Anticancer Potential of *Moringa oleifera* on BRCA-1 Gene: Systems Biology

Bioinformatics and Biology Insights
Volume 15: 1–7

DOI: 10.1177/11779322211010703

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ABSTRACT: Breast cancer has consistently been a global challenge that is prevalent among women. There is a continuous increase in the high number of women mortality rates because of breast cancer and affecting nations at all modernization levels. Women with high-risk factors, including hereditary, obesity, and menopause, have the possibility of developing breast cancer growth. With the advent of radiotherapy, chemotherapy, hormone therapy, and surgery in breast cancer treatment, breast cancer survivors have increased. Also, the design and development of drugs targeting therapeutic enzymes effectively treat the tumour cells early. However, long-term use of anticancer drugs has been linked to severe side effects. This research aims to develop potential drug candidates from *Moringa oleifera*, which could serve as anticancer agents. In silico analysis using Schrödinger Molecular Drug Discovery Suite and SWISS ADME was employed to determine the therapeutic potential of phytochemicals from *M oleifera* against breast cancer via molecular docking, pharmacokinetic parameters, and drug-like properties. The result shows that rutin, vicenin-2, and quercetin-3-O-glucoside have the highest binding energy of −7.522, −6.808, and −6.635 kcal/mol, respectively, in the active site of BRCA-1. The essential amino acids involved in the protein-ligand interaction following active site analysis are ASN 1678, ASN 1774, GLY 1656, LEU 1657, GLN 1779, LYS 1702, SER 1655, PHE 1662, ARG 1699, GLU 1698, and VAL 1654. Thus, we propose that bioactive compounds from *M oleifera* may be potential novel drug candidates in the treatment of breast cancer.

KEYWORDS: *Moringa oleifera*, breast cancer, in silico, BRCA-1, rutin

RECEIVED: December 25, 2020. **ACCEPTED:** March 29, 2021.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Breast cancer is the leading cause of death in women around the world. Several factors contribute significantly to the increased risk of breast cancer, including oral contraceptives, obesity, menopause, and elevation in serum estradiol concentration.[1] Ductal carcinoma is the most common type of breast cancer which developed from the ducts. Cancerous cells growing from lobules are called lobular cells.[2] Breast cancers are mainly diagnosed by physical examination by a health care provider or the use of mammography.[3] High occurrence of breast cancer has been reported to be prevalent in white women within the range of 40 years and above.[4]

Breast cancer gene 1 (BRCA-1), also called the caretaker gene, is a tumour suppressor gene that functions in cell cycle regulation, DNA repair mechanism, and other metabolic processes.[5,6] The BRCA-1 proteins interact with other essential proteins necessary to replicate and repair double-stranded DNA breaks.[7] It contains 1863 amino acid residues and helps inhibit the proliferation of cells lining the breast's milk ducts. Thus, BRCA-1 does not contribute to the pathogenesis of breast cancer. However, mutations in the breast cancer gene sequence can consequently increase breast cancer risk.[8] Mutations evolved when an individual's genetic makeup becomes damaged via exposure to environmental factors, including ultraviolet light, ionizing radiation, and genotoxic chemicals.[9] When the BRCA-1 is mutated, it cannot efficiently repair the broken DNA; thereby, breast cancer prevention will be hampered.[10]

Several treatment methods are available for breast cancers, but hormone-blocking agents, chemotherapy, and monoclonal antibodies are commonly used.[11,12] Hormone receptors (oestrogen ER+ and progesterone PR+ receptors) are a therapeutic target in breast cancer. Drugs such as tamoxifen and anastrozole act by blocking the hormone receptors.[13] Several medicinal plants such as *Camptotheca acuminate, Catharanthus roseus, Taxus brevifolia*, and many others have been used as anticancer therapy.[14]

Moringa oleifera, which belongs to the family of *Moringaceae*, has been reported to possess beneficial pharmacological properties such as anticonvulsant, antimicrobial, anticancer, and antiviral.[15] The extracts (phytochemicals) from the leaves, seeds, bark, and flowers of *M oleifera* have been used to treat several long-term diseases, including hypercholesterolemia, high blood pressure, diabetes, insulin resistance, nonalcoholic liver disease, cancer, and inflammation.[16] Bioactive compounds of *M oleifera* show inhibitory potential against cancerous cell line by inhibiting proliferation of carcinoma cells and malignant astrocytoma cells.[17,18] Pandey and Khan[19] reported the

inhibitory potential of methanolic extract of *M oleifera* leaves against cervical cancer cells by the downregulation of Jun activation domain-binding protein 1 and upregulation of p27 expression. It has been reported that the phytochemicals isolated from *M oleifera* leaves induced apoptosis of human keratin-forming cancer cells.[20] Furthermore, cold soluble aqueous extract of *M oleifera* leaves had demonstrated antitumour activity in A549 lung cancer cells via the mitochondrial-mediated pathway by pro-caspase activation 3 to caspase 3.[21] Nanoparticles derived from *M oleifera* demonstrated biological and pharmacological activity, including antimicrobial, anticancer, and antiplatelet activity.[22] The *M oleifera* shows critical anticancer potential on prostate cancer-3 (PC-3) carcinoma cells of prostate cancer in a dose-dependent manner. However, its cytotoxicity impact in typical Hek293 (human embryonic kidney 293) cells was minimal.[23]

In this study, in silico analysis via molecular docking and pharmacokinetic profiles were employed to screen the library of bioactive compounds from *M oleifera* to determine their anticancer property.

Materials and Method

Ligand preparation

The phytochemicals of *M oleifera* were retrieved from published literature,[15] and their crystal structures were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The PubChem Compound Identification Numbers (CIDs) for each ligands are rutin (CID: 5280805), vicenin-2 (CID: 5280805), quercetin-3-O-glucoside (Q3G) (CID: 5748594), chlorogenic acid (CID: 1794427), gallic acid (CID: 370), sinalbin (CID: 656568), isoquercetin (CID: 5280804), astragalin (CID: 5282102), quercetin (CID: 5280343), ferulic acid (CID: 445858), myricetin (5281672), and kaempferol (CID: 5280863). The ligands were prepared using the LigPrep module of Glide tool by using the OPLS 2005 force field.[24]

Protein preparation

The crystal structures of the BRCA-1 (PDB ID: 4OFB) was retrieved from Protein Data Bank (https://www.rcsb.org/) in complex with crystallized ligands. The protein was prepared using ProteinPrep Wizard of Maestro interface (11.5) by adding missing hydrogen atoms. Furthermore, the metal ionization was corrected to ensure formal charge and force field treatment. The protein was optimized and refined for docking analysis.[25,26]

Molecular docking

The docking analysis was conducted using the Glide tool from Schrödinger molecular drug discovery suite (version 2017-1). The grid was generated using the receptor grid generation module of the Glide tool. The coordinate (x, y, z) of the grid was centred to −9.07, 27.02, and −0.91, respectively. The refined *M oleifera* ligands were docked into the active site of BRCA-1. The energy calculation was achieved using the scoring function of the Glide tool. The compounds' drug-like properties were evaluated using the QikProp module and SWISS ADME Web tool following Lipinski five rule.[27]

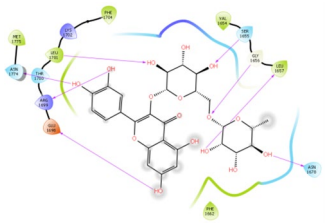
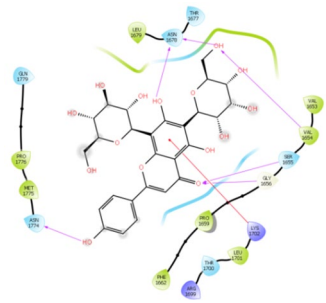
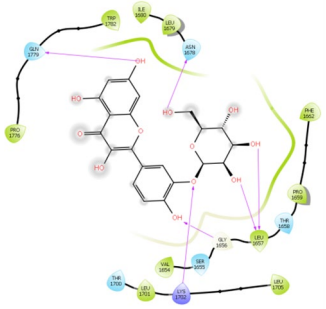
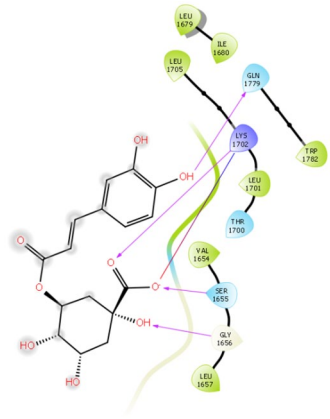
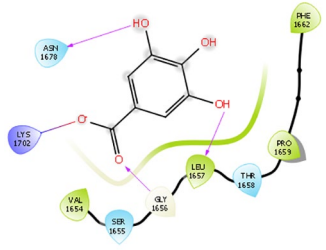
Results and Discussion

Molecular docking was employed to perform the library's virtual screening of phytochemicals from *M oleifera* against the targeted protein (BRCA-1).[28] The phytocompounds of *M oleifera* were ranked according to their binding poses and energy calculations.[29] The compounds were further subjected to pharmacokinetic study to predict their drug-able properties. The molecular docking analysis, which includes binding affinity (kcal/mol) predication, the interaction of the ligands within the binding pocket of BRCA-1, and their pharmacokinetic study, was shown (Table 1). Each ligand was analysed using Lipinski rule of five (ROF). The result confirms the ligands ROF with few violations. The ligand docking shows how the phytocompounds bind effectively with BRCA-1. Visualization of the protein-ligand complex was performed using the Glide tool's surface module (Figure 1). The interaction between the compounds and BRCA-1 identified the amino acid residues involved in the interaction and each amino acid residues' position in their ligand-binding site. The interaction was associated with a structure-based drug design depicting protein-ligand interaction.

The molecular docking demonstrates hydrophobic, pi-pi stacking, hydrogen bonding, and many others between the protein and the ligands.[26] Breast cancer gene 1 was cocrystallized with a natural inhibitor that defines its active site. This allows the binding of the ligands into the protein-binding domain. The primary amino acids involved in the protein-ligand interaction following active site analysis are ASN 1678, ASN 1774, GLY 1656, LEU 1657, GLN 1779, LYS 1702, SER 1655, PHE 1662, ARG 1699, GLU 1698, and VAL 1654. The phytoconstituents show a favourable interaction with BRCA-1. Rutin is a flavonoid found in natural products and has shown antitumour potential against various cancer cells.[30] Rutin's inhibitory potential against cervical cancer cells, majorly the human papillomavirus–negative C33A cell line, has been elucidated.[31] Following rutin's extra precision docking against BRCA-1, it shows hydrogen bonding interaction and pi-pi stalking with amino acid residues LEU 1701, ASN 1774, ARG 1699, GLU 1698, ASN 1678, LEU 1657, and SER 1655 and a binding affinity of −11.769 kcal/mol. Rutin's toxicity study confirms that it has low bioavailability and solubility, which has affected its application in the delivery system. It binds firmly to the human serum albumin, shows a high metabolic rate, and can be easily excreted.[32,33]

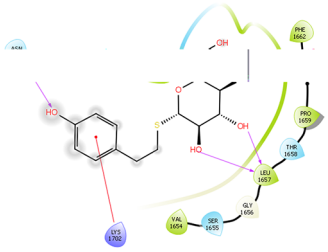
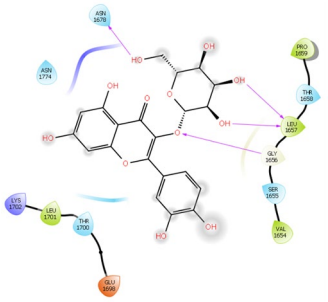
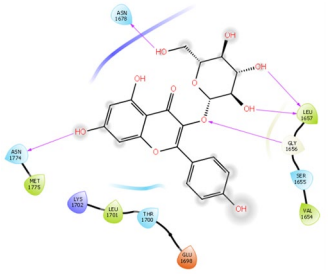
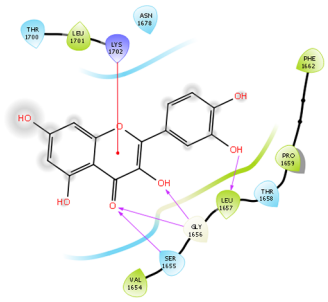
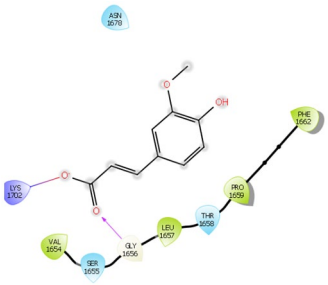
Vicenin-2 is a nontoxic flavonoid with pharmacological properties including antioxidant, hepatoprotective, anti-inflammatory, and anticancer.[34] It significantly inhibits vascular endothelial growth factor receptor tyrosine kinases in prostate

Table 1. Docking results of phytochemicals from *Moringa oleifera* in terms of binding affinity (kcal/mol), the interaction of the compounds with BRCA-1, and the drug-like properties.

PHYTOCHEMICALS	AFFINITY (KCAL/MOL)	STRUCTURE OF THE COMPOUNDS AND THEIR INTERACTION WITH BRCA-1	DRUG-LIKE PROPERTIES (LIPINSKI RULE OF FIVE)
Rutin	–7.522		Molecular weight (<500 Da): 610.52 Log P (<5): 2.43 H-bond donor (5): 10 H-bond acceptor (<10): 16 MlogP (<4.15): 3.89 Violations: 3
Vicenin-2	–6.808		Molecular weight (<500 Da): 594.52 Log P (<5): 1.27 H-bond donor (5): 8 H-bond acceptor (<10): 12 MlogP (<4.15): 2.59 Violations: 3
Quercetin-3-O-glucoside	–6.635		Molecular weight (<500 Da): 464.38 Log P (<5): 2.02 H-bond donor (5): 11 H-bond acceptor (<10): 15 MlogP (<4.15): 2.59 Violations: 2
Chlorogenic acid	–6.181		Molecular weight (<500 Da): 354.31 Log P (<5): 0.96 H-bond donor (5): 6 H-bond acceptor (<10): 9 MlogP (<4.15): 1.05 Violations: 1
Gallic acid	–5.771		Molecular weight (<500 Da): 170.12 Log P (<5): 0.21 H-bond donor (5): 4 H-bond acceptor (<10): 5 MlogP (<4.15): 0.16 Violations: 0

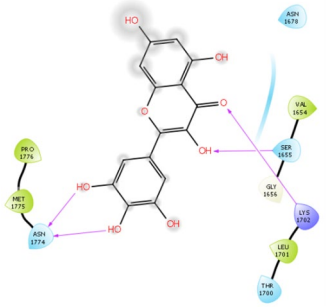
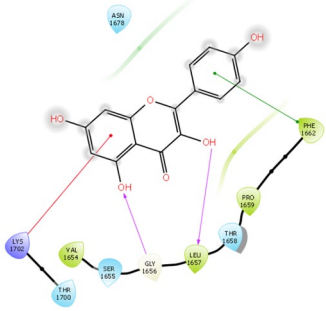
(Continued)

Table 1. (Continued)

PHYTOCHEMICALS	AFFINITY (KCAL/MOL)	STRUCTURE OF THE COMPOUNDS AND THEIR INTERACTION WITH BRCA-1	DRUG-LIKE PROPERTIES (LIPINSKI RULE OF FIVE)
Sinalbin	−4.893		Molecular weight (<500 Da): 425.43 Log P (<5): 0.49 H-bond donor (5): 6 H-bond acceptor (<10): 11 MlogP (<4.15): 2.14 Violations: 2
Isoquercetin	−4.766		Molecular weight (<500 Da): 464.38 Log P (<5): 2.11 H-bond donor (5): 8 H-bond acceptor (<10): 12 MlogP (<4.15): 2.59 Violations: 2
Astragalin	−4.492		Molecular weight (<500 Da): 448.38 Log P (<5): 0.53 H-bond donor (5): 7 H-bond acceptor (<10): 11 MlogP (<4.15): 2.10 Violations: 2
Quercetin	4.415		Molecular weight (<500 Da): 448.38 Log P (<5): 0.53 H-bond donor (5): 7 H-bond acceptor (<10): 11 MlogP (<4.15): 2.10 Violations: 2
Ferulic acid	−4.090		Molecular weight (<500 Da): 194.18 Log P (<5): 1.62 H-bond donor (5): 2 H-bond acceptor (<10): 4 MlogP (<4.15): 1.00 Violations: 0

(Continued)

Table 1. (Continued)

PHYTOCHEMICALS	AFFINITY (KCAL/MOL)	STRUCTURE OF THE COMPOUNDS AND THEIR INTERACTION WITH BRCA-1	DRUG-LIKE PROPERTIES (LIPINSKI RULE OF FIVE)
Myricetin	−3.819		Molecular weight (<500 Da): 318.24 Log P (<5): 1.08 H-bond donor (5): 6 H-bond acceptor (<10): 8 MlogP (<4.15): 1.08 Violations: 1
Kaempferol	−3.666		Molecular weight (<500 Da): 286.24 Log P (<5): 1.70 H-bond donor (5): 4 H-bond acceptor (<10): 6 MlogP (<4.15): 0.03 Violations: 0

Abbreviation: BRCA-1, breast cancer gene 1.

cancer cells.[35] It shows inhibitory potential against hepatocarcinoma cell proliferation via the signal transduction pathway involved in activating the signal transducer and activator of transcription 3 gene in a dose-dependent manner.[36] In addition, it reduced the growth of cancer cells by targeting the β-catenin pathway.[37] Vicenin-2 exhibited promising ligand interaction when complexed with BRCA-1. It binds with an energy of −6.808 kcal/mol by hydrophobic interaction with VAL 1654.

Aqueous Q3G extract isolated from medicinal plants has exhibited antiproliferative against different cancer cell lines.[38] The Q3G triggers apoptotic cell death through inhibition of the extrinsic pathway in caspase-3. Also, it is a potent inhibitor of DNA topoisomerase II involved in carcinogenesis.[39] The docking of Q3G with BRCA-1 shows a glide score of −6.635 kcal/mol by forming 5 hydrogen bonds with ASN 1774, GLY 1779, ASN 1678, GLY 1656, and Ser 1655 accompanied with pi-pi stacking at amino acid residue LYS 1702. A chlorogenic acid is an esterified form of caffeic acid via the shikimate pathway found naturally in plants. The molecular mechanism underlying the anticancer potential of chlorogenic acid involved inhibition of signalling transduction pathways (NF-κB, c-Jun NH2-terminal kinase, p38 kinase) to reduce the growth of cancer cells.[40] It binds well with the targeted protein with an affinity of −6.181 kcal/mol.

Gallic acid is a polyphenol known as 3,4,5-trihydroxy benzoic acid, with a significant anticancer property.[41] When A375 melanoma cancer cells were exposed to gallic acid in vitro, it stops cancer cells' growth. Synchronous treatment with low-level laser and subsequently gallic acid increases reactive oxygen species' production in both breast and melanoma cancer growth cells compared with gallic acid alone, which causes more apoptotic cells death in the tumour cells.[42] Sinalbin (a glucosinolate), quercetin, and isoquercetin are phenolic compounds that exhibit various biological functions, such as antioxidant, radical-scavenging, anti-inflammatory, antibacterial, antiviral, and anticancer. Khan et al[43] reported that quercetin and its derivatives inhibit cell proliferation in the colon (HCT-116) cancer cells. There was a favourable interaction of gallic acid, sinalbin, and isoquercetin against BRCA-1 with a binding energy of −5.771, −4.893, and 4.766 kcal/mol, respectively. The drug-like properties of gallic acid demonstrated that it does not violate Lipinski 5-year rule with a promising therapeutic potential. Isoquercetin interacts with an amino acid at GLY 1656. Astragalin and quercetin's pharmacokinetic profiles adhere to the ROF with only 2 violations and docking scores of 4.415 and −4.090 kcal/mol, respectively.

Ferulic acid (4-hydroxy-3-methoxy cinnamic acid) is a widely distributed phenolic compound in plants.[44] Furthermore, ferulic acid causes cell death by the downregulation of cyclin-dependent kinases and inhibiting the activation of the PI3K/Akt signalling pathway in proliferative cells.[45] Myricetin demonstrates anticancer activity against human acute leukaemia HL-60 cells in a dose-dependent manner while inhibiting tumour promoter–induced neoplastic cells in skin cancer.[46,47]

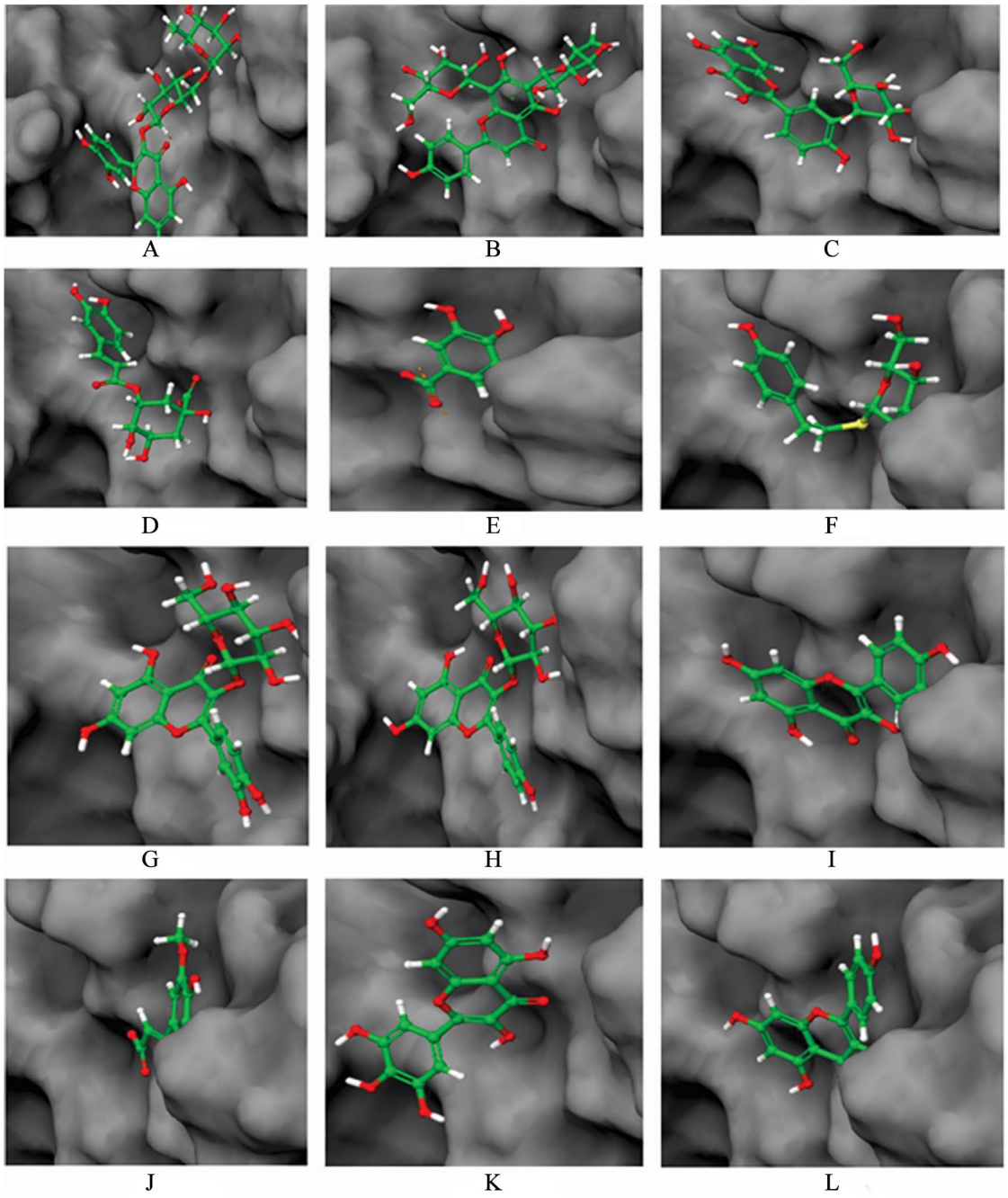


Figure 1. Visualization of docking results showing binding of (A) rutin, (B) vicenin-2, (C) quercetin-3-O-glucoside, (D) chlorogenic acid, (E) gallic acid, (F) sinalbin, (G) isoquercetin, (H) astragalin, (I) quercetin, (J) ferulic acid, (K) myricetin, and (L) kaempferol with BRCA-1. BRCA-1 indicates breast cancer gene 1.

Ferulic acid and myricetin have a binding energy of −4.090 and −3.819 kcal/mol, respectively, when complexed with the targeted protein. Kaempferol is an aglycone flavonoid that possesses anticancer activity against glioblastoma, breast cancer, hepatocellular carcinoma, colorectal cancer, and acute promyelocytic leukaemia pancreatic cancer, prostate cancer, and renal cell carcinoma.[48] Kaempferol has drug-like properties without violating Lipinski ROF and binding energy of −3.666 kcal/mol.

Conclusions

Several anticancer drugs, such as tamoxifen, anastrozole, and exemestane have been developed and are effective but posed severe side effects, including liver toxicity, cardiovascular diseases, and many others, following long-time use. In this study, we used computational modelling techniques to predict the inhibitory potential of *M oleifera* against BRCA-1. The binding of the compounds with BRCA-1, toxicity, and drug-like property as confirmed by docking analysis show that the *M oleifera* ligands

are promising anticancer agents. Following the phytocompound screening from *M oleifera* by docking technique, rutin was found to exhibit the highest degree of interaction and binding affinity with BRCA-1 accompanied by favourable drug-like properties. Thus, we proposed that the phytochemicals from *M oleifera* may be potential BRCA-1 inhibitors. Further biochemical analysis such as in vitro and in vivo study is required to establish the compounds' pharmacological properties.

Author Contributions

Toheeb A Balogun conceptualized and designed the study, performed the analysis and wrote the manuscript. Kaosarat D Buliaminu contributed to the drafting of the manuscript. Onyeka S Chukwudozie critically review the manuscript. Zainab A Tiamiyu and Taiwo J Idowu assisted with the editorial works.

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