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ORA- In silico study **OPEN ACCESS**

ANTI-CANCER POTENTIAL OF BIOACTIVE COMPOUNDS FROM *MORINGA OLEIFERA* AGAINST PARK2 IN ORAL CANCER PROTEIN: *IN SILICO* APPROACH

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ABSTRACT:

Background: Globally, oral cancer (OC) is one of the most common cancers and it is the second highest incidence in India. Medicinal plants are well known anticancer therapeutic agents since ages and considered alternative treatment of cancer diseases. Moringa oleifera, the most crucial medicinal plant contains a vast number of potential anti-cancer bioactive compounds. **Objective:** The aim of the current study is to investigate the therapeutic potential of five bioactive compounds kaempferol, niazimicin, niazinin, O-ethyl-4-(alpha-l-rhamnosyloxy) benzyl carbamate and quercetin of Moringa oleifera target PARK2 against OC proliferation via in silico study. **Methodology:** In silico approach via ADME/ProTox-II tools and molecular docking analysis have assessed to find binding affinity between PARK2 and Moringa oleifera selected compounds. **Results:** Our finding revealed that Kaempferol, bioactive compounds of Moringa oleifera shows Lipinski's Five Rules and is non-toxic to the liver. Besides, it also displays higher binding affinity -7.2kcal/mol and a lower binding energy followed by five selected compounds and also from 5-Flurouracil with the PARK2 interaction. **Conclusion:** The study provided insight into Kaempferol's possibilities of success as drug discovery candidates in the face of PARK2-related OC regulation. Thus, future in vitro, in vivo, and clinical studies are required to corroborate our findings.

Keywords: Bioactive compound, molecular docking, Moringa oleifera, oral cancer, PARK2, ADME

INTRODUCTION

Oral cancer (OC) is the most frequent disease among people, accounting for 177,757 fatalities and 377,713 new cases worldwide each year, according to Globocan 2020 [1]. In Asian countries south central region, including Sri Lanka, India, and, Pakistan has a high prevalence of OC, with India accounting for higher than 1/3rd of patients (135,929) and 1/5th of mortalities (75,290). Oral squamous cell carcinoma (OSCC) accounts for 90% of all OCs and is the sixth most frequent cancer in the world [2, 3]. Several studies have found that oral cancer is linked to lifestyle, dietary patterns, smoking, tobacco, alcohol intake, and physical inactivity, all of which have a direct impact on an individual's survival [4].

Chemotherapy is recognized as a helpful and promising approach for treating a variety of malignancies, including OSCC; nevertheless, if chemotherapeutic resistance results in failure of therapy, there is a risk of mortality [5,6]. To address this issue, multiple studies have discovered that natural plants and their bioactive compounds offer numerous qualities, including anti-cancer activity [7]. Natural plant bioactive compounds contain many potent polyphenols and flavonoids are able to regulate or reduce the risk of OC [8]. In contrast, the purposeful combination of bioactive compounds and chemo-preventive agents for successful therapeutic applications provides a crucial supply of pharmaceutical compounds with novel mechanisms for current medication development [9]. Many bioactive compounds can be obtained from plants, including glucosinolates, tannins, steroids, flavonoids, terpenes, saponins, alkaloids, and phenolic acids [10]. Several flavonoids found in plants, such as kaempferol, rhamnetin, quercetin, myricetin, apigenin, and rutin, have anti-oxidant, anti-cancer, antidiabetic, and anti-inflammatory activities [11,12]. This plant's anti-cancer activity is attributed to phytoconstituents such as, carbamates, kaempferol, quercetin, thiocarbamate, as well as, niazimicin, and nitrile glycosides. By changing the expression of downstream genes and proteins, bioactive compounds modulate multiple signalling pathways, including those involving toll-like receptors, tumour necrosis factor receptor, cytokine receptors and epidermal growth factor receptor, with anti-cancer properties [13]. Therefore, plants with therapeutic characteristics can be utilized to treat and manage OC.

Moringa oleifera is a member of the Moringaceae family that grows throughout India, Africa, and many other tropical and dry countries [14]. *Moringa oleifera* is rapidly increasing popularity in India as a medicinal herb owing to its effective bioactive compounds with anti-cancer properties. *Moringa oleifera* is also called as the "Drumstick Tree" and the 'Tree of Life' [15 ,16]. A vast number of studies have shown that bioactive compounds from *Moringa oleifera* interact with P^{53} which is a tumor suppressor gene such as in different malignancies, inhibiting cell growth in a way similar to some anti-cancer medications [17].

PARK2 is a ubiquitin-protein ligase, a tumor suppressor gene that stimulates expression and has a significant impact on the control of numerous human malignancies, including cervical cancer [18 ,19]. As a result, bioactive compounds from *Moringa oleifera* may increase the expression of PARK2 tumor suppressor proteins in response to a variety of malignancies.

To identify the impact and difficulty of developing various anti-cancer drugs, pharmacokinetics, computational and structural-based screening are some of the most significant methods that are very reliable and may meet the requirements as needed. In the current investigation, we identified physiochemical and toxicological properties of all five selected compounds of *Moringa oliefera* by using SwissADME and ProTox II web server online tools. Furthermore, the PARK2 gene's expression in OC pathogenesis was assessed using molecular docking analysis of its binding interaction with *Moringa oliefera's* five bioactive compounds

METHODOLOGY

The human PARK2 protein structure (PDB ID: 4I1H) was obtained from the online accessible Research Collaboratory for Structural Bioinformatics–Protein Data Bank (RCSB-PDB) [20] (Table 1, & Figure 1). BIOVIA Discovery Studio 2022 Client was used to save PARK2 protein data in.pdb file format after eliminating side chains, ligand molecules, water, and hetatm [21].

Table 1: 3-D structure of PARK2.

Molecule	PDB ID	Chains	Sequence Length	Gene Type	Organism	Details
PARK2	4I1H	A	325	TSG	Homo sapiens	Mutation(s): 0

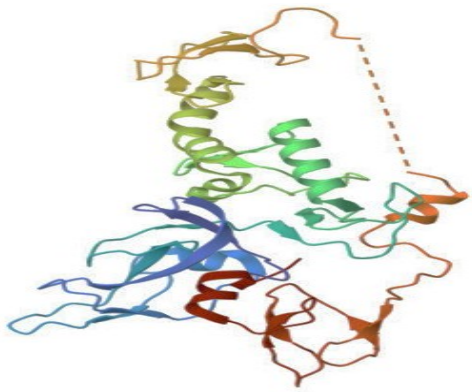


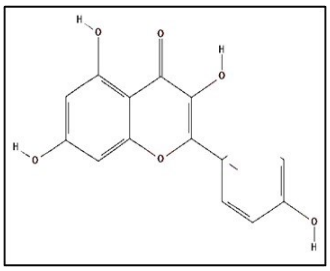
Figure 1: PARK2 (PDB: 4I1H)

Selection of bioactive compounds

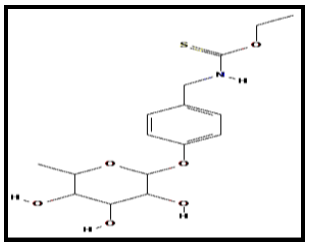
On the basis of previous review literature, five bioactive compounds from *Moringa oleifera* with anti-cancer activities were selected (table 2, figure 2). All of the compounds 3D structures were retrieved and saved in SDF file format from the PubChem database [22].

Table:2 Bioactive compounds of *Moringa oleifera* with their structure formula and molecular weight

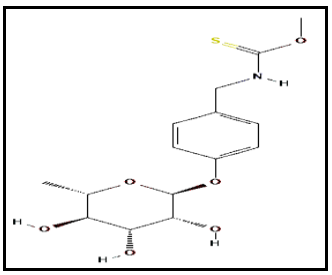
Bioactive Compound	Structure Formula	Molecular weight (g/mol)
Kaempferol	$C_{15}H_{10}O_6$	286.24
Niazimicin	$C_{16}H_{23}NO_6S$	357.42
Niazinin	$C_{15}H_{21}NO_6S$	343.40
O-ethyl-4-(alpha-l-rhamnosyloxy) benzyl carbamate	$C_{16}H_{23}NO_8$	357.36
Quercetin	$C_{15}H_{10}O_7$	302.24



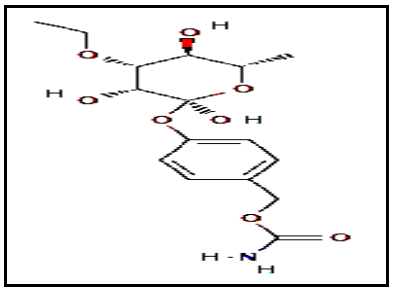
Kaempferol



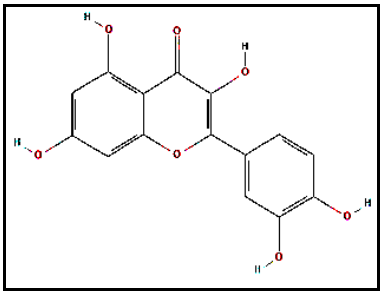
Niazimicin



Niazinin



O-ethyl-4-(alpha-l-rhamnosyloxy) -benzyl carbamate



Quercetin

Figure 2: Schematic representation of the 2D Structure of five bioactive compounds of *Moringa oleifera*

2.2 *In Silico* Study of Bioactive Compounds Pharmacokinetic Parameters by SwissADME

SwissADME [23] (http://www.swissadme.ch/) online web server tools was used to determine the pharmacokinetic characteristics to evaluate the drug-likeness of the five bioactive compounds. To be an orally active treatment, drug-like properties of selected phytochemicals was assessed by Lipinski and Veber's rule.

***In Silico* Study of Bioactive Compounds Toxicological Features Identification by ProTox-II**

The compounds' toxicological properties were predicted with the ProTox II online webserver tool [24, 25]. The toxicity profiles of five selected compounds based on various ways such as $LD_{50,}$ toxicity class, hepatotoxicity, immunogenicity, mutagenicity, and carcinogenicity was also determined.

Preparation of ligands

The 3D structures of all five bioactive compounds kempeferol (CID:5280863), niazimicin (CID:5471459), niazinin (CID: 10088810), O-ethyl-4-(alpha-l-rhamnosyloxy) benzyl carbamate (CID:129712240 and quercetin (CID:5280794), on the other side for comparison 5-flurouracil drug (CID:3385) were also retrieved from PubChem database in sdf format [22 , 28] . BIOVIA Discovery Studio 2022 used to convert and save the sdf file in pdb file format of all five bioactive compounds. **Figure 3** represents flow chart of the docking study.

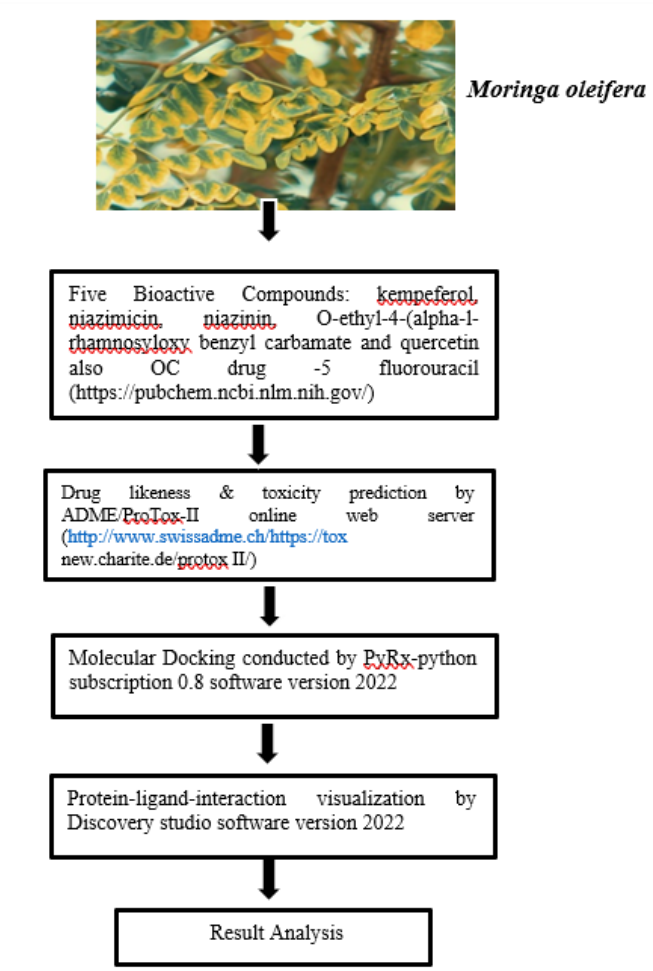


Figure 3: Flow chart of the docking study

Molecular docking studies

Human PARK2 protein binding mode and interaction with five individual phytoconstituents were performed using Pyrx-Python Prescription 0.8 software [26, 27]. The software was used to load the protein, defined as a macromolecule, and the drug, defined as a ligand. All five compounds, kaempferol, niazimicin, niazinin, O-ethyl-4-(alpha-l-rhamnosyloxy) benzyl carbamate and quercetin, were used as ligand for docking with the target protein PARK2. All of the ligand bonds were made rotatable. A grid box was created to define the docking site on the target protein that covered the whole protein in three dimensions (Angstrom) X:46.0283, Y: 55.6802, and Z:59.4971) and centre X: 60.3229, Y: 24.1522, Z: 16.8893. The best-docked pose with minimum energy has been selected and saved as the best conformation. The best average binding affinity has been determined as the final affinity value. The interactions of human PARK2- ligand conformations, including hydrogen bonds and several other bonds, were evaluated using BIOVIA Discovery Studio 2022.

RESULTS

ADME and toxicity analysis of selected bioactive compounds

On the basis of both Lipinski and Veber rules various features of ADME and markers of pharmacokinetic properties were used to observed the oral bioavailability of all selected compounds (Table 3). All five bioactive compounds were found to violate five of the parameters, as per Lipinski rule of five conditions that orally administered agents should covering some features such as H-bond donor (HBD) <5, lipophilicity value (Log P) ≤ 5, H-bond acceptor (HBA) <10, and molecular weight <500 amu. As per rules by Veber's mention TPSA (topological polar surface area) ≤140 as well as number of rotatable bonds ≤10. The results for all five compounds were gained from the SwissADME online server was shown in Table 3 for *Moringa oleifera*, respectively. After that using ProTox -II online web server tools were used to estimate the toxicity profiles of all selected compounds are displayed in Table 4. These data

presented that no any selected compounds from *Moringa olifera* are related with hepatotoxic properties. Niazimicin and niazinin were found to have immunotoxicity, while kaempferol and O-ethyl-4-(alpha-l-rhamnosyloxy) benzyl carbamate possess no toxicological properties. Only quercetin compounds were associated with both carcinogenic and mutagenic properties in all the compounds recognized in *Moringa olifera.*

Table 3: Pharmacokinetics features related with successful oral bioavailability of the bioactive compounds from *Moringa olifera*

	Lipinski's Rule of Five iLogP				**Veber Rule**			
Ligands	**Mol. wt.(g/mol) <500**	**iLogP <5**	**HBA <5**	**HBD <5**	**Drug-likeness Lipinski's rule follows (Yes/no)**	**Violation ≤1**	**nRB ≤10**	**TPSA ≤140**
Kaempferol	286.24	1.70	6	4	Yes	0	1	111.13
Niazimicin	357.42	3.06	6	4	Yes	0	7	132.50
Niazinin	343.40	2.55	6	4	Yes	0	6	132.50
O-ethyl-4-(alpha-l-rhamnosyloxy) benzyl carbamate	357.36	2.63	8	4	Yes	0	7	140.70
Quercetin	302.24	1.63	7	5	Yes	0	1	131.36

Table 4: Toxicological properties of the bioactive compounds of *Moringa olifera*

Bioactive compound	**LD_{50} (mg/kg)**	**Toxicity Class**	**Hepatotoxicity**	**Carcinogenicity**	**Immunotoxicity**	**Mutagenicity**
Kaempferol	3919	IV	No	No	No	No
Niazimicin	3750	V	No	No	Yes	No
Niazinin	3750	V	No	No	Yes	No
O-ethyl-4-(alpha-l-rhamnosyloxy) benzyl	4000	V	No	No	No	No

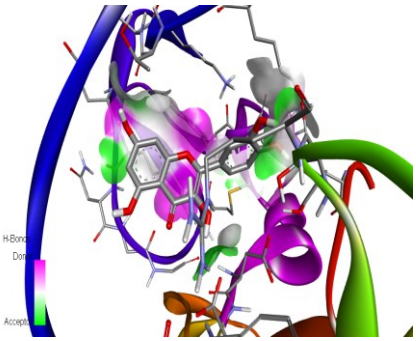
carbamate						
Quercetin	159	III	No	Yes	No	Yes

Molecular Docking Based Studies

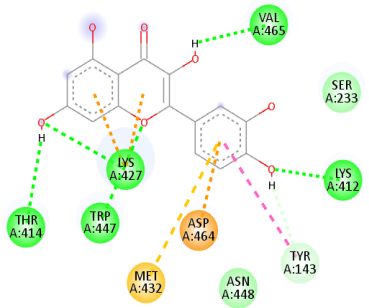
Structure-based drug design: PARK2 (PDB ID 4I1H) was docked with five bioactive compounds of Moringa *oleifera*: kaempferol, niazimicin, niazinin, O-ethyl-4-(alpha-l-rhamnosyloxy) benzyl carbamate and quercetin. Docked models with minimum energy were saved in pdb format using Pyrx software. Discovery Studio visualizer was used to study the molecular interaction between the target protein and the ligands and saved the best visual pose showing the hydrogen bond between the PARK2 protein and the ligands. To better understand interactions other than hydrogen bonds, which include van der Wal, pi-donor bonds, carbon-hydrogen bonds, alkyl bonds, conventional hydrogen bonds, alkyl bonds, and pi-alkyl bonds. 2D interaction was generated using one of the feature receptor-ligand interactions of Biodiscovery Studio which have displayed in **Figure 3**.

Molecular docking with PARK2 protein and five active compounds resulted in a stable docked complex as all the docking affinities were greater than -5 Kcal/mol, such as kaempferol-.7.2kcal/mol, niazimicin-6.6kcal/mol, niazinin-6.4kcal/mol, O-ethyl-4-(alpha-l-rhamnosyloxy) benzyl carbamate -7.0kcal/mol and quercetin -7.1 Kcal/mol. However, as per analysis among all compounds, kaempferol (CID:5280863) was found to have the highest binding affinity -7.2 Kcal/mol and comprised the least binding energy as compared to the rest of the compounds and root mean square density (RMSD) for both upper as well as lower bound was found to be zero **(Table 5)**. In addition, the five-hydrogen bond interaction has been analyzed between interacting residue Val465, Lys412, Lys427, Trp44, and Lys412 in kaempferol with PARK2 protein. However, docking of oral anti-cancerous synthetic drug 5-fluorouracil with PARK2 protein interaction, which contains the lowest binding affinity-4.6 kcal/mol and highest binding energy and contains only two hydrogen bond interacting residues between Phe304 and Lys299. So far, considering the lower binding energy as a more stable complex, we can assume kaempferol is a drug with oral anti-cancerous properties.

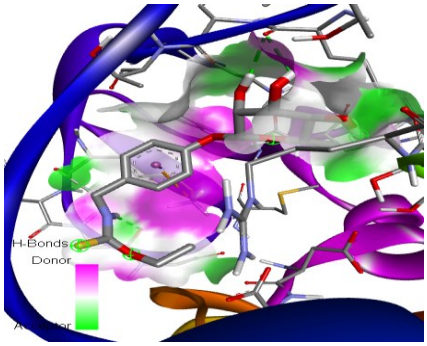
Protein-ligand interactions:



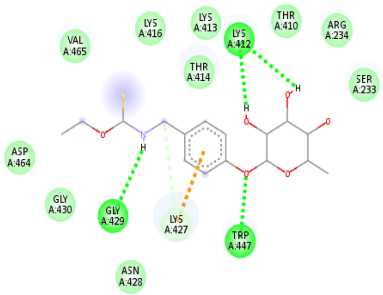
3D visualization docking of PARK2- Kaempferol interaction



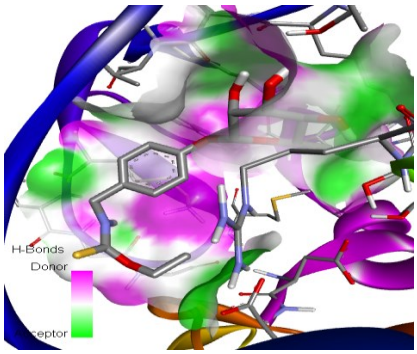
2D visualization docking of PARK2- Kaempferol



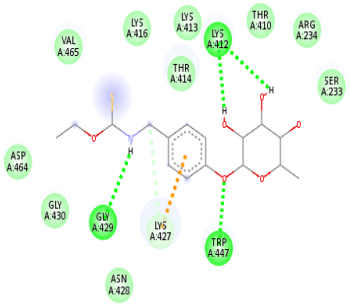
3D visualization docking of PARK2- Niazinin interaction



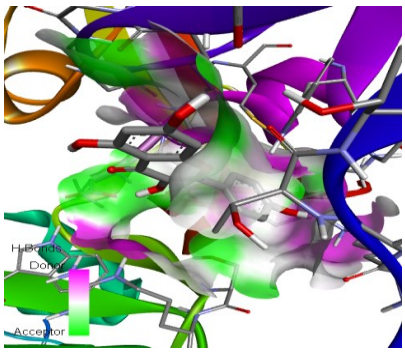
2D visualization docking of PARK2- Niazinin



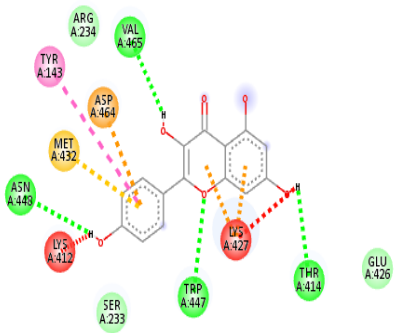
3D visualization docking of PARK2- Niazimicin interaction



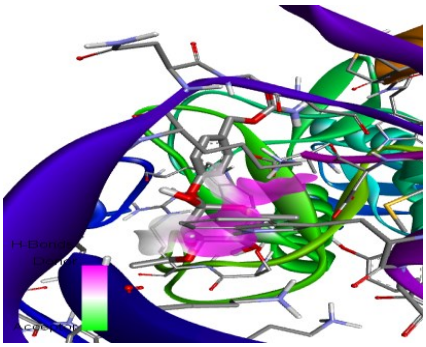
2D visualization docking of PARK2- Niazimicin



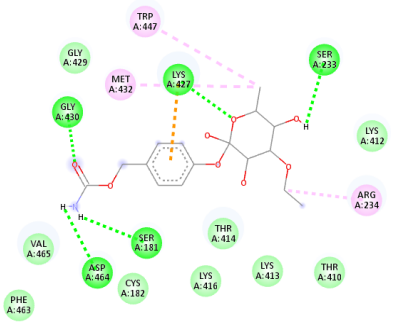
3D visualization docking of PARK2- Quercetin interaction



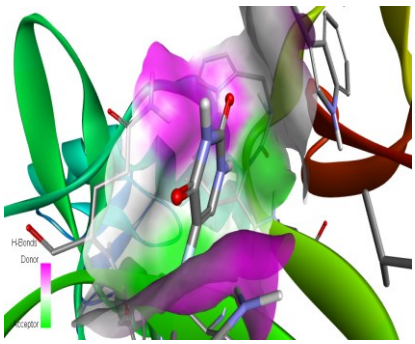
2D visualization docking of PARK2-Quercetin



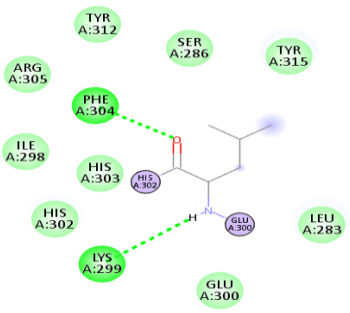
3D visualization docking of PARK2-((A-L-Rhamnosyloxy) benzyl) carbamate interaction



2D visualization docking of PARK2-((A-L-Rhamnosyloxy) benzyl) carbamate



3D visualization docking of PARK2-5-Flurouracil interaction



2D visualization docking of PARK2-5-Flurouracil

Figure 3: 3D and 2D images of docked complex of bioactive compounds of *Moringa oleifera* along with PARK2 protein with standard drug 5-Flurouracil (Green dotted line showing hydrogen bonding interaction)

Table 5: Energy-based dockings for selected five bioactive compounds with the target PARK2 protein

Protein	**PubChem CID**	**Bioactive compound**	**Binding affinity**	**RMSD (upper bound &Lower bound)**	**No. of H-bond**	**Interacting residues**
PARK2	5280863	Kaempferol	-7.2	0	5	Val465, Lys412, Lys427, Trp44, Lys412, Thr414
	5471459	Niazimicin	-6.4	0	3	Lys412, Trp 447, Gly429
	10088810	Niazinin	-6.8	0	3	Lys412, Trp 447, Gly429

	129712240	O-ethyl-4-(alpha-l-rhamnosyloxy) benzyl carbamate	-7.0	0	5	Lys427, Ser233, Ser181, Asp464, Gly430
	5280343	Quercetin	-7.1	0	4	Val465, Thr414, Trp447, Asn448
	3385	5-Flurouracil	-4.6	0	2	Phe304, Lys299

DISCUSSION

With the advancement of OC implication, there was a need to identify bioactive compound with anti-cancer properties and binding affinity with the PARK2 protein. Because of this urgency, several clinical researchers identified the concept of repositioning current chemotherapeutic medications as a powerful strategy for creating a new, effective therapeutic paradigm. This event provided an opportunity to investigate alternative treatment options, focusing on the potential use of medicinal herbs.

The primary goal of this research is to identify the five bioactive compounds found in *Moringa* oleifera that can efficiently interact with PARK2 to regulate the development of OC in an individual, hence reducing or avoiding OC metastasis. It is worth noting that previous research sought natural anti-cancer medications with pharmacological properties in plants, which have been identified in the literature for use in treating and preventing a variety of dangerous diseases.

In the current study, molecular docking was applied to inspect the anti-cancer potential of *Moringa oleifera* compounds with the PARK2 protein against OC. The bioactive compounds with the highest negative binding affinity and lowest binding energy to PARK2 proteins is thought to play an important role in oral cancer regulation. The results suggest that kaempferol has the largest molecular interactions with PARK2 protein (7.2 kcal/mol), while 5-fluorouracil, a synthetic commercial chemotherapeutic medication, has the lowest interactions (4.6 kcal/mol) with PARK2 protein. In consequently, screening demonstrated that these bioactive compounds may be effective anti-cancer medications with PARK2 protein against OC advancement, paving the way for novel and established treatments for this cancer.

The results show that five bioactive compounds, namely niazimicin, niazinin, O-ethyl-4-(alpha-l-rhamnosyloxy) benzyl carbamate, and quercetin, demonstrated lower molecular interactions with the PARK2 protein than kaempferol. Niazimicin exhibited the lowest binding affinity (-6.4 kcal/mol) and the highest binding energy among the five compounds. Other bioactive compounds, such as Niazinin (-6.8 kcal/mol), O-ethyl-4-(alpha-l-rhamnosyloxy) benzyl carbamate (-7.0 kcal/mol), and quercetin (-7.1 kcal/mol), have lower binding

affinity for PARK2 than kaempferol but higher binding affinity than 5-fluorouracil.

Kaempferol is a flavonoid found in many plants and is thought to be a potent natural compound with numerous biological functions [26]. *In silico* and *in vitro* studies show that this bioactive molecule has various health benefits, including cancer inhibition, inflammation reduction, diabetes prevention, neuroprotective, cardioprotective, and antibacterial properties [29, 30, 31].

The drug repositioning strategy, a standard procedure in pharmaceutical development research, aims to uncover new therapeutic applications for drugs that have been approved or are presently being tested [32]. Oral administration and high solubility are critical components of drug discovery plans that ensure complete absorption. In contrast, low solubility inhibits absorption in the digestive tract. Predictions of pharmacokinetic and toxicity characteristics (ADME/Pro-Tox-II) showed that the majority of drugs had appropriate water solubility. All five compounds that follow Lipinski's and Veber's rules have no infractions, a molecular weight of less than 500mg/kg, high solubility, and contain HBA and HBD. Veber's rule criteria specify a minimum of ten rotatable bonds and a TPSA of 140. This criterion shows that chemical or prospective therapeutic agents cannot violate entire of the requirements although keeping good oral bioavailability [33, 34] . Moreover, the toxicological features of the five compounds from *Moringa oleifera* ProTox-II tools evaluated mutagenicity, immunotoxicity, carcinogenicity, hepatotoxicity, and toxicity class.

In this study, we used *in silico* techniques to illustrate that bioactive compounds from *M. oleifera* and PARK2 may be useful in OC reduction. We used, ADME, ProTox II predictions, an online web tools and molecular docking analysis to evaluate the therapeutic potential of a bioactive molecule from *Moringa oleifera* against OC. It is important to note that our findings advocate strong anti-cancer potential; nevertheless, more experimental validation is required to confirm the efficacy of the tested *Moringa oleifera* bioactive compounds against OC.

CONCLUSION

Five bioactive compounds from *Moringa oleifera* shown anti-cancer activity with PARK2 protein against OC, which is critical for increasing PARK2 expression. Among the five compounds assessed, kaempferol, niazimicin, niazinin, O-ethyl-4-(alpha-l-rhamnosyloxy) benzyl carbamate, and quercetin, kaempferol was the most promising, with a high affinity for the PARK2 protein against OC. This compound also has a better molecular interaction than the usual oral anti-cancer medicine 5-fluorouracil for OC. Furthermore, pharmacokinetic studies reveal that kaempferol has a good solubility and low toxicity, indicating its potential as a treatment alternative for OC development. It is also worth noting that kaempferol showed no evidence of hepatotoxicity, mutagenicity, or carcinogenicity in our investigation. However, experimental validation such as *in vitro, in vivo* and

clinical studies are required before considering Kaempferol bioactive compounds of *Moringa oleifera* as prospective candidates for OC treatment and management.

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