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Pharmacokinetic predictions and molecular docking of phytocompounds derived from *Carissa edulis* on mutant p53 protein in breast cancer

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ABSTRACT

Globally, breast cancer is a leading cause of death, and the current chemotherapeutic agents are not devoid of drawbacks. Nevertheless, the potential of medicinal plants for cancer treatment and prevention remains immense. The current study aimed at elucidating the interactions between phytocompounds identified in *Carissa edulis* (*C. edulis*) and mutant p53, drug-likeness and potential toxicity. Molecular docking analysis was employed to analyse the interaction of compounds and the target protein. Lipinski's Rule of Five was used to analyse drug-likeness properties. Liquid chromatography-mass spectroscopy (LC-MS) and gas chromatography-mass spectroscopy (GC-MS) were employed to detected presence of phytocompounds in the extracts. Quantitative analyses revealed presence of phytocompounds which have been previously reported to have antiproliferative effects. The docked compounds had a binding efficiency ranging from -4.00 to -8.44 kcal/mol. Most of the studied phytocompounds were found to be within the "Rule of 5" without any violation. Regarding toxicity, rutin, catechin, betulin, tocopherol, sitosterol, beta-amyrin, menthol, and epicatechin exhibited no inhibitory effect on CYP450 enzymes. Moreover, most compounds had high intestinal absorption, whereas few compounds cross blood brain barrier. A bioavailability score of 0.55 was exhibited by most bioactive compounds analysed. These results underscore the therapeutic potential of C. edulis for future anticancer drug development.

Keywords: *Carissa edulis*, Phytocompounds, Breast cancer, p53, Molecular docking.

INTRODUCTION

Breast cancer is marked by uncontrolled growth and differentiation of normal cells, progressively transitioning to neoplastic cells [1]. The aetiology of breast cancer is multifactorial, with an intricate interplay between environmental risk factors and genetic predisposition. Uncontrolled cell proliferation arises from dysregulated activity and expression of proteins that regulate the cell cycle, including genes such as *TP53*. The gene, a critical regulator of cellular homeostasis and genomic integrity, orchestrates a network of cellular responses, including apoptosis, cell cycle arrest, senescence, and DNA repair [2]. Contrarily, mutant p53, prevalent in breast malignancies, loses its suppressive function and acquires oncogenic properties that promote tumorigenesis [3]. Consequently, restoration or reactivation of mutp53 to its wild-type form is a promising pharmacological approach for cancer treatment [4].

Targeting mutp53 with conventional agents has been a promising therapeutic strategy for breast cancer. However, these approaches are associated with a spectrum of adverse effects, such as cardiotoxicity and myelosuppression, some of which are attributable to the nonspecific nature of chemotherapeutic drugs [5]. The quest for effective therapies with the ability to improve survival outcomes and quality of life necessitates the need to explore alternatives. Increasing evidence suggests that medicinal plants hold significant potential as antineoplastic candidates due to the presence of phytocompounds [6].

Carissa edulis, of the Apocynaceae family, is a fast-growing, evergreen shrub reaching a scrambling height of about 5 meters. It occurs in bushveld, particularly in riverine, dry vegetation, and woodlands. *C. edulis* is renowned among various African communities for its substantial medicinal and nutritional benefits [7]. In African ethnomedicine, the plant is referred to as the 'magic herb' due to its use in treating myriad ailments, including cancer. Previous studies have also demonstrated its antiproliferative effect against breast cancer cell lines through upregulating p53 [5].

The study sought to elucidate the interactions between phytocompounds identified in *C. edulis* and mutant p53 (mutp53) within the apoptosis pathway through molecular docking analysis, assessing their binding affinities. In addition, the bioactive compounds were evaluated for adherence to Lipinski's Rule of Five, drug-likeness properties, and potential toxicity profile.

MATERIALS AND METHODS

Plant sample collection and preparation

The leaves of *C. edulis* were collected from Embu County and authenticated at the site by a taxonomist and a voucher specimen deposited in the Plant Science Departmental Herbarium (Voucher No. CE2023). The samples were shade-dried at room temperature and pulverized into fine powder before extraction. For ethyl acetate extraction, the sample was weighed (350 g) and steeped in 1L of the solvent (98%) for 24 h. The extracts were later decanted and resoaked for another 24 h, filtered, and concentrated under a vacuum rotary evaporator. For the aqueous extraction, 350 g of the powdered sample was soaked in 1L of double-distilled water and kept in a water bath for 2 hours at 60ºC. The extracts were then allowed to cool, decanted, and resoaked for a further 2 hours. Filtration was performed using filter paper and muslin cloth. The obtained filtrates were then freeze-dried to get the powdered extract.

Quantitative phytocompound analyses

Gas chromatography-mass spectrophotometer (GC-MS) and Liquid chromatography-mass spectrophotometer (LC-MS) facilitated the detection of phytocompounds present in the ethyl acetate and aqueous extracts of *C. edulis* [8,9].

Molecular docking for P53 transcriptional protein

Receptor preparation

The P53 transcriptional protein's crystal structure (PDB ID: 8EOM) was retrieved from the RCSB protein database (https://www.rcsb.org/) having a resolution of 1.70 Å. Using PyMOL 3D visualization software (https://pymol.org/), the protein was then stripped of the attached ligand (4-(4-methylpiperazine-1-sulfonyl) benzamide) as well as a sulphate ion and another unknown atom. Chain A residues were then separated from the other chains, and using AutoDock tools (ADT) and BIOVIA Discovery Studio, the protein was modified to remove water molecules (Hetatm) along with the native ligand and saved in the docking format (PDBQT).

Ligand selection and preparation

For this analysis, 14 phytocompounds of *C. edulis* with reported antiproliferative effects against breast cancer were used. All ligands were retrieved from NCBI PubChem databases (https://pubchem.ncbi.nlm.nih.gov/) in 3D SDF format. Using OPENBABEL-Chemical file format converter (https://openbabel.org/) desktop software, the files were optimized, and their energy was minimized with the force field set to mmff94 and converted to PDBQT format. Doxorubicin, a drug targeting the mutp53 protein was also retrieved to be used as the standard.

Preparation of the GRID parameter file (.gpf) and Docking parameter file

A grid box was established covering the whole of the protein using parameters Angstrom dimensions (A) (X, Y, Z) = (124, 86, 90), spacing (=0.375), and center (X, Y, Z) = (16.363, 1.841, 21.587). The grid box parameters were then saved in gpf format in the same folder where the protein and ligands (.pdbqt) files were saved. All the parameters for the docking parameter file were set to default, with the number of GA runs set to 10.

Docking process and analysis

The docking process was done using AutoDock4.2.6 (https://autodock.scripps.edu/download-autodock4/) in the Ubuntu Linux environment. An AutoDock docking log file (.dlg), containing the docking results for the compounds, was produced for each protein-ligand complex. The .pdbqt files of all the protein-ligand complexes were converted to.pdb format, and BIOVIA Discovery Studio and PyMOL software were used to visualize and compare the docked ligands to the standard. Binding interactions between the protein and the ligands were analysed using the BIOVIA Discovery Studio desktop software.

Compounds Pharmacokinetic Properties

Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET)

An ADMET analysis was done to determine the pharmacokinetic properties of the ligand compounds used in this study. All the ligands' SMILES (simplified molecular-input line-entry system) were retrieved from the NCBI PubChem database. The SMILES were used as input in the SwissADME program (http://www.swissadme.ch/), which was then used to compile the pharmacokinetic profiles of the ligand in terms of compound solubility, metabolism, distribution, and toxicity. Drug-like soft rule, Veber rule, the Lipinski rule of 5, solubility, permeability, and excretory indices were used to score and analyse the ligands' ADMET results.

RESULTS

Quantitative phytocompound analyses

In this study, LC-MS and GC-MS analyses detected various phytocompounds with reported antiproliferative effects in the aqueous and ethyl acetate extracts of *C. edulis*, respectively (Table 1 and 2, respectively) detected using GC-MS and LC-MS analyses with their respective chromatograms (Fig. 1 and 2, respectively).

Molecular docking analysis of phytocompounds present in *C. edulis*

Molecular docking analysis revealed that the docked compounds had binding efficiency ranging from -4.00 to -8.44 kcal/mol. Among the studied compounds, β-sitosterol and β-amyrin showed the highest docking scores of -8.44 and -8.10, whereas rutin and oleic acid had the least binding free energy values against targeted proteins. The reference standard drug, doxorubicin, exhibited a high affinity for the protein compared to the studied phytocompounds, with a docking score of -10.95 kcal/mol (Table 3).

Further analysis of the binding pattern revealed that the phytocompounds exhibited varying binding sites through various types of interactions, including hydrogen bonding, hydrophobic interactions, and alkyl interactions. Rutin, β-sitosterol, oleic acid, rutin, quercetin, apigenin, ellagic, and luteolin, docked at the active site similar to that of doxorubicin. However, the compounds revealed different degrees of bond interactions with different amino acids at the active site (Fig. 3).

Specifically, doxorubicin bound to mutp53 with 2 conventional hydrogen bonds (Lys1574 and Ile1572), 8 van der Waals interactions (with Glu1575, Gln1577, Glu1551, Ser1554, Ala1555, Gly1556, Glu1573, and Arg1578), 1 carbon-hydrogen bond (with Tyr1581), and 2 alkyls (with Ala 1546 and Lys 1579). Apigenin had 2 conventional hydrogen bonds (with Asp 1521 and Tyr 1552) and 5 van der Waals interactions (with Ser1497, Asp1498, Phe1553, Leu1547), whereas quercetin had 2 hydrogen interactions (with 2 Asp1521) and van der Waals interactions (Asn1498, Ser1497, Leu1547, Phe1553, Tyr-1552). Moreover, π-π stack, pi-pi T-shaped interactions were also observed between the ligands and the amino acid residues of the target protein (Fig. 4).

Pharmacokinetics and physicochemical properties of phytocompounds

Lipinski's Rule of 5 was used to estimate the drug potential properties of phytocompounds. All the compounds exhibited a molecular weight

of less than 500 g/mol, apart from rutin (Table 4). All the phytocompounds showed differing numbers of rotatable bonds with the highest being oleic acid. Apigenin and β-amyrin however, had no rotatable bonds. Except for rutin and doxorubicin, which had 16 and 12 acceptors, respectively, none of the remaining compounds had more than 10 hydrogen bond acceptors. The phytocompounds depicted varying TPSA values, with limonene exhibiting the lowest, whereas rutin had the highest value of 269.43 $Å^2$. The ratio of sp3 bonded carbon atoms (Fraction Csp3) ranged between 0.00 to 1.00. The lipophilicity (XLogP3) of phytocompounds ranged from -0.33 to 10.70 (Table 4).

As presented in Table 5, all the tested compounds, apart from menthol and limonene, had no ability to permeate the blood brain barrier. High GI absorption was observed however, for the polar compounds compared to the non-polar compounds, except for rutin and oleic acid which were found to have low and high GI permeability respectively. Rutin, catechin, epicatechin, tocopherol, as well as the standard doxorubicin were found to interfere with the activity of the P-glycoprotein drug efflux pump whereas the remaining compounds showed no effect. Apart from quercetin, apigenin and luteolin, limonene and, oleic acid, the rest showed no effect on the cytochromes. The skin permeability coefficient (log kp) of the compounds was found to be negative throughout with the polar compounds having higher negative values compared to the non-polar compounds. Most of the compounds depicted bioavailability of 0.55. All the polar compounds, with the exception of apigenin contained a PAIN alert to catechol_A while the non-polar compounds presented no PAIN alerts. The standard also had a PAIN alert to quinone_A (Table 5).

Table 1: Phytocompound profile of ethyl acetate extract of *C. edulis*

Class of compounds	Compound Name	Retention Time (min)	Conc. (µg/mg)
Monoterpenoids	Menthol	16.85	0.2
	Limonene	7.36	0.1
Diterpenoids	Phytol	25.14	0.46
Triterpenoids	β-Amyrin	40.61	9.14
	α-Amyrin	39.33	1.5
Phytosterols	β –Sitosterol	38.74	3.23
	Stigmasterol	0.44	0.44
Fatty Acid and Derivatives	Palmitic acid	23.71	2.66
	Oleic acid	25.38	1.15
Vitamin (Vitamin E)	α-Tocopherol	35.56	2.97
	β-Tocopherol	33.56	0.15

Table 2: Phytocompound profile of aqueous extract of *C. edulis*

Class of compounds	Compound Name	Retention Time (min)	Conc. (µg/mg)
Phenolics	P-coumaric acid	2.04	0.012
	Catechin	1.31	0.007
	Epicatechin	1.44	0.066
	Rutin	4.94	0.006
	Citric acid	1.58	0.120
Flavonoids	Apigenin	9.39	0.071
	Luteolin	9.42	0.091
	Quercetin	9.48	0.002

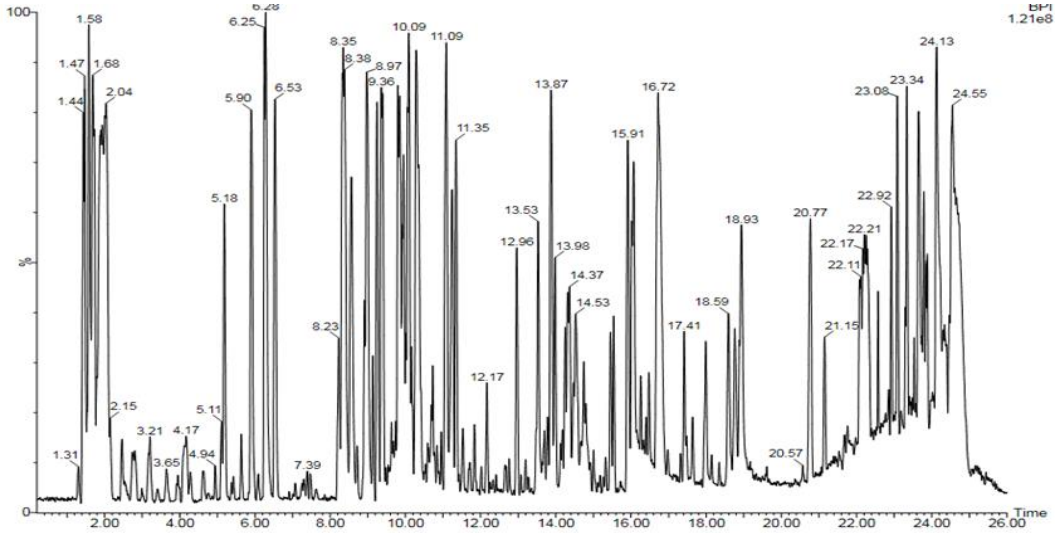

Figure 1: GC-MS chromatogram of ethyl acetate leaf extract of *C. edulis.* Retention times of compounds are shown above peaks

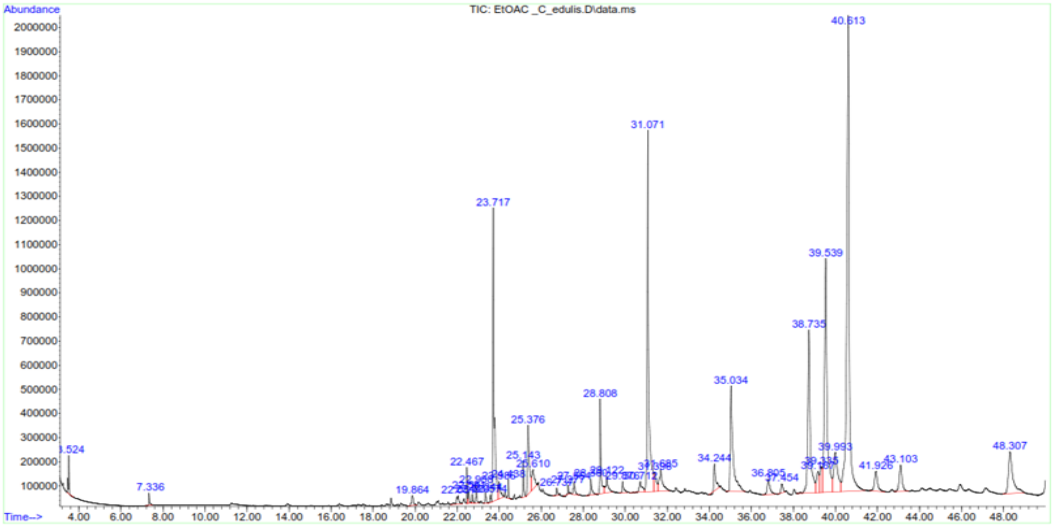

Figure 1: LC-MS chromatogram of an aqueous leaf extract of *C. edulis*. Retention times of compounds are shown above peaks

Table 3: Physicochemical properties of compounds from aqueous and ethyl acetate extracts of *C. edulis*

Ligands	Molecular weight (g/mol)	Rotatable bonds	Hydrogen acceptor	Hydrogen donor	TPSA Å^2	Fraction Csp3	XlogP3	LogS (ESOL)
Rutin	610.52	6	16	10	269.43	0.44	-0.33	-3.30
Catechin	290.27	1	6	5	110.38	0.20	0.36	-2.22
Quercetin	302.24	1	7	5	131.36	0.00	1.54	-3.16
Apigenin	270.24	0	5	3	90.90	0.00	3.02	-3.94
Ellagic	302.19	1	8	4	141.34	0.00	1.10	-2.94
Luteolin	286.24	1	6	4	111.13	0.00	2.53	-3.71
Epicatechin	290.27	1	6	5	110.38	0.20	0.36	-2.22
Menthol	156.27	1	1	1	20.23	1.00	3.40	-2.88
Limonene	136.23	1	0	0	00.00	0.60	4.57	-3.50
B-Amyrin	426.72	0	1	1	20.23	0.93	9.15	-8.25
Sitosterol	414.71	6	1	1	20.23	0.93	9.34	-7.90
Tocopherol	430.71	12	2	1	29.46	0.79	10.70	-8.60
Oleic acid	282.46	15	2	1	37.30	0.83	7.64	-5.41
Betulin	442.72	2	2	2	40.46	0.93	8.28	-7.67
Doxorubicin	579.98	5	12	6	206.07	0.44	2.07	-4.63

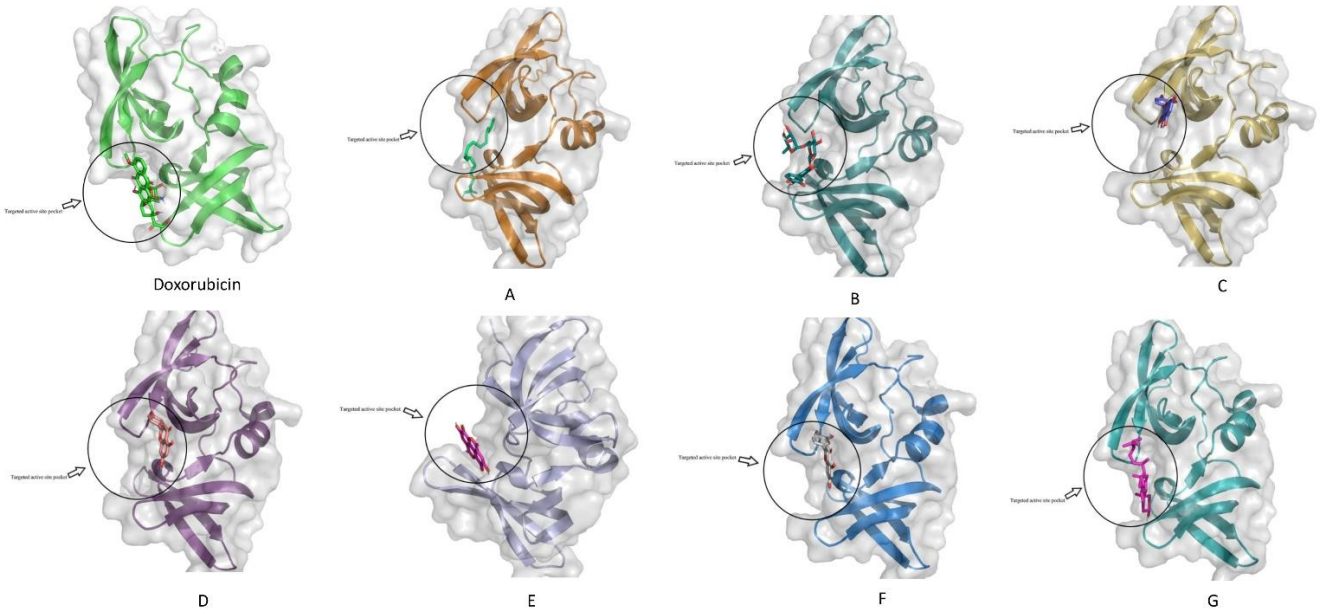

Figure 3: 3D docked poses of phytocompounds with active site region of p53 protein. Key: (A) Oleic acid, (B) rutin, (C) quercetin, (D) apigenin, (E) apigenin, (F) luteolin, (G) β-sitosterol. (In circle- Target active site pocket)

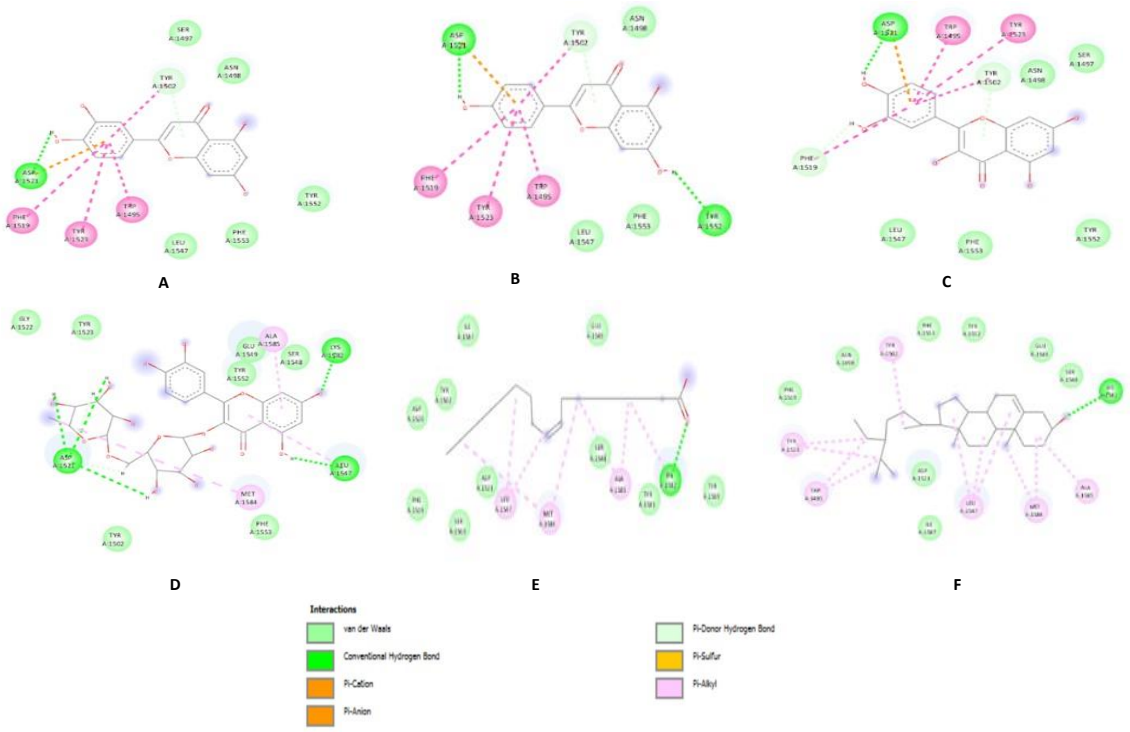

Figure 4: 3D docked poses of phytocompounds with active site region of p53 protein. Key: (A) Oleic acid, (B) rutin, (C) quercetin, (D) apigenin, (E) apigenin, (F) luteolin, (G) β-sitosterol

Table 5: Pharmacokinetic and Medicinal chemistry properties of compounds extracted from aqueous and ethyl acetate extracts of *C. edulis*.

Ligands	BBB permeant	GI absorption	P-gp	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	LogK_p (skin permeation) cm/s	Bioavailability score	PAINS
Rutin	No	Low	Yes	No	No	No	No	No	-10.26	0.17	1
Catechin	No	High	Yes	No	No	No	No	No	-7.82	0.55	1
Quercetin	No	High	No	Yes	No	No	Yes	Yes	-7.05	0.55	1
Apigenin	No	High	No	Yes	No	No	Yes	Yes	-5.80	0.55	0
Ellagic	No	High	No	Yes	No	No	No	No	-7.36	0.55	1
Luteolin	No	High	No	Yes	No	No	Yes	Yes	-6.25	0.55	1
Epicatechin	No	High	Yes	No	No	No	No	No	-7.82	0.55	1
Menthol	Yes	High	No	No	No	No	No	No	-4.84	0.55	0
Limonene	Yes	Low	No	No	No	Yes	No	No	-3.89	0.55	0
B-Amyrin	No	Low	No	No	No	No	No	No	-2.41	0.55	0
Sitosterol	No	Low	No	No	No	No	No	No	-2.20	0.55	0
Tocopherol	No	Low	Yes	No	No	No	No	No	-1.33	0.55	0
Oleic acid	No	High	No	Yes	No	Yes	No	No	-2.60	0.85	0
Betulin	No	Low	No	No	No	No	No	No	-3.21	0.55	0
Doxorubicin	No	Low	Yes	No	No	No	No	No	-8.37	0.17	1

DISCUSSION

Despite the recent dominance of synthetic chemistry in drug discovery, the potential of medicinal plants for cancer treatment and prevention remains immense. The plant *C. edulis* is reputed in traditional medicine due to its use in treating myriad ailments. Previous studies have reported its antiproliferative effects against various cancer cell lines including prostate and breast cancers by upregulating the w*tp53* [5]. In the current study, phytochemical profile analysis revealed the presence of compounds that have been demonstrated to possess antineoplastic effects. The potentiality of the phytocompounds to engage the active sites of mutated p53 cellular proteins was done through docking simulation.

To this effect, the compounds were docked with the mutated p53 protein, and various numbers of receptor-ligand positions were obtained with high binding affinities and complex interactions from the receptor pockets. Specifically, some compounds docked at the active site of the mutated p53 cellular tumour antigen in a manner analogous to doxorubicin, but with distinct conformational arrangements and unique amino acid interactions. The observed interaction could have resulted in the restoration of the *p53* antiproliferative activity as depicted in a previous study by Muruthi et al. [5]. Nevertheless, mutated p53 can also potentially be activated at different sites through various mechanisms, including targeting the core domain, zinc ion stabilization, targeting allosteric sites, and peptide-based approaches [10-12].

Moreover, most phytochemicals exhibited favourable binding affinities with the target protein, where increasingly negative binding energy values correlate with enhanced molecular interactions and optimal ligand orientation within the active site. More specifically, apart from rutin and oleic acid, which had binding energies of -4.03 and -4.00 kcal/mol, all other compounds exhibited values that fell within the range of FDA-approved drugs -5.63 to -6.85 kcal/mol [13]. Moreover, the compounds exhibited diverse interaction types with amino acid residues, including conventional hydrogen bonds, pi-pi stacks, and van der Waals forces leading to enhanced binding affinity with the target protein. The findings suggest that the phytochemicals have the potential to engage with the target protein like conventional anticancer drugs.

To further analyse the application of the compounds in cancer therapeutic applications, their drug-likeness was predicted using the physicochemical and pharmacokinetic parameters, which were analysed using the SwissADME program. The system investigates the molecular properties of a molecule to determine its similarity to known drugs, thereby assisting in predicting its drug-like properties [14]. The tools provide essential physicochemical information, including molecular weight, solubility, polarity, lipophilicity, and saturation of carbon fractions for compounds to prove their drug-likeness based on the rule of five as proposed by Lipinski et al. [15]. The "Rule of 5" states that a compound needs to have a molecular weight of less or equal to 500 g/ml, less or equal to 10 hydrogen bond acceptors, 5 hydrogen bond donors, log P less than 5, and a topological polar surface area (TPSA) value of less than 140 Å2. According to Rath et al. [16], these parameters are highly associated with intestinal permeability and dissolvable in the initial steps of oral bioavailability.

Findings revealed that apart from rutin, all the phytocompounds were found to be within the "Rule of 5" without any violation and, therefore, have a high probability of being drug candidates [17]. The compounds exhibited molecular weight less or equal to 500 g/mL, suggesting that they can be absorbed, diffused, and transported with ease. As for hydrogen acceptors and donors of the bioactive compounds, the numbers fell within the desirable range, indicating their potential for positive interaction with biological targets.

The lipophilic nature of a compound influences its selectivity, solubility, and permeability [15]. In this regard, XlogP3 values between -0.7 and +5.0 are satisfying lead molecules. High not deviate from the range. Consequently, the lipophilicity values of the latter compounds predict a balance between permeability and solubility, important for efficient drug delivery.

Regarding topological polar surface area (TPSA), the bioactive compounds exhibited a value lower than 140 $Å^2$, which is benchmarked for marketed drugs. However, rutin exhibited poor polarity as it had a TPSA higher than 140 $Å^2$, suggesting that its potential for dietary bioavailability may be constrained because a compound's solubility, absorption, and protein binding properties are dictated by TPSA [18]. Notably, previous studies have demonstrated that TPSA value has a positive correlation with a mass, whereby a compound with a mass higher than 500 g/mol is likely to have TPSA beyond 140 $Å^2$, which was evident with rutin [19]. As for water solubility, most of the compounds were soluble. It is well documented that soluble molecules simplify various aspects of drug development, more so in handling and formulation. In oral administration, solubility plays a significant role in determining absorption [20].

SwissADME also provides predictions for pharmacokinetic properties such as BBB permeation, P-glycoprotein, gastrointestinal (GI) absorption, and cytochrome P450 inhibition. These predictions are used to investigate the safety and potential efficacy of a particular molecule. In the present study, GI absorption of the polar and nonpolar compounds identified in the extracts of *C. edulis* revealed the ability to be well absorbed in the GI tract when administered orally. These findings suggest that the compounds with high GI absorption may have higher bioavailability than others, thereby increasing their therapeutic efficacy [14].

The compounds were also assessed for the potential to cross the brain-blood barrier. Some compounds showed the ability to cross, whereas others did not show any potential. As previously documented, penetration across the barrier is critical for compounds targeting the central nervous system. Nevertheless, compounds with less potential to cross BBB can be considered to cause fewer adverse effects in the central nervous system [13].

Permeability glycoprotein (P-gp) compounds act as membrane transporters in cells. It limits the cellular uptake of compounds through its unidirectional efflux pump effect to extrude its substrate from inside the cell. As a result, they influence drug absorption, distribution, excretion, and toxicity [15]. Phytochemicals rutin, epicatechin, catechin, and tocopherol are substrates for P-gp, implying that they are subject to efflux transport, limiting their therapeutic efficacy. Nevertheless, some of the studied compounds were non-substrate for the enzyme and thus have the potential not to be resisted in targeted cell sites.

In terms of drug metabolism, the study further analysed the toxicological characteristics of the phytocompounds by investigating their effects on the metabolic profile of liver inhibition of CYP family proteins. Cytochrome P450 enzymes have a significant role in drug metabolism and elimination in biological systems. The non-inhibitory effect of most compounds under study indicates that they have a high probability of being transformed and made bioavailable upon oral administration. On the contrary, a few compounds in this study with inhibitory effects can lead to poor bioavailability because of metabolic derangements and adverse effects due to their accumulation [13].

Pan-assay interference compounds (PAINS) are usually used to detect the presence of substructures in the compounds that might interfere with bioactivity detection technology. To enhance reliability of hit identifications PAINS are used to weed out false screening hits and detect suspect compounds from screening libraries (Capuzzi et al., 2017). Six of the polar compounds as well as the standard drug doxorubicin, from this study were flagged with the PAIN alerts suggesting presence of unattractive pharmacokinetic properties. These alerts however were derived from two most common substructures (frequent hitters) catechol and quinone which are present in many

phytocompounds thus suggesting that the alerts might have been phantom PAINS [21].

CONCLUSION

In the current study, various compounds with reported antiproliferative effects were detected in *C. edulis* extracts. The phytocompounds were demonstrated to interact with the target protein but with distinct conformational arrangements and unique amino acid interactions. The observed interaction could have resulted in the restoration of the *p53* gene's antiproliferative. Moreover, most phytochemicals exhibited favourable binding affinities with the target protein. The compounds also Findings from this study underscore the therapeutic potential of *C. edulis* for future anticancer drug development. Nevertheless, there is a need to isolate the compounds and carry out further preclinical studies.

Conflict of interest

The authors declared no conflict of interest.

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