
**DOCKING ANALYSIS OF PHENETHYL ISOTHIOCYANATE (PEITC) FROM
NASTURTIUM OFFICINALE (WATERCRESS), ON 4 - (METHYLNITROSAMINO) -1-
(3 - PYRIDYL) - 1- BUTANONE (NNK), CARCINOGENIC ACTION IN ORAL
CANCER**

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ABSTRACT

NNK (4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone), a nitrosamino compound present in tobacco cause cancer in oral cavity. NNK a potent procarcinogen, when metabolically activated by Cytochrome P450, the NNK procarcinogen was converted into NNK carcinogen. The Cytochrome P450 and NNK complex cause oral cancer. Watercress, (*Nasturtium officinale*) a green leafy cruciferous vegetable used in salads, sandwiches and as an herb. The chemo preventive agent Phenethyl Isothiocyanate (PEITC) present in Watercress (*Nasturtium officinale*) acts as an inhibitor of the metabolism of NNK with Cytochrome P450. Docking analysis was done to predict the binding affinity of PEITC to Cytochrome P450, which inhibits the binding action of NNK to Cytochrome P450 to prevent oral cancer.

KEYWORDS

NNK, Cytochrome P450, Watercress and Phenethyl Isothiocyanate

INTRODUCTION

Bioinformatics, defined as an intersection of biological science with computer application, necessary to manage, process and understand large amounts of data for instance from the sequencing of the human genome or from large databases containing information about plants and animals for use in discovering and developing new drugs.

Cancer is a complex group of over 100 different types of cancer. In those different types of cancer, Oral Cancer is the second most common disease in the world. Oral cancer is a sore in the mouth that doesn't heal which can be a warning sign of oral cancer. A

biopsy is the only way to know whether the abnormal area in the oral cavity is cancer.

Tobacco chewing and smoking use caused oral cancer. When the tobacco chews orally, the procarcinogenic NNK metabolically reacts with CytochromeP450. The procarcinogenic NNK is converted into carcinogenic NNK. Carcinogenic of NNK binds with DNA to form DNA adducts that result in the formation of tumors. Induction of some P450s is a risk factor in several cancers since these enzymes can convert procarcinogens to carcinogens. P450 enzymes play a major role in drug interactions [1, 2].

Cruciferous Vegetables are a member of the family of vegetables that include Kale, Watercress, broccoli, cabbage, Brussels sprouts and turnips. These Vegetables contain

substances that may protect against cancer. Of these Vegetables, watercress has anti cancer effects.

Watercresses (*Nasturtium officinale*) are fast growing, aquatic or semi-aquatic, perennial plants native from Europe to central Asia, and one of the oldest known leaf vegetables consumed by human beings. These plants are members of the Family Brassicaceae or cabbage family, botanically related to garden cress and mustard [3].

Phenethyl isothiocyanate is a substance being studied in the prevention of Cancer. It is a naturally occurring compound in Cruciferous Vegetables. Phenethyl isothiocyanate (PEITC) inhibits NNK tumorigenesis by blocking the activation of NNK. Phenethyl isothiocyanate may be an effective inhibitor of the carcinogenicity when activated by cytochromeP450 [4, 5].

MATERIALS AND METHODS

Protein Data Bank (<http://www.pdb.org>) The PDB contains information about experimentally determined structures of proteins, nucleic acids and complex assemblies. Protein Data Bank (pdb) file format, a textual file format describing the three dimensional structures of molecules held in the Protein Data Bank.

Swiss Pdb Viewer (<http://www.expasy.org/spdbv/>) Deep View – Swiss-Pdb Viewer is an application that provides a user friendly interface allowing to analyze several proteins at the same time. The proteins can be superimposed in order to

deduce structural alignments and compare their active sites or any other relevant parts. Amino acid mutations, H-bonds, angles and distances between atoms are easy to obtain.

Pubchem: Pubchem is a very large and growing (over 5 million unique chemical data entries) PUBLIC, online CHEMical database resource that invites chemical structure and annotated data submissions preferably of bioassay data. PubChem provides information on the biological activities of small molecules

ACD ChemsSketch ACD/ChemSketch is an advanced chemical drawing tool and is the accepted interface for the industries best NMR and molecular property predictions, nomenclature, and analytical data handling software. ACD/ChemSketch is also available as freeware.

Castp Castp is used to find the binding site of the protein. Castp is the **Computed Atlas of Surface Topography of proteins**. It includes annotated functional information of specific residues on the protein structure. These annotated residues are mapped to surface pockets, interior voids or other regions of the PDB structures. The CASTp web server can be used to study surface features, functional regions and specific roles of key residues of proteins.

Argus Lab The Argus Lab contains tools for building and visualising molecules as well as looking at the output from calculations. It has particularly good tools for interfacing with Gaussian 03 such as producing input files and reading output files.

RESULTS

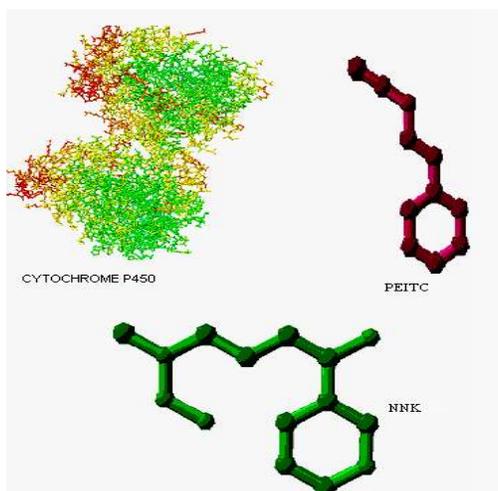


Figure 1
Structure of Cytochrome P450, NNK and PEITC

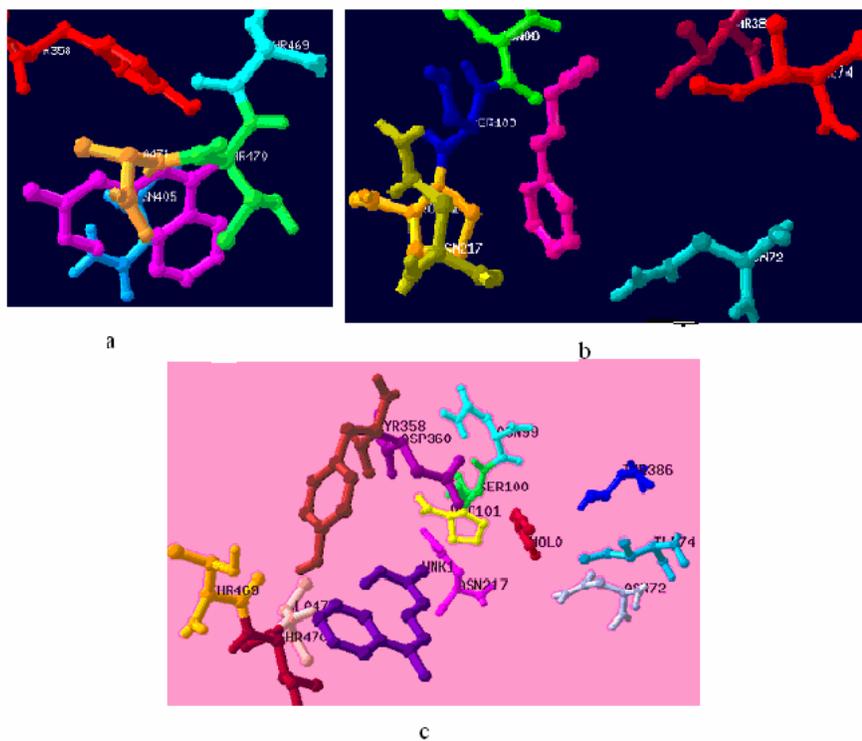


Figure2
Docking results of a) Cytochrome P450 with NNK, b) Cytochrome P450 with PEITC
c) Cytochrome P450 PEITC complex with NNK

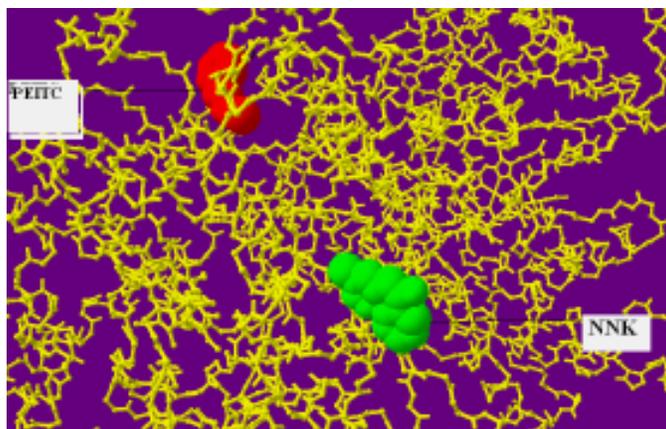


Figure 3
Binding site of PEITC and NNK to CYP450

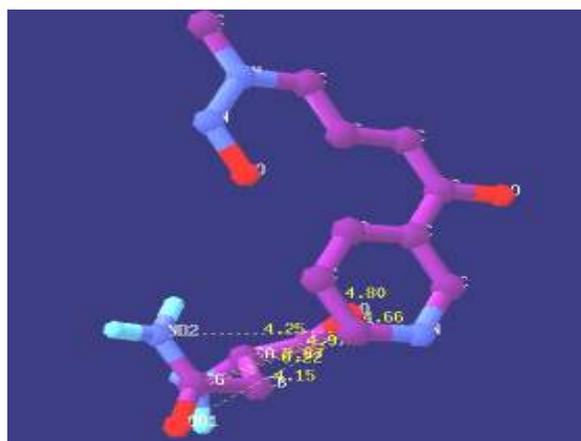


Figure 4
Interactions of CYP450 and NNK

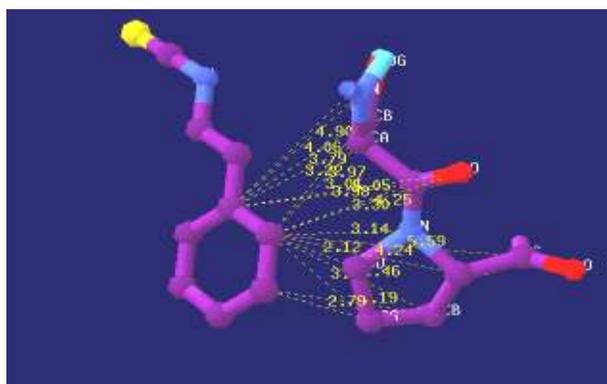


Figure 5
Interactions of CYP450 and PEITC

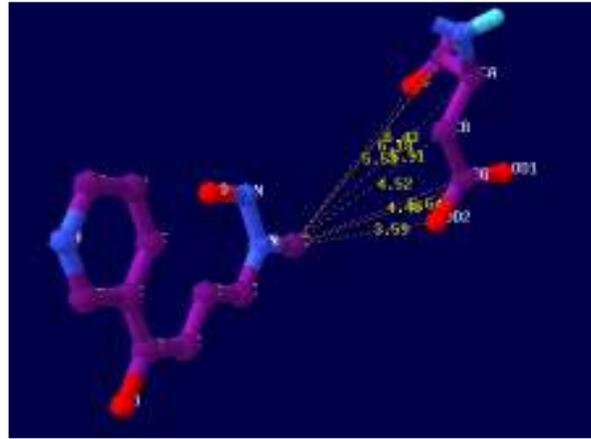


Figure 6
Interactions of CYP450, PEITC complex with NNK

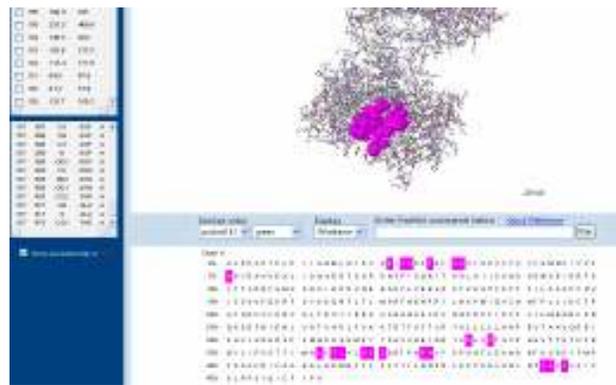


Figure 7
Binding sites results for NNK in CYP450

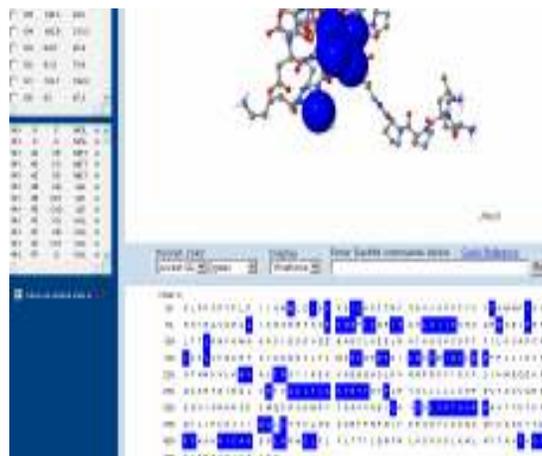


Figure 8
Binding sites results for PEITC in CYP450

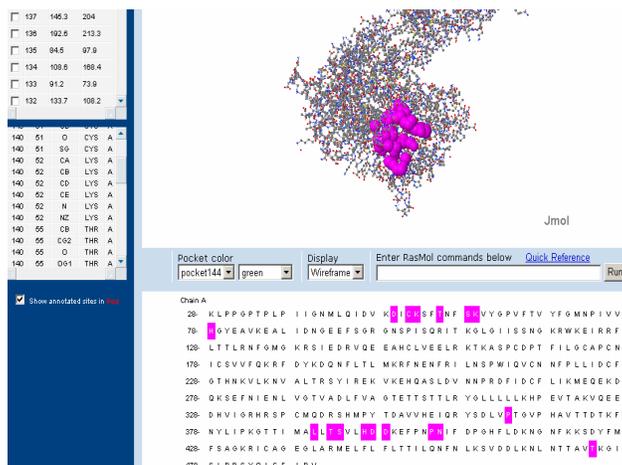


Figure 9
Binding sites results for NNK with CYP450, PEITC complex

DISCUSSIONS

Oral Cancer is caused by the tobacco consumption. This affects the mouth, throat, lips and jaws by causing cancer. Water cress (*Nasturtium officinale*), one of the cruciferous vegetables which have an anti-cancer effects. Watercress an excellent source of Phenethyl Isothiocyanate (PEITC), a naturally occurring compound in some cruciferous vegetables. CytochromeP450 (CYP450) was metabolically activated by the compound 4-(methyl-nitrosamine)-1- (3-pyridyl)-1-butanone (NNK) present in tobacco. NNK a nitrosamine and procarcinogenic compound. NNK a procarcinogen is converted to carcinogen by the activation of CYP450 which cause oral cancer. The binding of PEITC to CYP450 caused a

change to the native form of CYP450. This change inhibited the strong interaction of NNK to CYP450. The binding sites of NNK to CYP450 were in the position of amino acids at Tyrosine 'A' 358, Asparagine 'A' 405, Threonine 'A' 470, Alanine 'A' 471. The PEITC bind to CYP450 of the amino acids are Isoleucine 'A' 74, Asparagine 'A' 72, Asparagine 'A' 99, Serine 'A'100, Proline 'A'101, Asparagine 'A' 217, Threonine 'A'386. The CYP450, PEITC complex bind with NNK in the position of the amino acids are Isoleucine 'A' 74, Asparagine 'A' 72, Asparagine 'A' 99, Serine 'A'100, Proline 'A'101, Asparagine 'A' 217, Threonine 'A'386, Tyrosine 'A' 358, Aspartic acid 'A' 360, Threonine 'A' 470, Alanine 'A' 471. The native structure of CYP450 with NNK is Asparagine 'A'405.

	Interaction of CYP450 and NNK	Interaction of CYP450, PEITC complex and NNK
Interactions Value	3.22 A°, 4.15 A°, 4.25 A°, 4.80 A°.	5.55 A°, 5.64 A°, 5.91 A°, 6.18 A° and 6.43 A°.
Amino acids	Asparagine 'A' 405	Aspartic acid 'A' 360

The interaction formed between the CYP450 and NNK are with the amino acid Asparagine 'A' 405 with distance of 4.25 A°, 4.80 A°, 3.22 A° and 4.15 A°. The change in the amino acid and interaction formed between the complex structure of CYP450, PEITC with NNK are Aspartic acid 'A' 360 with distance of 5.55 A°, 5.64 A°, 5.91 A°, 6.18 A° and 6.43 A°. There was a changes found between the native form and the complex structure.

CONCLUSION

A sore in the mouth that does not heal can be a warning sign of Oral Cancer. Oral Cancer is caused by tobacco chewing and alcohol use. Watercress (*Nasturtium officinale*), one of the cruciferous vegetables. It has an anti-cancer effect. Watercress was one of the richest source of dietary PEITC (Phenethyl Isothiocyanate). Phenethyl Isothiocyanate (PEITC) was a strong inhibitor of carcinogenesis.

PEITC was a natural compound occurring in cruciferous vegetables. From that PEITC, the cruciferous vegetables of Watercress (*Nasturtium officinale*) were taken. 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) was a potent procarcinogenic compound in tobacco. It was activated with CytochromeP450 (CYP450) and converted procarcinogen into carcinogen. From that CYP450, PEITC complex docked with NNK, there was a changes in the complex structure compared to the native structure of CYP450 docked with NNK. This was occurred by the change of Asparagine 'A' 405 to Aspartic acid 'A' 360 in the CYP450, PEITC complex structure when docked with NNK. This showed that PEITC acted as a noncompetitive inhibitory effect on NNK induced oral cancer. Together these findings, suggest that PEITC plays important role in non competitive inhibitory effect and tobacco-related tumorigenesis in human oral cancer [6].

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