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Original Article

Structure-based Screening of *Bacopa monnieri* Compounds as Potential Anti-Breast Cancer Agents

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ABSTRACT

Background: Breast Cancer (BC) is a major global health concern, particularly among women, and the fatality rate is increasing. Cyclooxygenase-2 (COX-2) is a critical enzyme that is overexpressed in various human cancers, including BC. By performing efficient virtual screening of *Bacopa monnieri* bioactive compounds against COX-2 active sites, promising COX-2 inhibitors might be identified, leading to a novel prognostic approach in BC treatment. **Materials and Methods:** The *B. monnieri* compounds library was produced using data from the LOTUS database, and 94 compounds were identified. The LOTUS database provided information on the molecular properties and descriptors of the selected compounds. PyRx 0.8 was used to screen the prepared compound library against the target protein COX-2. **Results:** The compounds LTS0017052, LTS0104946, LTS0081157, and LTS0239184 demonstrated stronger binding to COX-2 than the positive control Celecoxib. The binding energy of the compounds LTS0017052, LTS0104946, LTS0081157, and LTS0239184 were -9.1, -8.9, -8.7, and -8.3 kcal/mol, respectively, while Celecoxib had a binding affinity of -7.4 kcal/mol. Furthermore, these compounds exhibited favorable molecular and drug-like characteristics. **Conclusion:** Compounds LTS0017052, LTS0104946, LTS0081157, and LTS0239184 can be used as COX-2 inhibitor to manage BC. However, additional experimental validation is required to optimize these compounds as COX-2 inhibitor.

Keywords: *Bacopa monnieri*, Breast cancer, COX-2, Drug-likeness, Molecular Docking.

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INTRODUCTION

Breast Cancer (BC) is a major worldwide health concern, particularly among women, and death rates are rising (Moris *et al*., 2016; Sahu *et al*., 2022). By 2025, the global incidence is expected to surpass 20 million new cases per year (Zugazagoitia *et al*., 2016). BC affects males as well as women due to its heterogeneity (Anderson and Matsuno, 2006; Zardavas *et al*., 2015). Cancer cells become aggressive during metastasis, multiplying and spreading throughout the body because of cellular malfunction and communication failures. Age, genetic predisposition, family history, and socioeconomic level are significant risk factors (Ganz and Goodwin, 2015; Pakseresht *et al*., 2009).

Cyclooxygenase-2 (COX-2), the enzyme that converts arachidonic acid to prostaglandin H2, is expressed in a variety of tissues. Its expression is triggered by inflammatory cytokines, growth factors, oncogenes, lipopolysaccharides, and tumor promoters. COX-2 promotes cancer by boosting epithelial cell proliferation, blocking apoptosis, promoting angiogenesis, increasing invasiveness, reducing immunological responses, and upregulating mutagen synthesis. Preclinical models and clinical trials in colon cancer show that COX-2 is a viable target for prevention and treatment. Furthermore, COX-2 overexpression has been associated with the pathogenesis of several epithelial malignancies, including BC (Hoellen *et al*., 2011; Singh-Ranger *et al*., 2008; Atalay, 2016), with studies emphasizing its involvement in disease progression and poor prognosis (Shim *et al*., 2003; Denkert *et al*., 2004). BC may be prevented and cured by targeting COX-2 (Harris *et al*., 2014; Falandry *et al*., 2009).

Drug development is a costly and time-consuming procedure. For many years, this method was based on empirical pharmacology. However, throughout time, the target-based approach enabled key discoveries in this discipline, ushering in the era of rational design. To save time and financial costs, rational drug design benefits from increased computer engineering and software development, with Computer-Aided Drug Design (CADD) emerging as a potential option (Niazi *et al*., 2023). Since the 1970s, this technique has identified several significant and revolutionary molecules, including protease inhibitors, antibiotics, and others. Many anticancer agents discovered using this method have demonstrated their value, making CADD crucial in any drug discovery campaign (Del Carmen Quintal Bojórquez and Campos, 2023). The present study aimed to find possible COX-2 inhibitors in *B. monnieri* compounds for the BC management.

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MATERIALS AND METHODS

Protein preparation

The crystal structure of COX-2 (PDB ID: 5F19) was obtained from the Protein Data Bank. The heteroatoms and water molecules were removed, and the protein was saved in .pdb format.

B. monnieri compounds library preparation

The first step in Virtual Screening (VS) is to build a library of possible compounds. One of the best and most extensive annotated resources on natural product occurrences, LOTUS, is freely accessible (Rutz *et al*., 2022). Using information from the LOTUS database (https://lotus.naturalproducts.net/), 94 compounds were identified for the *B. monnieri* compounds library. These substances were used for protein-ligand docking after being downloaded in .sdf format.

Virtual Screening (VS)

Drug development is increasingly using VS, a computer method for finding structurally distinct and potentially active lead compounds, because of its faster computation speed and lower cost (Zhang *et al*., 2023; Guo *et al*., 2023). In order to create pharmacologically significant compounds, academic research organizations frequently employ the VS technique in drug development (Sankar *et al*., 2021). Following the preparation of the ligand and protein, the grid box parameters were set up to fully cover the active site of the protein. A scoring system was then used to assess possible ligand conformations within the binding region using the VS tool PyRx 0.8. The unit of measurement for the binding affinity score is Kcal/mol.

Analysis of docked models

The Discovery Studio visualizer was used to investigate the interaction of *B. monnieri* compounds with COX-2. Hydrogen and hydrophobic bonding interactions, as well as others, were considered.

Molecular Properties

The LOTUS database provided information on the molecular properties and descriptors of the hit compounds (Rutz *et al*., 2022).

RESULTS

COX-2 overexpression has been linked to the development of several epithelial malignancies, including BC. The purpose of this study was to identify natural inhibitors of COX-2 for BC treatment. *B. monnieri*, a well-known medicinal plant that has been used for human health since ancient times in the history of ayurveda, was chosen for research because it is an enriched source of alternative drug development in a non-toxic manner. The LOTUS database was used to access the bioactive compounds (n=94) of *B. monnieri*. These compounds were virtually screened against the COX-2 active sites, with Celecoxib serving as the control compound. Notably, 4 compounds (LTS0017052, LTS0104946, LTS0081157, and LTS0239184) had stronger binding affinity values for COX-2 than Celecoxib (Table 1).

The binding pattern of these compounds (LTS0017052, LTS0104946, LTS0081157, and LTS0239184), and the control (Celecoxib) in the COX-2 binding pocket exhibited that they interact in the same pocket (Figure 1).

The 2D view of interacting residues analysis of these four compounds (LTS0017052, LTS0104946, LTS0081157, and LTS0239184), and the control (Celecoxib) showed that they bind with several residues of COX-2. LTS0017052 bind with the Phe381, Phe209, Phe205, Thr206, Leu352, Val523, Phe518, Met522, Trp387, Ala527, Leu384, Gly526, Leu531, Leu534, Tyr385, Val349, Gly533, Lys532, Phe529, and Val228 residues of COX-2 (Figure 2); while Phe381, Leu534, Tyr385, Tyr348, Gly526, Leu384, Trp387, Met522, Phe518, Val349, Val523, Ser353, Leu352, Ala527, Phe529, Leu531, Phe209, Phe205, and Val344 residues were bind with the LTS0104946 (Figure 2). LTS0081157 was found to interact with Phe381, Phe529, Leu531, Tyr348, Val344, Tyr385, Trp387, Gly526, Leu384, Met522, Val349, Ala527, Phe518, Val523, Val352, Ser353, His90, Arg513, Gly533, Phe209, Phe205, Val228, and Leu534 residues of COX-2 (Figure 2). LTS0239184 interacted with Phe381, Gly533, Ile377, Phe209, Phe205, Phe529, Gly526, Val344, Tyr348, Tyr385, Leu384, Trp387, Met522, Phe518, Gln192, Ala516, Ile517, Ser353, Tyr355, Val523, Ala527, Val349, Leu534, and Leu531 residues of COX-2 (Figure 2). Furthermore, control Celecoxib was found to bind with Ser353, Val349, Tyr355, Val116, Arg120, Leu359, Leu531, Leu352, Leu384, Ala527, Tyr385, Trp387, Gly526, Met522, Phe518, Val523, Ile517, Gln192, Ala516, Gly354, Thr94, His90, and Arg513 residues of COX-2 (Figure 2).

The compounds LTS0017052, LTS0104946, LTS0081157, and LTS0239184 exhibited favorable molecular properties (Table 2). The probability of a compound being natural ranges from -5 (less likely) to 5 (very likely). Interestingly, these compounds had ratings of 1 or +1, indicating a strong preference for characteristics found in natural products. Furthermore, Lipinski's Rule of Five revealed a comprehensive profile of these compounds by assessing the drug's chemical structure to predict its oral bioavailability, and the compounds LTS0017052, LTS0104946, and LTS0239184 met the criteria with no violations (Table 3).

DISCUSSION

Cancer remains a serious public health issue globally, and studies showed that BC is one of the most common among women, accounting for over 2.3 million new cases and 685,000 deaths in 2020 (Arnold *et al*., 2022). COX-2 is a new diagnostic and therapeutic biomarker for cancer monitoring. COX-2 is a well-known tumor-associated inflammatory factor that is extensively expressed in human tumor cells, particularly BC. The

expression of COX-2 promotes tumor development, metastasis, and recurrence (Li *et al*., 2021). This study screened the *B. monnieri* bioactive compounds against the COX-2 active sites. Notably, the compounds LTS0017052, LTS0104946, LTS0081157, and LTS0239184 had stronger binding affinity for COX-2 than the control Celecoxib.

The compounds LTS0017052, LTS0081157, and LTS0239184 including control Celecoxib demonstrated H-bonding with COX-2 residues. LTS0017052 was H-bonded with Leu534, and Phe529 residues of COX-2; while LTS0081157 was H-bonded with Ser353 residue of COX-2. LTS0239184 was H-bonded with Gly526, and Leu353 residues of COX-2. Furthermore, Celecoxib was H-bonded with Phe518, Gln192, and His90 residues of COX-2.

Celecoxib is a selective COX-2 inhibitor that was used as a control in this study. Studies have shown that celecoxib plays a promising role in the treatment and prevention of various cancer types, including BC (Toloczko-Iwaniuk *et al*., 2019). Ser353, Val349, Tyr355, Val116, Arg120, Leu359, Leu531, Leu352, Leu384, Ala527, Tyr385, Trp387, Gly526, Met522, Phe518, Val523, Ile517, Gln192, Ala516, Gly354, Thr94, His90, and Arg513 residues of COX-2 have been shown to be important in the binding with Celecoxib. Interestingly, the compounds LTS0017052, LTS0104946, LTS0081157, and LTS0239184 bind to these COX-2 residues, with Val349, Leu531, Leu384, Ala527, Trp387, Gly526, Met522, Phe518, and Val523 residues being common in binding with these compounds and Celecoxib. This implied that these compounds bind to the same pocket of COX-2 as control Celecoxib.

Strong binding between the ligand and protein complex is indicated by a high negative binding affinity value (Sait *et al*., 2019; Nazam *et al*., 2020; Sait *et al*., 2020; Alqahtani *et al*., 2024). It's interesting to note that the compounds LTS0017052, LTS0104946, LTS0081157, and LTS0239184 have stronger interactions with COX-2 than the control Celecoxib, as evidenced by their higher negative binding affinity values.

Since ancient times, medicinal plants have been used to treat a wide range of illnesses and are a valuable source of pharmacologically active compounds (Ansari and Iqbal, 2023). About 3.3 billion people in developing countries use traditional medicine on a daily basis, and they are its mainstay. These plants have a significant influence on human cultures all over the world and offer excellent resources for medical research. Worldwide, approximately 80,000 species of flowering plants are used in pharmaceuticals, according to the International Union for Conservation of Nature. Brahmi, also called Brahmi, is a significant Ayurvedic medicinal plant that has been used for more than 3,000 years and is a member of the Scrophulariaceae family (Gohil and Patel, 2010). In addition to treating anxiety, neurological conditions, skin conditions, and digestive issues, it has long been used as a cognitive enhancer to help with memory, learning, and focus. *B. monnieri* may be used as an anti-cancer agent as a result of studies into its biological effects (Ghosh *et al*., 2021).

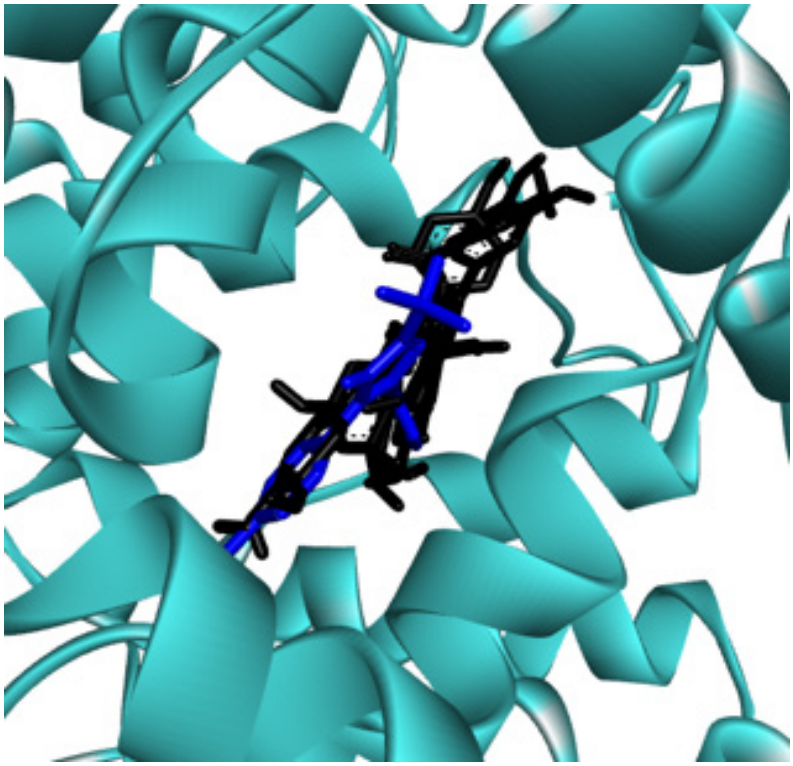
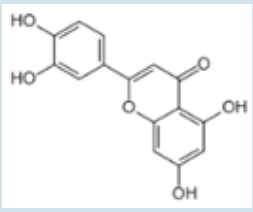
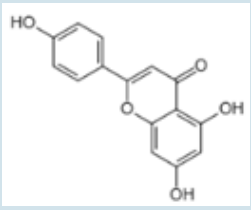
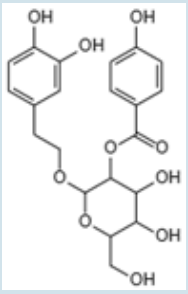
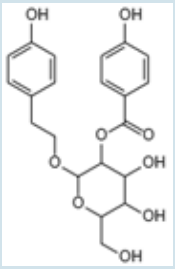


Figure 1: Binding representation of top 4 compounds (black) and Celecoxib (green) with the COX-2 protein.

Table 1: Top screened compounds of *B. monnieri* that have high binding affinity values than the control Celecoxib.

Sl. No.	Compounds	Structure	Binding affinity (kcal/mol)
1.	LTS0017052		-9.1
2.	LTS0104946		-8.9
3.	LTS0081157		-8.7
4.	LTS0239184		-8.3
5.	Celecoxib	-	-7.4

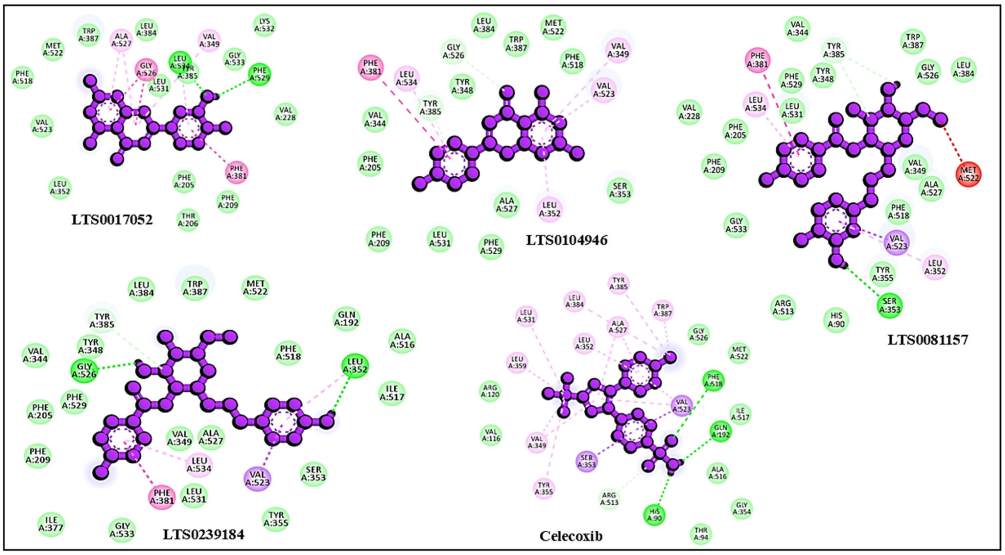


Figure 2: Interacting residues of COX-2 with top 4 compounds LTS0017052, LTS0104946, LTS0081157, and LTS0239184) and the control Celecoxib. The compounds has been shown in ball and stick representations.

Table 2: Molecular properties of the selected compounds LTS0017052, LTS0104946, LTS0081157, and LTS0239184.

Molecular properties	LTS0017052	LTS0104946	LTS0081157	LTS0239184
Total atom number	31	30	55	54
Heavy atom number	21	20	31	30
Bond count	23	22	33	32
Number of carbons	15	15	21	21
Minimal number of rings	3	3	3	3
Maximal number of rings	4	4	3	3

Table 3: Molecular descriptors of the selected compounds LTS0017052, LTS0104946, LTS0081157, and LTS0239184.

Molecular descriptors	LTS0017052	LTS0104946	LTS0081157	LTS0239184
NP-likeness score	1	1	1	1.6
Alogp	2.76	3.03	1.04	1.31
Alogp2	7.62	9.16	1.08	1.71
Apol	37.8799	37.0779	60.983	60.181
Bpol	13.8061	13.8061	32.943	32.943
EccentricConnectivityIndexDescriptor	355	338	783	754
Fmf Descriptor	0.7619	0.8	0.7419	0.7667
Fsp3	0	0	0.381	0.381
Fragment Complexity Descriptor	669.06	644.05	2319.1	2266.09
Petitjean Number	0.5	0.5	0.5	0.5
Lipinski's Rule (Failures)	0	0	1	0
WienerPathNumber	896	788	2906	2660
Xlogp	3.423	3.668	1.232	1.477
Zagreb Index	114	108	158	152
TopoPSA	111.13	90.9	166.14	145.91

CONCLUSION

A well-known inflammatory factor linked to tumors, COX-2 is widely expressed in human tumor cells, especially BC. The expression of COX-2 stimulates the growth, spread, and recurrence of tumors. The bioactive compounds of *B. monnieri* were screened in this study against the COX-2 active sites. The compounds LTS0017052, LTS0104946, LTS0081157, and LTS0239184 had strong binding with COX-2. In addition, these compounds possessed advantageous molecular and druglike characteristics. These compounds can be used to treat BC by acting as COX-2 inhibitors.

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ABBREVIATIONS

BC: Breast cancer; **COX-2:** Cyclooxygenase-2; **CADD:** Computer-aided drug design; **VS:** Virtual screening; **PDB:** Protein Data Bank; **H-bonding:** Hydrogen bonding;

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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