INNOVARE JOURNAL OF MEDICAL SCIENCES

Vol 10, Issue 4, 2022

ISSN - 2321-4406

Research Article

IN SILICO ANALYSIS OF PHYTOCHEMICALS FROM ZINGIBER OFFICINALE FOR THE INHIBITION OF TUMOR PROTEIN-53 BINDING PROTEIN 1 ASSOCIATED WITH HEPATOCELLULAR CARCINOMA

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Received: 01 May 2022, Revised and Accepted: 15 June 2022

ABSTRACT

Objectives: The bioactive phytocompounds present in *Zingiber officinale* were assessed for their tumor-suppressing activity against TP-53 BP1 linked to hepatocellular carcinoma.

Methods: The study investigates the interaction of the phytochemicals from Ginger (*Zingiber officinale*) with the tumor protein TP53. Drug likeness of the chosen ligand was evaluated using SWISS ADME. The Autodock tools were used to investigate the interactions of the ligands with that TP-53 BP1 protein. The docking interactions were visualized using PLIP (Protein-Ligand Interaction Profiler).

Results: It is observed that all the ligands show high gastrointestinal absorption along with the presence of blood-brain barrier permeability and have moderate solubility whereas Gingerenone A exhibits high solubility up to par. Docking analysis shows high-efficiency binding of the ligand (Gingerol) to the receptor.

Conclusion: The bioactive ligand gingerol is a beta-hydroxy ketone compound that displays better binding with the tumor proteins.

Keywords: Hepatocellular carcinoma, Phytochemicals, Ginger, Molecular docking, Lipinski rule, Ramachandran plot, Visualisation.

 DOI: http://dx.doi.org/10.22159/ijms.2022v10i4.45113. Journal homepage: https://innovareacademics.in/journals/index.php/ijms

INTRODUCTION

Hepatocellular carcinoma (HCC) is a type of hepatic cancer that represents 80–90% of all hepatic malignancies and is among the most common carcinomas globally, with 600,000 fatalities per year [1]. The condition has a significant pathogenetic link with viral hepatitis (HBV and HCV), hemochromatosis, recognized hepatic toxins like aflatoxin B1 (AFB1), mycotoxins, etc. The condition is more prominent in regions of Africa and Asia than in North and South America and Europe. As it is commonly identified at an advanced phase, the ailment has an abysmal prognosis [2,3].

HCC is closely correlated with hepatic fibrosis and cirrhosis as it developed as a result of existing hepatic problems [4]. The best restorative treatments for treating hepatic malignancies are hepatectomy and liver transplantation. Furthermore, in individuals who had undergone hepatectomy, resurgence or metastases are extremely prevalent, and the 5-year survival rate averages to 30–40%. The hepatic tumor progression is a multi-step process that entails the aggregation of genetic alterations that emerge during the cancer onset, development, and exacerbation [5,6]. Overexpression of many proteins that repress apoptosis and regulate the cell cycle is frequently associated with cellular functions that impact the survival of the malignant cells. HCC is a complicated illness with various pathogenic pathways that are triggered by a multitude of variables. Aflatoxin, which affects the Wnt/-catenin and p53 pathways, is one of the cellular signaling pathways known to be altered in HCC induced by diverse factors. TP53-binding protein 1 is important for DNA repair, particularly during the G1 phase of the cell cycle. For appropriate positioning of 53BP1 and genomic stability, nuclear import of 53BP1 is necessary [7,8].

Zingiber officinale is a flowering plant whose tuber, sometimes known as ginger root or ginger, is extensively utilized as a condiment and Folk medicine (Figs. 1 and 2). It is a herbaceous plant with one-meter-tall annual pseudostems carrying slender leaf blades. The pale-yellow flowers are outlined with purple hues and emerge on individual branches that emerge independently from the rhizome [9-11].

Ginger is a common condiment used worldwide, it is used for flavoring, and as a therapeutic in herbal medicine. The phytocompounds from ginger display advantageous pharmacological properties such as anti-oxidant, anti-diabetic, anti-oxidant, anti-inflammatory, hepatoprotective, and anti-cancer. These remarkable properties are the basis for the current study to illustrate its activity toward the tumor binding protein.

METHODS

Protein retrieval

The protein receptor FASTA sequence was procured from RCSB PDB and it was used to obtain the structure from the SWISS-MODEL template library (Fig. 3) [12].

The chosen receptor from the SWISS-MODEL was subjected to energy minimization using the Swiss PDB Viewer (SPDBV).

Ligand preparation

The structure data file (SDF) of the chosen ligands Gingerenone A, Zingerone, Paradol, Gingerol, and Shogoals was obtained from PubChem [13]. The conversion of SDF to PDB was done using Marvin Sketch. Ligand cleaning is achieved using Marvin's sketch.

Analysis of drug likeness of the ligand

SWISS ADME is considered to be a conventional drug discovery tool. All the properties of the chosen ligands were investigated using this tool. It includes Lipinski filter analysis, and pharmacokinetic behavior, that is, the blood-brain barrier [14].

Fig. 1: *Zingiber officinale* plant

Fig. 2: Ginger root

Docking evaluation

Molecular docking of the ligand's ligands Gingerenone A, Zingerone, Paradol, Gingerol, and Shogoals with the TP53 receptor protein was achieved using Pyrx and AutoDockTools. The process of docking allows us to interpret the active binding site of each specific ligand along with its orientation. The entire receptor is placed within the grid box to produce a blind docking with each ligand. The result generates binding affinity and RMSD values [15].

Visualization of the interaction

The interaction of the ligand with that of the protein was visualized to determine the bond length [16].

RESULTS AND DISCUSSION

Ligand retrieval

The selected ligands were downloaded from PubChem in.sdf format. This two-dimensional structure of all the selected ligands is displayed in Fig. 4.

Ramachandran plot analysis

The Ramachandran plot shows the statistical distribution of the combinations of the backbone dihedral angles ϕ and ψ. ϕ values are plotted on the X-axis and the ψ values are presented on the Y-axis. Ramachandran's plot explains what kind of phi and psi angles are preferred in a particular secondary structure of the protein.

Fig. 3: 3D structure of tp53 protein

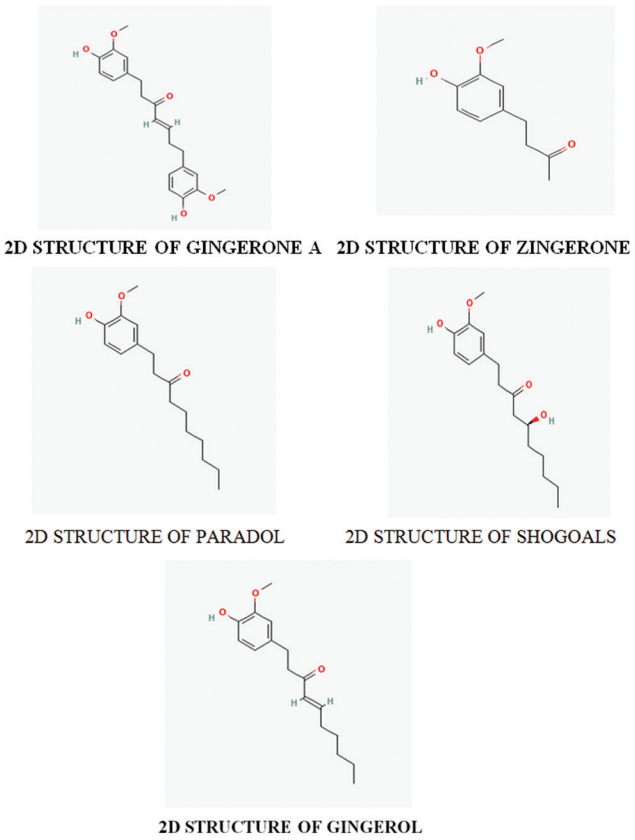

Fig. 4: 2D structure of the phytochemicals selected from the ginger plant

The Ramachandran plot result exhibits that the majority of the amino acids in tumor protein TP53 are concentrated on the top left; this explains they form beta sheets (Antiparallel) and the amino acids at the bottom depict the formation of right-handed alpha-helical secondary structure (Fig. 5). The most of the amino acids present in the two quadrants are considered highly preferred regions with a percentage of 99.738. Hence, this protein is acceptable.

Lipinski filter analysis

The drug-likeness was analyzed using a Lipinski filter (Table 1). It presents the pharmacokinetic properties, molecular mass, hydrogen bond donor, and bond acceptor of the selected ligand.

Table 1: Lipinski filter analysis

Phytochemicals	Molecular weight	High lipophilicity	No. of hydrogen atom donor	No. of hydrogen atom acceptor	Molecular refractivity	violations
Gingernone A	356.41	3.60	2	5	101.49	0 VIOLATION
Zingerone	194.23	2.09	1	3	54.54	0 VIOLATION
Paradol	278.39	3.65	1	3	83.39	0 VIOLATION
Gingerol	294.39	3.48	2	4	84.55	0 VIOLATION
Shogoals	276.37	3.28	1	3	82.91	0 VIOLATION

Table 2: ADME analysis

Ligand	Blood-brain barrier	GI absorption	Permeability glycoprotein substrate	Log S
Gingernone A	Yes	High	No	−4.15
Zingerone	Yes	High	No	−1.80
Paradol	Yes	High	No	−3.72
Gingerol	Yes	High	No	−2.96
Shogoals	Yes	High	No	−3.70

Table 3: Docking of TP53 with selected ligands from ginger

Ligand	Binding affinity	Mode	RMSD lower bound	RMSD upper bound
Gingernone A	−5.3	0	0.0	0.0
Gingerol	−5.4	0	0.0	0.0
Zingerone	−4.7	0	0.0	0.0
Paradol	−5.3	0	0.0	0.0
Shagoal	−4.7	0	0.0	0.0

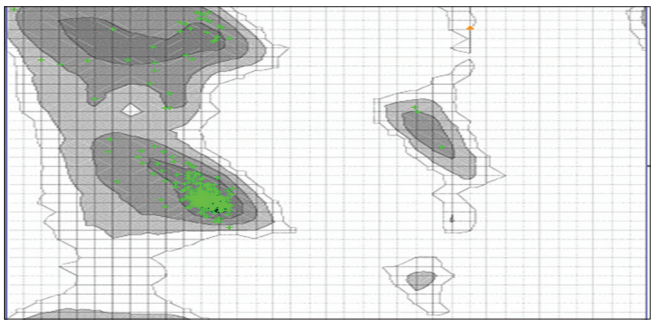

Fig. 5: Ramachandran plot

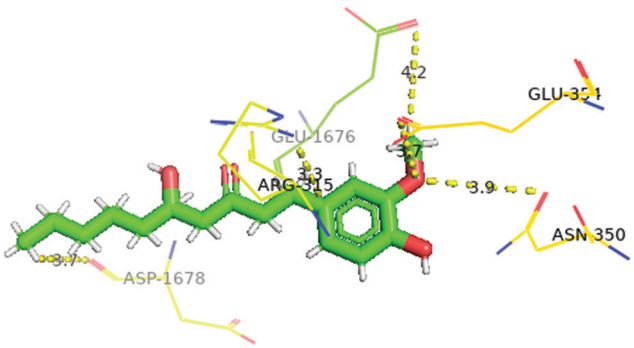

Fig. 6: Interaction of gingerol with TP53

Criteria: Molecular weight in the range 194–356, H-bond donors ≤ 2, and H-bond acceptors ≤ 5. The selected ligands exhibit an acceptable range for human use. It also presents potential drug-like properties (Table 2).

Docking results

Autodock analysis

Results of docking were interpreted using AutoDockTools-1.5.6. The RMSD table includes 10 outcome values for each specific Ligand. AutoDock assists in analyzing the interactions of ligand molecules at the specified target site of the protein. The docking procedure was displayed for a rigid macromolecule and here the docking is faster than that of a flexible macromolecule. From the results of autodock, the binding sites in the protein for ligand interaction can be identified. Gingerol presents the least value of binding affinity (i.e., −5.4) followed by Gingernone A and Paradol (i.e., −5.3) and Zingerone and Shagoal (i.e., −4.7). High binding efficiency is displayed by the phytochemical Gingerol (Table 3).

The measurement of the bonds in visualization for GLU-354 is 3.7, ARG-315 is 3.3, ASN-350 is 3.9, GLU-1676 is 4.2 and ASG-1678 is 3.7 (Fig. 6).

CONCLUSION

Based on in-silico studies, the phytochemicals Gingerenone A, Zingerone, Paradol, Gingerol, and Shogaol have presented favorable outcomes. Through SWISS ADME analysis, it is observed that all the ligands show high gastrointestinal absorption along with the presence of blood-brain barrier permeability and have moderate solubility whereas Gingerenone A exhibits high solubility up to par. Docking analysis shows high-efficiency binding of the ligand (Gingerol) to the receptor (Tumor protein TP53). Zingerone and Shogaol displayed a lower efficiency binding as compared to Gingerol, Gingerenone A, and Paradol. Taking all these factors, it can be concluded that Gingerol is the most suitable one and can be brought into play as a drug against hepatocellular carcinoma (HCC).

ACKNOWLEDGMENT

We hereby acknowledge the sincere support and help extended by BioNome, the project guide, and the staff in carrying out the project work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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