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Harnessing Insilico Techniques for Breakthroughs in Breast Cancer Drug Discovery

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ABSTRACT
Breast cancer is the most common and deadly cancer globally, with over 1.6 million new cases in 2010 and over 50,000 deaths annually. It is the leading cause of cancer-related fatalities worldwide and is characterized by various molecular subtypes. In India, the incidence is projected to surpass 90,000 cases in the near future. Insilico molecular docking is a computational technique that simulates interactions between nucleic acids and target molecules to validate the binding of potential aptamer candidates and identify specific binding sites. A total of 28 phytochemical constituents were screened using various software's to identify drug-likeness and toxicity prediction. Molecular docking studies were performed between protein 4zzz and the phytochemical constituents and recorded. The top five compounds were selected based on their docking scores and e energy, with Berberine having the highest score of -9.80847 and e energy of -46.469. The study compared 28 phytochemical constituents with standard drugs Kaempferol and Quercetin, revealing five constituents with high docking scores and e energy. Berberine, ellagic acid, Hispidulin, Theaflavin, and Genkwanin were found to have good anti-cancer activity. Insilico studies identified berberine as a lead molecule for breast cancer, which can be used as a cocrystal for further studies. The anticancer activity of these compounds could be enhanced by adding substituents to the pharmacophore structure in the future.

KEYWORDS: Computer Aided Drug Design, Insilico molecular Docking, Breast cancer, Phytochemical constituents, Protein 4zzz, Interactions.

1. INTRODUCTION

Cancer stands as a significant global health challenge, causing a substantial number of deaths across nations regardless of their income levels. The incidence and mortality rates of cancer are projected to escalate rapidly due to factors such as population growth, aging demographics, and the adoption of lifestyle habits that heighten cancer risk. This trend is particularly noteworthy in low- and middle-income countries (LMICs) undergoing economic transitions, which bring about changes such as increased mechanization, shifts in gender roles, and greater exposure to global markets. Consequently, many risk factors associated with lifestyle choices, such as tobacco consumption, sedentary behavior, obesity, and reproductive patterns, prevalent in high-income countries (HICs), are becoming more widespread in

LMICs. Cancer encompasses a diverse group of diseases characterized by the uncontrolled proliferation and dissemination of abnormal cells. Metastasis, the stage at which cancer cells spread beyond their original site, poses a grave threat as it can lead to fatal outcomes if left unchecked. The causes of cancer are multifaceted, stemming from external factors like tobacco use, exposure to chemicals and radiation, and infectious agents, as well as internal factors including genetic mutations, hormonal influences, immune disorders, and random genetic alterations.[1]

Breast cancer ranks among the most commonly diagnosed and deadliest cancers globally, following closely behind lung cancer in terms of mortality rates, particularly among women. Worldwide, it was responsible for over 1.6 million new cases in 2010. In India, the incidence or prevalence of breast cancer is projected to surpass 90,000 cases in the near future, with over 50,000 women succumbing to the disease each year. Among cancers affecting women, breast cancer stands out as the most prevalent and the leading cause of cancer-related fatalities globally. It is characterized by a heterogeneous nature, with various molecular subtypes, including Basal-like, Luminal-A, Luminal-B, Human Epidermal Growth Factor 2 (HER2)-positive/HER2-enriched/HER2-overexpressing, and normal-like cancers, identified through genomic profiling.[2]

Contemporary drug development heavily relies on computational techniques, known as in silico methods, to comprehend how drugs interact with receptors and their quantum chemical characteristics. In this study, a computational approach called de novo design was employed to verify the binding mode for antibacterial activity, as well as to elucidate quantum chemical properties and assess the drug-likeness according to ADMET criteria.[3]

In silico molecular docking is a computational technique used to simulate interactions between nucleic acids and their target molecules. The primary focus of in silico docking methods is to validate the binding of potential aptamer candidates and identify the specific binding sites between aptamers and their targets. In vitro SELEX (Systematic Evolution of Ligands by Exponential Enrichment) is conducted up to a certain round, after which the resulting pool of nucleic acids undergoes sequencing. These sequences are then subjected to computational docking simulations to evaluate the binding affinity of each nucleic acid sequence to its target. The nucleic acids demonstrating the strongest binding affinity to the target molecule are selected as the most promising aptamers.[4]

Docking refers to computational methods designed to anticipate the structure of the complex formed when two or more molecules interact: typically, a receptor and a ligand. The receptor is commonly a protein, while the ligand can vary and may include proteins, nucleic acids, or small molecules such as drugs, substrates, or inhibitors. The fundamental challenge of molecular docking involves predicting the precise configuration of the bound complex, based on the atomic coordinates of the molecules involved.[5]

The earliest known record of utilizing plant substances for medicinal purposes dates back to around 5000 years ago, as documented on a Sumerian clay tablet discovered in Nagpur, India. This ancient text discusses the therapeutic use of well-known plants such as poppy, henbane, and mandrake, which remain popular remedies in modern times.[6]

During the early 1800s, the emergence of sophisticated synthetic chemistry techniques facilitated our understanding of the mechanisms, isolation, and synthesis of active compounds found in well-known medicinal plants like poppy, ipecacuanha, strychnic, quinine, and pomegranate. Despite the long-established history and efficacy of medicinal plants, research in this field experienced a slowdown during the late 1800s and early 1900s. Pharmaceutical industries showed reluctance towards utilizing plant-

derived components, leading to a substantial shift in focus from plant-based remedies to synthetic chemistry in drug development.[6]

The success achieved with antimalarial drugs derived from traditional herbal medicine is not an isolated occurrence but rather represents a small fraction of the potential pharmaceutical benefits offered by plant-based compounds. Consequently, the National Cancer Institute (NCI) in the United States has directed significant efforts towards identifying therapeutic agents for cancer treatment from plant sources. Through initiatives like the Cancer Moonshot project, which aims to expedite cancer research and broaden the availability of cancer therapeutics, the focus has been placed on phytochemicals. As part of this endeavor, the NCI has compiled a collection of natural products and their purified chemical constituents, providing researchers with resources to discover novel anticancer medications.[6]

Quercetin, chemically known as 3,3',4',5,7-pentahydroxyflavone, belongs to a broad category of polyphenolic flavonoid compounds commonly found in various plants and plant-based food sources. Often, quercetin exists in glycoside forms, such as rutin, where a disaccharide replaces the hydrogen of the R-4 hydroxyl group. Quercetin is referred to as the aglycone or sugarless form of rutin. In experiments conducted on human breast cancer cell lines, it was observed that quercetin at a concentration of 248 microM significantly decreased the expression of mutant p53 protein to nearly undetectable levels. Lower concentrations of quercetin resulted in less reduction of mutant p53 expression. The suppression of p53 expression was found to arrest the cells in the G2-M phase of the cell cycle. However, this downregulation was considerably less pronounced in cells with an intact p53 gene. It's worth noting that mutations of p53 are among the most prevalent genetic abnormalities observed in human cancersKaempferol represents one of the most encountered aglycone flavonoids in the form of glycoside. It is a tetrahydroxyflavone in which the four hydroxy groups are located at positions 3, 5, 7, and 40, and it is a yellow compound.[7], [8], [9], [10]

Kaempferol is among the most common aglycone flavonoids found in glycoside form. It is a tetrahydroxyflavone, with hydroxy groups positioned at 3, 5, 7, and 40, lending it a yellow hue. Kaempferol is widely distributed across various plant parts, including seeds, leaves, fruits, flowers, and vegetables. Both kaempferol and its glycosylated derivatives have demonstrated a range of beneficial effects, including cardioprotective, neuroprotective, anti-inflammatory, antidiabetic, antioxidant, antimicrobial, antitumor, and anticancer properties.[11], [12], [13], [14]

2. MATERIALS AND METHODLOGY

2.1 Molecular docking study

Protein is downloaded from Protein Data Bank (PBD ID: 4ZZZ). It was later generated using the Schrodinger suite 2022-1's protein manufacturing wizard.[15], [16], [17] By eliminating crystal fluids and modifying bond ordering with hydrogen additions, the protein was produced. Prime was used to create protonation and tautomeric states for acidic and basic residues at pH 7.0 after replacing any missing side chains and loops.[18], [19], [20], [21] The protein was reduced using the molecular force field OPLS3e (Optimized Potentials for Liquid Simulations), and the RMSD of the crystallographic heavy atoms was set to 0.30. The docking procedure was confirmed by re-docking the Co-crystal ligand and calculating the RMSD difference between the initial energy-reduced posture and the Co-crystal ligand's XP docked positions. The overlay of the XP docked attitude with the RMSD difference and the energy-minimized starting stance. LigPrep was used to prepare the ligands, and the prefilter option was used to get rid of any extraneous ligands before starting the virtual procedure. The ligands were docked sequentially using the

default parameters for the XP (extra precision) modes into the catalytic pocket of PARP-1 (4ZZZ.pdb). The ideal docking point was selected using glide g-score, glide energy values, and hydrogen bond evaluations.[18], [22]

2.2 Insilico drug likeness

Physical and pharmacokinetic prediction of relevant characteristics for the design compound was done by online tool SWISSADME. Molecular weight, Total Polar Surface Area (TPSA), Hydrogen Bond Acceptor and Donor Count, log P, log D, log S, Molar Volume, Dissociation Constant, Number of Violations of Lipinski's Rule of Five, Log P, Log D, Log S the Van der Waals volume, and other properties were computed.[23]

2.3 Insilico toxicity predictions

The organ toxicities and toxicological endpoints of the ligands and their LD50 were predicted using PREADMET. Only compounds without violation are used for further studies.[24]

3. RESULT AND DISCUSSION

Ligands of phytoconstituents are drawn using marvin chemaxon are displayed in **figure;1**. Various insilico studies for breast cancer using PARP 1 protein i.e 4zzz are studied and reported in **figure 1 and Tables 1-3.**

3.1 Molecular docking

The docking score of standard kaempferol and quercetin were -9.1837, -7.92728, g score; -9.223, -7.916, lipo; -3.0865, -2.90084, H bond; -0.539326, -0.192552, eVdw; -29.9528, -42.7164, e coul; -19.0928, -10.6034, e model; -72.1775, -79.1941 and glide energy; -49.0456, -53.3198. These values are compared with other 26 phytochemical constituents. Among these 26 compounds top 5 compounds Berberine, Ellagic acid, Theaflavin, Hispidulin and Genkwanin were selected based on their docking score and e energy. Their docking scores: -9.80847, -8.95606, -8.90836, -8.87821, -8.82576 and e energy; -46.469, -52.0005, -29.8589, -50.2323, -46.6698. In this Berberine has docking score of -9.80847 and e energy of -46.469, Ellagic acid and Hispidulin has second high docking score of -8.95606 and -8.87821 and e energy -52.0005 and 50.2323 are displayed in table 1.

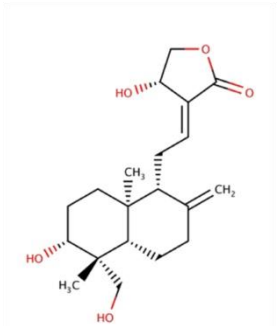
3.2 Docking interaction

The interaction of top five compounds with the protein 4zzz was described. Berberine has one hydrogen bond interaction with Serine 864 and Pi-Pi bond interaction with Tyrosine 907. Kaempferol has two hydrogen bond interaction with the amino acid Serine 864, 904 and Aspartate 766, 770, one Pi-Pi interaction with Tyrosine 907. Ellagic acid has three hydrogen bond interaction with aspartate 766, glycine 863, GOL 2018, one pi-pi interaction with tyrosine 907 and this compound also have solvent exposure. Hispidulin has three hydrogen bond interaction with aspartate 766, phenylalanine 869, histidine 862, one pi-pi interaction with tyrosine 907 and has a solvent exposure. Theaflavin has three hydrogen bond interaction in which one bond is interacted through the water molecule with the amino acid arginine 878 and the other two interaction with amino acid are aspartate 770, serine 864 and 904, glycine 863, one pi-pi interaction tyrosine 907 and salt bridge interaction with glutamic acid 988. Quercetin has two hydrogen bond interaction with aspartate 770and serine 904, one pi-pi interaction tyrosine 907 and has a solvent exposure. Genkwanin two hydrogen bond interaction with aspartate 766, phenylalanine 897, one pi-pi interaction with tyrosine 907 and also has a solvent exposure. These results are displayed in figure 2

3.3 SWISS ADME

All the phytochemical constituents are screened for Swiss ADME and based on the docking score, the 5

compounds which are comparable with standard and better than standards are checked and among that, all 5 phytochemical constituents; Molecular weight for phytochemical constituents must be less than 500 Daltons satisfied by 4 of 5 constituents except Theaflavin which has 564.49 Da. All 5 molecules such as Berberine, Ellagic acid, Theaflavin, Hispidulin and Genkwanin has Rotatable bonds less than 10 and obeys the rule, H-bond acceptors are less than 10 for all compounds except Theaflavin which has 12, H-bond donors are less than 5 for all compounds except Theaflavin which has 9, Topological Polar Surface Area (TPSA) with range Varies, typically less than 140 Å² where Berberine, Hispidulin, Genkwanin are in range, Ellagic acid violated by little elevated value of 141.34 and Theaflavin have 217.6. Log P (cLog P) greater than 5 likely had poor absorption or permeation. Among the selected top 5 compound, all have the Consensus Log P value of 1 to 4 and have better absorption. GI permeation, an important characteristics for a compound to formulate it as an oral absorbable formulation, where out of 5, except theaflavin, all have relatively high GI Permeation. BBB Permeation is an important character for a cancer, especially in metastasis as it may penetrate CSF. Among the top 5 phytochemical constituents, Berberine have BBB Permeation and where others doesn't. The Lipinski violations of 1 or less is acceptable where the 4 constituents among 5 have 0 violation except theaflavin which has 3 violations. Bioavailability Score for the drugs are 0.55, which means around 55% except Theaflavin 0.17, which is not acceptable. The Pain alerts is nil for Berberine, Hispidulin and Genkwanin and 1 for Ellagic acid and Theaflavin. The Synthetic Accessibility for Berberine, Ellagic acid, Theaflavin, Hispidulin and Genkwanin are 3.14, 3.17, 5.03, 3.26 and 3.03. are displayed in Table 2 and figure 3.



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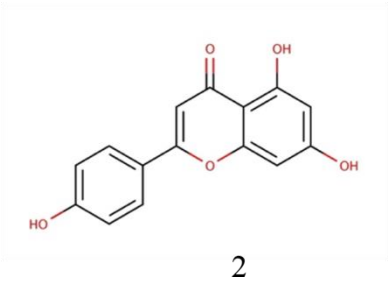

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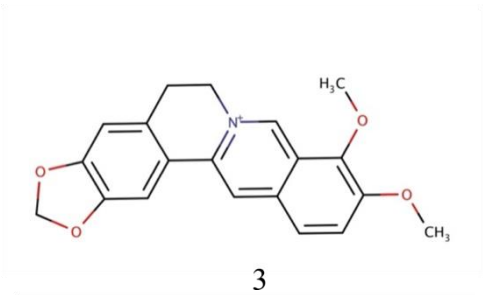

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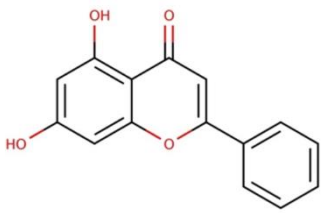

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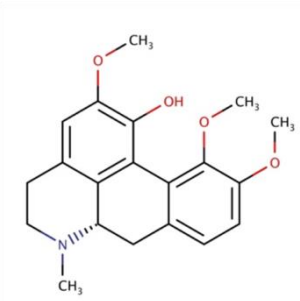

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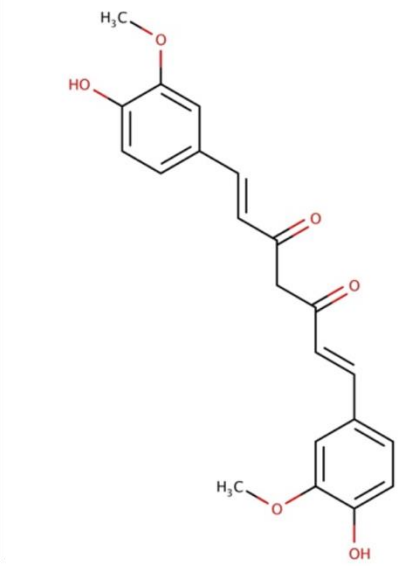

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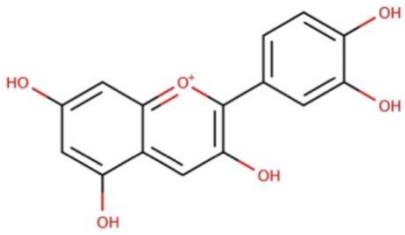

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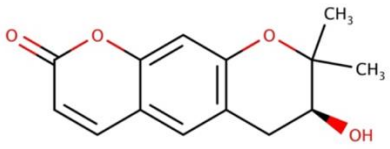

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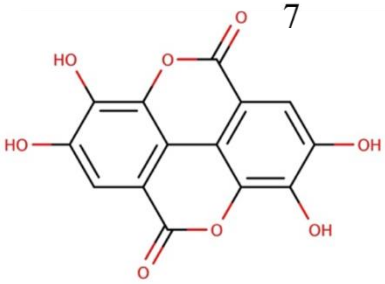

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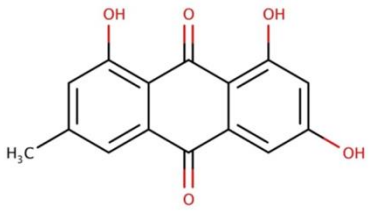

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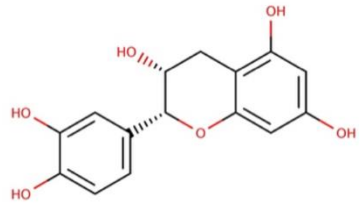

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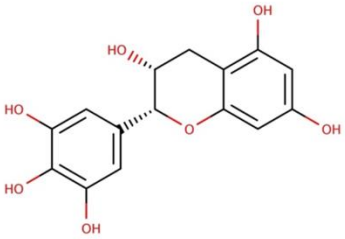

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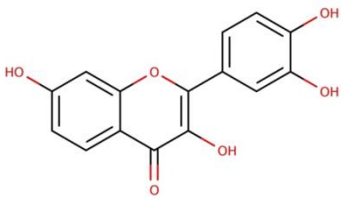

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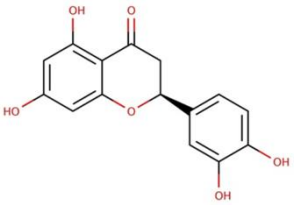

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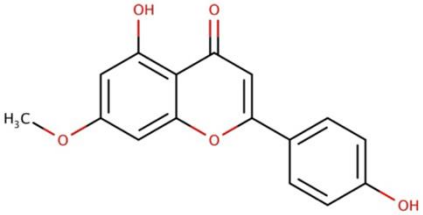

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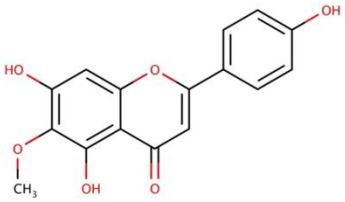

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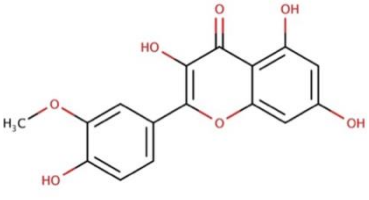

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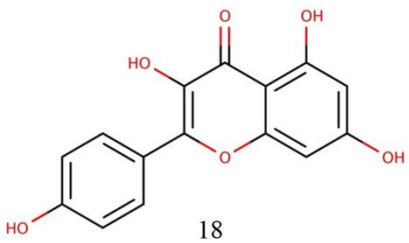

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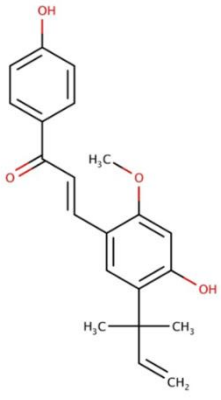

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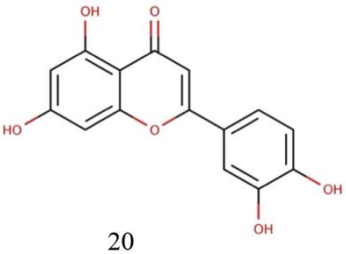

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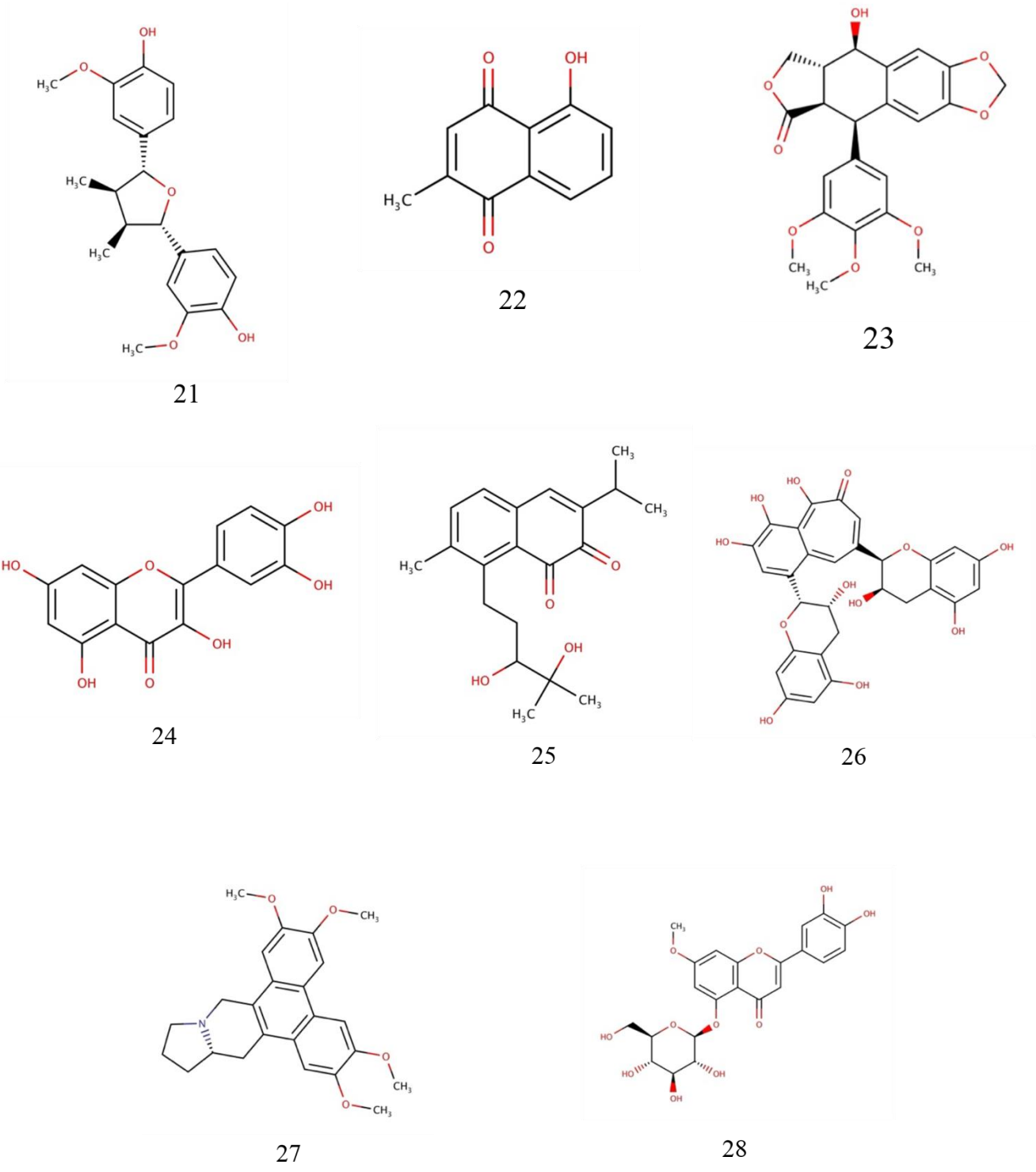

Figure 1: Phytochemical Constituents

1 -Andrographolide; 2 –Apigenin; 3 -Berberine; 4-Chrysin; 5 –Corydine; 6 -Curcumin; 7 -Cyanidin; 8 -Decursinol; 9 -Ellagic acid; 10 -Emodin; 11 -Epicatechin; 12-Epigallocatechin; 13-Eriodyctiol; 14-Fisetin; 15-Genkwanin; 16-Hispidulin; 17-Isorhamnetin; 18-Kaempferol; 19-Licochalcone; 20-Luteolin; 21-Nectandrin B; 22-Plumbagin; 23-Podophylotoxin; 24-Quercentin; 25-salvicine; 26-Theaflavin; 27-Tylophorine; 28-Yuanhuanin

TABLE 1: Docking result

Title	Compound name	docking_score	r_i_glide_gscore	r_i_glide_lipo	r_i_glide_hbond	r_i_glide_evdw	r_i_glide_ecoul	r_i_glide_emodel	r_i_glide_energy
1	Andrographolide	-7.77318	-7.77348	-3.88445	-0.100593	-27.3434	-9.44799	-53.0613	-36.7914
2	Apigenin	-8.05755	-8.10545	-2.95851	-0.432452	-38.5947	-9.75375	-70.4692	-48.3485
3	Berberine	-9.80847	-9.80847	-3.94989	-0.0643633	-38.764	-7.70503	-66.3287	-46.469
4	Chrysin	-8.24925	-8.30125	-3.11856	-0.211716	-33.7063	-12.2692	-68.7962	-45.9755
5	Corydine	-7.23584	-7.29294	-3.85688	-0.051034	-31.2478	-4.98771	-50.7113	-36.2355
6	Curcumin	-7.59045	-7.96325	-3.28257	-0.252403	-37.7824	-14.4871	-73.9948	-52.2696
7	Cyanidin	-8.78638	-8.90708	-2.7871	-0.290524	-34.698	-19.0947	-88.176	-53.7927
8	Decursinol	-7.53279	-7.53279	-2.9918	-0.16	-38.3196	-4.45527	-63.146	-42.7749
9	Ellagic acid	-8.95606	-9.02956	-3.61847	-0.299294	-40.7863	-11.2142	-78.6925	-52.0005
10	Emodin	-8.38193	-8.48543	-2.74199	-0.146225	-37.2075	-9.39531	-71.4788	-46.6028
11	Epicatechin	-8.2674	-8.2674	-2.49475	-0.683502	-35.3594	-14.0498	-74.6936	-49.4091
12	Epigallocatechin	-8.58161	-8.59061	-2.67957	-0.682812	-40.3369	-13.9159	-81.9486	-54.2528

13	Eriodyctiol	-8.62975	-8.65335	-3.05334	-0.303671	-40.2303	-11.5054	-79.8655	-51.7357
14	Fisetin	-7.82573	-7.86323	-2.66606	0	-35.1334	-14.6976	-74.3037	-49.8309
15	Genkwanin	-8.82576	-8.82576	-3.28064	-0.579795	-33.347	-13.3228	-70.0187	-46.6698
16	Hispidulin	-8.87821	-8.92611	-3.47759	-0.288	-36.2398	-13.9925	-74.3647	-50.2323
17	Isorhamnetin	-8.61159	-8.65089	-3.59747	-0.303614	-44.1964	-9.82225	-80.1501	-54.0186
18	Kaempferol	-9.1837	-9.223	-3.08625	-0.539326	-29.9528	-19.0928	-72.1775	-49.0456
19	Licochalcone	-8.15834	-8.23834	-4.26737	-0.350452	-40.2169	-8.36122	-63.1827	-48.5781
20	Luteolin	-8.21043	-8.25833	-2.90588	-0.246484	-38.7293	-12.8908	-77.2295	-51.6201
21	Nectandrin B	-8.22828	-8.22828	-3.89473	-0.0505477	-46.0047	-7.90451	-77.9753	-53.9093
22	Plumbagin	-7.90097	-7.91307	-2.57884	-0.172338	-32.9622	-3.74142	-54.0382	-36.7036
23	Podophyllotoxin	-7.88977	-7.88977	-3.9797	-0.479482	-37.1445	-5.76974	-69.6406	-42.9143
24	Quercentin	-7.92728	-7.96658	-2.90084	-0.192552	-42.7164	-10.6034	-79.1941	-53.3198
25	salvicine	-8.67369	-8.67369	-3.41979	0	-41.2246	-11.6847	-76.1263	-52.9094
26	Theaflavin	-8.90836	-8.90836	-5.23193	-0.390256	-11.4774	-18.3815	-55.9947	-29.8589

27	Tylophorine	-8.21423	-8.21993	-4.24427	-0.32	-44.8054	-4.63973	-60.116	-49.4451
28	Yuanhuanin	-6.88513	-6.88753	-2.66325	-0.32	-35.1241	-14.7527	-50.7822	-49.8768

Table 2: Swiss adme result

Compound name	**Canonical SMILES**	**Formula**	**MW**	**Rotatable bonds**	**H-bond acceptors**	**H-bond donors**	**TPSA**	**Consensus Log P**	**GI absorption**	**BBB permeant**	**Lipinski #violations**	**Bioavailability Score**	**PAINS #alerts**	Synthetic Accessibility
Andrographolide	OC[C@]1(C)[C@H](O)CC[C@@]2([C@@H]1CCC(=C)[C@H]2C/C=C\1/[C@H](O)COC1=O)C	C20H30O5	350.45	3	5	3	86.99	2.23	High	No	0	0.55	0	5.06
Apigenin	Oc1ccc(cc1)c1cc(=O)c2c(o1)cc(cc2O)O	C15H10O5	270.24	1	5	3	90.9	2.11	High	No	0	0.55	0	2.96
Berberine	COc1c(OC)ccc2c1c[n+]1CCc3c(c1c2)cc1c(c3)OCO1	C20H18NO4+	336.36	2	4	0	40.8	2.53	High	Yes	0	0.55	0	3.14
Chrysin	Oc1cc(O)c2c(c1)oc(cc2=O)c1ccccc1	C15H10O4	254.24	1	4	2	70.67	2.55	High	Yes	0	0.55	0	2.93
Corydine	COc1cc2CCN([C@@H]3c2c(c1O)c1c(C3)ccc(c1OC)OC)C	C20H23NO4	341.4	3	5	1	51.16	2.77	High	Yes	0	0.55	0	3.8
Curcumin	COc1cc(/C=C/C(=O)CC(=O)/C=C/c2ccc(c(c2)OC)O)ccc1O	C21H20O6	368.38	8	6	2	93.06	3.03	High	No	0	0.55	0	2.97
Cyanidin	Oc1cc(O)c2c(c1)[o+]c(c(c2)O)c1ccc(c(c1)O)O	C15H11O6+	287.24	1	6	5	114.29	0.32	High	No	0	0.55	1	3.15
Decursinol	O=c1ccc2c(o1)cc1c(c2)C[C@@H](C(O1)(C)C)O	C14H14O4	246.26	0	4	1	59.67	2.11	High	Yes	0	0.55	0	3.36
Ellagic acid	Oc1cc2c(=O)oc3c4c2c(c1O)oc(=O)c4	C14H6O8	302.19	0	8	4	141.34	1	High	No	0	0.55	1	3.17

	cc(c3O)O													
Emodin	Cc1cc(O)c2c(c1)C(=O)c1c(C2=O)c(O)cc(c1)O	C15H10O5	270.24	0	5	3	94.83	1.87	High	No	0	0.55	1	2.57
Epicatechin	Oc1cc2O[C@H](c3ccc(c(c3)O)O)[C@@H](Cc2c(c1)O)O	C15H14O6	290.27	1	6	5	110.38	0.85	High	No	0	0.55	1	3.5
Epigallocatechin	Oc1cc2O[C@H](c3cc(O)c(c(c3)O)O)[C@@H](Cc2c(c1)O)O	C15H14O7	306.27	1	7	6	130.61	1.47	High	No	1	0.55	1	3.53
Eriodyctiol	Oc1cc2O[C@H](CC(=O)c2c(c1)O)c1ccc(c(c1)O)O	C15H12O6	288.25	1	6	4	107.22	1.71	High	No	0	0.55	1	3.11
Fisetin	Oc1ccc2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O	C15H10O6	286.24	1	6	4	111.13	1.55	High	No	0	0.55	1	3.16
Genkwanin	COc1cc(O)c2c(c1)oc(cc2=O)c1ccc(cc1)O	C16H12O5	284.26	2	5	2	79.9	2.5	High	No	0	0.55	0	3.03
Hispidulin	COc1cc(ccc1O)c1oc2cc(O)cc(c2c(=O)c1O)O	C16H12O7	316.26	2	7	4	120.36	1.65	High	No	0	0.55	0	3.26
Isorhamnetin	Oc1ccc(cc1)c1oc2cc(O)cc(c2c(=O)c1O)O	C15H10O6	286.24	1	6	4	111.13	1.58	High	No	0	0.55	0	3.14
Kaempferol	C=CC(c1cc(/C=C/C(=O)c2ccc(cc2)O)c(cc1O)OC)(C)C	C21H22O4	338.4	6	4	2	66.76	3.93	High	Yes	0	0.55	0	3.23
Licochalcone	Oc1cc(O)c2c(c1)oc(cc2=O)c1ccc(c(c1)O)O	C15H10O6	286.24	1	6	4	111.13	1.73	High	No	0	0.55	1	3.02
Luteolin	COc1c(O)cc2c(c1O)c(=O)cc(o2)c1ccc(cc1)O	C16H12O6	300.26	2	6	3	100.13	2.12	High	No	0	0.55	0	3.12
Nectandrin B	COc1cc(ccc1O)[C@@H]1O[C@@H]([C@H]([C@H]1C)C)c1ccc(c(c1)OC)O	C20H24O5	344.4	4	5	2	68.15	3.14	High	Yes	0	0.55	0	3.88

Plumbagin	CC1=CC(=O)c2c(C1=O)cccc2O	C11H8O3	188.18	0	3	1	54.37	1.72	High	Yes	0	0.55	2	2.41
Podophylotoxin	COc1cc(cc(c1OC)OC)[C@H]1[C@H]2C(=O)OC[C@@H]2[C@H](c2c1cc1OCOc1c2)O	C22H22O8	414.41	4	8	1	92.68	2.28	High	No	0	0.55	0	4.64
Quercentin	Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O	C15H10O7	302.24	1	7	5	131.36	2.97	High	No	0	0.55	1	3.23
salvicine	OC(C(O)(C)C)CCc1c(C)ccc2c1C(=O)C(=O)C(=C2)C(C)C	C20H26O4	330.42	5	4	2	74.6	2.93	High	Yes	0	0.55	2	4.13
Theaflavin	Oc1cc2O[C@@H]([C@@H](Cc2c(c1)O)O)c1cc2c(cc(c(c2c(=O)c(c1)O)O)O)[C@H]1Oc2cc(O)cc(c2C[C@H]1O)O	C29H24O12	564.49	2	12	9	217.6	1.07	Low	No	3	0.17	1	5.03
Tylophorine	COc1cc2c3C[C@@H]4CCCN4Cc3c3c(c2cc1OC)cc(c(c3)OC)OC	C24H27NO4	393.48	4	5	0	40.16	4.03	High	Yes	0	0.55	0	3.48
Yuanhuanin	OC[C@H]1O[C@@H](Oc2cc(OC)cc3c2c(=O)cc(o3)c2ccc(c(c2)O)O)[C@@H]([C@H]([C@@H]1O)O)O	C22H22O11	462.4	5	11	6	179.28	0.42	Low	No	2	0.17	1	5.34

Table 3: Toxicity result

COMPOUND	algae_at	Ames_test	Carcino_Mouse	Carcino_Rat	daphnia_at	hERG_inhibition	medaka_at	minnow_at	TA100_10RLI	TA100_NA	TA1535_10RLI	TA1535_NA
drographolide	0.0310296	mutagen	positive	negative	0.0877455	low_risk	0.0129787	0.0167863	negative	negative	negative	negative

Apigenin	0.0527482	mutagen	positive	positive	0.130131	medium_risk	0.0280583	0.0152727	positive	positive	negative	negative
Berberine	0.0784197	mutagen	negative	negative	0.185293	medium_risk	0.06102	0.104081	negative	negative	negative	negative
Chrysin	0.0688194	mutagen	negative	negative	0.12158	medium_risk	0.0238541	0.0149208	positive	positive	positive	negative
Corydine	0.0288311	mutagen	negative	negative	0.079269	low_risk	0.0106507	0.0155893	negative	negative	negative	negative
Curcumin	0.0188401	non-mutagen	negative	positive	0.0387851	medium_risk	0.0030707	0.00751345	negative	negative	negative	negative
Cyanidin	0.0304475**	mutagen	negative	negative	0.123147**	medium_risk	0.027012**	0.016145**	negative	positive	negative	negative
Decursinol	0.0750157	mutagen	negative	negative	0.261483	low_risk	0.0943837	0.0943487	positive	negative	negative	negative
Ellagic acid	0.043818	mutagen	negative	positive	0.15038	low_risk	0.0399862	0.021897	negative	positive	negative	negative
Emodin	0.0351931	mutagen	negative	positive	0.110756	medium_risk	0.0203803	0.00947176	negative	negative	negative	negative
Kaempferol	0.0483223	mutagen	negative	positive	0.196882	medium_risk	0.0642539	0.0294885	negative	positive	negative	negative
Quercetin	0.0378136	mutagen	negative	positive	0.214345	medium_risk	0.0778806	0.0335026	negative	positive	negative	negative

4. CONCULSION

In this study 28 phytochemicals constituents were compared with standard drug kaempferol and quercetin. Among these the berberine, ellagic acid, Hispidulin, Theaflavin and Genkwanin are the five phytochemicals constituents that have high docking score and e energy when compared with the standard drug Kaempferol and Quercetin. The anti-cancer activity of berberine were checked by invivo and invitro methods were found to be good. The anticancer activity of these 26 compounds were compared with the standard compounds and comes to know the lead compound within a short period of time through the insilico work. Using Insilico studies we identified berberine as a lead molecule for breast cancer. Which can be used as a cocrystal for further studies. The anticancer activity of these compounds can be enhanced by adding substituents to the pharmacophore structure of the compound in future.

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