excellent bioavailability, good absorption, minimal toxicity, and were permeable. This study provides solid scientific evidence that AI has traditionally been utilized as a traditional herbal medicine to treat infections and cancer.

Author Contributions

PP, GE and GA Conceptualization, Data curation, writing - original draft, Preparation, Writing – review & editing. KAP performed the molecular docking and simulations. PP, RM and KS wrote the article. AT,HAA,MAA,AAH,VM, MAD, BV, AAH, MC and BR all authors reviewed the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jksus.2021.101679.

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