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In Silico Evaluation of Phytochemicals as PI3K/AKT/mTOR Inhibitors for the Treatment of Breast Cancer

Srivarshini Sankar[1], Rama Jayaraj[2, 3], Nalini Easwaran[1] and Gothandam Kodiveri Muthukaliannan[1]*

[1]School of BioSciences and Technology, Vellore Institute of Technology (VIT), Vellore, Tamil Nadu, India
[2]Jindal Institute of Behavioral Sciences, Jindal Global Institution of Eminence Deemed to Be University, Sonipat 131001, India
[3]Director of Clinical Sciences, Northern Territory Institute of Research and Training, Darwin, NT 0909, Australia
*Corresponding author: gothandam@gmail.com

Abstract

Breast cancer is the most common type of cancer and the second most common cause of death. Influential and widely accepted breast cancer prevention strategies are still elusive. Aspirin and other nonsteroidal anti-inflammatory drugs, such as ibuprofen, are frequently recommended to treat fever, pain, and inflammation. Studies have shown that these medications also have anticancer effects. A key target of tumor-targeted therapy has been discovered in recent years, and it is the PI3K/AKT/mTOR signalling pathway. In order for tumour cells to proliferate, develop, migrate, and survive, the PI3K/AKT/mTOR signalling system is essential. So, using *in silico* analysis, we chose to determine whether the NSAID Diclofenac and other phytochemicals have anticancer properties and also act as PI3K/AKT/mTOR inhibitors. We conducted docking analyses for the drugs diclofenac, piperine, naringin, eugenol, d-limonene, cinnamaldehyde, and curcumin versus the FDA-approved AKT/PI3K and mTOR inhibitors alpelisib, rapamycin, and afuresertib. Both bioactivity and ADMET profiling were done for these drugs. We concluded from our *in silico* analysis that diclofenac, d- limonene, and piperine do not contradict any of Lipinski's rules and can be effective AKT/PI3K/mTOR inhibitors.

Keywords: Breast cancer, AKT/PI3K/mTOR inhibitors, Diclofenac, Piperine, d-Limonene

Introduction

The most prevalent kind of cancer and the second most prominent causation of death is breast cancer. This disease is the leading cause of death in women aged 45–55 and is also the second major cause of cancer-related mortality (1). Breast cancer affects about 1-in-8 women and, in the majority of cases, demands complete tissue excision, chemotherapy, radiation, and hormonal therapy (2). Breast cancer is a form of epithelial cancer that primarily affects the inner lining of the milk glands, lobules, and the ducts (3). Age, elevated hormone production (4), ethnicity, economic circumstances, and iodine deficiency in the diet are all major cancer risk factors. Breast cancer is a grouping of several cancers that appear in the mammary glands. Malignant tumors account for most breast malignancies, with sarcomas such as phyllodes tumours and angiosarcomas uncommon (5).

Breast cancer is a malignant tumor that may spread to various body organs, such as the bone, liver, lung, and brain, making it nearly im-

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possible to cure. An excellent diagnosis and a higher recovery percentage can be attained if the cancer is detected early. Because of prompt discovery of this malignancy, the 5-year survival rate of breast cancer patients in North America is above 80% (6). Mammography is a frequently used screening method for identifying breast cancer that has been shown to reduce mortality successfully. Additional screening modalities, like as MRI, which is much more accurate and specific than mammography, are also used and investigated throughout the previous decade (7). Physical exercise, managing postmenopausal obesity weight gain (8), dietary modification, and multivitamin intake have all been promoted as ways to prevent breast cancer, based on studies linking these variables to a decreased risk. Long-term lifestyle change is debatable, although motivated women are likely to be able to make small changes. A randomized study of dietary fat reduction/management conducted by the Women's Health Initiative found a slight (9%) decrease in the risk of breast cancer that was borderline statistically significant; a more enormous effect was shown among more consistent women (9). There was no indication of a decrease in breast cancer incidence in randomized studies of vitamin D therapy. Breast cancer prevention that is both efficient and widely accepted is still unattainable. Healthy women have a lower tolerance for toxicity, especially catastrophic diseases like cancer and thrombosis. Finding both successful ways and have a reasonable hazard- benefit ratio will remain a problem (10).

NSAIDs (Nonsteroidal anti-inflammatory drugs) like ibuprofen as well as aspirin are commonly prescribed for the treatment of inflammation, discomfort, and fever, and they may also have anticancer properties (11). The restriction of one or both of the cyclooxygenase enzymes is assumed to be the mechanism through which NSAIDs reduce cancer risk; cyclooxygenase-1 is found in almost all the cells, whereas cyclooxygenase-2 is triggered by tumour oncogenes as well as promoters and is highly expressed in mammary tumours (12, 13). In recent years, the PI3K/AKT/mTOR signalling pathway has emerged as a prominent target for tumor-targeted treatment. The PI3K/AKT/mTOR signalling system plays a key role in tumour cell proliferation, growth, migration, and survival. In recent years, the PI3K/AKT/mTOR signaling pathway has been identified as a key target of tumor-targeted therapy (14). Diclofenac suppresses the development of tumour xenografts (15) and also the proliferation of cancer cells in a dosage-dependent manner, according to research (16). Because the function of the superoxide dismutase enzyme in mitochondria is inhibited, diclofenac suppresses melanoma cell development by raising the cellular concentration of reactive oxygen species (17).

Phytochemicals in the prevention of breast cancer

Plants and herbs have been used in the treatment of a multitude of diseases for centuries. Plants create phytochemicals, also known as secondary metabolites, which are non-nutritive chemical molecules created by various chemical pathways (18). They are a good source of bioactive material, which can be extracted and purified to be used against diseases. Their biological significance is still being researched, discovering the active components of the various plants. These active compounds are known as phytochemicals, they exhibit a wide range of important properties such as antioxidant, antimicrobial, and anticancer (19). Some phytochemicals that have anticancer qualities include curcumin from turmeric, genistein from soybean, and tea polyphenols from green tea. Due to their dietary origin, phytochemicals are thought to be safer and better tolerated with less toxicity than conventional treatments (20). Phytochemicals are better suited as preventative measures rather than cures (21). The methods by which phytochemicals can help protect against cancer are: 1. Modulation of Oxidative Stress 2. Inhibition of Inflammation 3. Modulation of Tumor Metabolism. The phytochemicals that are used in this study are piperine, nar-

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10.5530/ctbp.2023.3s.59

ingin, curcumin, D-limonene, cinnamaldehyde and eugenol. Piperine is the major bio-active component of black pepper and it is an alkaloid derived from the genus Piperum, is often employed in folk medicine and it has been widely consumed (22). A study by Chen et al. (23) showed that piperine decreased SNU-16 cell growth and promoted apoptosis. Piperine increased the expression of Bax, Bad, Cyto C, cleaved PARP, and cleaved caspase-3 proteins while decreasing the expression of Bcl-2, Bcl-xl, pPI3k, and pAkt proteins. Piperine inhibits metastasis in DU145 cells by partially blocking the Akt/mTOR/MMP-9 signalling pathway, suggesting that it might be a promising chemotherapeutic drug option in future treatment drugs for prostate cancer patients (24).

Grapefruit and some other citrus fruits contain the flavonoid naringin, which is a key flavonoid. Naringin has the ability to suppress tumour biological activity by reducing the excessive activation of the PI3K/AKT/mTOR signalling pathway. Naringin reduced the PI3K/AKT/mTOR signalling pathway, which decreased CRC cell growth and promoted death (25). Curcumin is a chemical component found in Curcuma longa (turmeric) rhizomes as well as other Curcuma spp, also referred to as diferuloylmethane. Curcumin-mediated inhibition of nuclear Factor-B (NF-kB), the primary device in the inflammatory cascade, was one of the most important discoveries in medicine (26). Curcumin also impacts several signaling pathways linked to cancer (27). Curcumin binds to a variety of cell key proteins, including transcription factors, cytokine signaling receptors, growth factors, and anti-apoptotic proteins, and has even been shown to suppress metastasis.

Eugenol is generally found in essential oils extracted from certain spices like clove, bay leaf, cinnamon, etc. External application of eugenol could efficaciously ameliorate or suppress breast premalignant condition by inducing apoptotic cell death and S-phase cycle arrest via the HER2/PI3K-AKT pathway, suggesting that eugenol could be a hopeful exterior implementation drug to prevent and reduce breast premalignant condition (28). d-Limonene is a chemical that may be found in the peels of citrus fruits such as oranges. d-limonene blocked Akt activation and triggered the intrinsic mitochondrial apoptotic signalling pathway in LS174T cells, according to the findings of Jia et al. (29). Cinnamaldehyde (CA) is a bioactive chemical obtained from the stem bark of Cinnamomum cassia which was seen in vitro to have antiproliferative and pro-apoptotic actions on cancer cell lines. Cinnmaldehyde significantly increased E-cadherin expression while decreasing the levels of MMP-2 (Matrix metalloproteinases) and MMP-9. Cinnamaldehyde, as well as IGF-1, which works as an anti-apoptotic factor, significantly decreased the transcriptional activities of PI3K/AKT(30).

Materials and methods

Preparation of ligand structure

The FDA- approved inhibitors of AKT (Afuresertib: PubChem ID- 46843057), mTOR (Rapamycin: PubChem ID- 5284616), and PI3Kα (Alpelisib: PubChem ID- 56649450) are used as a control to find the difference among the binding energies of the approved inhibitor and the compounds diclofenac (PubChem ID- 3033), piperine (PubChem ID- 638024), naringin (PubChem ID- 442428), eugenol (PubChem ID- 3314), d-limonene (PubChem ID- 440917), cinnamaldehyde (PubChem ID- 637511), and curcumin (PubChem ID- 969516). The structure of the ligands were downloaded from PubChem. The files are obtained in the SDF format and then converted into the PDB format using the PyMOL software (The PyMOL Molecular Graphics System, Version 1.2r3pre, Schrödinger, LLC) for further screening procedures.

Preparation of protein structure

The three-dimensional structures of PI3Kα (PDB ID: 5DXT, Chain A), AKT (PDB ID: 4GV1, Chain A), and mTOR (PDB ID: 4JT6, Chain A, B, C) proteins were retrieved from the Protein Data Bank and were used as the target

Vol. 17(Supplementary issue - 3B) 1232-1244,September 2023, ISSN 0973-8916 (Print), 2230-7303 (Online)
10.5530/ctbp.2023.3s.59

for the compounds. The selected chains of the proteins were edited for missing hydrogens and for assigning proper bond orders. The H-bonds were optimized using sample orientations. All the polar hydrogens were displayed. Finally, protein structure was energy minimized using SPDBViewer software (http://www.expasy.org/spdbv/).

Bioactivity and ADMET Profiling of compounds

A chemical compound's drug-likeness is defined as a balance between its molecular characteristics, which directly impacts the drug's biological activity, pharmacodynamics, and pharmacokinetics in the human body. To screen possible drug-like compounds, the LIPINSKI rule of five (RO5) was first used (31). Compounds' "drug-likeness" was assessed using molecular weight distributions, estimated lipophilicity, number of hydrogen bond acceptors, and donors. The strategy provides a prediction regarding potential absorption difficulties based on these four chemical descriptors; the rule indicates that molecules must have log≤ P5, molecular weight ≤500, number of hydrogen bond acceptors ≤10, and number of hydrogen bond donors≤5. Molecules that fail in more than one of these criteria may have oral bioavailability complications (32). The pharmacokinetics, drug-likeliness, and medicinal chemistry compatibility of small molecules were tested using the SWISS-ADME server (33). The SWISS-ADME server (http://www.swissadme.ch) was also used to estimate the physicochemical characteristics and drugability of the chosen compounds. Bioavailability is one of the fundamental pharmacokinetic properties of drugs and it is the absorption rate of a drug available at the site of physiological activity after administration. The ligands' bioavailability was studied with the pkCSM software (https://biosig.lab.uq.edu.au/pkcsm/).

Boiled egg plot

As a consequence of lipophilicity as well as evident polarity, a strong and uncomplicated Boiled Egg plot observation is made for both brain penetration and passive intestinal absorption. The Boiled Egg Plot was predicted using Molecular Weight (MW), Total Polar Surface Area (TPSA), MLOGP, Gastro-intestinal (GI), and Blood-Brain Barrier (BBB) characteristics in this study. The yolk of the egg-plot represents BBB permeability, the white space represents compound absorption in the human intestine, and the outer grey zone represents minimal absorption and restricted brain penetration capabilities of the drug (34).

Active site prediction

CASTp server (Computed Atlas of Surface Topography of Proteins) http://cast.engr.uic.edu aids in the identification of active sites in the proteins, which will be employed later in the docking process.

Virtual screening

The optimum orientations of diclofenac, piperine, naringin, limonene, curcumin, eugenol, cinnamaldehyde, alfelisib, rapamycin, and afuresertib with the lowest binding affinities were investigated utilizing Virtual screening for ligands and target structures on the PyRx platform using Auto Dock vina (version4, The Scripps Research Institute, USA). The active sites of proteins associated with binding pockets with high affinity, as well as non-covalent interactions for potential ligands, were displayed in Discovery studio visualizer for each protein-ligand complex (version 16.1.0.15350, Biovia, USA) and the 3D structure of the protein-ligand complex were displayed in UCSF Chimera (35) (developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco, with support from NIH P41-GM10331.

Softwares and web servers used

The Protein data bank was used to retrieve the proteins of interest for this study. The PubChem database was utilised to search for and construct a collection of ligands for virtual

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10.5530/ctbp.2023.3s.59

screening on PyRx platform using Auto Dock vina (version4, The Scripps Research Institute, USA). CASTp server was used to predict the active sites of the proteins. Molecular graphics were performed with UCSF Chimera (developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco, with support from NIH P41-GM103311), and interactions of the complex structures were displayed using Discovery studio visualizer (version 16.1.0.15350, Biovia, USA). The SWISS-ADME server and the pkCSM software were also used to calculate the physicochemical properties, drugability, and bioavailability of the ligands in interest.

Results and Discussion

Drug-likeliness and physicochemistry of selected ligands

The drug-likeness of the proposed drug was investigated using computational sensitivity and structural analysis. The size of a molecule determines its transport qualities, such as intestinal absorption or blood-brain barrier permeability. The molecular properties of the chosen compounds were evaluated using the SWISS-ADME server and the results are attached in table 1.

Table 1: Evaluation of molecular properties of the compounds using SWISS-ADME

Ligand	Pubchem CID	Molecular weight (g/mol)	Lipinski's rule	Bioavailability score
Diclofenac	3033	296.15	Yes; 0 violation	0.85
Piperine	638024	285.34	Yes; 0 violation	0.55
Naringin	442428	580.53	No; 3 violations: MW>500, N or O>10, NH or OH>5	0.17
Rapamycin	5284616	914.17	No; 2 violations: MW>500, N or O>10	0.17
Alpelisib	56649450	441.47	Yes; 0 violation	0.55
Afuresertib	46843057	427.32	Yes; 0 violation	0.55
d-Limonene	22311	136.23	Yes; 0 violation	0.55
Eugenol	3314	164.20	Yes; 0 violation	0.55
Curcumin	969516	368.38	Yes; 0 violation	0.55
Cinnamaldehyde	637511	132.16	Yes; 0 violation	0.55

Pharmacokinetic and toxicity properties of the ligands

After administration, bioavailability refers to the rate of absorption of a medicine at the location of physiological action. The pkCSM is a free and open source web interface used for the analysis and optimization of pharmacokinetic and toxicity properties, a useful tool that helps research groups to find the balance among efficacy, safety, and pharmacokinetic properties. The results obtained from the software is mentioned in table 2.

Vol. 17(Supplementary issue - 3B) 1232-1244,September 2023, ISSN 0973-8916 (Print), 2230-7303 (Online)
10.5530/ctbp.2023.3s.59

Table 2: Efficacy, safety, and pharmacokinetic properties of the compounds

S.No	Ligand	Absorption-Intestinal absorption (human) %	Distribution-BBB Permeability (log BB)	Metabolism (Cytochrome enzymes)	Excretion- Total clearance (log ml/min/kg)	Toxicity-AMES/ Hepatotoxicity
1	Diclofenac	91.923	0.236	No	0.291	No/No
2	Piperine	94.444	-0.102	Yes (CYP3A4 substrate, CYP2C19 inhibitor)	0.232	No/Yes
3	Naringin	25.796	-1.6	No	0.318	No/No
4	Rapamycin	62.002	-1.674	Yes (CYP3A4 substrate)	0.558	No/Yes
5	Alpelisib	86.367	-1.275	No	0.031	No/Yes
6	Afuresertib	87.974	-0.73	Yes (CYP3A4 substrate, CYP1A2 inhibitor, CYP2D6 inhibitor)	0.537	No/Yes
7	d-Limonene	95.898	0.732	No	0.213	No/No
8	Eugenol	92.041	0.374	Yes (CYP1A2 inhibitor)	0.282	Yes/No
9	Curcumin	82.19	-0.562	Yes (CYP3A4 substrate, CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP3A4 inhibitor)	-0.002	No/No
10	Cinnamaldehyde	95.015	0.436	Yes (CYP1A2 inhibitor)	0.203	No/No

Human Intestinal absorption

Generally, the Intestine is the principal location of medication absorption from an orally delivered solution. This approach is designed to estimate the percentage of substances absorbed by the mammalian small intestine. It calculates the proportion of a substance that would be absorbed via the human gut. A compound that has an absorbency of less than 30% is said to have been absorbed poorly. Here, d- Limonene has the highest intestinal absorption percentage (95.898), and Naringin has the lowest intestinal absorption percentage (25.796).

Blood brain barrier

The blood-brain barrier protects the brain from external chemicals (BBB). The potential of a drug to penetrate into the brain is a critical criterion to examine when reducing adverse effects and toxicity or enhancing the potency of treatments having pharmacological action in the brain. A logBB > 0.3 indicates that a substance may easily pass the blood-brain barrier, whereas molecules with a logBB of <-1 are sparsely dispersed in the brain. Here, d- Limonene with a log value of 0.732 can be easily penetrated into the brain, when compared to other com-

Vol. 17(Supplementary issue - 3B) 1232-1244,September 2023, ISSN 0973-8916 (Print), 2230-7303 (Online)
10.5530/ctbp.2023.3s.59

pounds, whereas, Rapamycin with the log value of -1.674 is poorly distributed in the brain.

Cytochrome enzymes

P-glycoprotein substrate

The P-glycoprotein is an ABC transporter (ATP-binding cassette), extruding poisons and xenobiotics from inside to outside of the cells, it acts as a biological barrier. Piperine, rapamycin, afuresertib, and curcumin are found to be a substrate of Pgp.

P-glycoprotein I and II inhibitors

Alteration of P-glycoprotein-mediated movement has important pharmacokinetic consequences for Pgp substrates, which might be used for particular therapeutic benefits or cause complications. P-glycoprotein I and P-glycoprotein II transport inhibition is a characteristic of piperine, eugenol, afuresertib, curcumin, and cinnamaldehyde.

Total clearance

The proportionality constant CLtot is used to calculate clearance of the drug, which is essentially a blend of hepatic clearance and renal clearance. It has something to do with bioavailability and is crucial for establishing dosage rates in order to obtain relatively stable concentrations. The total clearance rate of curcumin is higher (-0.002) when compared to other compounds.

AMES toxicity

The Ames test is a frequently used bacteria-based method for determining a compound's mutagenic ability. A positive test shows that the substance is mutagenic and so might cause cancer. Eugenol is the only compound that shows AMES positive and so it is predicted to be a mutagen.

Hepatotoxicity

Drug-induced hepatic damage is a prominent source of medication retention and a major safety issue for drug discovery. A chemical was classified as hepatotoxic if it caused at least one clinical or physiological liver event that is heavily correlated to altered normal liver function. Piperine, Rapamycin, Alpelisib, and Afuresertib are said to be hepatotoxic from the results given in the table 2.

Boiled-egg plot method

Numerous drug discovery setbacks, besides from ADMET, toxicity, and effectiveness, are to blame for poor bioavailability and pharmacokinetics. The primary two pharmacokinetic techniques critical for evaluation at different phases of the drug development processes are gastrointestinal intake and Brain permeation. The Brain or Intestinal estimated permeation approach (BOILED-Egg) is characterized as a precise prediction method that calculates the polarity and lipophilicity of small compounds (36). Estimates for both gut and brain permeation were obtained using the same two physicochemical features and then transformed into synthetic approaches due to the model's reliability, conceptual clarity, speed, and simple visual display. Here, diclofenac, piperine, d- limonene, eugenol and cinnamaldehyde can be readily cross the blood brain barrier, whereas, the phytochemical naringin is out of the range of Boiled-egg plot and it is represented in Fig. 1.

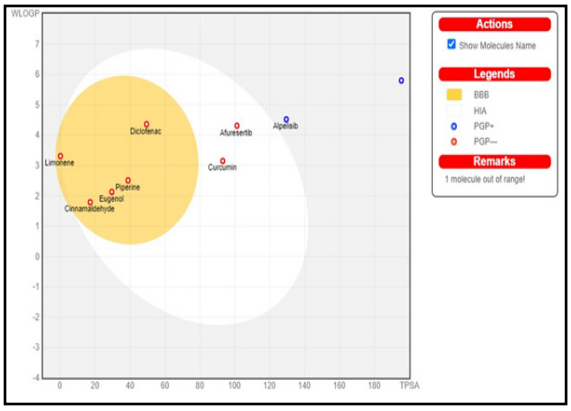

Fig. 1. Boiled egg plot representation of the compounds

Vol. 17(Supplementary issue - 3B) 1232-1244,September 2023, ISSN 0973-8916 (Print), 2230-7303 (Online)
10.5530/ctbp.2023.3s.59

Analysis and Visualization of Docking Study

Virtual screening based on molecular docking is one of the most widely used methods of structure-based drug discovery. PyRx software and UCSF chimera are used in the analysis and visualization of the protein-ligand complex and the binding energies are given in table 3. This method gives molecular information regarding protein-ligand interactions, and their binding energy (kcal/mol) which is useful for drug discovery and development.

Table 3: Binding energies of the protein-ligand complex

Compounds	**PI3K-** Binding energy (kcal/mol)	**AKT-** Binding energy (kcal/mol)	**mTOR-** Binding energy (kcal/mol)
Diclofenac	-5.5	-5.0	-6.4
Piperine	-6.2	-5.3	-5.9
Naringin	-6.8	-6.2	-6.8
Eugenol	-6.2	-4.5	-5.1
d-Limonene	-6.6	-4.5	-4.8
Curcumin	-8.6	-5.1	-7.0
Cinnamaldehyde	-6.1	-4.3	-5.0
Alpelisib	-6.8	-	-
Afuresertib	-	-5.6	-
Rapamycin	-	-	-6.8

The virtual screening of these selected compounds against the PI3K/AKT/mTOR pathway receptors were performed. The compounds were utilized to uncover interactions of molecules with these protein targets. The affinities between the ligands and their respective proteins were recorded, and their 2D and 3D structures are showcased in Fig. 2-7. Most of the compounds showed moreover the same binding energy when compared to the FDA- approved drugs Alpelisib, Afuresertib and Rapamycin. But curcumin showed the best binding energy PI3K (-8.6 kcal/mol), AKT (-5.1 kcal/mol), mTOR (-7.0 kcal/mol) when compared to diclofenac, piperine, d-limonene and other compounds. Naringin showed the highest binding energy -6.2 kcal/mol against AKT protein, compared to the FDA approved AKT inhibitor Afuresertib. d- limonene showed its best binding energy (-6.6 kcal/mol) against PI3K protein.

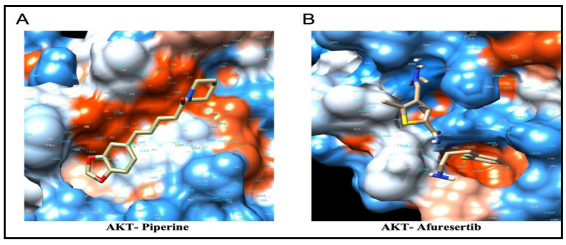

Fig. 2. 3D representation of the Protein-ligand docked complex. A) AKT-Piperine, B) AKT-Afuresertib

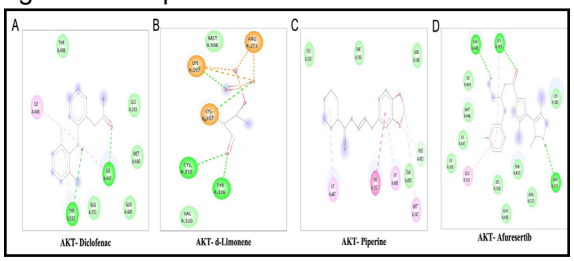

Fig. 3. 2D representation of the interaction between ligand molecules. a) Diclofenac, b) d-Limonene, c) Piperine, d) Afuresertib with the target molecule AKT. Light greenish color represents the van der Waals interaction, Pi-Pi stacking interaction is represented in solid pink, bright green color represents the conventional hydrogen bond interaction.

Vol. 17(Supplementary issue - 3B) 1232-1244,September 2023, ISSN 0973-8916 (Print), 2230-7303 (Online)
10.5530/ctbp.2023.3s.59

The free energy of binding sites is a key criterion for determining how they interact. Positive free energy values indicate that energy is needed to originate the interactions or linkages, and that binding will not occur on its own. All of the values in this investigation are negative, implying that binding will happen spontaneously. Drug discovery and development is the most common procedure nowadays, and it starts with target and lead identification, then leads optimization and pre-clinical in vitro and in vivo investigations to identify the most effective compounds that fulfill the major criteria for drug development (37).

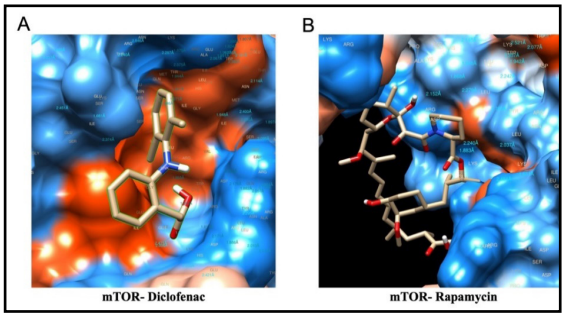

Fig. 4. 3D representation of the Protein-ligand docked complex. A) mTOR -Diclofenac, B) mTOR- Rapamycin

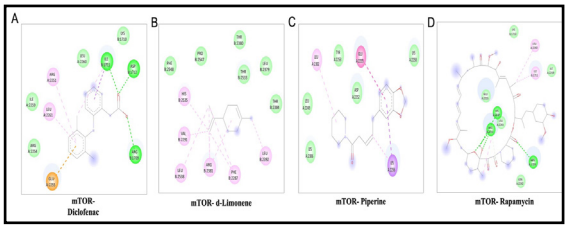

Fig. 5. 2D representation of the interaction between ligand molecules. a) Diclofenac, b) d-Limonene, c) Piperine, d) Rapamycin with the target molecule mTOR. Light greenish color represents the van der Waals interaction, Pi-Pi stacking interaction is represented in solid pink, bright green color represents the conventional hydrogen bond interaction.

It takes a long time and a lot of capital to develop a therapeutic drug using in vivo and in vitro methodologies. Using bioinformatics techniques, computational drug discovery can aid in the identification of effective therapeutic agents and targets. Bioinformatics tools can also be used to analyze target protein structures for the potential active site, develop pharmaceutical active drug compounds, and inspect their flexibility and kinetic characteristics. Molecular docking studies of these molecules or compounds with protein targets will allow us to understand the sensitivity and effectiveness of newly developed molecules. There are several programs that assist us in developing an active therapeutic compound. Furthermore, high-performance computers, data management software, and networking are assisting us in the development of high-quality data and the translation of large amounts of complicated biological data into usable information in recent trends to identify innovative therapeutic compounds (38).

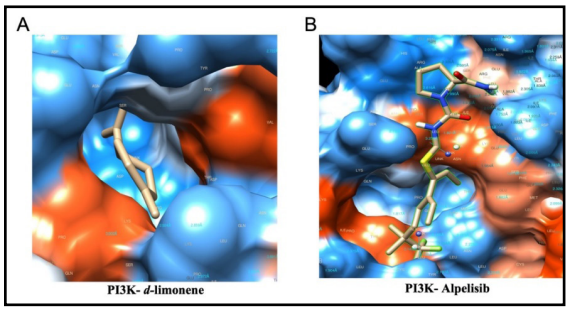

Fig. 6: 3D representation of the Protein-ligand docked complex. A) PI3K -d-Limonene, B) PI3K – Rapamycin

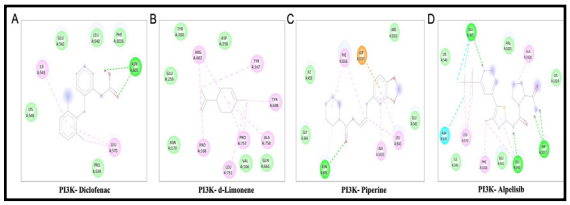

Fig. 7: 2D representation of the interaction between ligand molecules. a) Diclofenac, b) d-Limonene, c) Piperine, d) Alpelisib with the target molecule PI3K. Light greenish color represents the van der Waals interaction, Pi-Pi stacking interaction is represented in solid pink, bright green color represents the conventional hydro-

Vol. 17(Supplementary issue - 3B) 1232-1244,September 2023, ISSN 0973-8916 (Print), 2230-7303 (Online)
10.5530/ctbp.2023.3s.59

gen bond interaction.

Among the fundamental cellular signalling pathways, phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signalling plays a vital role in core cellular activities. Cell motility, metabolism, development, and division are all regulated by the PI3K/Akt/mTOR pathway. Human malignancies have been found to deteriorate when this route is inhibited, a finding that has been investigated in preclinical settings and examined at varying degrees in numerous clinical studies (39). The Food and Drug Administration approves certain inhibitors for this pathway provided clinical trials demonstrate their potency and safety.

With the proteins that have been looked into, each one of the compounds have a binding affinity. The maximum binding energies to all of the targeted proteins were shared by curcumin and naringin when compared to other compounds. Curcumin's drug-likeness property and ADMET results were satisfactory, while naringin's weren't. Curcumin, on the other hand, has received extensive research and has been employed as a drug conjugate. Therefore, Diclofenac was chosen to combine with piperine and d-limonene to test their synergism on breast cancer cells based on the binding energy with AKT, PI3K, and mTOR proteins, as well as their drug-like characteristic and ADMET results.

Conclusion

The aim of this study was to compare the binding energies of the phytochemicals were compared to those of the FDA-approved drugs afuresertib, alpelisib, and rapamycin against AKT, PI3K, and mTOR proteins. The findings will assist in the development of novel drugs with enhanced inhibitory activity against various tumour types. Based on the ADMET studies, drug likeness property, and docking results, we may conclude from the current study that the compounds diclofenac, d-limonene, and piperine are effective. To prove this, extensive in vitro and in vivo research together with clinical trials are required.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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