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Molecular Interaction Study between Gentamicin and the Cancer Protein Target (TP53) using *in silico* Tools

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The most prevalent mutation in hepatocellular carcinoma (HCC), TP53 mutations impacts the course and prognosis of HCC. 3D *in silico* drug docking techniques were employed to make the possible mutant target tumor protein 53 (TP53) interact with benzene acetic acid (Gentamicin) and non-steroidal anti-inflammatory drugs (NSAIDs). To carry out drug docking techniques, the translated amino acid sequence and three-dimensional chemical compound were obtained from the NCBI database. The use of sophisticated 3D molecular visualization tools was employed in post-docking experiments. The docking study results unequivocally show that gentamicin directly suppresses amino acid mutational sites. TP53 and Gentamicin's electrostatic force is depicted in a three-dimensional manner using notions from molecular dynamics techniques. In the end, it was

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determined that gentamicin, an Antibiotic medication, helps treat liver cancer. Most chemotherapy medications cause pain. Therefore, Gentamicin shall be used to lessen discomfort while minimizing the symptoms of cancer.

Keywords: Hepatocellular carcinoma; tumor protein 53; gentamicin and drug docking.

1. INTRODUCTION

According to data from the Global Cancer Observatory (GLOBOCAN) for 2020, liver cancer ranks tenth among all cancers in India, accounting for 34,743 new cases and 33,793 deaths annually [1]. According to currently available data, age-adjusted incidence rates of HCC in India range from 0.7 to 7.5 per 1,000 individuals annually for men and from 0.2 to 2.2 per 1,000 women. In India, the proportion of cirrhotic patients with HCC rises by 1.6% annually. Though less than 5% of people with cirrhosis go on to acquire HCC each year, 90% of HCC cases have a history of cirrhosis [2]. However, the yearly recurrence rate of HCC is 15%–20%, higher than that of any other malignant tumor with a high fatality rate. Male-to-female ratios for HCC presentations in India range from 4:1 and the patients' ages range from 40 to 70. In India, the age-standardized HCC death rate is 6.8/1,00,000 for men and 5.1/1,00,000 for women. HBV is the main etiological factor associated with HCC in India. But right now, India lacks access to thorough HCC data [3].

A prominent tumor suppressor gene in humans, TP53, is found on chromosome 17p13.1. With 11 exons that together encode 393 amino acid residues, it is one of the most commonly changed genes in African-Asian cultures [4]. Because it is necessary to maintain both the integrity of the genome and intracellular homeostasis, it is known as the guardian of the genome. Numerous processes related to cell survival are triggered by it, such as differentiation, senescence, apoptosis, cell cycle arrest, and DNA damage [5]. In a physiological sense, the p53 protein is kept low and unstable by negative regulatory factors in cells [6]. Furthermore, TP53 can mutate by point mutation, deletion, frameshift, rearrangement, and other mechanisms in all types of cancer [7]. The lengthy half-life and high stability of the encoded P53 protein are caused by a mutation in TP53; eventually, the protein accumulates in the nucleus and loses its monitoring capacity. A mutant p53 mutation can cause cancer by improving migration, invasion, and metastasis. It can also make cells more resistant to chemotherapy and more likely to multiply [5].

Gentamicin is an antibiotic that is prescribed most frequently worldwide. In 1963, gentamicin, an aminoglycoside with antibacterial properties, was identified and extracted from *Micromonospora purpurea.* Because of its availability, affordability, and broad range of activity, it is one of the aminoglycosides that is prescribed the most. Although gentamicin works well against gram-positive and gram-negative bacteria, it is most helpful in treating severe gram-negative infections, such as those brought on by *Pseudomonas aeruginosa*. When beta-lactam antibiotics and gentamicin are taken together, there is an additional advantage known as synergy [8-10]. According to the existing literature, the majority of the premature termination codon (PTC) readthrough activity is attributed to the pharmaceutically generated minor component of gentamicin (B1), which has the potential to cure patients with nonsense mutations [11]. However, the study focused primarily on Nonsense mutations and did not take missense mutations into account which are the significant mutations in HCC patients [12].

Today, Liver cancer is a challenge faced by medical and surgical oncologists. Identification of a potential cancer target is a major task in the field of pharmacology and drug design. This research work elucidates how the existing general antibiotics help in reducing the effects of hepatocellular carcinoma-induced protein TP53.

2. METHODOLOGY

2.1 HCC Protein Selection

The data was obtained from the NCBI Genpept database (AZI94701.1 _TP53_HUMAN). Gentamicin (CID: 3467) was obtained from NCBI- PubChem [13] (https://pubchem. ncbi.nlm.nih.gov) to do molecular drug docking research. The 3D structure was obtained using the online SMILES translator hosted by the National Cancer Institute (https://cactus.nci.nih.gov/translate/) [14]. A

powerful molecular visualization tool named Discovery Studio was used to predict Three-Dimensional structures.

2.2 Drug Docking

HDOCK, an automated molecular drug docking server (http://hdock.phys.hust.edu.cn/) [15] has been used in studies on molecular drug docking. Using a 3D molecular dynamics methodology, the molecular affinities of Gentamicin and the cancer protein TP53 (tumor protein p53) in human Hepatocellular Carcinoma (HCC) were ascertained.

2.3 3D Ligand Interaction Studies

The Discovery Studio software was used to conduct post-docking studies. The molecular dynamics concept was utilized to thoroughly examine the Three-dimensional image based on the docking score (3D H-bond/Electrostatic interactions).

3. RESULTS AND DISCUSSION

3.1 Protein Sequence

TP53 gene-coded protein sequence is represented in the FASTA format below:

>AZI94701.1 tumor protein p53, partial [Homo sapiens]

CQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQS QHMTEVVRRCPHHERCSDSDGEQQ

3.2 Gentamicin

The molecular properties of Gentamicin are as follows: (MW: 477.600 g/mol MF: C21H43N5O7, 2-[4, 6-diamino-3-[3-amino-6-[1-(methylamino) ethyl] oxan-2-yl] oxy-2-hydroxycyclohexyl]oxy-5-methyl-4-(methylamino)oxane-3,5-diol). The canonical smiles of gentamicin were retrieved from the Pubchem database and converted into the 3D structure using the online smiles translator which is depicted below in Fig. 1.

3.3 Molecular Docking

The 3D docking score of -115.32 kcal/mol between Gentamicin and the tumor protein obtained from the H-Dock server is shown in complex form in Fig. 2 and the 3D complex form after docking is shown in Fig. 3.

3.4 Interactions between Gentamicin and TP53

The H-bond interaction, electrostatic interactions, and the hydrophobic interactions between Gentamicin and the tumor protein are shown in detailed view using Discovery Studio Software (Fig. 4-7).

The length of the TP53 gene-coded protein sequence amino acids length is 58 aa. This sequence was validated for analysing the drug docking studies. The most significant tumor suppressor gene is thought to be the TP53 gene, which plays a significant role in the development of cancer. The p53 protein is involved in DNA repair, senescence, cell cycle regulation, autophagy, and apoptosis. It also functions as a transcription factor. Evidence links TP53 to aging, longevity, and fertility in addition to cancer. Furthermore, there is increasing evidence linking TP53 genetic variations to environmental adaptation. Pathogenic TP53 mutations or unique TP53 amino acid residues appear to be adaptive for animals exposed to malnutrition or living in cold, hypoxic conditions, respectively. It has recently been established that several cancer genes, including TP53, are subject to positive selection in human tissues that are healthy at the somatic level [16-18].

The docking score along with the interactions of Gentamicin and TP53 from the above results illustrates that non-covalent interactions have taken place between the Gentamicin chemical structure and the tumor protein, TP53. Hence, it can be mentioned that tumor protein will be downregulated as proved by previous studies. Various previous literature coincides with the docking studies [19-26].

The human genome contains only about 1.5% protein-coding genes, therefore protein-ligand interactions found in traditional paradigms might not be sufficient to meet the urgent needs of illness treatment. Increased quantities of the protein known as the p53 tumor suppressor are present in a wide range of altered cells. It is either undetectable or only slightly present in resting cells, but it is detectable in many proliferating non-transformed cells as well. It is typically absent or mutated in a variety of cancer forms. In certain cancer types, although most likely not all of them, p53 appears to function as a tumor suppressor [27]. The functional domain region of the retrieved protein is 1-52

(PTHR11447: CELLULAR TUMOR ANTIGEN P53). From the findings, it is clear that the antibiotic, Gentamicin directly interacts with the domain regions. This research work proved that the amino acids present at the binding region between the drug and the protein are the following: SER: 32, GLN: 31, SER: 32, SER: 32, THR: 21, ARG: 40.

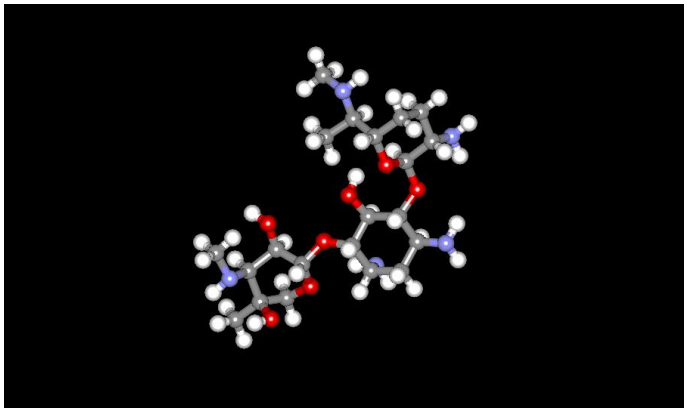

Fig. 1. 3D structure of Gentamicin in ball and stick model viewed using Discovery Studio Software

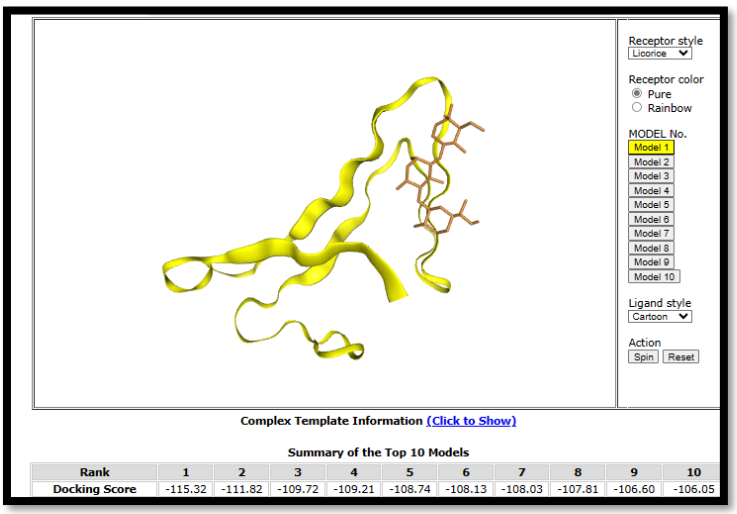

Fig. 2. Complex form of Gentamicin with tumor protein, TP53 using H-Dock server showing the corresponding binding scores

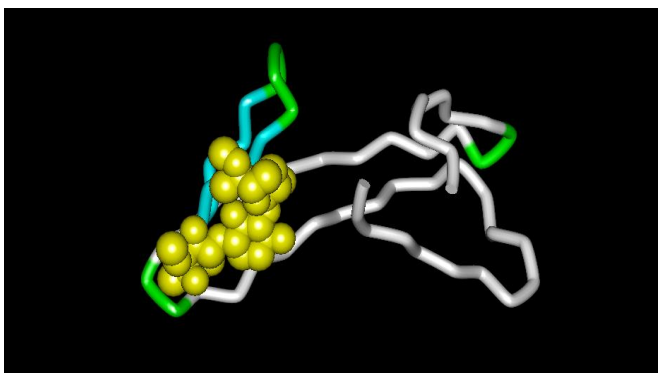

Fig. 3. Complex form of Gentamicin in spacefill model view (yellow color) with tumor protein, TP53 in tube model viewed using Discovery Studio software

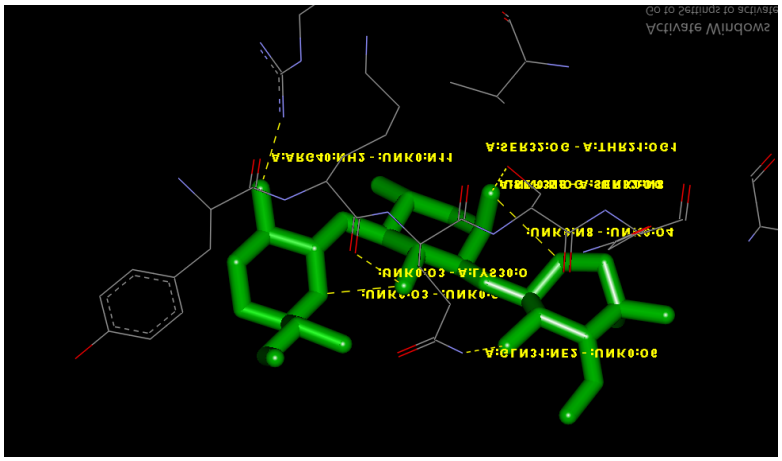

Fig. 4. Complex form of Gentamicin with TP53 showing H-bond interaction along with the corresponding binding amino acids with position number

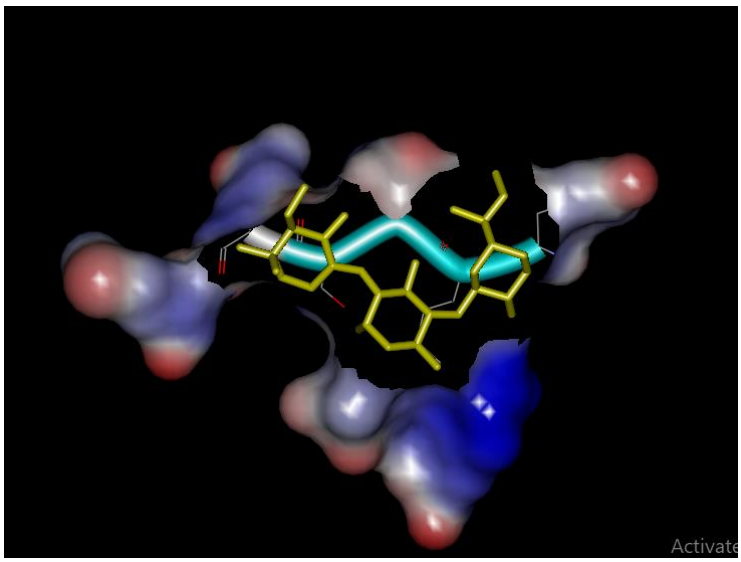

Fig. 5. Complex form of Gentamicin with TP53 showing 3D electrostatic interaction

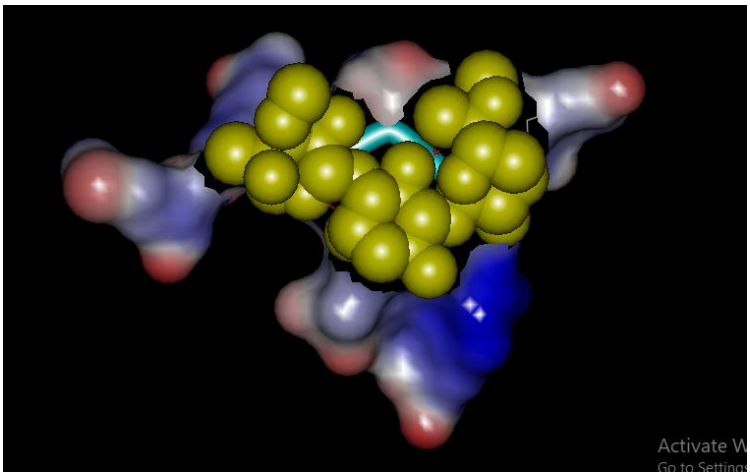

Fig. 6. Complex form of Gentamicin with TP53 showing 3D hydrophobic interaction

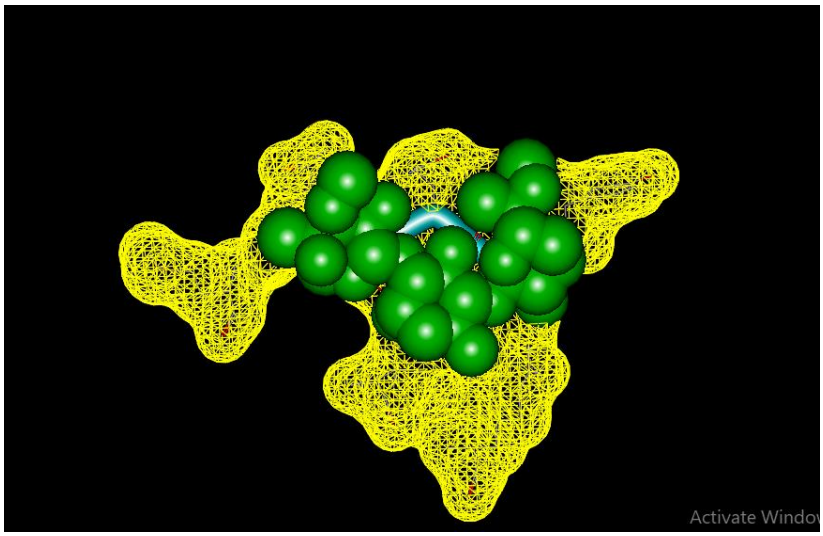

Fig. 7. Complex form of Gentamicin (green color) with TP53 (yellow color) showing the electrostatic force of attraction using Discovery Studio software

4. CONCLUSION

The research clearly shows how an antibiotic responds to a tumor protein responsible for Hepatocellular Carcinoma (HCC). The docking results clearly revealed that Gentamicin binds well to the functional domain region of the TP53 protein, where it attaches and suppresses the expression of the liver cancer protein. The binding interaction between gentamicin and the TP53 protein, as determined by docking scores, distinctly clarifies the 3D electrostatic interaction. Thus, gentamicin has the potential to be an antibiotic medication (aminoglycoside) that helps to treat the consequences of cancer. This *in silico* investigation unequivocally demonstrates that gentamicin, an antibiotic medication, may have pharmacological effects on the TP53 liver cancer protein.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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