International Journal of Biomedical Investigation

journal homepage: https://ijbi.edwiserinternational.com

Original Article

Identification of potential inhibitors of PTEN tumor suppressor gene from phytochemical constituents found in tomato (Solanum lycopersicum) *via* biocomputational analysis

Atreyee Majumder[#], Satavisha Ghorui[#], Sudeshna Sengupta[#] and Malavika Bhattacharya[*]

Department of Biotechnology, Techno India university, EM-4, Sector-V, Salt Lake, Kolkata, West Bengal -700091, India
#Authors contributed equally

ARTICLE INFO

Received 29 April 2024
Revised 26 June 2024
Available Online 30 June 2024

Keywords:
Bioinformatics
PTEN Tumor Suppressor Gene
Endometrial Cancer
Tomato
Solanum lycopersicum
Lenvatinib Mesylate

ABSTRACT

The research investigates the potential of phytochemical constituents found in tomatoes (Solanum lycopersicum) to inhibit the PTEN tumor suppressor gene, which is frequently mutated in endometrial cancer. Endometrial cancer, primarily adenocarcinomas, is often linked to genetic mutations, particularly in the PTEN gene, which is crucial for regulating cell proliferation and apoptosis through the PI3K/AKT pathway. This study leverages biocomputational analysis to identify bioactive compounds in tomato peel, pulp, and seeds that could serve as alternative inhibitors to the PTEN gene, comparing their efficacy to the control drug Lenvatinib mesylate. The methodology involved preparing the PTEN protein structure, retrieving phytochemicals from tomatoes, and performing molecular docking to assess binding affinities. The top three ligands from each tomato component were selected based on their binding energies and underwent ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis to evaluate their drug-likeness. Results indicated that several tomato-derived compounds exhibit binding energies comparable to or better than Lenvatinib mesylate, suggesting potential as natural therapeutic agents. The study concludes that tomato phytochemicals, particularly those with high binding affinities, hold promise for developing dietary supplements aimed at treating endometrial cancer with potentially fewer side effects than conventional drugs.

Introduction

Endometrial cancer is the most commonly diagnosed form of cancer, occurring in female reproductive organs [1].

The inner lining of the uterus is called the endometrium, and endometrial cancer develops when cells in the endometrium start to proliferate out of control, leading to the growth and development of tumours in the uterus. It is to be noted, however, that endometrial cancer is not the same as uterine sarcoma, which is cancer of the uterus's muscle or connective tissue. Adenocarcinomas account for about 80% of all endometrial cancer cases.

*Corresponding author: Malavika Bhattacharya, Department of Biotechnology, Techno India university, EM-4, Sector-V, Salt Lake, Kolkata, West Bengal -700091, India.

https://doi.org/10.31531/2581-4745.1000152

This indicates that the endometrial gland-developing cells are where this cancer starts. These tumours are pathogenetically connected to an excess of unopposed oestrogen, developed from endometrial hyperplasia, and express hormone-receptor activity. When detected early, endometrial cancer is highly curable [2-4].

Endometrial carcinoma (Figure 1) is thought to be caused by several genetic changes, including signalling system disruption, proto-oncogene activation, and tumour suppressor gene inactivation. Each category of endometrial cancer develops and progresses using separate molecular processes of oncogenesis, indicating type-specific genetic changes. While there are long-standing surgical, radio-, and chemotherapeutic therapies, the detection and classification of biological markers are often required to enhance the comprehension of molecular pathways of the disease and for the advancement of particular novel targeted treatments to achieve higher levels of specificity in tumour growth as well as metastatic processes, and to appropriately assess the long-term outlook, especially in situations involving recurring and poor disease history [5-8].

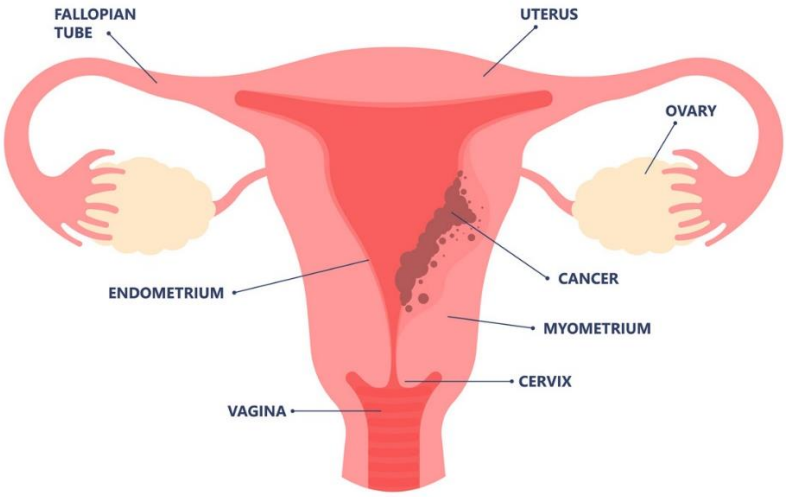

Figure 1: Diagram of Endometrial Cancer (Picture: Vejthani Hospital).

Endometrial carcinoma's most common genetic mutation [9], about 30-80%, occurs in the PTEN gene [10]. First identified in 1997, the Phosphatase and Tensin homolog or PTEN gene is a tumour-suppressor gene found in chromosome 10 (10q23). The protein suppresses cell proliferation and differentiation and is involved in the insulin signalling pathway. It also participates in several cellular processes, including translocation and amplification [9,11]. PTEN inactivation is caused by alterations that result in loss of expression and, to a lesser extent, by loss of heterozygosity [12,13]. The PTEN protein is known to regulate the PI3K/AKT pathway by phosphorylation of PIP3 at the cellular membrane. Loss of operating PTEN protein thus results in continuous generation of tumorigenic PIP3. MTOR is the primary activator of the PI3K/AKT pathway, boosting the G1 cell division phase as well as regulating apoptosis through protein interactions [14]. The bulk of PTEN gene mutations in cancers are located in the phosphatase domain, which affects phosphatase activity [15]. PTEN gene expression has been found to be diminished in a variety of human malignancies, including endometrial cancer, glioblastoma, lung cancer, breast cancer, prostate carcinoma, ovarian cancer, etc [16]. Furthermore, prior investigations have demonstrated that PTEN expression is on the lower end in endometrial hyperplasia and endometrial cancer as opposed to proliferative endometrium [17-19].

The role of nutritional factors in carcinogenesis is generally accepted to be important [20,21]. Epidemiologic studies have provided compelling evidence that diets rich in fruits and vegetables are linked to a decreased risk of various malignancies [22, 23]. Several organizations, such as the National Cancer Institute, the National Research Council of the National Academy of Sciences, the World Cancer Research Fund, as well as the American Institute for Cancer Research [24], have made dietary suggestions to increase the consumption of citrus fruits [25], cruciferous vegetables, especially green and yellow vegetables and fruits that are high in vitamins A and C

to lower the likelihood of developing cancer. What is still undetermined, though, is which components contribute to this advantage [26].

Up until now, the health benefits or medicinal value of tomatoes (*Solanum lycopersicum*) had received relatively little attention, with tomatoes not going beyond the usual usage in different cuisines across the world or at most as homemade herbal facial masks, applied topically on the recommendations of our mothers and grandmothers. But recently, the antioxidant and anti-carcinogenic properties of biocompounds lycopene, a carotenoid-rich phytocompound found in abundance in tomatoes, have raised interest in tomatoes being seen as a nutraceutical source with potential anticancer properties [27]. Higher consumption of tomatoes is consistent with current dietary recommendations aimed at increasing the intake of various fruits and vegetables for a healthy lifestyle.

This study compares epidemiological evidence that links the ingestion of tomatoes, specifically the peel, pulp, and seeds (as shown in Figure 2), to a decreased risk of cancer, particularly endometrial carcinoma, in the human body. The main objective of this study is to evaluate the evidence produced and investigate the potential advantages of bioactive compounds present in the peel, pulp, and skin of tomatoes. Additionally, it aims to analyse the strengths and limitations of the studies in order to determine whether the observed associations are causally related or statistically significant. The criteria evaluated in this study encompass the magnitude of associations, the uniformity of results across different study designs (case-control or cohort), the molecular assessment method using biocomputational techniques, the factors controlled for through matching or data analysis and docking, and the possibility of residual or uncontrolled confounding. The potentially beneficial properties of the phytochemical constituents retrieved from tomatoes are then compared to the same benefits and effects derived from an existing endometrial cancer prescription drug, Lenvatinib mesylate, to conclude the possibility of developing any alternative herbal remedies with comparatively lesser medical side effects. Finally, the implications of utilizing phytocompounds found in tomatoes as dietary supplements for the probable treatment and cure of endometrial cancer by inhibiting the hallmark PTEN Tumor Suppressor gene have been discussed [28,29].

Figure 2: Peel, Pulp and Seeds of Tomato (*Solanum lycopersicum*) (Picture: Almost Practical).

Materials and Methods

Preparation of Target Protein

The PTEN Tumor Suppressor (PDB ID: 1D5R) was obtained from the RCSB PDB web server (https://www.rcsb.org/) [30] in its 3D crystal form.

It was noted that the 3D structure showed a crystal resolution of 2.10 Å, with a single chain A of 324 amino acids. The protein was then cleaned in the UCSF Chimera software for further docking studies following the standard protein preparation protocol.

Analysis of Stereochemical Properties of the Target Protein

The three-dimensional structure (Figure 3) of the target protein PTEN Tumor Suppressor (PDB ID: 1D5R) was studied thoroughly to understand its stereochemistry (Table 1). The different spatial arrangements of its atoms and molecules were observed via the Phi-Psi (Φ-Ψ) torsional angles graphical plot, also known as the Ramachandran Plot, that gave us a statistical representation of the amino acids present in the protein's peptides. This analysis was carried out via the EMBL-EBI PDB sum site [31] and its inbuilt PROCHECK web server.

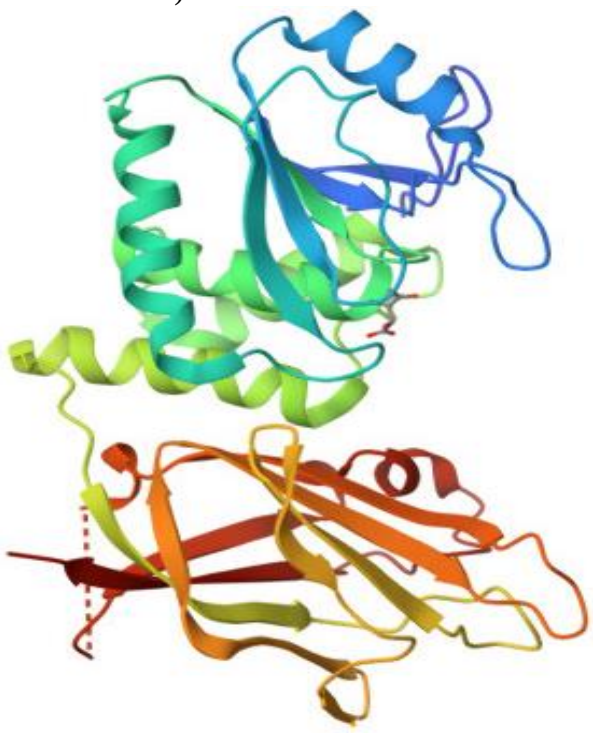

Figure 3: 3D Structure of PTEN Tumor Suppressor (PDB ID: 1D5R).

Table 1: Information on the Stereochemistry of the Target Protein

Protein ID	Macromolecule	Method	Classification	Organism	Unique Ligands
1D5R	Phosphoinositide Phosphatase PTEN	X-Ray Diffraction	Hydrolase	Homo sapiens	L(+)-Tartaric Acid

Prediction of the Secondary Structure of the Target Protein

The secondary structure of the protein PTEN Tumor Suppressor was predicted (Figure 4) using the protein prediction tool PSIPRED (PSI-blast based secondary structure PREDiction) web server (http://bioinf.cs.ucl.ac.uk/psipred/). This online tool incorporates artificial neural network machine learning mechanisms within its algorithm and is known to use very stringent cross-validation methods to predict the secondary structure of proteins from their sequence of amino acids. The predicted secondary structure's image showed highlighted helices, strands and signal peptides of the protein.

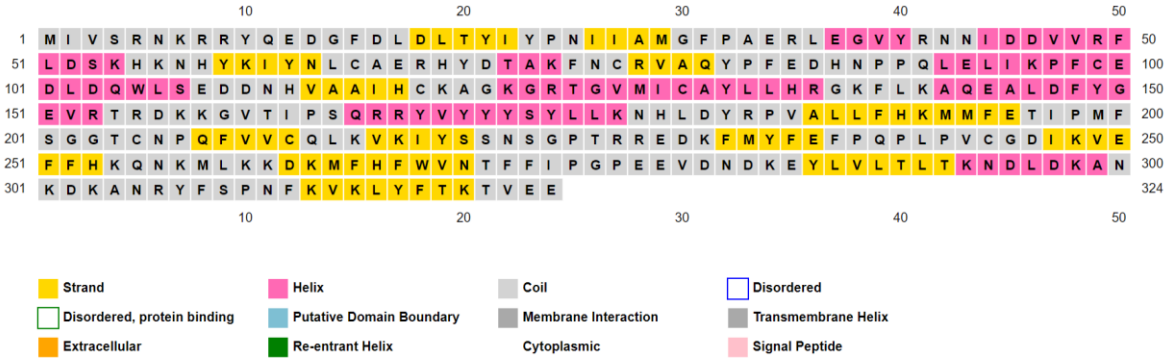

Figure 4: Secondary Structure of PTEN Tumor Suppressor (PDB ID: 1D5R)

Retrieval of the Control Drug and Ligands Found in Peel, Pulp and Seeds of Tomato

After studying various literature, the active phytocompounds found in the peel, pulp and seeds of tomato (*Solanum lycopersicum*) were retrieved from the PubChem database (Table 2) with the goal of identifying potential inhibitors of the PTEN Tumor Suppressor as compared to existing control drugs used in the treatment of endometrial cancer. A total of 55, 37, and 225 bioactive compounds were selected from the peel, pulp, and seeds of tomatoes, respectively, and downloaded in the 3D SDF file format [32]. After this, the phytocompounds were prepared by optimization of ligands and minimization of energy. Additionally, a known PTEN inhibitor, Lenvatinib mesylate, a methane sulfonate salt obtained by the reaction of Lenvatinib with one molar equivalent of methanesulfonic acid, was used as the control drug in this experiment. Worldwide, Lenvatinib mesylate is permitted to be used alone or in combination with other medications, such as Keytruda, for the treatment of endometrial carcinoma that has reached an advanced stage despite the employment of other systemic therapies.

Table 2: List of the Number of Ligands and the Control Drug

	Tomato Peel	Tomato Pulp	Tomato Seeds	Control Drug
Phytocompounds	55	37	225	Lenvatinib mesylate

Molecular Docking Analysis

Molecular Docking is an essential tool in computer-assisted drug design and structural molecular biology. Docking is a computational method employed in molecular modelling to predict the optimal arrangement of a ligand and a target molecule when they bind together to form a stable complex. By employing scoring functions, it is possible to predict the level of connection or binding affinity between two molecules by utilising information about their preferred orientation. The main goal of ligand-protein docking is to forecast the principal binding mode(s) of a ligand with a protein that possesses a known three-dimensional structure. [33]. For this study, a well-known virtual screening software called PyRx was used [34]. The collective bioactive compounds retrieved from the peel, pulp and seeds of tomatoes were docked separately with the PTEN Tumor Suppressor. Following the completion of the docking process, a table displaying each ligand's binding affinity was studied. The top three ligands from each of the pulp, peel and seeds data were chosen for additional analysis based on the ligand's highest binding affinity and saved in the PDB file format. In addition to this, the control drug in our study, Lenvatinib mesylate, was also docked with the target protein and its binding energy was duly noted for future comparative analysis. After this, Discovery Studio Visualizer 21.1 was used

to visualize the 2D-3D interactions of the ligands and the control drug [35].

Analysis of the Suitability of Ligands as Potential Drug Targets

An ADMET analysis refers to the assessment of a drug's pharmacokinetics, which includes its absorption, distribution, metabolism, excretion, and toxicity [36]. Forecasting the destiny of a medication and its impact on the body, encompassing the extent of oral absorption and gastrointestinal passage, is a crucial aspect of drug exploration. Likewise, inadequate absorption could impact distribution and metabolism, potentially resulting in neurotoxicity and nephrotoxicity. The ultimate goal of the research is to comprehend how a medication molecule behaves inside an organism. Consequently, ADMET analysis [37] is considered to be one of the most crucial aspects of computational drug design. The top 3 phytocompounds from the docking results of peel, pulp and seeds, showing the highest binding energies, were chosen for this study. A drug-likeness test as well as ADMET analysis was carried out via the web-based software SWISS-ADME tool(http://www.swissadme.ch/) [38] and ADMETLab 2.0 server [39] respectively. Furthermore, a Boiled-Egg Analysis [40] was done using the SWISS-ADME tool.

Formulated by Christopher A. Lipinski in 1997, Lipinski's Rule of 5 or simply Rule of Five, observed that since most orally administered drugs are relatively small and moderately lipophilic molecules, they must conform to a set of five major criteria, having not more than one violation in total. The set of five rules states that an orally active drug-like compound must follow the following:

i. No more than 5 hydrogen bond donors
ii. No more than 10 hydrogen bond acceptors
iii. Molecular weight less than 500 g/mol
iv. The molar refractivity value lies between 40 and 10, and
v. The value of the calculated LogP or C LogP is greater than 5

This rule of five was considered for the drug-likeness test and ADMET analysis.

Results and Discussion

Statistical Analysis of the Phi-Psi Graphical Plot

A statistical analysis was conducted on the Phi-Psi (Φ - Ψ) Ramachandran Plot (Figure 5) of the PTEN Tumor Suppressor (PDB ID: 1D5R), and its detailed protein geometry was retrieved from the EMBL-EBI PDBsum web server and tabulated below (Table 3).

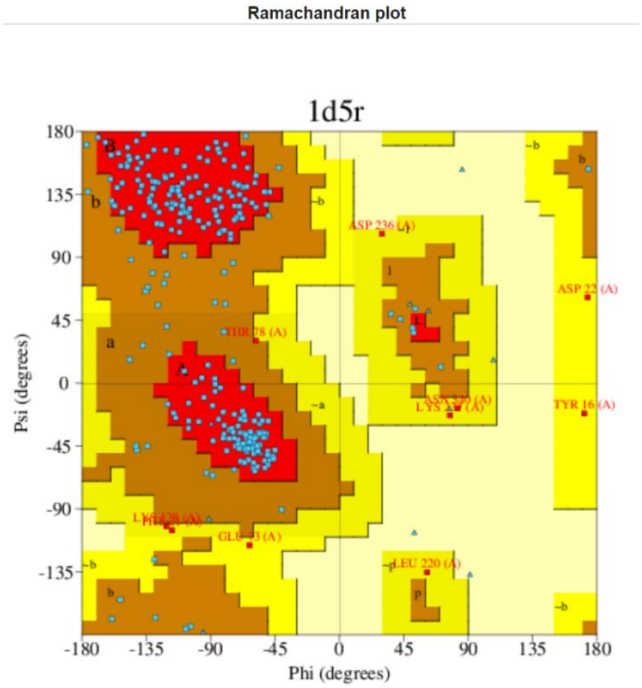

Figure 5: Ramachandran Plot of PTEN Tumor Suppressor (PDB ID: 1D5R)

Table 3: Ramachandran Plot Geometry of Protein (PDB ID:1D5R)

	Number of Residues	Percentage
Most favoured regions [A,B,L]	222	80.7%
Additional allowed regions [a, b, l, p]	43	15.6%
Generously allowed regions [~a, ~b, ~l, ~p]	10	3.6%
Disallowed regions [XX]	0	0.0%
Non-glycine and non-proline residues	275	100.0%
End-residues (excl. Gly and Pro)	3	
Glycine residues	13	
Proline residues	16	
Total number of residues	307	

Molecular Docking of Ligands and Control Drug

The ligands from the peel, pulp, and seeds of tomatoes were docked via the PyRx software application, revealing a list of several bioactive compounds that displayed high binding energies with the target protein. Only the compounds showing a binding affinity value of more than 7 Kcal/mol with PTEN Tumor Suppressor were considered from this list. The top three phytocompounds from each of peel, pulp, and seeds were taken into consideration. Similarly, the control drug, Lenvatinib mesylate, was docked with the target protein. The final results of the complete docking study were tabulated (Table 4) for imminent drug-likeness tests and ADMET analysis.

Table 4: Molecular Docking Results Showing Binding Energies.

	Sl. No.	Name of Phytocompounds	PubChem ID	Binding Energy After Docking With 1D5R (Kcal/mol)
Peel	1.	Kombetin	637579	-9.8
	2.	Flavanone	10251	-8.1
	3.	Naringenin	439246	-7.9
Pulp	1.	2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)	5815211	-8
	2.	2,2'-Azino-bis-(3-ethylbenzothiazoline-6-sulfonate)	6871216	-7.9
	3.	Flavylium	145858	-7.8
Seeds	1.	Cryptochrome	5375760	-10.2
	2.	Phytosterols	12303662	-9.6
	3.	Solanacol	102417064	-9.6
Control Drug	Lenvatinib mesylate		9823820	-8.4

Analysis of Docking Results and Visualization of Different Molecular Interactions

Following the completion of the molecular docking, the most advantageous configurations were chosen from the cluster RMSD table for further assessment. The docking data (Table 4) indicated that the binding energy between

Lenvatinib mesylate, our control medication, and PTEN Tumour Suppressor was -8.4. It is a well-established fact that compounds with lower binding energy exhibit higher stability in terms of their binding capability. According to this theory, researchers observed that a total of 9 phytocompounds, with 3 taken from the peel, pulp, and seeds of tomatoes respectively, exhibited binding energies that were either close to or lower than that of the control drug. Therefore, these compounds could be considered as potential drug candidates against the PTEN Tumour Suppressor protein. The molecular interactions between the 9 selected biocompounds of tomatoes and the control medication were visualised using Discovery Studio Visualizer 21.1. Each phytocompound exhibited distinct 2D and 3D interactions with the study protein, including typical hydrogen bonds, pi-donor hydrogen interactions, and various hydrophobic interactions with Pro, Phe, and Leu, Gln side chains.

Analysis of Ligands using Lipinski's Rule of Five Filter

Lipinski's Rule of Five, sometimes referred to as the Rule of Five or RO5, is a set of standards used in drug development and discovery to assess a chemical compound's suitability as a medication. These guidelines, which were developed by medicinal chemist Dr. Christopher A. Lipinski, are frequently used to forecast a compound's likelihood of having advantageous oral bioavailability and pharmacokinetic characteristics. The Rule of Five is a broad heuristic rather than a rigid set of rules.

The rationale for these guidelines is that substances that don't meet them could find it difficult to pass through cell membranes, which is necessary for efficient oral absorption. It is crucial to remember, however, that the Rule of Five is simply a recommendation rather than a hard and fast rule. These standards are often not entirely met by many effective medications, and other elements like target specificity, metabolism, and formulation can also be very important when it comes to drug design and development. Lipinski's Rule of Five is, therefore, not the only method for determining a compound's potential as a therapeutic candidate, even though it is a helpful tool in drug creation.

For this study, the chosen 9 bioactive compounds, along with the control drug, were evaluated via the Swiss ADME web server. The tool was intended to forecast the physicochemical and pharmacokinetic characteristics of small molecules, especially those connected to medication development. The Lipinski's filtered evaluations were tabulated in Table 5.

Table 5: Analysis of Ligands using Lipinski's Rule of Five Filter.

Name of Ligand	Molecular Formula	Molecular Weight (g/mol)	H-bond Donors	H-bond Acceptors	MLOGP	Molar Refractivity	Lipinski's Rule of Five Violations
Kombetin	$C_{29}H_{44}O_{12}$	584.65	8	12	-1.11	140.66	3
Flavanone	$C_{15}H_{12}O_2$	224.25	0	2	2.47	65.5	0
Naringenin	$C_{15}H_{12}O_5$	272.25	3	5	0.71	71.57	0
2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)	$C_{18}H_{18}N_4O_6S_4$	514.62	2	8	3.07	122.61	1
2,2'-Azino-bis-(3-ethylbenzothiazoline-6-sulfonate)	$C_{18}H_{16}N_4O_6S_4^{--}$	512.60	0	8	3.07	118.91	1
Flavylium	$C_{15}H_{11}O^+$	207.25	0	1	3.28	66.06	0
Cryptochrome	$C_{40}H_{56}O_3$	584.87	1	3	6.23	184.56	2
Phytosterols	$C_{29}H_{50}O$	414.71	1	1	6.73	133.23	1
Solanacol	$C_{19}H_{18}O_6$	342.34	1	6	1.82	87.1	0
Lenvatinib mesylate	$C_{21}H_{19}ClN_4O_4$	426.85	3	5	2.10	112.86	0

In addition to this, the compounds were also evaluated for their permeability ability to the blood-brain barrier (BBB) as well as the human intestinal absorption (HIA) factor via the Boiled-Egg analysis conducted on the SwissADME website. The molecules or spots found within the white ellipse in the Boiled-Egg image (Figure 6) represented substances with a high chance of being passively absorbed by the digestive system. Conversely, the spots found in the yolk, or the yellow ellipse represented the substances with a high likelihood of penetrating through the BBB and accessing the central nervous system. However, the yellow and white ellipses were not exclusive of one another. Molecules not predicted to be well-absorbed, nor BBB-permeant were understood to be in the grey zone, that is, further outside the range of the referential and thus counted in 'Remarks'.

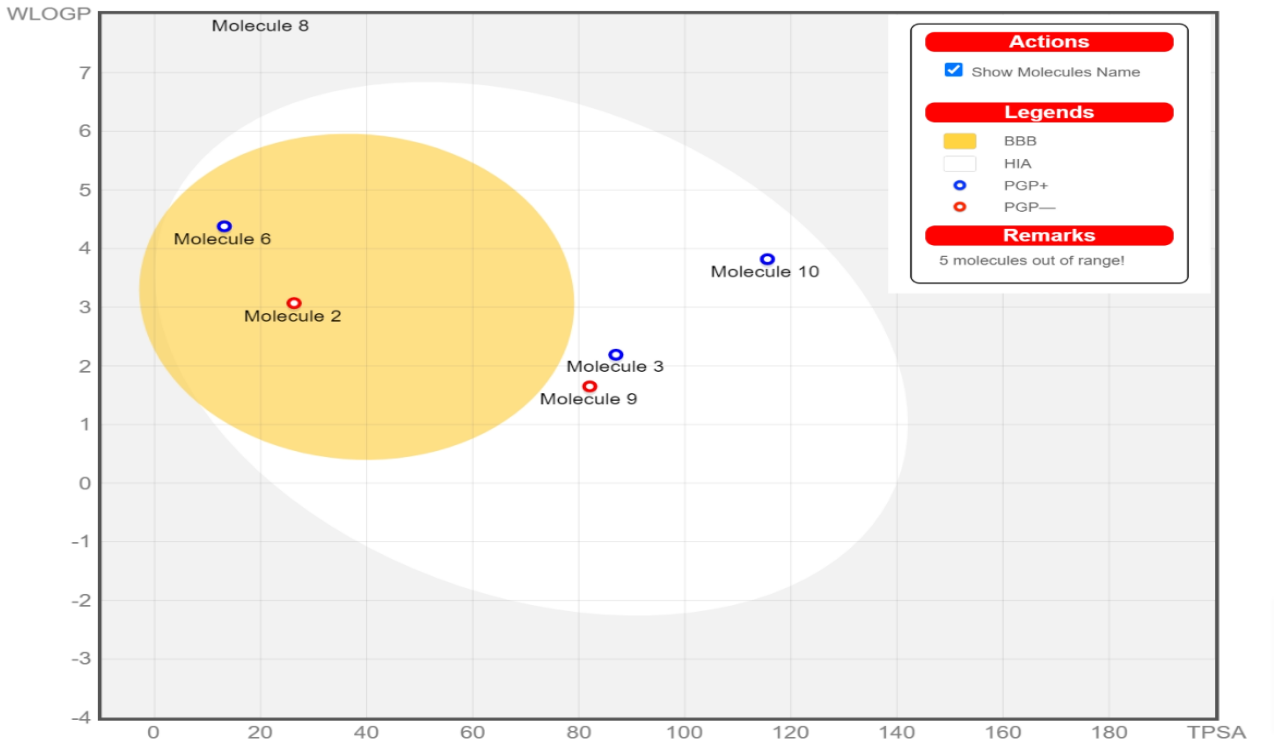

Figure 6: Boiled-Egg Analysis of the 9 Phytocompounds and the Control Drug

Drug-Likeness Test, Toxicity Prediction and ADMET Analysis

Absorption, Distribution, Metabolism, Excretion, and Toxicity are the acronyms for ADMET. It is a set of operations that are essential for comprehending the actions of a medication or other chemical substances in the human body. ADMET analysis is a crucial component of drug development and discovery since it enables scientists to assess the toxicological and pharmacokinetic characteristics of possible therapeutic candidates. Comprehending the absorption, distribution, metabolization, excretion, and possible hazardous consequences of a molecule aids researchers in optimizing medication design, mitigating the likelihood of adverse effects, and increasing overall prospects for drug development success. ADMET analysis frequently uses computational models and in vitro experiments to supplement conventional in vivo research. For our study, the 9 chosen ligands and the control drug were put through the ADMET analysis via the ADMET Lab 2.0 web-based tool. The results of the evaluation were tabulated in Table 6. Furthermore, the toxicity of the biocompounds was predicted using the ProTox 2 web server, their characteristics being scrutinized within the standard scale of evaluation for water solubility (Logs), glycoprotein substrate permeability, HIA, BBB, and carcinogenic properties (Table 7).

Table 6: ADMET Analysis of Ligands via ADMET Lab 2.0

	Sl. No.	Name of Ligand	Log S	Pgp-sub	HIA	BBB	Carcinogenicity	Lipinski's Rule of Five
Peel	1.	Kombetin	-2	0.728	0.99	0.218	0.496	Rejected
	2.	Flavanone	-4.32	0	0.008	0.257	0.73	Accepted
	3.	Naringenin	-3.876	0.001	0.018	0.042	0.576	Accepted
Pulp	1.	2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)	-0.605	0.014	0.798	0.146	0.992	Accepted
	2.	2,2'-Azino-bis-(3-ethylbenzothiazoline-6-sulfonate)	-0.605	0.014	0.798	0.146	0.992	Accepted
	3.	Flavylium	-5.914	0.087	0.004	0.104	0.786	Accepted
Seeds	1.	Cryptochrome	-6.332	0.554	0.023	0.055	0.031	Rejected
	2.	Phytosterols	-7.052	0.001	0.004	0.84	0.047	Accepted
	3.	Solanacol	-3.098	0.026	0.014	0.147	0.962	Accepted
Control Drug	Lenvatinibmesylate		-7.121	0.996	0.006	0.503	0.597	Accepted

Table 7: Prediction of Ligand Toxicity via ProTox 2 Webserver.

	Sl. No.	Name of Ligand	Predicted LD50 (mg/kg)	Predicted Toxicity Class	Average Similarity (%)	Prediction Accuracy (%)
Peel	1.	Kombetin	5	1	100	100
	2.	Flavanone	2000	4	73.92	69.26
	3.	Naringenin	2000	4	76.8	69.26
Pulp	1.	2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)	200	3	48.54	54.26
	2.	2,2'-Azino-bis-(3-ethylbenzothiazoline-6-sulfonate)	200	3	48.54	54.26
	3.	Flavylium	2500	5	71.67	69.26
Seeds	1.	Cryptochrome	6060	6	58.18	67.38
	2.	Phytosterols	890	4	89.38	70.97
	3.	Solanacol	2000	4	45.9	54.26
Control Drug	Lenvatinib mesylate		3000	5	53.43	67.38

Conclusion

This study revealed that the peel, pulp, and seeds of tomato (*Solanum lycopersicum*), a common fruit used for a variety of purposes and in multiple different cuisines across the world, harboured certain bioactive constituents showing anti-carcinogenic, anti-inflammatory, and antioxidant potential against the target protein PTEN Tumor Suppressor (PDB ID: 1D5R). The molecular docking results ascertained that the compounds Kombetin, Cryptochrome, Phytosterols, and Solanacol showed lower binding energies than the commercially used endometrial cancer drug Lenvatinib mesylate (binding energy -8.4 Kcal/mol). On the other hand, two phytocompounds, namely Flavanone and 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), bound with PTEN Tumor Suppressor with almost similar binding energies to those of the control drug, while the rest of the compounds, namely Naringenin, 2,2'-Azino-bis-(3-ethylbenzothiazoline-6-sulfonate), and Flavylium demonstrated slightly higher binding energies for the same.

Thus, these phytocompounds, whether used alone or in combination with other bioactive components, could be considered potential drug candidates against the target protein PTEN Tumor Suppressor. Additionally, the results of the drug-likeness test conducted using Lipinski's Rule of Five filter significantly demonstrated their fitness for human consumption. The resulting ADMET analysis, undertaken to evaluate pharmacokinetic properties, and the Boiled-Egg analysis further strengthened our findings. It was worth noting that commercially available prescription medicines for endometrial cancer, such as Lenvatinib mesylate, Keytrude, etc., often imparted significant side effects to our body that could prove fatal and have consequences when used long-term. Because of this, it was all the more crucial to take advantage of the widely accessible, well-established qualities of natural ingredients and investigate the prospect of employing them as viable candidates for the creation of herbal medications. It was anticipated that this preliminary assessment might lead to the launch of future research on designing reasonable derivatives from naturally occurring phytochemical constituents found in tomatoes, which could eventually substitute commercially available drugs to reduce existing adverse reactions and possibly aid in the treatment and cure of endometrial cancer. However, the binding stability of bioactive compounds might need to be further improved before they are utilized as potential drug candidates.

Acknowledgement

The authors are thankful to the Chancellor, Techno India University, West Bengal, for providing the necessary infrastructural facilities to bring this work to the light of the day.

Statement of Informed Consent

We, the authors of this manuscript titled "Identification of Potential Inhibitors of PTEN Tumor Suppressor Gene from Phytochemical Constituents Found in Tomato (*Solanum lycopersicum*) Via Biocomputational Analysis," hereby give our informed consent for the submission and publication of this document.

Conflict of Interest

The authors declare no conflict of interest.

Funding

The authors did not receive any fundings from any private or government sources.

References

1. Endometrial cancer. (2021, August 8). Johns Hopkins Medicine. https://www.hopkinsmedicine.org/health/conditions-and-diseases/endometrial-cancer
2. What is endometrial cancer? Uterine cancer. (n.d.). American Cancer Society. https://www.cancer.org/cancer/types/endometrial-cancer/about/what-is-endometrial-cancer.html
3. Qiu M, Bao W, Wang J, Yang T, He X, Liao Y, Wan X. FOXA1 promotes tumor cell proliferation through AR involving the Notch pathway in endometrial cancer. BMC cancer. 2014 Dec;14:1-7.
4. Gu X, Liu Q, Yang N, Shen JF, Zhang XG, Cao F, Ding HZ. Clinicopathological significance of increased ZIC1 expression in human endometrial cancer. Journal of Huazhong University of Science and Technology [Medical Sciences]. 2015 Dec;35:898-903.
5. Elbasateeny SS, Salem AA, Abdelsalam WA, Salem RA. Immunohistochemical expression of cancer stem cell related markers CD44 and CD133 in endometrial cancer. Pathology-Research and Practice. 2016 Jan 1;212(1):10-6.
6. Agopiantz M, Forgez P, Casse JM, Lacomme S, Charra-Brunaud C, Clerc-Urmès I, Morel O, Bonnet C, Guéant JL, Vignaud JM, Gompel A. Expression of neurotensin receptor 1 in endometrial adenocarcinoma is correlated with histological

grade and clinical outcome. Virchows Archiv. 2017 Oct;471:521-30.
7. Bansal N, Yendluri V, Wenham RM. The molecular biology of endometrial cancers and the implications for pathogenesis, classification, and targeted therapies. Cancer control. 2009 Jan;16(1):8-13.
8. Dohi S, Ohno S, Ohno Y, Kyo S, Soma GI, Sugiyama H, Inoue M. WT1 expression correlates with angiogenesis in endometrial cancer tissue. Anticancer research. 2010 Aug 1;30(8):3187-92.
9. Guo C, Song WQ, Sun P, Jin L, Dai HY. LncRNA-GAS5 induces PTEN expression through inhibiting miR-103 in endometrial cancer cells. Journal of biomedical science. 2015 Dec;22:1-9.
10. Lee H, Choi HJ, Kang CS, Lee HJ, Lee WS, Park CS. Expression of miRNAs and PTEN in endometrial specimens ranging from histologically normal to hyperplasia and endometrial adenocarcinoma. Modern Pathology. 2012 Nov;25(11):1508-15.
11. Shawana S, Kehar SI, Masood S, Aamir I. Immunoexpression of cyclin D1 and PTEN in various endometrial pathologies. J Coll Physicians Surg Pak. 2016 Apr 1;26(4):277-82.
12. Yuan TL, Cantley L. PI3K pathway alterations in cancer: variations on a theme. Oncogene. 2008 Sep;27(41):5497-510.
13. Li LI, Ross AH. Why is PTEN an important tumor suppressor?. Journal of cellular biochemistry. 2007 Dec 15;102(6):1368-74.
14. Djordjevic B, Hennessy BT, Li J, Barkoh BA, Luthra R, Mills GB, Broaddus RR. Clinical assessment of PTEN loss in endometrial carcinoma: immunohistochemistry outperforms gene sequencing. Modern pathology. 2012 May 1;25(5):699-708.
15. Kimura F, Watanabe J, Hata H, Fujisawa T, Kamata Y, Nishimura Y, Jobo T, Kuramoto H. PTEN immunohistochemical expression is suppressed in G1 endometrioid adenocarcinoma of the uterine corpus. Journal of cancer research and clinical oncology. 2004 Mar;130:161-8.
16. Chen J, Li S, Yang Z, Lu G, Hu H. Correlation between NDRG1 and PTEN expression in endometrial carcinoma. Cancer science. 2008 Apr;99(4):706-10.
17. Erkanli S, Kayaselcuk F, Kuscu E, Bagis T, Bolat F, Haberal A, Demirhan B. Expression of survivin, PTEN and p27 in normal, hyperplastic, and carcinomatous endometrium. International Journal of Gynecologic Cancer. 2006 Apr 1;16(3).
18. Lacey Jr JV, Mutter GL, Ronnett BM, Ioffe OB, Duggan MA, Rush BB, Glass AG, Richesson DA, Chatterjee N, Langholz B, Sherman ME. PTEN expression in endometrial biopsies as a marker of progression to endometrial carcinoma. Cancer research. 2008 Jul 15;68(14):6014-20.
19. Merritt MA, Cramer DW. Molecular pathogenesis of endometrial and ovarian cancer. Cancer Biomarkers. 2011 Jan 1;9(1-6):287-305.
20. U.S. National Research Council, Committee on Diet and Health. Diet and health: implications for reducing chronic disease risk. Washington (DC): National Academy Press; 1989.
21. American Cancer Society. Nutrition and cancer: causation and prevention. An American Cancer Society special report. CA Cancer J Clin 1984 ; 34 : 5 -10.
22. Potter JD. Vegetables, fruit, and cancer. The Lancet. 2005 Aug 13;366(9485):527-30.
23. World Cancer Research Fund American Institute for Cancer Research. Food, nutrition and the prevention of cancer: a global perspective. Washington (DC): American Institute for Cancer Research; 1997.
24. American Cancer Society 1996 Advisory Committee on Diet, Nutrition, and Cancer Prevention. Guidelines on diet, nutrition, and cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA: A Cancer Journal for Clinicians. 1996 Nov;46(6):325-41.
25. Sengupta S, Ghorui S, Bhattacharya M. Molecular docking Analysis of the phytocompounds found in Citrus seeds and their effects on the hallmark gene of HNSCC. Asian Journal of Pharmaceutical and Health Sciences. 2023;13(3).
26. Giovannucci E. Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. Journal of the national cancer institute. 1999 Feb 17;91(4):317-31.
27. Di Mascio P, Kaiser S, Sies H. Lycopene as the most efficient biological carotenoid singlet oxygen quencher. Archives of biochemistry and biophysics. 1989 Nov 1;274(2):532-8.
28. Jumaah AS, Al-Haddad HS, Mahdi LH, Hatem E, Al-Janabi AA, McAllister K, Yasseen AA. Increased PTEN gene expression in patients with endometrial carcinoma from areas of high risk depleted uranium exposure. BMC Research Notes. 2019 Dec;12:1-6.
29. Stavropoulos A, Varras M, Vasilakaki T, Varra VK, Tsavari A, Varra FN, Nonni A, Kavantzas N, Lazaris AC. Expression of p53 and PTEN in human primary endometrial carcinomas: Clinicopathological and immunohistochemical

analysis and study of their concomitant expression. Oncology letters. 2019 May 1;17(5):4575-89.
30. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, et al. The protein data bank. Nucleic Acids Res 2000;28:235-42. 19.
31. European Bioinformatics Institute. PDBsum Home Page. Cambridge: European Bioinformatics Institute. Available from: https://www.ebi.ac.uk/pdbsum
32. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, Li Q, Shoemaker BA, Thiessen PA, Yu B, Zaslavsky L. PubChem in 2021: new data content and improved web interfaces. Nucleic acids research. 2021 Jan 8;49(D1):D1388-95.
33. McConkey BJ, Sobolev V, Edelman M. The performance of current methods in ligand–protein docking. Current Science. 2002 Oct 10:845-56.
34. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of computational chemistry. 2010 Jan 30;31(2):455-61.
35. Biovia DS. Discovery Studio Modeling Environment, Dassault Syst. Release, San Diego. 2015;4.
36. Guan L, Yang H, Cai Y, Sun L, Di P, Li W, Liu G, Tang Y. ADMET-score–a comprehensive scoring function for evaluation of chemical drug-likeness. Medchemcomm. 2019;10(1):148-57.
37. Dong J, Wang NN, Yao ZJ, Zhang L, Cheng Y, Ouyang D, Lu AP, Cao DS. ADMETlab: a platform for systematic ADMET evaluation based on a comprehensively collected ADMET database. Journal of cheminformatics. 2018 Dec;10:1-1.
38. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific reports. 2017 Mar 3;7(1):42717.
39. Xiong G, Wu Z, Yi J, Fu L, Yang Z, Hsieh C, Yin M, Zeng X, Wu C, Lu A, Chen X. ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties. Nucleic acids research. 2021 Jul 2;49(W1):W5-14.
40. Daina A, Zoete V. A boiled-egg to predict gastrointestinal absorption and brain penetration of small molecules. ChemMedChem. 2016 Jun 6;11(11):1117-21.