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# *In Silco* Docking Studies of Bioactive Compounds from *Musa acuminata* Extract and Potential Inhibitors for Bone and Colon Cancer

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**Abstract:** This study examined the ethanol extracts of *Musa acuminata* pulp for phytochemical screening based on the reported GCMS analysis. The chosen compounds were then evaluated for their anti-cancer activity against bone and colon cancer through an *in silico* approach. In an *in silico* study, among the 19 selected compounds, guanosine and beta-sitosterol demonstrated the highest docking score, binding free energy, and satisfactory pharmaceutical properties. A molecular study was conducted on the two primary compounds, guanosine and beta-sitosterol. The analysis provided insights into the stability of the protein-ligand interactions, ultimately concluding that the lead compounds exhibit the highest stability. This study indicated that the specific bioactive compounds derived from *M. acuminata* pulp demonstrated anti-cancer properties, as evidenced by *in silico* analysis.

**Keywords:** Bone cancer, Colon, Banana pulp, Bioactive compound, *In silico* analysis, Guanosine, Beta-sitosterol

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## Introduction

Cancer, recognized as the second leading cause of mortality, is defined by the atypical growth and division of cells, the interruption of programmed cell death, and the unchecked proliferation, invasion, formation of new blood vessels, and dissemination to various regions of the body (Monda *et al*., 2021). Cancers develop as a result of the build-up of mutations in critical genes, which can lead to changes in cellular behaviour and the onset of malignancy. The Global Cancer Statistics 2020 indicate that there are now 19.3 million new cancer cases and 10 million deaths related to cancer. The global cancer burden is projected to increase significantly, reaching an estimated 28.4 million cases by 2040, which represents a staggering rise of 47% (Das and Agarwal, 2024).

Osteosarcoma represents a cancer variant that predominantly impacts adolescents, marked by the development of immature bone and osteoid tissue. It frequently manifests in the lengthy bones of the arms and legs and has the potential to be life-threatening. This condition is observed more frequently in males and may manifest with or without any underlying pathology. The symptoms consist of inflammation, impaired joint function, and localized apprehension (Varadarajan *et al*., 2023).

Colorectal cancer (CRC) ranks as the third most prevalent cancer and holds the position of the second highest in mortality rates for both genders globally. In 2020, it represented 10% of all new cases and was responsible for 9.4% of cancer-related deaths worldwide. In Latin America and the Caribbean, CRC accounted for approximately 7% of cancer incidence and mortality during the same period. In Colombia, it represented 9.5% of all new cancer cases and 9.7% of cancer-related deaths among both women and men (Ferlay *et al*., 2020; Ruiz-Grajales *et al*., 2024).

Precise identification of cancer is essential for delivering suitable and effective treatment. The conventional approach to cancer treatment includes a blend of surgical interventions, radiation therapy, and chemotherapy (Wayteck *et al*., 2014). The prognosis is unfavourable when cancer exhibits resistance to radiotherapy and chemotherapy, and the side effects significantly limit the effectiveness of these conventional treatments. Therefore, it is essential to investigate alternative therapeutic targets for cancer and natural compounds that demonstrate greater efficacy and reduced adverse effects.

Knowing the over-expressed cancer biomarkers holds significant promise, as they can potentially be suppressed through targeted inhibition. Transcriptomic studies have revealed numerous differentially expressed genes across various cancer types (Mirza and Karim, 2023). A group of genes collaborates in networks and pathways to oversee cellular functions. Nonetheless, identifying a crucial therapeutic gene remains a significant challenge.

Significantly, Bcl-xL, which belongs to the Bcl-2 protein family known for its crucial role in regulating apoptotic cell death, has been documented to have important implications in malignant transformation and tumorigenesis (Wei *et al*., 2023). Reports indicate that Bcl-xL is up-regulated in various human malignancies, and its over-expression leads to the development of resistance against multiple chemotherapeutic agents or radiation (Wang *et al*., 2010). Given the significant role of Bcl-xL in the development and advancement of tumors, numerous initiatives are currently focused on targeting this molecule. Nonetheless, the role and clinical importance of Bcl-xL mRNA expression in human osteosarcoma remain ambiguous, and it is still uncertain whether Bcl-xL could serve as a viable therapeutic target for the treatment of osteosarcoma. Focal adhesion kinase (FAK) is a 125 kDa protein that plays a crucial role in focal adhesion dynamics, acting as a signaling scaffold for the assembly and maturation of focal contacts. Discovering novel FAK binding proteins may uncover potential signaling targets and aid in the advancement of therapeutic drugs for the treatment of breast, lung, prostatic, osteosarcoma, and colorectal cancer (Ren *et al*., 2015; Nguyen *et al*., 2019; Feng *et al*., 2020). FAK is essential in tumor progression and cancer metastasis through its regulation of cancer cells and their activities, including migration, invasion, and epithelial-mesenchymal transition (Schaller, 2010).

Cyclin-dependent kinase 2 (CDK2) has been noted for its over-expression in human colorectal cancer; it plays a crucial role in the transition from the G1 to S phase in the cell cycle, and its deregulation is a defining characteristic of cancer (Shi *et al*., 2015). CDK2 is mainly associated with the regulatory subunits, particularly cyclin A or E, and has been observed to be overexpressed in multiple forms of human cancer, including breast, ovarian, lung, endometrial, and thyroid carcinomas, along with osteosarcoma and

melanoma (Peyressatre *et al*., 2015). Multiple studies indicate that indole exhibits notable anti-cancer effects, in part because of its ability to inhibit cyclin-dependent kinase 2 (CDK2), a crucial regulator of the cell cycle (Gomha *et al*., 2023). The B cell lymphoma 2 (Bcl-2) family proteins, which play a crucial role in the regulation of apoptotic cell death, are linked to the advancement and progression of various cancers. Thorough investigation into new cancer treatment targets has resulted in the recognition of Bcl-2 overexpression as a defining characteristic of cancer, with Bcl-2 inhibition emerging as a potential therapeutic strategy (García-aranda *et al*., 2018).

Research indicates that phytochemicals serve as potent anticancer agents, offering advantages over synthetic compounds, including reduced toxicity, simpler extraction processes, and greater availability (Qawoogha *et al*., 2020). Approximately 35% of cancer cases can be managed through the implementation of a suitable diet, primarily focusing on the intake of plant-based foods like vegetables, fruits, and whole grains that are rich in carotenoids, flavonoids, and phenolics (Mendie and Hemalatha, 2022). *Musa acuminata* Colla, commonly known as banana, is particularly abundant in bioactive compounds including phenolics, carotenoids, biogenic amines, phytosterols, and volatile oils. These compounds are present in different sections of the plant, such as the stem, fruit, pseudostem, leaf, flower, sap, inner trunk, root, and inner core (Mondal *et al*., 2021). The fruits of *Musa* species exhibit a diverse array of pharmacological activities, encompassing antioxidant, immunomodulatory, antimicrobial, anticancer, antiulcerogenic, hypolipidemic, hypoglycemic, leishmanicidal, and anthelmintic properties (Mathew and Negi, 2017). Banana extracts have demonstrated promising results in the prevention and treatment of various cancers, including skin, colorectal, esophageal, hepatic, oral, prostate, and breast cancer (Mondal *et al*., 2021)

β-sitosterol, a plant sterol, has been acknowledged for its diverse biological effects, which encompass antinociceptive, immune-modulatory, anti-proliferative, anti-inflammatory, lipid-lowering, liver protective, metastatic, antioxidant, and anti-diabetic properties (Jayaraman *et al*., 2023). Guanosine and guanosine-derived nucleotides exhibited no cytotoxic effects on peripheral blood mononuclear cells (PBMCs) or acute lymphocytic leukemia (ALL) xenograft cells. The effects of guanosine and its derived compounds on HuT-78 cells, specifically their anti-proliferative and apoptotic properties, were negated by the nucleoside transport inhibitor NBMPR (S-(4-Nitrobenzyl)-6-thioinosine) (Schneider *et al*., 2020).

Molecular docking is a structure-based method to identify and screen novel compounds of therapeutic interest (Ferreira *et al*., 2015). The *in silico* molecular docking experiment efficiently organizes extensive compound libraries more quickly, logically, and at a considerably lower cost than conventional drug screening techniques (Torres *et al*., 2019). This study assessed potential herbal compounds with anti-cancer properties through structure-based molecular docking, aiming to predict interactions and propose an alternative treatment strategy or a complementary approach to current therapies. This study assessed the inhibitory effects of phytochemical compounds derived from the ethanol extract of *M. acuminata* (banana) pulp on bone cancer proteins, specifically BcL-XL and FAK Domine kinase, as well as colon cancer proteins, including CDK2 and BCL-2 (PDB-4LXD), utilizing molecular docking techniques.

## Materials and Methods

### *Sample collection and preparation*

The *M. acuminata* Colla fruit was gathered from Kerala, India. The banana sample underwent a meticulous cleaning process with water to eliminate any foreign particles. A knife was employed to cut the entire banana, which was subsequently allowed to dry at room temperature under sunlight for several days. The dried samples

were meticulously ground with a dry grinder and then carefully stored in an airtight container in a freezer at -20°C until the extraction process commenced. A 10% ethanol concentration was utilized to extract the dried sample (10 g) over a period of 36 h, with gentle agitation at 37°C. A solution was prepared by diluting the stock with sterile dimethyl sulfoxide, achieving a concentration of 1 mg/ml of the solvents (DMSO) (Duraipandiyan *et al*., 2006).

### *Gas chromatography-mass spectrometry (GC -MS) analysis*

This study utilized the Agilent 7890A gas chromatograph and the Agilent 5975C inert mass spectrometer, both produced by Agilent technologies and equipped with triple-axis detectors, to perform a GC-MS analysis of the ethanol extract from *M. acuminata* Colla. The spectrum values and associated components were analyzed, and the database of the acquired spectrum was preserved in the GC-MS NIST (2008) library, with materials accessible (Augustine *et al*., 2024).

### *Compound Collection*

The dataset utilized in this investigation comprised 19 compounds derived from the ethanolic extract of *M. acuminata* Colla, as identified in a previously published article (Augustine *et al*., 2024). However, only two compounds were suitable for analysis due to their interaction with bone and colon cancer targets.

### *In silico potential bioactivity prediction of ethanolic extract of M. acuminata pulp against target cancer protein*

### *Software and hardware*

The RCSB Protein Data Bank (https:// www.rcsb.org) and the PubChem database (https://pubchem.ncbi.nlm.nih.gov) were used in this investigation, as well as online applications such as ADMET lab 2.0 and Swiss ADME. Employing PyRx and Auto Dock Vina 0.8 (Dallakyan and Olson, 2015) software; alternatively, utilizing the BIOVIA Discovery Studio (RRID:SCR_015651) protein visualizer (Pawar and Rohane, 2021). Each structure underwent analysis using PLIP v1.1.1 (Salentin *et al*., 2015).

### *Protein Preparation*

The crystal structures of proteins associated with bone cancer, specifically BcL-XL (PDB-1R2D) and FAK Domine kinase (PDB-4GU6), as well as colon cancer target proteins CDK2 (PDB-6GU6) and BCL-2 (PDB-4LXD), were obtained from the RCSB Protein Data Bank (PDB) (https://www.rcsb.org/) for the purpose of docking studies. The process of preparing a chosen protein entails modifying its macromolecular structure to create a more appropriate configuration for executing a computational experiment (Opo *et al.,* 2021). The description of various proteins involved in the study is mentioned in Table 1.

### *Ligand Preparation*

The compounds identified using GC-MS from ethanolic extract of *M. acuminata* were used as ligands to study their possible interactions against the bone cancer target proteins and Colon cancer target proteins using site-specific molecular docking. For ligand structures available in PubChem, the NIST (Mass Spectrometry Database), IMPPAT (Indian Medicinal Plants and Phytochemistry Database), and ChEMBL were consulted (Linstrom and Mallard, 2001; Papadatos and Overington, 2014; Vivek-Ananth *et al*., 2023). There are 2 ligand (Guanosine and beta-sitsterol natural compounds) which were used for the docking energy analysis and pharmacokinetics analysis. Each structure was analysed with PLIP v1.1.1. PLIP allows for comprehensive detection and visualization of protein–ligand interaction patterns.

### *Molecular Docking*

Molecular docking is a widely utilized computational method recognized for its efficiency, affordability, and prevalent application in forecasting binding modes and affinities in molecular recognition processes. A molecular docking study was performed to investigate the potential mechanisms by which selected ligand

Table 1: Target proteins and their respective functions

| Cancer | Target protein | PBB ID | Protein Function |
|---|---|---|---|
| **Bone cancer** | BcL-XL | 1R2D | It acts as an anti-apoptotic protein |
| | FAK Domine ki nase protein | 4GU6 | Tumour growth is enhanced through the pro-proliferative and anti-apoptotic functions of FAK. |
| **Colon cancer** | CDK2 protein | 6GUE | Major cell cycle component that controls the G1/S and S/G2 Transitions. |
| | apoptosis prote in (BCL-2) | 4LXD | control the intrinsic apoptosis pathway |

Table 2: Grid box parameters selected for target protein, based on the binding site residues

| Target protein | Active Site Residues | Grid Box Parameter | |
|---|---|---|---|
| **BcL-XL** | 101 TYR,103 ARG,105 PHE,107 ASP,108 LED,111 GLN,129 GLU ,130LEU ,132 ARG ,16 LYS,20LYS,98 GLU,101 TYR,104 ALA, 105 PHE,145 SER,148 GLY, 149 ALA,152 VAL | 12.472 X -0.861 X78.083 | 40 X 66 X 40 |
| **FAK Domine Kinase protein** | 563 GLY,550 ARG,506 GLU, 551 ASN,568 SER, 430 GLU,567 LEU,429 GLY,436 VAL, 564ASP,499 MET,428 ILF,484 VAL,500 GLU, 502 CYS,452 ALA,501LEU,553 LEU,GLY 505, 503 THR | -17.389 X -0.528 X -18.861 | 76 X 76 X 76 |
| **CDK2 protein** | 18 VAL, 33 LYS,15 TYR,51 GLU, 158 ARG, 146 ASP,64 VAL,ASN 133, GLN 132, LEU 135, 88 LYS, 86 ASP,89 LYS,83 LEU,81 GLU, 80PHE,31 ALA,10 ILE,82 PHE,83 LEU | 26.806 X -14.833 X 0.667 | 86 X -68 X -84 |
| **Apoptosis Protein (BCL-2)** | 101 PHE,105 TYR,108 ASP, 109 PHE, 111 GLU,112 MET, 115 GLN,116 LEU, 126 ARG, 130 VAL, 133 GLU, 134 LEU, 146 ALA, 149 GLU, 150 PHE, 153 VAL | 10.472 X -1.333 X 4.139 | 40 X 62 X 40 |

molecules may exhibit anti-cancer effects. The target proteins underwent analysis through PyRx software, leveraging the advanced capabilities of Autodock Vina (Dallakyan and Olson, 2015). The ligands' SDF files were converted to pdbqt file format, and flexible docking was performed. In addition, a receptor grid was generated by selecting the active site of the protein using the PyRx software (Opo *et al.*, 2021). Table 2 presents the Vina Search Space, detailing the grid center and the dimensions between the ligand and target protein atoms. The ligand molecules were docked one by one with each target cancer protein. The final docked conformations were obtained in the PDB format and preserved for additional analysis. The binding sites of Guanosine and beta-sitosterol were examined and contrasted with all target protein molecules utilizing BIOVIA Discovery Studio (Pawar and Rohane, 2021). The final outcome of each docked molecule to protein is represented by the final minimum score, commonly known as the dock score interaction or docking energy of the receptor-ligand (Abdulfatai *et al.*, 2018).

### *Drug-likeness and ADMET profiling*

It is very important to evaluate the Drug-likeness and ADMET profile of selected compounds earlier to avoid waste of time/resources (Isyaku *et al.*, 2020). The drug-likeness properties of the

selected ligand molecules were determined using *in silico* Swiss ADME. These properties include molecular weight (MW ≤ 500 Dalton), octanol–water partition coefficient (iLOGP), number of hydrogen donors (HBD ≤ 5), number of hydrogen acceptors (HBA ≤ 10), Topological Polar Surface Area (TPSA), and number of rotatable bonds (nROT) (Alam *et al.,* 2020). Swiss ADME is an online tool used to determine the drug-like properties of selected ligand molecules. It works by uploading an SDF file of the ligand and converting its structure into Smiles. The file can then be run using a command. Once the run command is applied, all the properties of the uploaded ligand are displayed on the screen. The crucial molecular properties were according to Lipinski Rules of five (RO5) (Beg and Athar, 2020).

## Results and Discussion

Bone and colon cancer ranks among the most lethal diseases globally. This initiative employs diverse computational methods to uncover possible inhibitors for bone and colon cancer. An investigation centered on various proteins associated with the progression of bone and colon cancer, which is thought to be potential therapeutic targets, was conducted using several phytochemicals extracted from *M. acuminata* Colla. This procedure examined the spatial and energetic alignment of the ligand with the receptor's active site, facilitating the discovery of promising new drug candidates, enhancing existing compounds, and deepening our understanding of the intricate relationships between drugs and receptors (Chaudhary, 2023). This approach to drug design employs mathematical algorithms to evaluate the optimal biological binding conformation between the drug and the target molecule, aided by computational tools. The drug design under consideration is fundamentally based on the molecular structure, facilitating the modeling and prediction of molecular interactions, along with the assessment of biochemical processes (Meng *et al*., 2011; Phillips *et al*., 2017).

Data on *M. acuminata* Colla ethanol extraction and GC-MS analysis were retrieved from Augustine *et al.* (2024). The peaks encompass the entire area percentage and exhibit different retention times. Various compound fragments were identified in different regions, including Glycerol, beta-palmitate (27.02%), Guanosine (14.71%), 5-Methyl-2-ethylamino-2-thiazoline (10.49%), 3-Deoxy-d-mannoic lactone (9.23%), 5-Hydroxymethylfurfural (8.97%), 2-Ethylbutyric acid, eicosyl ester (4.79%), Di(1-methyl-1-silacyclobutyl) amine (3.55%), and Beta-sitosterol (2.02%). A recent investigation by Liu *et al.* (2019) involved a thorough examination of more than 1000 established small molecular compounds. The study focused on 15 compounds, analyzing their effects on the viability and migration of breast cancer cells.

### *In silico potential bioactivity prediction of ethanolic extract of M. acuminata pulp against target cancer protein*

The docking study was used to identify phytochemical components from M. *acuminata* pulp as ligands. Nineteen distinct chemicals were successfully isolated from the ethanolic extract of the fruit. The structural information of the identified phytochemicals was obtained from the PubChem and Drug Bank databases. The control group received lonsurf in colon cancer and dasatinib for bone cancer. A variety of lipophilic substances were identified (Table 3). A number of proteins have been recognized as possible drug targets for managing the advancement of cancer. The inhibition of proteins such as PR, EGFR, mTOR, p53R2, CTLA-4, BARD1, BRCA1, BCL-xL, FAK, CDK2, Bcl-2, and CDK8 has demonstrated potential in various studies (Gurung *et al.,* 2001).

Docking experiments were carried out utilizing Auto dock software to assess the binding energy of bioactive chemicals to specific target proteins associated with bone cancer, namely BcL-XL (PDB-1R2D) and FAK Domine kinase protein (PDB-4GU6), as well as colon cancer target proteins CDK2 (PDB-6GU6) and BCL-2 (PDB-

Table 3: Docking scores of the twenty compounds from the ethanol extract against breast cancer protein along with the standard drugs

| Ligands | Ligand code | Bonding enrgy (kcal/mol) | | | |
|---|---|---|---|---|---|
| | | IR2D | 4GU6 | 6GUE | 4LXD |
| 5-Methyl-2-ethylamino-2-thiazoline | L1 | -3.7 | -4 | -4.5 | -4.7 |
| ETHYL CAPRYLATE | L2 | -4.2 | -4 | -5.4 | -4.6 |
| N-(1,1-Dimethylpropyl)-2,2,3-trimethylaziridine-1-carboxamide | L3 | -4.9 | -5.1 | -6.5 | -5.6 |
| 5-Hydroxymethylfurfural | L4 | -4.7 | -4.7 | -4.9 | -4.2 |
| ETHYL CAPRINATE | L5 | -4.3 | -4.1 | -5.3 | -4.7 |
| PENTADECANE | L6 | -4 | -3.7 | -5.2 | -4.8 |
| Di(1-methyl-1-silacyclobutyl)amine | L7 | 0 | 0 | -5.2 | -4.8 |
| GUANOSINE | L8 | -6.1 | -7.1 | -7.8 | -6.1 |
| TETRADECANE | L9 | -4.4 | -3.3 | -5.3 | -4.7 |
| HEXADECANE | L10 | -4.2 | -4.7 | -5.8 | -5 |
| 3-Deoxy-d-mannoic lactone | L11 | -4.4 | -5.2 | -5.5 | -4.9 |
| ETHYL PALMITATE | L12 | -3.9 | -4.3 | -5.5 | -4.8 |
| ETHYL LINOLATE | L13 | -5.2 | -3.3 | -5.5 | -5 |
| ETHYL MARGARATE | L14 | -4.2 | -4.2 | -5.5 | -5.2 |
| Heptadecyl acetate | L15 | -4.5 | -3.5 | -5.2 | -4.5 |
| 2-Ethylbutyric acid, eicosyl ester | L16 | -3.5 | -3.6 | -5.1 | -5 |
| Glycerol .beta.-palmitate | L17 | -4.3 | -3.5 | -5.8 | -5.1 |
| 2-methyloctacosane | L18 | -4.1 | -3.8 | -3.9 | -4.5 |
| beta.-Sitosterol | L19 | -7.7 | -9.1 | -8.6 | -7.2 |
| Dasatinib (BONE Cancer Standard) | L20 | 7.1 | -6.8 | | |
| Lonsurf (Colon cancer Standard) | L20 | | | -6.7 | -5.4 |

Table 4: Interaction of amino acid residues with ligands at receptor sites

| Protein | Ligands | Amino acids involved and distance (Å) | |
|---|---|---|---|
| | | **Hydrogen-Binding Interaction** | **Hydrophobic Interaction** |
| **1R2D** | L8 | 101 TYR(3.90),103 ARG (3.73),108 LEU(4.08),129 GLU(2.94),132 ARG(4.05) | _____ |
| | L19 | 11 GLN (3.17),129 GLU (3.25) | 97 PHE (3.59),100 (3.93),101 TYR(3.7),105 PHE (3.63),108 LEU (3.80),129 GLU (3.64),139 ARG(3.76),142 ALA (3.70). |
| | L20 | 100 ARG (3.14),194 LEU (3.09),195 TYR (3.90) | 97 PHE (3.69),101 TYR(3.81),105 PHE (3.51),108 LEU(3.94),130 LEU 3.87 |
| **4GU6** | L8 | 550 ARG (3.17),564 ASP (3.24) | ---------- |
| | L19 | ---------- | 428 ILE (3.37),501 LEU (3.51),506 GLU (3.43),550 ARG (3.78),553 LEU (3.20),567LEU (3.36),570 TYR(3.56) |
| | L20 | 598 ARG (3.18),601 SER(2.52),668 ARG (2.96) | 541 ARG(3.65),663 PRO (3.74) |
| **6GUE** | L8 | 180 TYR (2.57) | 163 VAL (3.68) |
| | L19 | 180 TYR (2.57) | 163 VAL (3.68) |
| | L20 | 180 TYR (2.57) | 163 VAL (3.68) |
| **4LXD** | L8 | 130 VAL (3.26), 149 GLU (4.08) | ---------- |
| | L19 | ---------- | 97 ALA (3.24),101 PHE (3.46),104 ARG (3.95),105 TYR (3.43),145 VAL (3.69),199 TYR (3.51) |
| | L20 | 96 GLN (2.81),97 ALA (3.20) | 97 ALA (3.99),100 ASP (3.32),101 PHE(3.94),105 TYR (3.86),199 TYR(3.64) |

4LXD). The binding affinity was evaluated by docking the selected receptors with the screened compounds. The optimal ligands identified among the 19 phytochemical substances evaluated were guanosine and beta-sitosterol, exhibiting the highest binding affinity. Table 4 and Figs. 1 to Fig. 4 show the specifics of the interactions between different receptors' amnio acid residues and ligands. Based on the docking score, the substances guanosine and beta-sitosterol (L8, L19, respectively) were chosen for further investigation.

*Screening of drug for BcL-XL protein* (*Bone Cancer*)

Among the 19 phytochemical substances evaluated, guanosine and beta-sitosterol emerged as the most effective ligands, demonstrating the highest binding affinity. The binding energies of these two primary compounds vary between -7.1 and -9.1 kcal/mol. The average binding energy of this drug is measured at -7.1 kcal/mol. In the context of receptor 1R2D, ligand L8 demonstrates a hydrogen bond interaction, while ligand L19 shows both hydrogen and hydrophobic interactions. Additionally, ligand L20, which

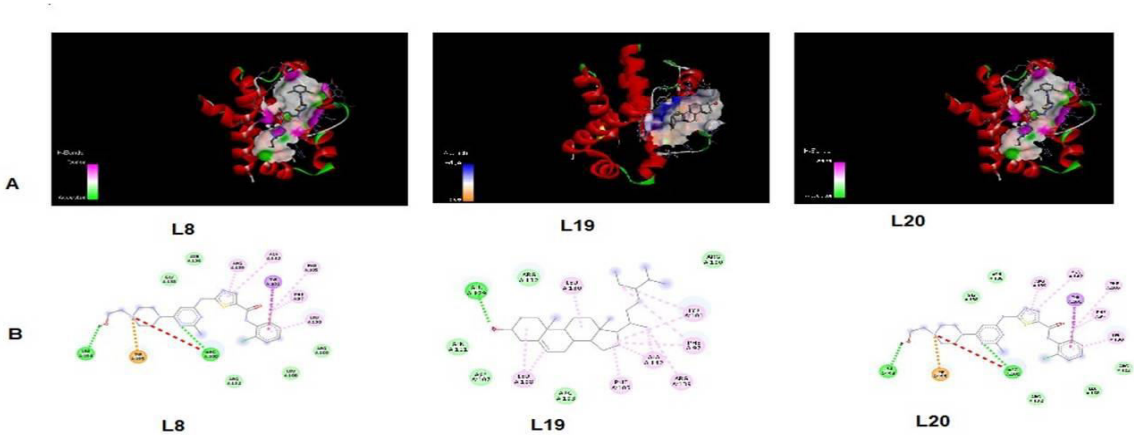



Fig. 1: Interaction of L8, L19, and L20 with amino acid residues present in 1R2D.(A) Docking pose of Guanosine (L8), Beta-sitosterol (L19), Dasatinib (L20) within the cavity of BcL-XL,(B) 2D interaction plot of BcL-XL-L8,L19,L20 complex visualized using Biovia.

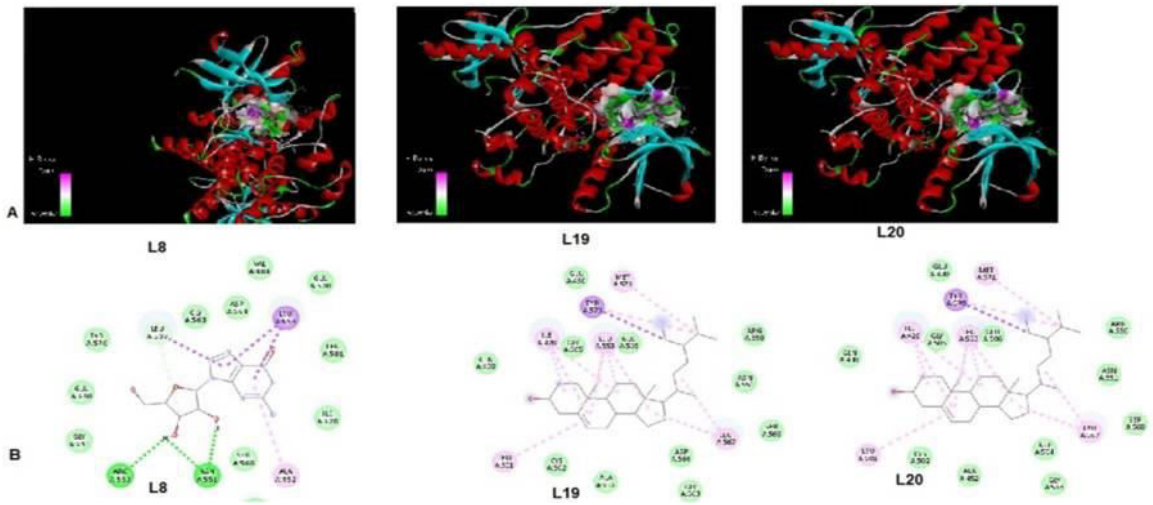



Fig. 2: Interaction of L8,L19, and L20 with amino acid residues present in 4GU6. (A) Docking pose of Guanosine (L8),Beta-sitosterol (L19), Dasatinib (L20) within the cavity of FAK Domine kinase protein,(B) 2D interaction plot of FAK Domine kinase protein -L8,L19,L20 complex visualized using Biovia.

serves as the standard, also displays hydrogen and hydrophobic interactions (Figs. 1A, B).

### *Screening of drug for FAK Domine kinase protein*

The two most prevalent phytonutrients, beta-sitosterol and guanosine, exhibit the lowest binding affinities, with values ranging from -7.3 to -8.3 kcal/mol. The average drug exhibits a binding energy of -7.8 kcal/mol. The L8 and L20 molecules exhibit hydrophobic interactions with hydrogen atoms. The L19 exhibits hydrophobic interactions with receptor 4GU6 (Figs. 2A, B).

### *Screening of drug for CDK2 protein (Colon cancer)*

The two most promising treatment possibilities, guanosine and beta-sitosterol, have binding affinity scores that range from -7.1 to -7.5 kcal/mol. The phytochemical Guanosine formed hydrogen bond, beta-sitosterol formed hydrophobic bond and Lonsurf (standard) formed

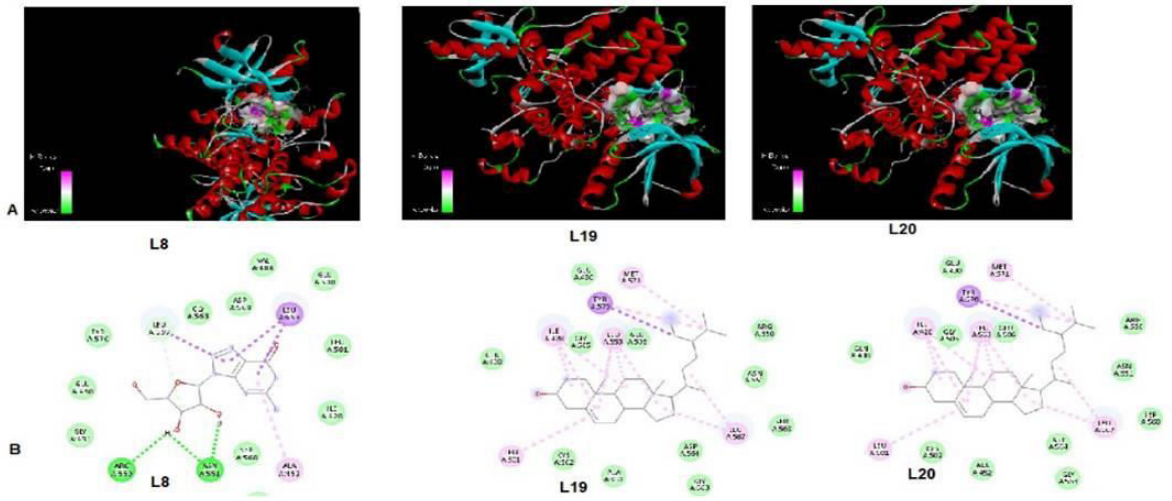



Fig. 3: Interaction of L8,L19, and L20 with amino acid residues present in 4LXD. (A) Docking pose of Guanosine (L8), Beta-sitosterol (L19), Lonsurf (L20) within the cavity of CDK2,(B) 2D interaction plot of CDK2 -L8,L19,L20 complex visualized using Biovia

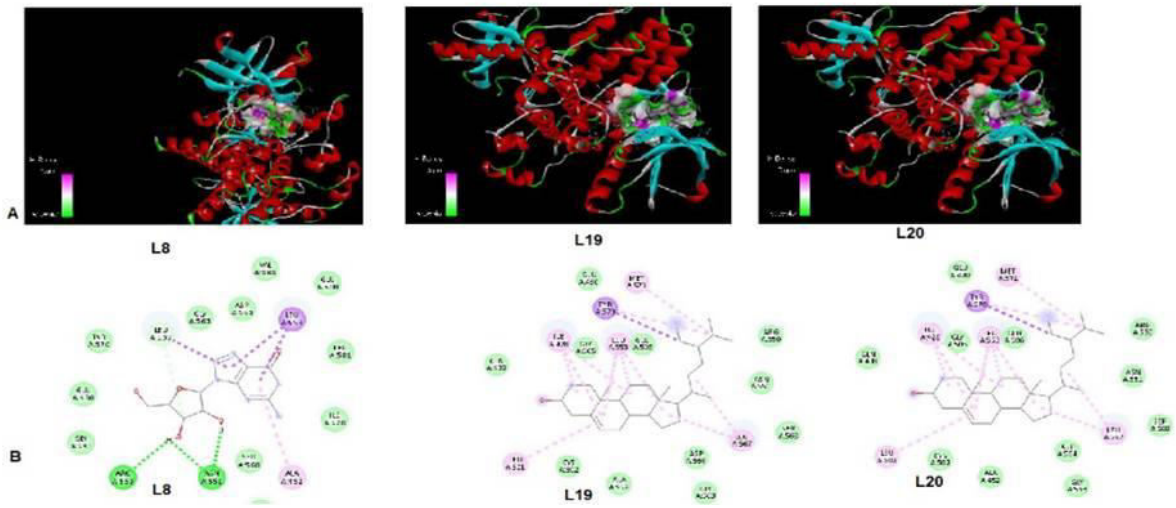



Fig. 4: Interaction of L8, L19, L20 with amino acid residues present in 6GUE. (A) Docking pose of Guanosine (L8), Beta sitosterol (L19), Lonsurf(L20) within the cavity of BCL-2,(B) 2D interaction plot of BCL-2 -L8,L19,L20 complex visualized using Biovia.

both hydrogen and hydrophobic bond with receptor 6GUE (Figs. 3A, B).

*Screening of drug for apoptosis protein* (*BCL-2*)

The compounds with the weakest binding strengths to BCL-2 were guanosine (-7.8 kcal/mol) and beta-sitosterol (-7.2 kcal/mol). Within a range of -5.8 kcal/mol, the reference medication interacts. Ligand 8 formed a hydrogen bond,The ligand 19 and standard formed hydrophobic interaction with 4LXD (Figs. 4A, B).

A recent study conducted by Gurung *et al*. (2021) explored the drug-likeness of the active constituents of the plant and analyzed their interactions with specific receptors linked to anticancer medications. The receptors of interest comprised cyclin-dependent kinase 2 (CDK-2),

Table 5: ADMET parameters and Drug likeness of the screened compound

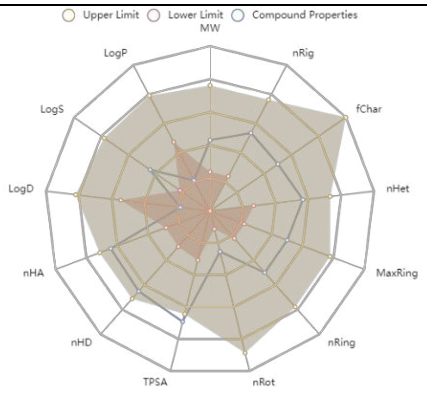
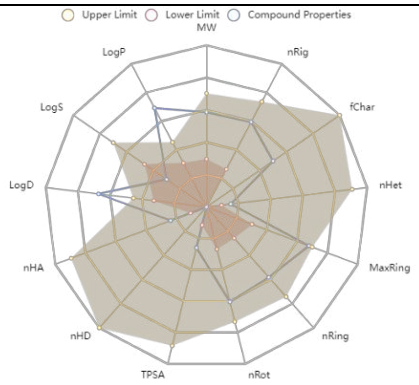
| **Molecule** | L8 | **L19** |
|---|---|---|
| **Bioavailability Radar** |  |  |
| **AMES Toxicity** | **Negative** | **Negative** |
| **Carcinogenicity** | **Positive** | **Negative** |
| **Rat Oral Acute Toxicity** | **Positive** | **Negative** |

Table 6: Phytochemical and pharmacokinetic properties of screened compound

| **Compound** | **L8** | **L19** |
|---|---|---|
| **Formula** | $C_{10}H_{13}N_5O_5$ | $C_{31}H_{52}O_2$ |
| **MW** | 283.24 | 456.74 |
| **Heavy atoms** | 20 | 33 |
| **Aromatic heavy atoms** | 9 | 0 |
| **Fraction Csp3** | 0.5 | 0.9 |
| **Rotatable bonds** | 2 | 8 |
| **HBA** | 9 | 1 |
| **HBD** | 6 | 1 |
| **MR** | 63.9 | 128.21 |
| **TPSA** | 159.51 | 26.3 |
| **iLOGP** | -0.23 | 5.19 |
| **PAINS #alerts** | 0 | 0 |
| **Brenk #alerts** | 0 | 1 |
| **Bioavailability Score** | 0.55 | 0.55 |

cyclin-dependent kinase 6 (CDK-6), topoisomerase-I (Topo I), topoisomerase-II (Topo II), B-cell lymphoma 2 (Bcl-2), and vascular endothelial growth factor receptor 2 (VEGFR-2). A docking study was also carried out to evaluate the efficacy of phytocompounds in comparison to the synthetic drug doxorubicin. The binding affinity of ergost-25-ene-3,6-dione,5,12-dihydroxy-, (5. alpha.,12.beta.) exceeds that of the synthetic drug doxorubicin (−7.2 kcal/mol), with other compounds showing comparable binding affinities to the drug (Saravanan *et al*., 2022). The previous

section described the interaction of amino acids with inhibitors at the molecular level. In this section, we tried to present the interaction of amino acids with inhibitors at the atomistic level. Hydrogen bonding (H-bond) analysis is the main ligand–protein interaction (Salentin *et al*., 2014; Kongkaew *et al*., 2015).

### *ADMET analysis*

In the process of developing medication, it is essential to meticulously evaluate bioavailability to ensure that even a treatment with significant potential can achieve the necessary therapeutic effect within the body. After analyzing the binding affinity scores of 19 different compounds, the top two candidates for each receptor were identified. Analyses of bioavailability and toxicity profiles were conducted to evaluate these two medications. Beta-sitosterol and Guanosine exhibited the highest effective binding affinity for nearly all receptors (Table 5).

As shown in Table 6 the fundamental phytochemical characteristics are outlined. The selected compounds exhibit molecular weights ranging from 283.24 to 456.74 g/mol. The lipophilicity of the chosen compounds varies from 2.76 to 6.89. Guanosine (L8) is soluble in water, while beta-sitosterol (L19) is not. The topological polar surface area (TPSA) measures approximately 26.3 $Å^2$ for L19 and 159.51 $Å^2$ for L8. The efficacy of the synthesized drugs was evaluated using pharmacokinetic ADMET characteristics. The results indicate no BBB permeability and limited GI absorption for both compounds.The properties of guanosine (L8) consist of a molar refractivity of 63.984, with 6 hydrogen bond donors and 9 hydrogen bond acceptors. Its log p-value is -2.815, and it has a molecular weight of 283 Dalton, following the rule of five. Similarly, the molecular weight of beta-sitosterol (L19) is 414 Dalton, with 1 hydrogen bond donor and 1 hydrogen bond acceptor. The Log P value is 8.024, and the molar refractivity is 128.216. The bioactive compounds in question have the potential to contribute to the development of effective therapeutic drugs, adhering to Lipinski's rule without any violations. A recent study by Raju *et al*. (2023) involved a thorough examination of various terpenoid phytoconstituents alongside five proteins associated with breast cancer. The proteins selected for further investigation include EGFR, ERα, HER2, NF-κB, and TopoIIa, chosen meticulously from various databases. A total of 235 compounds were eliminated following an evaluation of their molecular characteristics following Lipinski's rule of five. Following a comprehensive analysis utilizing pkCSM and SwissADME web servers, it was concluded that 43 compounds failed to satisfy the drug-likeness criteria and exhibited PAINS alert properties, resulting in their exclusion. Following a comprehensive evaluation of the remaining 222 compounds, predictions were made regarding their ADMET properties.

## Conclusion

This study showed that *M. acuminata* pulp may serve as a potential inhibitor for bone and colon cancer, as demonstrated through an *in silico* approach. Our investigation revealed that guanosine and beta-sitosterol demonstrate enhanced binding affinity to bone cancer target proteins - BcL-XL (PDB-1R2D) and FAK Domine kinase protein (PDB-4GU6); as well as colon cancer target proteins - CDK2 (PDB-6GU6) and BCL-2 (PDB-4LXD), in comparison to alternative ligands. The compounds guanosine and beta-sitosterol exhibit stability during the simulation period and are regarded as potential inhibitors for bone and colon cancer. The guanosine and beta-sitosterol compounds exhibit excellent stability and possess notable pharmacokinetic and pharmaceutical properties, making them highly regarded as promising inhibitors for bone and colon cancer.

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