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COMPUTATIONAL APPROACH FOR ANTI-CANCER LEAD DISCOVERY USING SELECTED NATURAL SOURCES CONTAINING COUMARIN NUCLEUS

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ABSTRACT

Natural compounds with coumarin derivatives from selected natural sources hold potential as anti-cancer agents. Present study is designed to employ computational approaches such as molinspiration, Swiss ADME, pass analysis, Osiris property explorer and autodock to identify lead compounds in natural drugs containing the coumarin nucleus with specific activity against breast cancer which seems to time saving and cost effective. Pass analysis activity reported that angelicin was having less membrane integrated activity when compared to all other lead molecules. Osiris property explorer studies reported that angelicin was mutagenic, tumorigenic, and irritant; genistein was mutagenic, tumorigenic; kumatakenin and alpha mangostin were mutagenic whereas remaining lead molecules are safe. Docking studies reported that the binding score of hyperoside, naringenin, alpha mangostin, quercetin 3- O – α arabinopyranoside, kaempferol 3-O- α -d galactoside, genistein were lowest whereas remaining kumatakenin, eriodictyol hispidulin, luteolin 7- glucoside were highest in comparision with angelicin.

KEYWORDS

Coumarin, Molinspiration, Swiss ADME, Pass analysis, Osiris property and Docking.

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INTRODUCTION

Cancer continues to pose a significant challenge to global health, affecting millions of lives every year. Despite advances in conventional therapies, the development of resistance and unwanted side effects have prompted a growing interest in exploring alternative treatment strategies. The most common type of cancer on the list is Breast cancer with 3,00,590 new cases expected in US and third most prevalent cancer (14%) in India. (Uniyal, 2023)[1]. Breast cancer primarily affects women, but

men can also develop breast cancer, although it is much less common (Gadag, Sinha, Nayak, Garg, Nayak, 2020)[2]. Breast cancer occurs when abnormal cells in the breast multiply and grow out of control, forming a tumor. These cancerous cells can invade nearby tissues and, in advanced stages, spread to other parts of the body through the lymphatic system or bloodstream. For the current study, a few natural drugs containing coumarin ring that possess anti-cancer activity have been selected as shown in the Table No.1 (Agnihotri, Wakode, 2012[3], Sree Nath, Khan, Ahmad 2014[4], Levitsky, Dembitsky, 2015[5]). Natural compounds were often perceived as safer than synthetic compounds. The activity of these drugs was compared with a commercially available natural furanocoumarin agent called angelicin (Acharya, Chacko, Bose, 2019)[6] that is used as adjuvant in treatment of Breast cancer.

***In-silico* approaches**

Drug discovery and development is an intense, lengthy and interdisciplinary venture. There are many factors responsible for the failure of drugs, such as lack of effectiveness, side effects, poor pharmacokinetics and marketable reasons. A trend towards the use of *insilico* chemistry and molecular modelling for computer-aided drug design has gained significant momentum in recent times.

Molinspiration

Drug likeness is defined as a complex balance of various molecular properties and structural features that determine whether a particular molecule is like known drugs (Duffy, Devocelle, Shields, 2015)[7]. These properties include hydrophobicity, electronic distribution, hydrogen bonding characteristics, and flexibility. There are various rules such as Lipinski's Rule of 5, Veber rule, Ghose rule, Ergan rule, Muegge rule, Opera rule of 3, Norinder rule of 2, Monika rule, Veber rule describing the molecular properties that are important for the pharmacokinetics of the drugs.

Swiss ADME

The significance of the synthetic accessibility score is to determine the ease of synthesis of compounds and the scale ranges from 1 to 10. The value toward 1 denotes that compound can be easily synthesized and the value approaching 10 denotes that it's difficult to synthesize the compound. It is based on 1024 fragmental contributions (FP 2) modulated by size and complexity penalties, trained on 12, 782,590 molecules, and tested on 40 external molecules.

PASS Analysis

PASS Online predicts over 3500 kinds of biological activity, including pharmacological effects, mechanisms of action, toxic and adverse effects, interaction with metabolic enzymes and transporters, influence on gene expression, etc.

OSIRIS Property explorer

OSIRIS (Optical and Spectroscopic Information System) is a software tool used for predicting and evaluating the properties and behaviour of organic compounds. It is widely employed in the field of drug discovery and development to assess the drug-likeness, toxicity and other key properties of chemical compounds.

Auto Dock

Auto Dock utilizes a grid-based energy evaluation approach combined with a search algorithm to explore the conformational space of the ligand within the receptor's binding site.

METHODOLOGY

Molinspiration

Open the internet search engine (google/ explorer) and type www.molinspiration.com in the address bar. Then the home page of molinspiration will appear

Select calculation of molecular properties and prediction of bioactivity. Enter the a) smiles notation of the chemical structure or b) draw the structure using given applet. Click on Calculate properties – to determine drug- likeness properties. Predict bioactivity- to determine binding affinity.

Swiss ADME

Open the internet search engine (google/ explorer) and type http://www.swissadme.ch in the address bar. Then home page of Swiss ADME will appear. Draw structure of the compound for which molecular properties to be determined in the left

side window (a) or enter smiles notation in the right-side window (b). Click on Run at the bottom of the page.

PASS analysis

Open the internet search engine (google/explorer) and type https://www.way2drug.com/PassOnline/predict.php . Then the home page of pass analysis will appear where you should enter your email id for registration. Click on go for prediction where a interface appears to enter a password sent to your mail. Click on predict new compound. Select an option to enter molecule in the format of smiles/ MOL file/ Marvin JS (where you can draw molecule). Enter a molecule smiles notation (a) and click on get prediction (b). A page will open giving the (a) results of biological activity of the molecule Pa (probability of activity) and Pi (probability of inactivity). You can (b) get information about possible adverse effects.

OSIRIS- Property Explorer

Open the internet search engine (google/explorer) and type http://www.cheminfo.org/flavor/cheminformatics/Utility/Property_explorer/index.html_in the address bar [26]. Then the home page of Osiris will appear. Click on the utility option and select property explorer. A page to draw the structure at the left side of the page will appear (a). After drawing the structure of the molecule predicted properties will appear.

AutoDock

Software required to be installed for Autodock: Autodock, MGLTools and Open Babel.

The target protein was downloaded in PDB format from Protein Data Bank.

The ligands were drawn in Chemsketch and saved in MOL/MDL format and converted to PDB format using Open Babel.

To convert ligand to PDB format, select input format as MOLMDL → select ligand →select output format as PDB→ Convert.

A docking folder was created with all the required files: autodock4.exe, autogrid4.exe, AD4.1_bound.dat, AD4 parameters.dat, ligand, and protein.

Procedure for docking using AutoDock

Open AutoDock → File → Preferences → Set → Startup Directory- copy and paste the docking folder pathway→ Set →Dismiss.

Preparation of Protein

I. All molecules (right click) → Read molecule → Select Protein →Open.

II. To delete the extra chain of protein: Select 'S' for B chain →Edit → Delete →Delete selected Atoms→ Continue.

III. Removal of water molecules: Edit → Delete water.

IV. Add hydrogen: Edit →Hydrogens → Add → Polar only → Ok.

V. Addition of Charges: Edit → Charges → Add Kollman charges → Ok.

VI. Save protein in pdbqt format: Grid → Macromolecule → Choose → Select protein → Select molecule →Ok → add .pdbqt extension→ Save

Preparation of Ligand

I. Ligand →Input →Open → Select → ligand.pdb → Open → Ok

II. Ligand →Torsion tree →Choose root

III. Ligand → Torsion tree → Detect root

IV. Ligand → Output → add '.pdbqt' extension → Save

Grid-box generation

I. Grid → Macromolecule →Choose →Protein (Ex: leqg) → Select molecule→ Ok

II. Grid → Set map types → Choose ligand → ligand name→ Select ligand

III. Grid → Grid box → Grid options→ 'spacing'- increase to 1 Å→ increase x, y, and z dimensions to fit the entire protein into the grid box

IV. File → Close saving current.

V.Grid → Grid box → File → Output grid dimensions file → Name as 'grid.txt' → Save

VI. Grid → Output →Save GPF→ name the file with 'gpf extension (ligand. gpf) → Save

Docking

I. Docking → Macromolecule → Set Rigid Filename →select protein → Open

II. Docking → Ligand → Choose→ ligand name → select ligand→ Accept
III. Run → Run AutoGrid
Program pathname → Browse → autogrid4 → Open.
Parameter File name- Browse → ligand.gpf →Open → Launch.
IV. Docking→ Search parameters → Genetic Algorithm→ Accept.
V. Docking →Docking parameters →Accept.
VI. Docking → Output → Lamarckian → name file with .dpf extension (ligand.dpf) →Save.
VII. Run → Run Autodock → Browse → Select AutoDock→ Open
Program pathname→ Browse autodock4 → Open
Parameter File name→ Browse → ligand.dpf → Open → Launch
After docking was completed, the least binding energy and the corresponding conformation were noted from the DLG file.

RESULTS AND DISCUSSION

Physicochemical Properties

According to Lipinski rule of five, the oral absorption of a drug is effective, when the following criteria is met**:** Molecular weight (MW) not more than 500 D, Hydrophobicity (log P) not more than 5, Number of hydrogen bond donors (HBD) not more than 5, Number of hydrogen bond acceptors(HBA) not more than 10. Any deviation from this rule will be notified as violation and gives indications for the possible structural modifications of the molecule so that it will evolve as the best fit to exhibit the desired pharmacological activity. From the Table No.2, it is reported that out of selected eleven, six compounds such as Angelicin, Hispidulin, Genistein, Kumatakenin, Naringenin, Eriodictyol, are in accordance with the Lipinski rule of five with zero violations whereas Alpha mangostin showing one violation with 6.32 log P value, Luteolin 7 glucoside, Hyperoside, Kaempferol -3-O-α-d- galactoside, Quercetin 3 o-alpha- arabinopyranoside showing 2 violations with 11, 12, 11, 11 hydrogen bond acceptor groups and 7, 8, 7, 7, hydrogen bond donor groups respectively.

Bioactivity

Bioactivity is predicted by molinspiration; measure of the ability of the drug molecule to interact with different receptors such as GPCR ligands, Kinase inhibitors, Protease inhibitors, Ion channel modulators, or to interact with enzymes and nuclear receptors. Larger the bioactivity score, higher is the probability that the proposed molecules will be active. The compounds are considered to be active with a score more than 0.00, moderately active between -0.50 to 0.00 and inactive less than -0.50.
From the Table No. 3, it is reported that all the selected compounds found to be more active towards nuclear receptor and enzymes compared to other elements.

Swiss ADME

Synthetic accessibility of the selected compounds was obtained using Swiss ADME open software which measures on a scale of 1 to 10; very easy to synthesise towards one and difficult towards ten. From table 4, it is inferred that Angelicin, Hispidulin, Genistein, Kumatakenin, Naringenin, Eriodictyol, Alpha mangostin can be easily synthesised compared to Luteolin 7 glucoside, Hyperoside, Kaempferol -3-O-α-d- galactoside, Quercetin 3 o-alpha- arabinopyranoside**.**

Pass Analysis Based on Membrane Integrated Agonistic Activity

PASS analysis is predicted by (www.way2drug.com/passonline) software tools. *PASS (Prediction of Activity Spectra for Substances)* is used for evaluating the biological potential of the drug-like molecule. *PASS* provides contemporaneous prediction of many types of biological activity based on the structure of the proposed drug molecule. Thus, by performing *PASS* analysis one can predict the bioactivity profiles for proposed molecules before the chemical synthesis and biological testing. The probable bioactivity profiles for compounds under study can be predicted based on their structural formulae presented in MOLfile or SDfile format. PASS prediction is based on the knowledge base about structure-activity relationships for more than 1,000,000 compounds with known biological

activities. *Pa (probability "to be active")* evaluates the probability that the proposed compound is active. *Pi (probability "to be inactive")* evaluates the probability that the proposed compound is inactive.

Pa – atom promotes activity (Pa =1, Pi =0)

Pi – atom promotes inactivity (Pa = 0, Pi =0)

It is identified that all the selected compounds have an impressive membrane integrated agonistic activity compared to angelicin as reported in the Table No.5.

OSIRIS Property explorer

The toxicity parameters calculated using OSIRIS were represented in the Table No.6. The results are represented with colour codes such as red, green and yellow. Green colour indicates the compounds with low toxicity, yellow indicates mild toxicity and red colour indicates high probability of toxicity. From table 6, it can be observed that all the compounds except Angelicin Genistein, Kumatakenin and Alpha mangostin are considered to be safe and are expected to show low or no toxicity in terms of mutagenicity, tumorigenicity, irritant effect and effect on reproductive system. Compounds like Angelicin, Genistein, Kumatakenin and Alpha mangostin possess the potential risk of mutagenicity while Angelicin, Genistein, shows tumerogenicity. Angelicin and Genistein might produce irritant and toxic effects on reproductive system respectively. The drug scores ranged from 0.11-0.88. The greater score was observed for Naringenin and the lowest was for Angelicin. The order of drug scores obtained were:

Naringenin > Eriodictyol > Hispidulin > Hyperoside > Luteolin-7 glucoside > Kumatakenin> Kaempferol- 3-O-α-d- galactoside, Quercetin 3-o-alpha- arabinopyranoside> Alpha mangostin> Genistein> Angelicin.

Green - Low toxicity; Yellow - Mild toxicity; Red - High toxicity.

Binding Energies

By using AutoDock, it is observed that Luteolin 7-glucoside and Kaempferol- 3-O-α-d- galactoside were having the highest and lowest values respectively when compared with the reference drug Angelicin which is a natural anticancer agent. Compounds with the lowest binding energy will show more affinity towards receptors, thus displaying more activity. Naringenin, Hyperoside, Genistein, Alpha mangostin, Quercetin3-o-alpha arabinopyranoside, and Kaempferol- 3-O-α-d-galactoside have less binding energy compared to the other natural products and reference drug; Angelicin as shown in the Table No.7.

Discussion

Molinspiration studies revealed various physicochemical properties and bioactivity scores of the selected set of compounds among which luteolin 7 – glucoside, hyperoside, kaempferol 3-O-α -d galactoside, alpha mangostin, quercetin 3- O – α arabinopyranoside were found to violate Linpinski's rule of five**(**R05) in terms of number of hydrogen bond donors and acceptors. It was found that all lead molecules have greater affinity towards nuclear receptor ligand except angelicin.

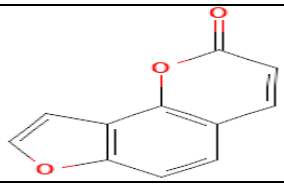
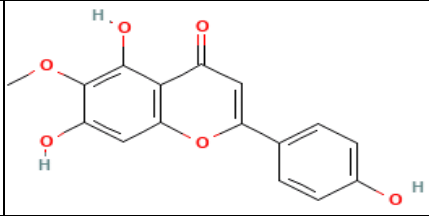
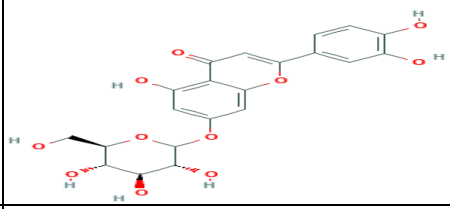
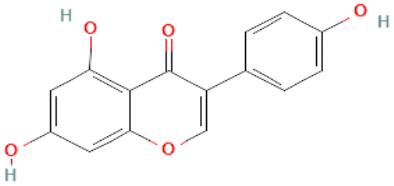
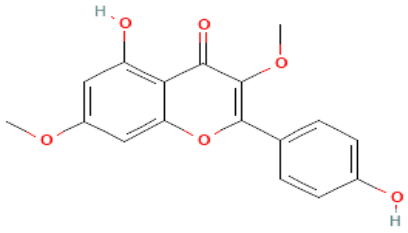
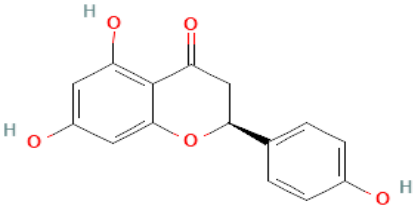
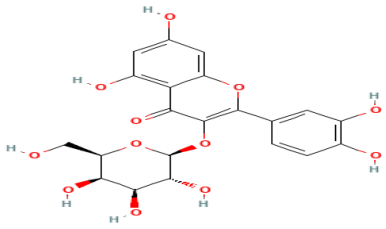
Swiss ADME studies revealed that angelicin, hispidulin, eriodictyol, kumatakenin, naringenin, genistein, alpha mangostin were easy to synthesize and remaining hyperoside, luteolin 7 – glucoside, kaempferol 3-O- α -d galactoside, quercetin 3- O – α arabinopyranoside were difficult to synthesize.

Pass analysis activity reported that angelicin was having less membrane integrated activity when compared to all other lead molecules.

Osiris property explorer studies reported that angelicin was mutagenic, tumorigenic, and irritant; genistein was mutagenic, tumorigenic; kumatakenin and alpha mangostin were mutagenic whereas remaining lead molecules are safe.

Docking studies reported that the binding score of hyperoside, naringenin, alpha mangostin, quercetin 3- O – α arabinopyranoside, kaempferol 3-O- α -d galactoside, genistein were lowest whereas remaining kumatakenin, eriodictyol hispidulin, luteolin 7- glucoside were highest in comparision with angelicin.

Table No.1: Various natural compounds containing coumarin nucleus selected for *In-silico* studies

S.No	Drug	Structure	Biological Source	Family
1	Angelicin		Angelica archangelica	Apiaceae
2	Hispidulin		Eupatorium arnottianum	Asteraceae
3	Luteolin,7-glucoside		Achillea millefolium	Asteraceae
4	Genistein		Glycine max	Fabaceae
5	Kumatakenin		Chrysanthemum morifolium	Asteraceae
6	Naringenin		Citrus paradisi	Rutaceae
7	Hyperoside		Eupatorium arnottianum	Asteraceae

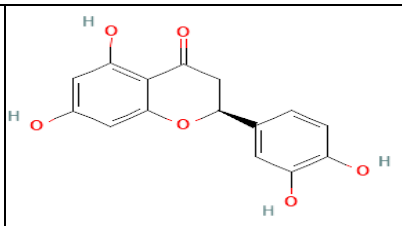
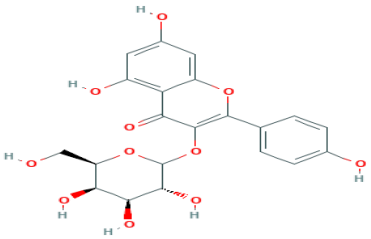
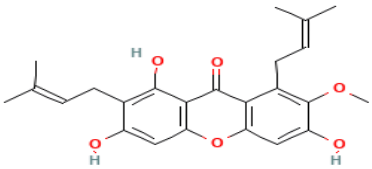
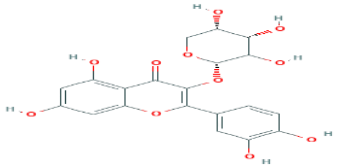
8	Eriodictyol		Eupatorium arnottianum	Asteraceae
9	Kaempferol-3,O-alpha-galactoside		Calluna vulgaris	Ericaceae
10	Alpha mangostin		Garcinia mangostana	Guttiferae
11	Quercetin 3 o-alpha-arabinopyranoside		Geranium pratense	Geraniaceae

Table No.2: Physicochemical properties of the selected compounds by using molinspiration

S.No	Drug	miLogp	TPSA	natoms	MW	nOH	nOHNH	nviolations	nrotb	volume
1	Angelicin	2.29	43.35	14	186.17	3	0	0	0	154.15
2	Hispidulin	2.48	100.13	22	300.27	6	3	0	2	249.59
3	Luteolin, 7-glucoside	0.19	190.28	32	448.38	11	**7**	2	4	364.19
4	Genistein	2.27	90.89	20	270.24	5	3	0	1	224.05
5	Kumatakenin	2.98	89.14	23	314.29	6	2	0	3	267.12
6	Naringenin	2.12	86.99	20	272.26	5	3	0	1	230.26
7	Hyperoside	-0.36	210.5	33	464.38	12	**8**	2	4	372.21
8	Eriodictyol	1.63	107.22	21	288.25	6	4	0	1	238.28
9	Kaempferol -3-O-α-d- galactoside	0.12	190.28	32	448.38	11	**7**	2	4	364.19
10	Alpha mangostin	6.32	100.13	30	410.47	6	3	1	5	376.86
11	Quercetin 3 o-alpha-arabinopyranoside	0.80	190.28	31	434.35	11	**7**	2	4	347.36

Table No.3: Bioactivity scores of selected compounds using molinspiration

S.No	Drug	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Angelicin	-0.87	-0.48	-0.88	-0.93	-1.15	-0.28
2	Hispidulin	-0.07	-0.22	0.21	0.20	-0.33	0.17
3	Luteolin,7-galactoside	0.09	-0.02	0.15	0.27	-0.01	0.42
4	Genistein	-0.22	-0.54	-0.06	0.23	-0.68	0.13
5	Kumatakenin	-0.10	-0.21	0.13	0.22	-0.26	0.17
6	Naringenin	0.03	-0.20	-0.26	0.42	-0.12	0.21
7	Hyperoside	0.06	-0.04	0.13	0.20	-0.06	0.42
8	Eriodictyol	0.07	-0.20	-0.22	0.46	-0.09	0.21
9	Kaempferol- 3-O-α-d- galactoside	0.06	-0.05	0.10	0.20	-0.05	0.41
10	Alpha mangostin	-0.01	-0.12	-0.10	0.45	-0.19	0.39
11	Quercetin 3-o-alpha-arabinopyranoside	0.20	-0.04	0.21	0.06	-0.01	0.53

Table No.4: Synthetic accessibility score of the selected compounds by using Swiss ADME

S.No	Drug	Synthesis accessibility
1	Angelicin	3.07
2	Hispidulin	3.12
3	Luteolin 7- glucoside	5.17
4	Genistein	2.87
5	Kumatakenin	3.34
6	Naringenin	3.01
7	Hyperoside	5.32
8	Eriodictyol	3.11
9	Kaempferol- 3-O-α-d- galactoside	5.29
10	Alpha mangostin	3.91
11	Quercetin 3-o-alpha- arabinopyranoside	5.04

Table No.5: Pa and Pi score of the selected compounds by using Pass analysis

S.No	Drug	Pa	Pi	Other activities
1	Angelicin	0.623	0.069	CYP2A 11 substrate, antimutagenic, oxidoreductase inhibitor, photosensitizer
2	Hispidulin	0.945	0.004	Kinase inhibitor, chlordecone reductase inhibitor, Aldehyde oxidase inhibitor
3	Luteolin-7-glucoside	0.975	0.001	Hemostatic , Vaso protector, Membrane permeability inhibitor
4	Genistein	0.913	0.008	HIF 1 A expression inhibitor, chlordecone reductase inhibitor, CYP 1 A substrate
5	Kumatakenin	0.976	0.002	Chlordecone reductase inhibitor, Antimutagenic, CYP1A inhibitor
6	Naringenin	0.964	0.003	HMOX 1 expression enhancer, CYP1 A substrate, chlordecone reductase inhibitor

7	Hyperoside	0.989	0.001	Hemostatic, cardio protectant, Monophenol monooxygenase inhibitor
8	Eriodictyol	0.962	0.002	UGT 1A 10 substrate, CYP 1A substrate, chlordecone reductase inhibitor
9	Kaempferol- 3-O-α-d-galactoside	0.989	0.001	Hemostatic, Cardio protectant, Membrane permeability inhibitor
10	Alpha mangostin	0.950	0.004	Apoptosis agonist, UGT 1A9 substrate, Lipid peroxidase inhibitor
11	Quercetin 3 O- Alpha Arabinopyranoside	0.980	0.001	Monophenol Monooxygenase Inhibitor, Membrane Permeability Inhibitor, Free Radical Scavenger

Table No.6: Toxicity profile of the selected compounds

S.No	Drug	Mutagenic	Tumorigenic	Irritant	Reproductive Effective	Drug likeness	Drug-Score
1	Angelicin	red	red	red	green	-3.14	0.11
2	Hispidulin	green	green	green	green	1.11	0.81
3	Luteolin-7 glucoside	green	green	green	green	0.76	0.69
4	Genistein	red	red	green	red	1.16	0.18
5	Kumatakenin	red	green	green	green	0.89	0.47
6	Naringenin	green	green	green	green	1.90	0.88
7	Hyperoside	green	green	green	green	1.58	0.72
8	Eriodictyol	green	green	green	green	1.49	0.86
9	Kaempferol- 3-O-α-d- galactoside	green	green	green	green	-2.43	0.44
10	Alpha mangostin	red	green	green	green	-1.11	0.20
11	Quercetin 3-o-alpha-arabinopyranoside	green	green	green	green	-2.58	0.44

Table No.7: Binding energies of the selected compounds using Autodock

S.No	DRUG	Binding Energy
1	Angelicin	-5.33
2	Luteolin 7- glucoside	-3.66
3	Hispidulin	-4.86
4	Eriodictyol	-4.96
5	Kumatakenin	-5.03
6	Naringenin	-5.71
7	Hyperoside	-5.77
8	Genistein	-5.95
9	Alpha mangostin	-6.64
10	Quercetin 3-o-alpha- arabinopyranoside	-7.20
11	Kaempferol- 3-O-α-d- galactoside	-8.32

CONCLUSION

Various computational approaches have been employed to derive several parameters like physicochemical properties, bioactivity scores, synthetic accessibility, membrane integrated activity, toxicity profile and binding score with a selected set of coumarin rings containing natural anticancer agents. This study provided the basis for the selection of compounds to carry out synthesis and pharmacological activity studies on the selected compounds.

CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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