Elucidation of Scavenging Properties of Nanoparticles in the Prevention of Carcinogenicity Induced by Cigarette Smoke Carcinogens: An In Silico Study

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Abstract Nanotechnology, a science dealing with particles at nano scale, is currently used in many fields including environmental management and medicine for welfare of human being. The economic development and quality of life have been improved through nanotechnology. The Polycyclic aromatic hydrocarbons (PAHs)

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and other toxicants have higher affinity to scaveng by nanopartilces. The structural properties and surface chemistry of nanoparticles are the players, further, extremely high surface area to volume ratio results in multiple enhancement of many beneficial properties. Hence, we have followed a methodology to compare the binding efficiency of nanoparticles and cigarette smoke carcinogens with selected enzymes involved in DNA repair pathways. The molecular interactions have been accomplished using PatchDock server and interestingly got significant interacting results for our hypothesis. PatchDock results showed nanoparticles could be able to trap cigarette smoke carcinogens efficiently in the cellular system. The highest obtained binding efficiency between 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) versus Single wall carbon nanotube (SWcNT) is 2632 score in contrast with NNK versus Human MDC1 BRCT T2067D in complex (PDB ID: 3K05) shows 2454 score, which means NNK could interact with SWcNT more efficiently than 3K05. Another part of the study shows that the highest binding efficiency 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) versus SWcNT = 2746 score and NNAL versus Titanium dioxide (TiO_2) Rutile = 2110 score in contract with NNAL versus Human Thymine DNA Glycosylase(PDB ID: 2RBA) shows 1696 score. It is also signified that NNAL interact with SWcNT and TiO_2 rutile more efficiently than 2RBA. The results clearly signifying that **SWcNT/TiO_2** are binding with NNK/NNAL more efficiently than biomolecules.

Keywords Cancer · Cigarette smoke · Nanoparticles · TiO_2 · In silico

1 Introduction

1.1 Environmental Chemical Causing Cancer

Human population is constantly exposed to many environmental chemical compounds and exprimentaly, they have been reported to cause cancer or mutation (Wogan et al. 2004).

The mutagenic and carcinogenic factors are commonly found in environmental air, water including soil which can affect exogenously and endogenously. The pathological and physiological activities such as production of some metabolic products may also cause certain changes in cellular activities which result into human cancer (Wogan et al. 2004). A food associated primary cancer of liver has been reported by aflatoxin. A causal association between contact to aflatoxin, a strongly cancer causing mycotoxin of dietary staples in Asia and Africa, and elevated risk for primary liver cancer has been reported through the application of well-valida (Kensler et al. 2011).This research has also been reported a striking synergistic interaction between hepatitis B virus infection a flat and oxinin elevating liver cancer.

Chuang et al. have reported the risk of cancer by the consumption of tobacco products (Chuang et al. 2010). It has also been reported well that tobacco carcinogens

and their DNA adducts play a significant role to induce a specific tobacco mediated cancer like polycyclic aromatic hydrocarbons (PAHs) and NNK reported for lung cancer (Hecht 2012).

1.2 Prevention of Carcinogenesis by Using Nanoparticles as Scavenger

Nanotechnology, actually means the use of the substances at their nano scale, is expected to improve the economic development and quality of life globally. Understanding of metabolic processes of nanoparticles is a strong powerful force in the development of nanotechnology. The nanoparticles offers not only size-dependant physical properties but also offer beneficial optical and magnetic effects which have been used for a number of biological/medical applications, like as a fluorescent biological marker, for the gene and drug delivery, for the detection of proteins, pathogens, Probing of DNA structure, for the treatment of cancer by tumor destruction via heating (hyperthermia), in tissue engineering, for the purification of biological molecules and cells, in the contrast enhancement of MRI, and phagokinetic studies etc. (Kudr et al. 2017). The list of utilities of nanomaterials to biology or medicine is ever escalating. Recently, some of the nanoparticles have been used in soil remediation to remediated the high molecular weight PAHs from the contaminated soils (Karnchanasest and Santisukkasaem 2007). Amphiphilic polymer nanoparticles have also been used as nano-absorbent for pollutants in aqueous phase (Shim et al. 2007).

The hunting capacities of the nanoparticles for PAHs and other toxicants could probably be credited to their higher affinity towards the xenobiotics. The structural properties and surface chemistry of nanoparticles are the players, further, extremely high surface area to volume ratio results in multiple enhancements of such properties (Dhasmana et al. 2014).

1.3 Potential of Nanoparticles (TiO_2) in Reduction of Harmful Compounds

TiO_2 is biological Inert but in ultrafine form and in high conc. TiO_2 causes the fibrosis in tissues which may lead the cancer (Chen et al. 2014). In 2006, the carcinogenic risk of TiO_2 reviewed by International Agency for Research on Cancer (IARC) and remarked that it is "possibly carcinogenic to humans" (Group 2B) based primarily on studies in rats indicating lung tumors (IARC 2006). However, epidemiology studies conducted in North America and Europe, on more than 40,000 workers in the titanium dioxide industry at manufacturing locations reported neither link with an amplified risk of lung cancer nor with any other adverse lung effects (Council 2013).

However, study conducted on inhalation exposures to TiO_2 in rats can result in lung tumors and lung effects (Bermudez et al. 2004). It is generally thought that the rat is exclusively sensitive to the effects of "lung overload", with the production of chronic lung inflammation and lung fibros which result into tumor formation but it

was not observed in other species including humans (Warheit et al. 2016). The IARC conclusion was based on studies that involved rat "lung overload" effects. But in low and definite conc., Ultra Fine TiO_2 significantly reduced the harmful compounds from the cigarette smoke (Deng et al. 2011). A number of chemical compounds have been found in Cigarette smoke aerosol which are present in both vapour phase as well as particulate (Rodgman and Perfetti 2013). Some important compounds of cigarette smoke are tar, nicotine and water. The toxic nature and health risk have been observed with Tar, PAHs and tobacco-specific nitrosamines (TSNAs) (Lee et al. 2012).

Titanate Nano Tubes (TNT) and Titanate nanosheets (TNS) have also been synthesized and used to extract harmful compounds in CS (Deng et al. 2011). Thus, TNS and TNT were introduced into cigarette filter to reduce harmful compounds including nicotine, tar, hydrogen cyanide, ammonia, phenolic compounds and selected carbonyls. Interestingly, TNT exhibits highly efficient reduction capability for the most of the harmful compounds. This might be related to the intrinsic properties of TNT (Deng et al. 2011).

Hence, we have followed a methodology to analyse the binding efficiencies of nanoparticles and cigarette smoke carcinogens. The molecular interactions have been accomplished using PatchDock server and interestingly got significant binding results for advantageous contribution of our hypothesis in the field of carcinogens.

2 Materials and Methods

The minimum system requirement for the completion of computational study is as follows.

2.1 Supported Operating Systems

Discovery Studio Visualizer is supported on the following operating systems:

- Microsoft® Windows 7 Professional
- Red Hat® Enterprise Linux® 4.0, Updates 4-7
- Red Hat Enterprise Linux 5, Retail, Updates 1-2
- SUSE® Linux Enterprise 10 (SP2).

2.2 Processor and RAM Requirements

- Processor: An Intel-compatible $\geq$2 GHz is required.
- RAM: A minimum of 2 GB of memory for the visualizer.

2.3 Disk Space Requirements

A standard installation of Discovery Studio Visualizer requires 272 MB of disk space on Windows and 454 MB on Linux.

2.4 Software

- Accelrys discovery studio visualizer (*Designing of crystal structure, visualizing and manipulating protein and crystal 3D structures*) (Dassault Systemes, BIOVIA Corp., San Diego, CA, USA).
- PatchDock (Docking server).
- Open Babel (File converter) (O'Boyle et al. 2011).
- PyMol 3D structure visualizer (The PyMOL Molecular Graphics System, Version 2.0 Schrödinger, LLC.).
- An Internet Browser and valid internet connection.

2.5 Preparation of 3D Structures of Nanoparticles

After studying the anatase crystal structure, using Accelrys Discovery studio, we have designed the TiO_2 rutile (Fig. 1a), TiO_2 anatase (Fig. 2a), fullerene (Fig. 3c) and single wall carbon nanotube (SWcNT) (Fig. 3d) 3D crystal structure.

2.5.1 The 3D Structure of Cigarette Smoke Carcinogens

The chemical structures of carcinogens NNK (Fig. 2a) and NNAL (Fig. 2b) (Jamal et al. 2012, 2017) were drawn on Chemsketch (www.acdlabs.com) followed by generation of their PDB structures by (http://accelrys.com/products/discovery-studio/) Discovery Studio visualizer and their PDB structures were generated using link (http://www.molecular-networks.com) for tool CORINA. CharMM force field was application and optimized, subjected to single step minimization through smart minimize algorithm for 1000 steps at RMS gradient of 0.01 s (Brooks et al. 2009).

2.5.2 Preparation of 3D Structures of Proteins

From the our earlier study we have selected DNA repair enzymes 1CKJ (mammalian protein casein kinase I), 2O8B (DNA mismatch repair protein Msh2), 3K05 (human MDC1 BRCT T2067D in complex), 3GQC (human Rev1-DNA-dNTP ternary complex), 1Q2Z (the 3D solution structure of the C-terminal region of Ku86), 1T38 (human o6-alkylguanine-dna alkyltransferase) and 2RBA (Human Thymine DNA Glycosylase) and their crystal structures of DNA repair enzymes were downloaded from protein data bank (www.pdb.org) (Jamal et al. 2012, 2017). Further the selected enzymes were interacted with nanoparticles using PatchDock analysis.

2.6 Docking Studies Using PatchDock Server

We have performed comparative interaction analysis between nanoparticles and selected enzymes using PatchDock server (Fig. 3).

PatchDock server (http://bioinfo3d.cs.tau.ac.il/PatchDock/).

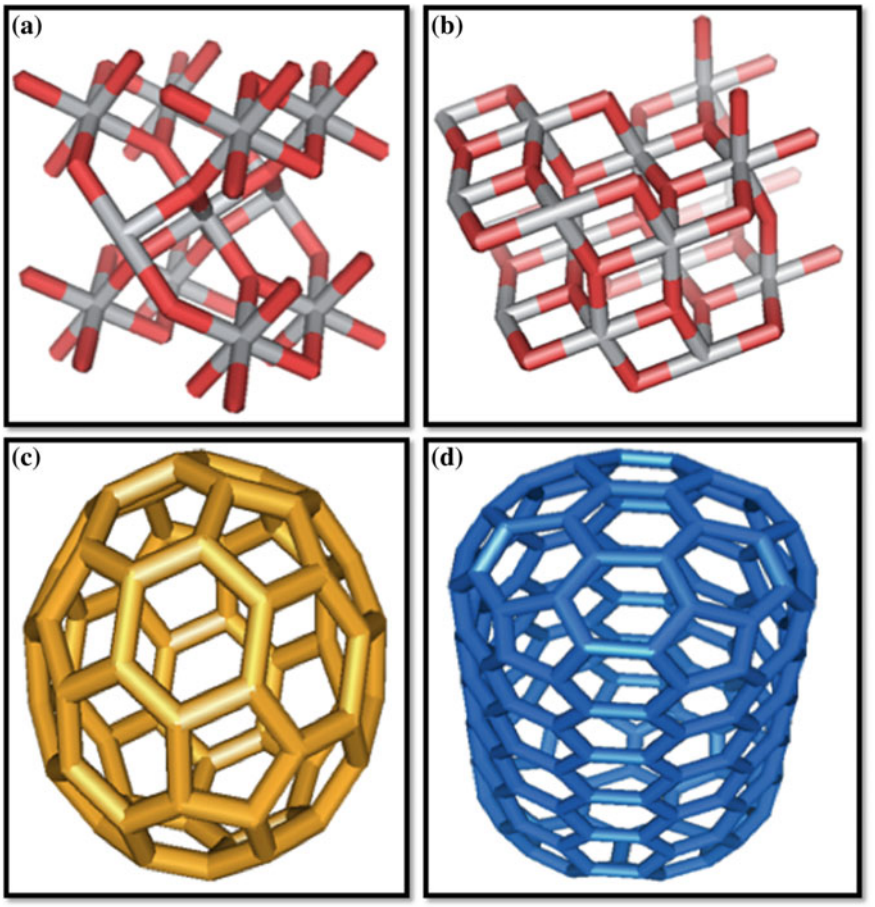

Fig. 1 Shows the structural variations of **a** TiO_2 rutile, **b** TiO_2 anatase, **c** fullerene and **d** SWcNT

- In the receptor molecule option click "choose file" button, and select the protein file "model.pdb", from the location where it has been saved. Then in the Ligand molecule option "choose file", and select the ligand file "Ligand.pdb", from the location where it has been saved.
- Give your e-mail address in the space provided where the results would be sent.
- Keeps the default clustering RMSD value , i.e., 4.0.

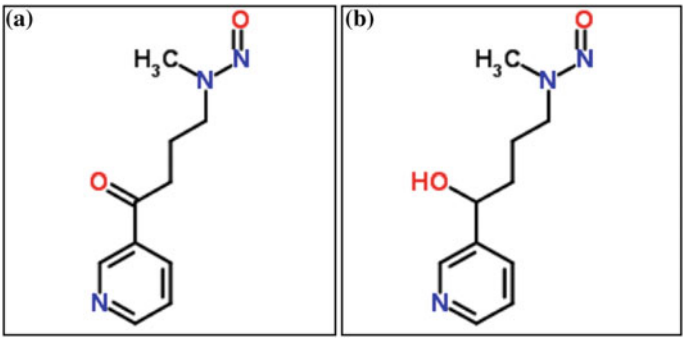

Fig. 2 Cigarette smoke carcinogens NNK and NNAL as a ligand for analysis, where structural compositions are **a** 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (PubChem Compound ID-47289, ChemSpider ID-43038), and **b** 4-(methylnitrosamino)-1-(3-pyridyl)-1-butan-1-ol (PubChem Compound ID-104856, ChemSpider ID-94646)

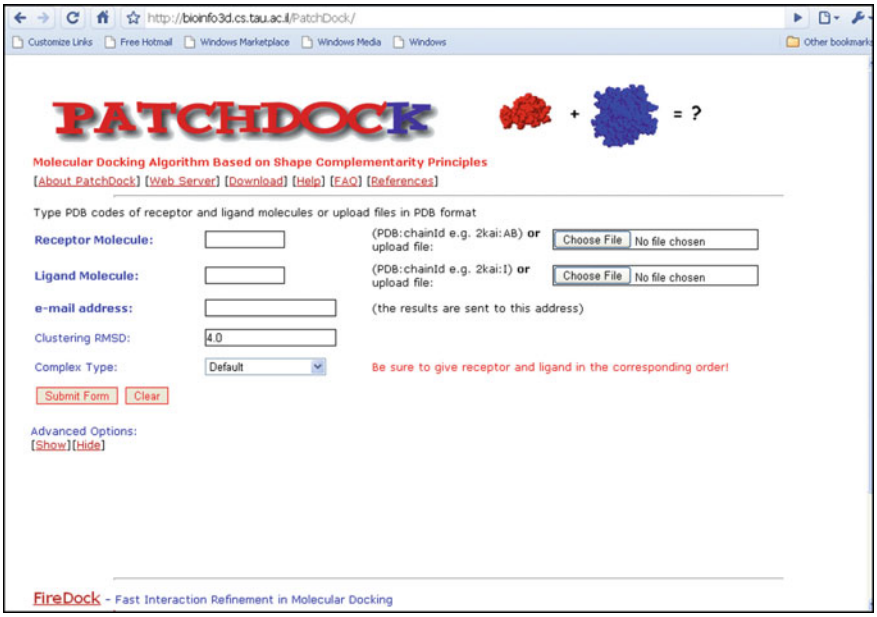

Fig. 3 Home page of PatchDock for the molecular docking algorithm

- Select complex type from the drop down menu as Protein-Small Ligand.
- Press "submit form" button. Results would be sent to the provided e-mail address after sometime.

3 Results and Discussion

We have performed molecular docking method using PatchDock server to find out the interaction between NNK versus Nanoparticles and NNK versus proteins involved in DNA repair Pathways (Table 1) and the interaction between NNAL versus Nanoparticles and NNAL versus proteins involved in DNA repair Pathways (Table 2).

The implemented hypothesis suggest that if NNK/NNAL and nanoparticles would be present in the cellular system than nanoparticles could interact with carcinogens like NNK and NNAL firstly on the basis of obtained binding energy using PatchDock tool and visualization of interaction pattern in Fig. 4a–u. All graphic were generated by PyMol 3D visualizer (*The PyMOL Molecular Graphics System, Version 2.0 Schrödinger, LLC.*).

The molecular surfaces are divided into shape-based patches by The PatchDock algorithm. This division deals the efficiency as well as discriminate between residue types (polar/non-polar) in the patches. Moreover, we also have created the use of

Table 1 Comparison of PatchDock scores obtained from docked NNK versus proteins and NNK versus nanoparticles conformations

S. No.	Protein's name	Protein versus NNK	SWcNT versus NNK	TiO_2 anatase versus NNK	TiO_2 rutile versus NNK	Fullerene versus NNK
1	1CKJ	2790	2632	2068	1360	910
2	2O8B	2720	2632	2068	1360	910
3	**3K05**	**2454**	**2632**	2068	1360	910
4	3GQC	3054	2632	2068	1360	910

Table 2 Comparison of PatchDock scores obtained from docked NNAL versus proteins and NNAL versus nanoparticles conformations

S. No.	Protein's name	Protein versus NNAL	SWcNT versus NNAL	TiO_2 anatase versus NNAL	TiO_2 rutile versus NNAL	Fullerene versus NNAL
1	1CKJ	3688	2746	2110	1360	954
2	1Q2Z	3374	2746	2110	1360	954
3	1T38	3240	2746	2110	1360	954
4	**2RBA**	**1696**	**2746**	**2110**	1360	954

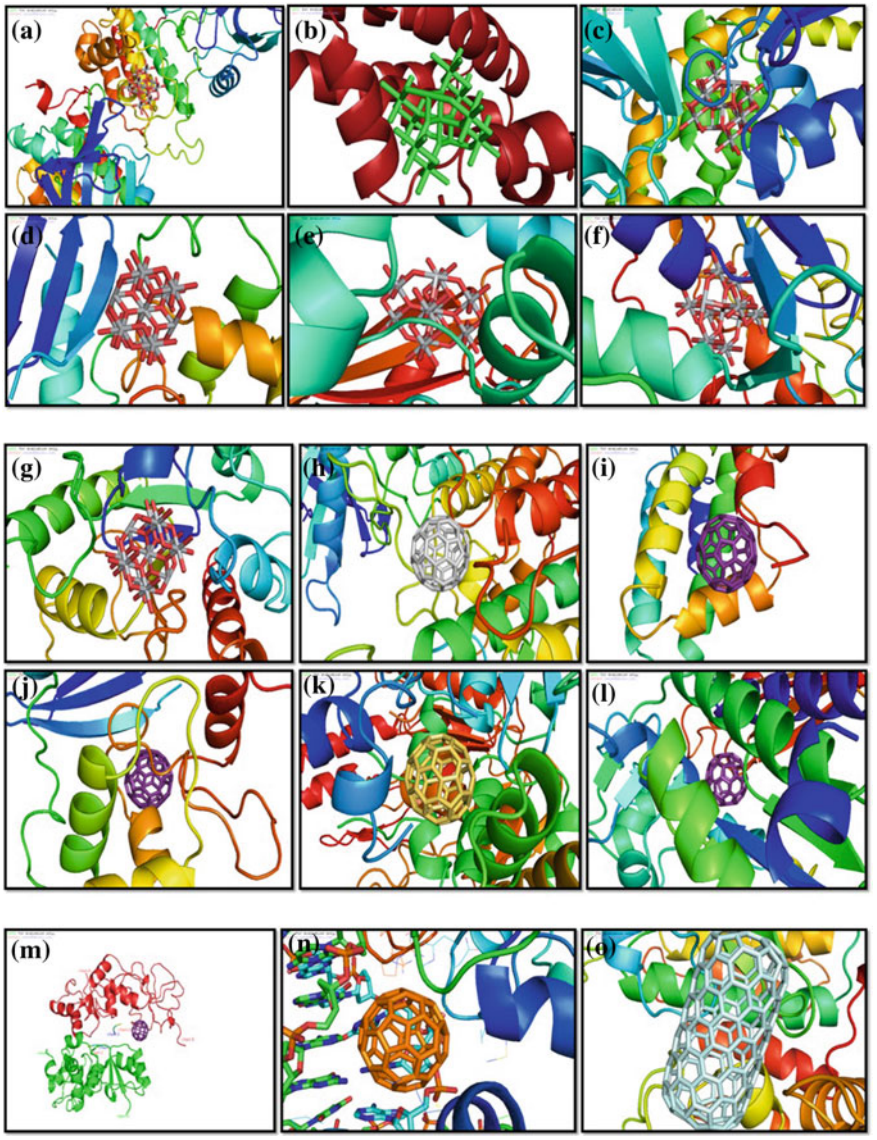

Fig. 4 **a** TiO_2 docked with 1CKJ; **b** TiO_2 docked with 1Q2Z; **c** TiO_2 docked with 2O8B; **d** TiO_2 docked with 1T38; **e** TiO_2 docked with 3GQC; **f** TiO_2 docked with 3K05; **g** TiO_2 docked with 2RBA; **h** fullerene docked with 1CKJ; **i** fullerene docked with 1Q2Z; **j** fullerene docked with 1T38; **k** fullerene docked with 2O8B; **l** fullerene docked with 3GQC; **m** fullerene docked with 3K05; **n** fullerene docked with 2RBA; **o** SWcNT docked with 1CKJ; **p** SWcNT docked with 1Q2Z; **q** SWcNT docked with 1T38; **r** SWcNT docked with 2O8B; **s** SWcNT docked with 3GQC; **t** SWcNT docked with 3K05; **u** SWcNT docked with 2RBA; **v** visualization of SWcNT and NNAL interaction; **w** visualization of SWcNT and NNK interaction

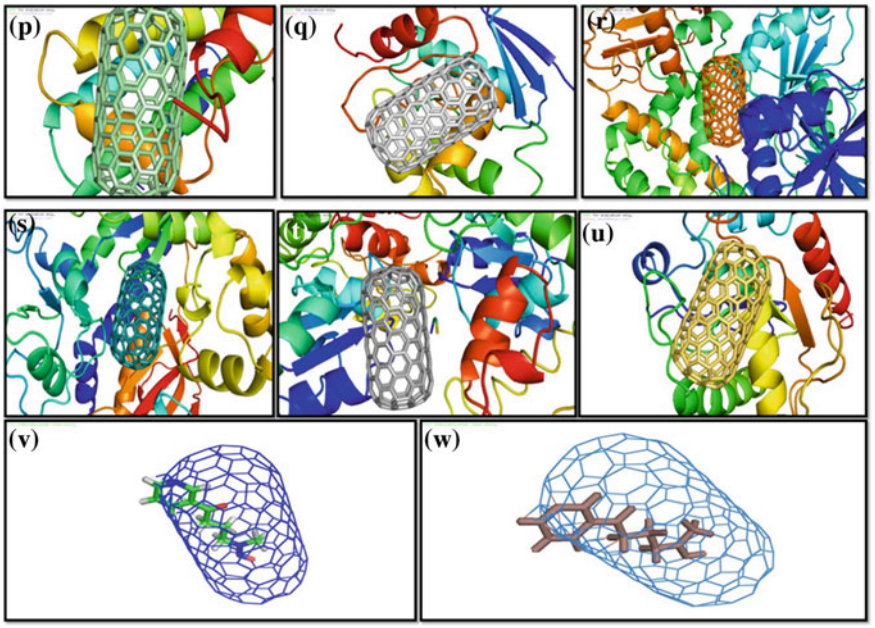

Fig. 4 (continued)

residue and hot spots in the patches. In the next step, improvement for the shape complementarily function are carried out by method by utilizing distance transform.

Moreover, it implements faster scoring, based on multi-resolution surface data structure. Our improved shape complementarily function further helps to improve the quality of the results. However, here the docking is rigid, the utilization of the last three components enables us to permit more liberal intermolecular penetration. PatchDock results showed nanoparticles could be able to trap cigarette smoke carcinogens efficiently in the cellular system. The highest obtained binding efficiency between NNK versus SWcNT is 2632 score (Table 1 and Fig. 4w) in contrast with NNK versus 3K05 shows 2454 score (Table 1), which means NNK could interact with SWcNT more efficiently than 3K05 (Fig. 4t). Another part of the study shows that the highest binding efficiency NNAL versus SWcNT = 2746 (Table 2 and Fig. 4v) score and NNAL versus TiO_2 Rutile = 2110 score (Table 2) in contract with NNAL versus 2RBA shows 1696 score (Table 2). It is also signified that NNAL interact with SWcNT and TiO_2 rutile more efficiently than 2RBA (Fig. 4g, u).

4 Conclusion

As mentioned earlier, the fact that technical TiO_2 has been very often of the (metastable) anatase form; and in many cases anatase is photocatalytically more active than rutile. This has provoked theoretical study of anatase, but there are hardly any experiments on well-characterized surfaces that would enable verification of these theoretical predictions. This lack of experimental research data is mostly because of the limited availability of anatase crystals of adequately large size.

This study of anatase [1, 0, 1] surface may establish valuable way for biotechnological researchers since this aspect of biotechnology has yet not been explored. The surface is also for interactions, this surface is also found over TiO_2 nanotubes, which are presently the subject of interest of the research community of electronics and nanotechnology innovators. In low and definite conc., TiO_2 significantly reduced the harmful compounds from the cigarette smoke (Deng et al. 2011).

The scavenging capacities of the nanoparticles for PAHs and other toxicants could probably be attributed to their higher affinity towards the xenobiotics. The structural properties and surface chemistry of nanoparticles are the players, further, extremely high surface area to volume ratio results in multiple enhancements of such properties.

Our study is conformity of study of Deng et al. (2011), who reported the use of titanate nanosheets and nanotubes are significantly reduces the harmful compounds in tobacco smoke. Our study confirmed this action in Biological system that by using of Bioinformatics tools we have done the comparative docking study between Nanoparticles-biomolecules and NNK/NNAL-Nanoparticles, we concluded that **SWcNT**, **TiO_2-Biomolecules** binding shown **lower** scores and **NNK/NNAL-Nanoparticles** binding shown **higher** scores. Hence, Results are clearly signifying that **SWcNT/TiO_2** binding with NNK/NNAL is more efficiently than biomolecules.

5 Future Scope

There is a lot to be done in this research work. We are just at the beginning; yet have much to be studied. Further studies can be done by applying force fields like crystal-CHARMm (Chemistry at HARvard Molecular Mechanics) (Brooks et al. 2009), SIBFA (Sum of Interactions Between Fragments Ab initio computed) (Gresh et al. 2002) (these are the few force fields which deals with metals and crystal structures) and then going for various interaction studies and energy calculations. The major hurdle in this work is that most of the softwares currently available do not recognize, i.e., they do not contain information regarding crystallographic bonding (or arrangements) and metallic atoms, their physical, chemical and quantum mechanical properties for molecular dynamic simulations of the same. There is an urgent require-

ment for a complete software package which can be used to design and manipulate inorganic or organic crystals as well as the biomolecules.

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