EXCELLENT PUBLISHERS

International Journal of Current Research and Academic Review

ISSN: 2347-3215 Special Issue-3 (August-2016) pp. 134-147

Journal home page: http://www.ijcrar.com

Comparative In-Silico Docking Analysis of SOD1 against Natural Synthetic Antioxidant

M. Victoriya Salomi[1,2]*, R. Aishwarya[2] and N. Saranya[2]

[1]Department of Biotechnology, Mother Teresa Women's University, Kodaikanal, India
[2]Department of Biochemistry and Bioinformatics & Clinical Trial Managements, Dr. MGR Janaki College of Arts and Science, Chennai, Tamilnadu, India

Corresponding author

KEYWORDS

Free radicals, superoxide dismutase, antioxidants, *Murraya koenigii*, docking, therapeutic agents.

A B S T R A C T

Free radicals and other ROS (Reactive Oxygen Species) are derived as a result of endogenous metabolisms, exposure to certain physiochemical conditions or pathological states. These free radicals are unpaired (O_2^-) and reacts with DNA, Proteins, Carbohydrates and lipids to satisfy themselves as a paired electron (O_2) and results in various diseases. Superoxide dismutase is a metalloprotein which catalyzes the dismutation of the superoxide radicals (O_2^-) into ordinary molecular oxygen (O_2) or hydrogen peroxide (H_2O_2) and prevents cell damage. SOD consists of three isoforms in mammals : (i) cytoplasmic Cu/Zn SOD (SOD1),(ii) mitochondrial Mn SOD (SOD2) and (iii) extracellular Cu/Zn SOD (SOD3).All of which requires catalytic metal ions for their activation.Antioxidants are chemical substances which prevents/inhibits cellular damages caused by oxidation. Plants are rich source of antioxidants. These antioxidants can also be artificially synthesized, called as synthetic antioxidants. ButylatedHydroxytoluene (BHT) is one such synthetic antioxidant, widely used in food industries to prevent/inhibit oxidative damage and thereby increases the shelf life of packed or canned food. *Murrayakoenigii* (curry leaves) is an essential species known for its distinct flavor, belongs to the family *Rutaceae*. The phytochemical constituents extracted from the leaf of *M.koenigii* are lutein, tocopherol, carotene, koenimbine, O-methyl murrayamine A, O-methylmahanine, isomahanine, bismahanine, bispyrafoline, euchrestine, bismurrayafoline E, mahanine, shows antioxidant activity. This article provides a comprehensive overview of how far the activity of superoxide dismutase 1 is enhanced by both natural antioxidant compounds from *M.koenigii* (O-methylmurrayamine A & O-methylmahanine) and synthetic antioxidant compounds (butylatedhydroxytoluene) through their binding to the allosteric site of the SOD1. This binding interaction can be calculated by using the AutoDock software. Several chronic and degenerative diseases were found to evolve as a result of oxidative stress.In the current research, Insilco docking studies of both natural antioxidants such as o-methylmurrayamine A & O-methyl mahanine and synthetic antioxidants ButylatedHydroxytoluene (BHT) was performed. The results indicated that in o-methylmurrayamine and O-methylmahanine the binding energies and hydrogen bond formation were stronger than in the synthetic antioxidant ButylatedHydroxytoluene (BHT). Thus, we conclude that natural antioxidants such as o-methylmurrayamine A and O-methylmahanine could be used as potent natural therapeutic agents to combat oxidative stress.

Introduction

A free radical is an atom or group of atoms that have one or more unpaired electrons; collectively known as Reactive Oxygen Species (Bowen, 2003). These Reactive Oxygen Species (O_2^-, H_2O_2 and OH^-) are known to be the mediators of oxidative stress. ROS are highly reactive, they are capable to react with membrane lipids, DNA, proteins and other small molecules, resulting in cellular damage.

Types of ROS include superoxide anion radical, hydrogen peroxide, hydroxyl radical, singlet oxygen, nitric oxide radical, hypochlorite radical, and various lipid peroxides (Douglas Darr and Irwin Fridovich, 1994). Oxygen derived free radicals are generated constantly as part of normal aerobic life, formed in mitochondria as oxygen molecule which is reduced along the electron transport chain. ROS are also formed as necessary intermediates in a variety of enzyme reactions. Examples of situation in which oxygen radicals are overproduced in cells include: (i) oxygen radicals produced by white blood cells such as neutrophils, which are used in host defense to kill invading pathogens, (ii) cells exposure to abnormal environments such as hypoxia generate abundant and often damaging ROS.

A number of drugs have oxidizing effects on cells and lead to production of oxygen radicals, and (iii) ionizing radiation is well known to generate oxygen radicals within the biological systems (Bowen, 2003).Free radicals are involved in the initiation of cellular injury observed in neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, Parkinson's disease and even can act in all stages of carcinogenesis leading to cancer development (Lien Ai Pham-Huy *et al*, 2008).

Free radical development is unavoidable but human system adapted by setting up and maintaining defense mechanisms that reduce their impact. There are three major detoxifying enzymes, they are as follows: (i) Superoxide dismutase (SOD)-scavenges superoxide anions and converts them into hydrogen peroxides, (ii) Catalase-this enzyme contains iron as cofactors and converts hydrogen peroxide to water and oxygen, thereby finishing the detoxification reaction started by SOD and (iii) Glutathione peroxidase-the majority of enzymes within this family is dependent on the micronutrient selenium. Similar to catalase, these enzymes convert hydrogen peroxide to water and oxygen (Bowen, 2003 *et al*., Douglas Darr and Irwin Fridovich, 1994). TheSuperoxide dismutases, (EC 1.15.1.1) are a family of enzymes characterized by the metals they contain and by their localization. Three isoforms of SOD in mammals: (i) cytoplasmic Cu/Zn SOD (SOD1), (ii) mitochondrial SOD (SOD2) and (iii) extracellular Cu/Zn SOD (SOD3). SOD catalyzes the dismutation of the superoxide radicals (O_2^-) into ordinary molecular oxygen (O_2) or hydrogen peroxide (H_2O_2) and prevents cell damage, where H_2O_2 is substantially less toxic than superoxide, later catalase converts hydrogen peroxide into oxygen and water. SOD accelerates this detoxifying reaction roughly 10,000 fold over the non-catalyzed reaction (James d. Crapo, 1992 *et al*., Bowen, 2003).On the current research, we are focusing on SOD1. Cu/Zn superoxide dismutase (SOD1) is a highly conserved enzyme which is the cytoplasmic scavenger of superoxide (O_2^-).SOD1 is a dimer, molecular weight of 32 kDa, each of the subunit contains the active site. The active site is funnel shaped dinuclear metal cluster constituted by copper and zinc ions. The strong positive charge of the metal ions, along with two nearby positively charged

amino acids; serve to draw the negatively charged superoxide into the funnel(Azfar AliBajwa,2012 *et al*., Rishi Rakhit *et al*, 2006).

Apart from the endogenous antioxidant enzymes, an antioxidant can be a vitamin, mineral or phytochemical naturally present in Vegetables and fruits, known as dietary supplements which includes beta-carotene, lutein, lycopene, selenium, vitamin A, vitamin C and vitamin E (Chinwe Elochukwu, 2015 *et al*.,). Antioxidants are a man-made or natural substance that prevents/inhibits oxidation or reactions promoted by free radicals. These antioxidants are electron donors, neutralize free radicals and also terminate the chain reaction produced by oxidation leading to cellular damages.

These antioxidants can also be artificially synthesized, called as synthetic antioxidants. Butylated Hydroxytoluene (BHT) is one such synthetic antioxidant also known as dibutylhydroxytoluene, a lipophilic organic compound which is a chemical derivative of phenol. BHT is widely used in food industries to prevent/inhibit oxidative damage and thereby increases the shelf life of packed or canned food. Each BHT consumes two peroxy radicals. However, oral studies on BHT some renal and hepatic damagewas seen in male rats (Lanigan and Yamarik, 2002; SeppHasslberger, 2007).

Murrayakoenigii(curry leaves) belongs to the Rutaceae family, natural flavoring plant with a number of important health benefits, which makes our food both healthy and tasty along with pleasing aroma. They contain various antioxidant properties and have the ability to ail various diseases.

Amongst the green leafy vegetable the total antioxidant activity was highest in *Murraya koenigii* as compared to that of methanol extracts of *Amaranthus* sp., *Centella asiatica* and *Trizonella f oenumgraecum*. The phytochemical constituents extracted from the leaf of *M.koenigii* are lutein, tocopherol, carotene, koenimbine, O-methylmurrayamine A, O-methylmahanine, isomahanine, bismahanine, bispyrafoline, euchrestine, bismurrayafoline E, mahanine, shows antioxidant activity (Vandana Jain *et al*., 2012). Studies conducted by Mitra*et al*., 2012 indicated that the aqueous extracts of *M.koenigii*leaf confer significant protection to rat cardiac tissue against cadmium induced oxidative stress probably due to its antioxidant activity (Prasan Bhandari, 2016).

Materials and Methods

Uniprot

UniProt is a comprehensive, high-quality and freely accessible database of protein sequence and functional information, many entries being derived from genome sequencing projects. It contains a large amount of information about the biological function of proteins derived from the research literature. The UniProt/Swissprot Knowledgebase (UniProtKB) is the central access point for extensive curated protein information, including function, classification, and cross-reference. http://www.uniprot.org/

PDB

The Protein Data Bank (PDB) is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. The data, typically obtained by X-ray crystallography or NMR spectroscopy and submitted by biologists and biochemists from around the world, are freely accessible

on the Internet via the websites of its member organizations. The PDB is a key resource in areas of structural biology, such as structural genomics. http://www.rcsb.org/pdb/home/home.do

ACD Chem Sketch

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. It contains tools for 2D structure cleaning, 3D optimization and viewing.

Open Babel

Open Babel is a chemical toolbox designed to speak the many languages of chemical data. It's an open, collaborative project allowing anyone to search, convert, analyze, or store data from molecular modeling, chemistry, solid-state materials, biochemistry, or related areas. http://openbabel.org/

AutoDock

Auto Dock is a suite of automated docking tools. The software is used for modeling flexible small molecule such as drug molecule binding to receptor proteins of known three dimensional structures. It uses Genetic Algorithms for the conformational search and is a suitable method for the docking studies. The technique combines simulated annealing for conformation searching with a rapid grid based method of energy evaluation. Auto Dock tools are used to prepare, run and analyze the docking simulations, in addition to modeling studies. http://autodock.scripps.edu/resources/tools

PyMOL

PyMOL is an open-source tool to visualize molecules available from (www.pymol.org). It runs on Windows, Linux and MacOS equally well. PyMOL has excellent capabilities in creating high-quality images from 3D structures; it has well developed functions for manipulating structures and some basic functions to analyze their chemical properties. The possibilities to write scripts and plugins as well as to incorporate PyMOL in custom software are vast and superior to most other programs. PyMOL has been written mostly in the Python language (www.python.org), while the time-critical parts of the system have been coded in C. This way, Python programs interact most easily with the PyMOL GU

Results and Discussion

Sequence retrieval: Superoxide dismutase 1

The sequence of human SOD1 (Homo sapiens) was retrieved from UNIPROT database, its sequence accession number is P00441.

Structure retrieval

The 3D structure (crystal structure) of superoxide dismutase 1 was derived from PDB database. From the PDB databank (Berman *et al*., 2000: www.pdb.org), the PDB file was collected and its PDB ID is 2xjk. The structure was visualized using RASMOL. The final stable structure of the SOD1 protein obtained was shown in Figure 4.

Preparation of ligands

Both natural and synthetic antioxidant compounds are used as ligands and were retrieved from NCBI PubChem Compound database (Bolton *et al*., 2008)

(http://pubchem.ncbi.nlm.nih.gov/). For further docking analysis, the ligands were designed using ChemSketch and their 2d structure was converted to 3D structures. These data are saved as a molecular format file (MDL MOL format). The molecular format converter tool (Open babel) is used to convert this file into the PDB format during the docking analysis. The structure and molecular formula of antioxidant compounds was shown in Table 1 and 2.

Molecular docking study of both natural and synthetic antioxidant compounds

The two natural antioxidant compounds from Murrayakoenigii (O-methylmahanine and O-methylmurrayamine A) and synthetic antioxidant compound (butylatedhydroxy-toluene) are docked against SOD1 protein.

The Graphical User Interface program "Auto-Dock Tools" was used to prepare, run, and analyze the docking simulations. Koll man united atom charges, solvation parameters and polar hydrogen were added into the receptor PDB file for the preparation of protein in docking simulation.

Auto Dock (Goodsell *et al*., 1996; Jones *et al*., 1996; Rarey *et al*., 1996)requires pre-calculated grid maps, one for each atom type present in the flexible molecules being docked and its stores the potential energy arising from the interaction with rigid macromolecules. This grid must surround the region of interest in the rigid macromolecule. The grid box size was set at 126, 126 and 126A° (*x*, *y*, and *z*) to include all the amino acid residues that present in rigid macromolecules. Auto Grid 4.2 Program, supplied with AutoDock 4.2 was used to produce grid maps. The spacing between grid points was 0.375 angstroms. The Lamarckian Genetic Algorithm (LGA) (Morris *et al*., 1998) was chosen search for the best conformers. During the docking process, a maximum of 10 conformers was considered. The population size was set to 150 and the individuals were initialized randomly. Maximum number of energy evaluation was set to 25,00,000, maximum number of generations 27,000, maximum number of top individual that automatically survived set to 1, mutation rate of 0.02, crossover rate of 0.8, Step sizes were 0.2 A for translations, 5.0° for quaternions and 5.0° for torsions. Cluster tolerance 0.5Ao, external grid energy 1,000.0, and max initial energy 0.0, max number of retries 10,000 and 10 LGA runs was performed. The best ligand-receptor structure from the docked structures was chosen based on the lowest energy and minimal solvent accessibility of the ligand.

The binding energy of natural antioxidant compounds from *Murrayakoenigii* (O-methylmahanine and O-methylmurrayamine A) and synthetic antioxidantcompound (butylatedhydroxytoluene) and SOD1 are shown in fig 5(a), 6(a) and 7(a) respectively. The interaction between protein and ligand is visualized using AutoDock is shown in fig 5(b), 6(b) and 7(b). The hydrogen bond interaction between protein and ligand using pyMol is shown in fig 5(c), 6(c) and 7(c). Distance of hydrogen bond between donor and acceptor is shows in Table 5, 6 and 7 respectively.

Table.1 The Ligand (promoter) molecules used for docking studies from *Murraya koenigii*

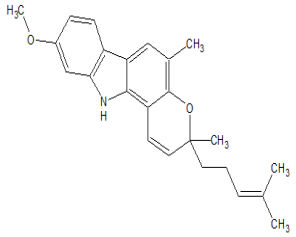
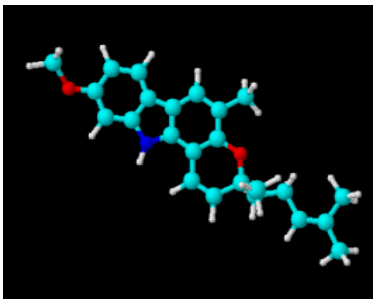
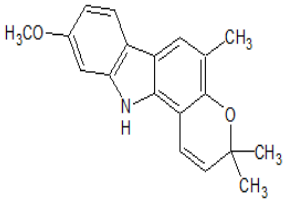
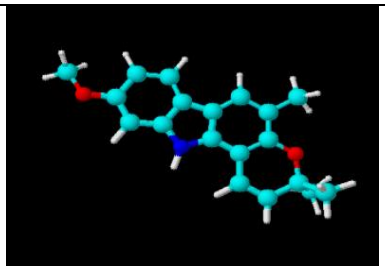
s.no.	Compounds	Molecular formula	2D structure	3D structure
1.	**O-methyl mahanine**	$C_{24}H_{27}NO_2$		
2.	**O-methyl murrayamine A**	$C_{19}H_{19}NO_2$		

Table.2 The synthetic Ligand molecule used for docking studies

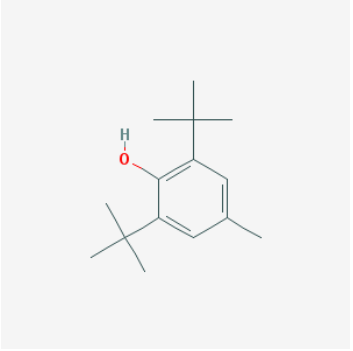
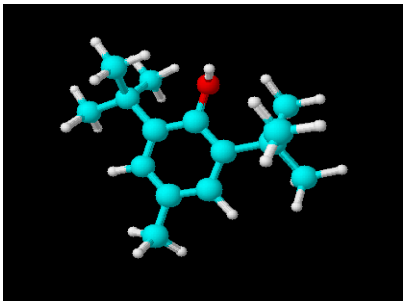
s.no.	Compounds	Molecular formula	2D structure	3D structure
1.	**Butylatedhydroxytoluene**	$C_{15}H_{24}O$		

Table.3 Lipinski's properties of the compounds of *Murraya koenigii*

Ligand molecule	Molecular weight	Xlogp3 value(<=5)	H-bond donor	H-bond acceptor
O-methylmahanine	361.476 g/mol	6.6	1	1
O-methylmurrayamine A	293.359 g/mol	4.6	2	2

Table.4 Lipinski's properties of the synthetic antioxidant compound

Ligand molecule	Molecular weight	Xlogp3 value(<=5)	H-bond donor	H-bond acceptor
Butylatedhydroxytoluene	220.350 g/mol	5.3	1	1

Table.5 The docking interaction between SOD1 and O-methylmahanine

SOD1		**O-methylmahanine**	**Distance**	**Binding energy**
Residue	**atom**	**O**	**3.2**	**-6.61**
THR-88	**N**			

Table.6 The docking interaction between SOD1 and o-methylmurrayamine

SOD1		**O-methylmurrayamine**	**Distance**	**Binding energy**
Residue	**atom**	**O**	**2.9**	**-6.69**
LYS-23	**NZ**			

Table.7 The docking interaction between SOD1 and o-methylmurrayamine

SOD1		**Butylatedhydroxytoluene**	**Distance**	**Binding energy**
Residue	**atom**	**H**	**1.9**	**-4.56**
ASN-86	**O**			

Table.8 The mode of binding interactions of the ligands with the Superoxide dismutase 1

Ligands	**Number of Hydrogen Bonds**	**Amino acid and atoms involved in Hydrogen bond interaction**	**Binding Energy (Kcal/mol)**
O-methylmahanine	1	THR-88 (N)	-6.61
O-methylmurrayamine A	1	LYS-23 (NZ)	-6.69
Butylatedhydroxytoluene	1	ASN-86 (O)	-4.56

Fig.1 Mechanism of oxidative stress caused by free radicals

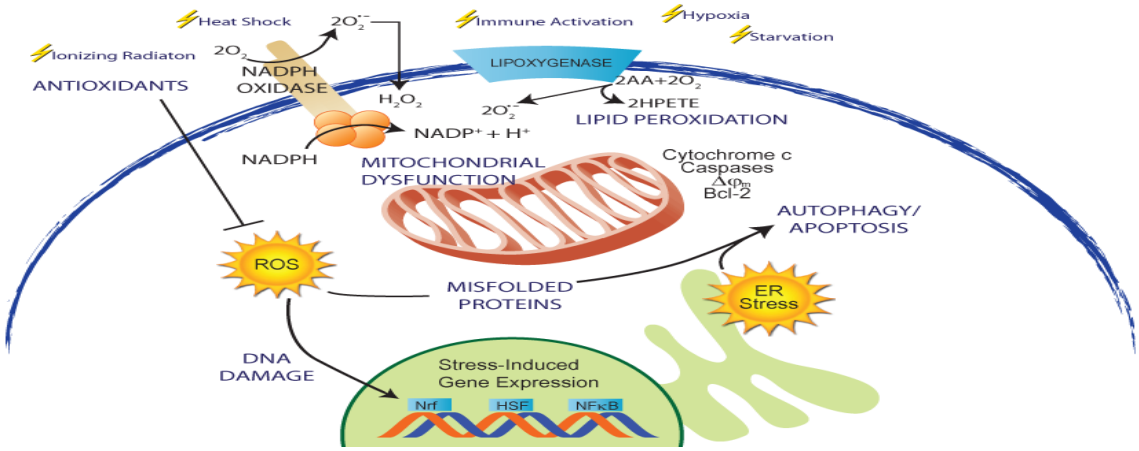


Fig.2 Representation of antioxidant activity

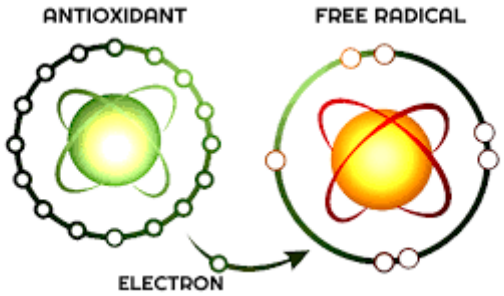


Fig.3 *Murraya koenigii* (curry leaves)

Fig.4 Crystal Structure of superoxide dismutase 1

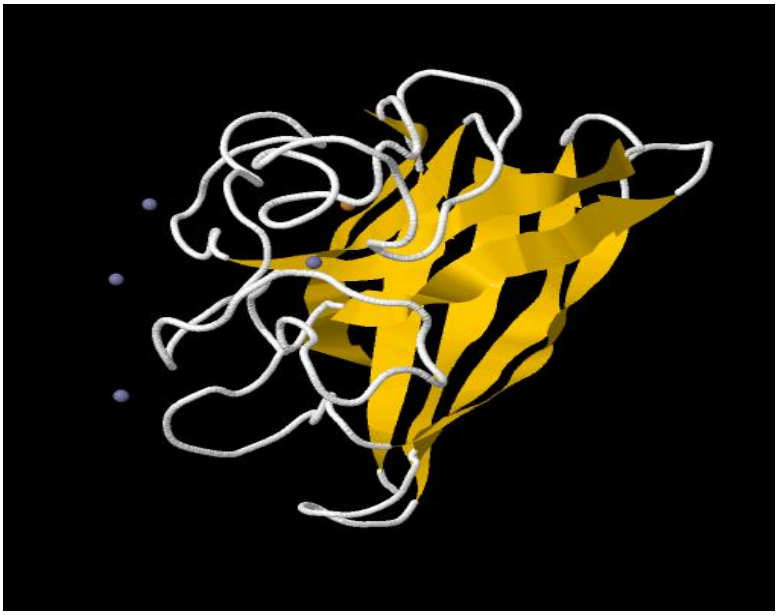
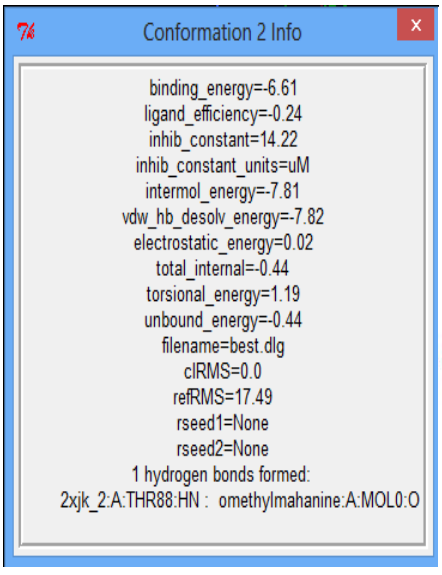
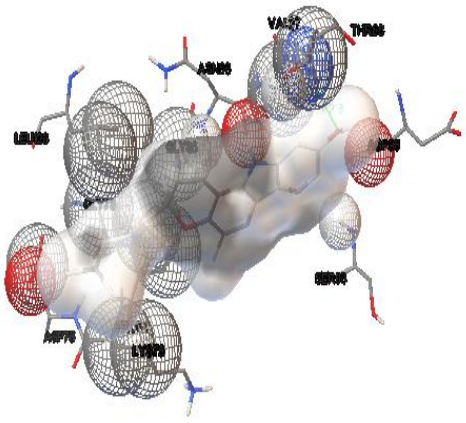
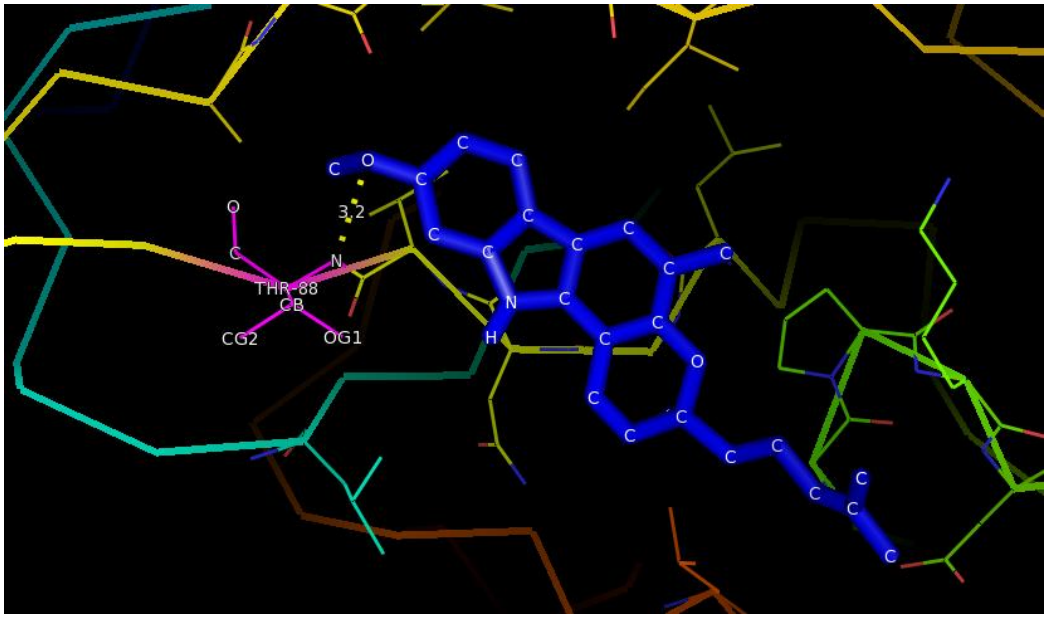


Fig 5 Docking of 2xjk with O-methylmahanine (a)Binding energy score(b)Interaction between SOD1 and O-methylmahanine is visualized using AutoDock (c)Hydrogen bond interactionsbetween SOD1 and O-methylmahanine is visualized using PyMol. The protein shown in magenta color is represented using wireframe model and ligand molecule shown in blue color is represented using stick model.The hydrogen bond interaction is mentioned as yellow dotted line.



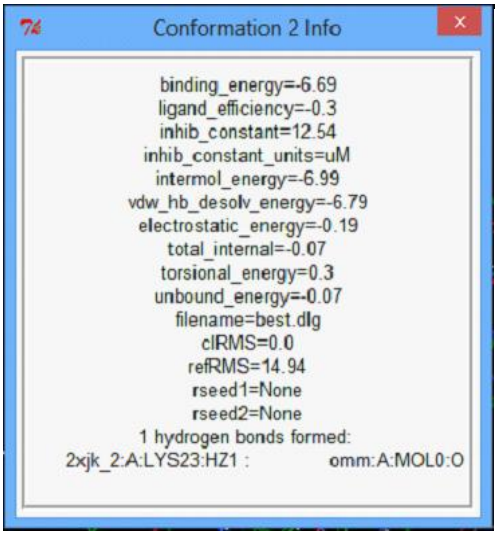


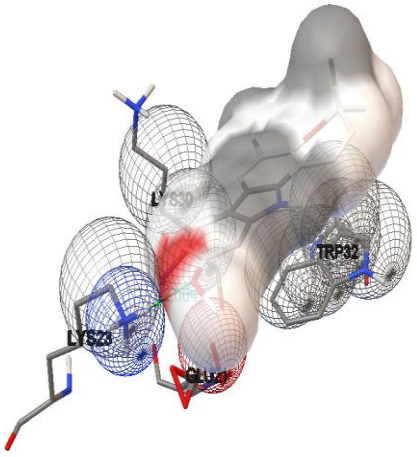
(a) (b)



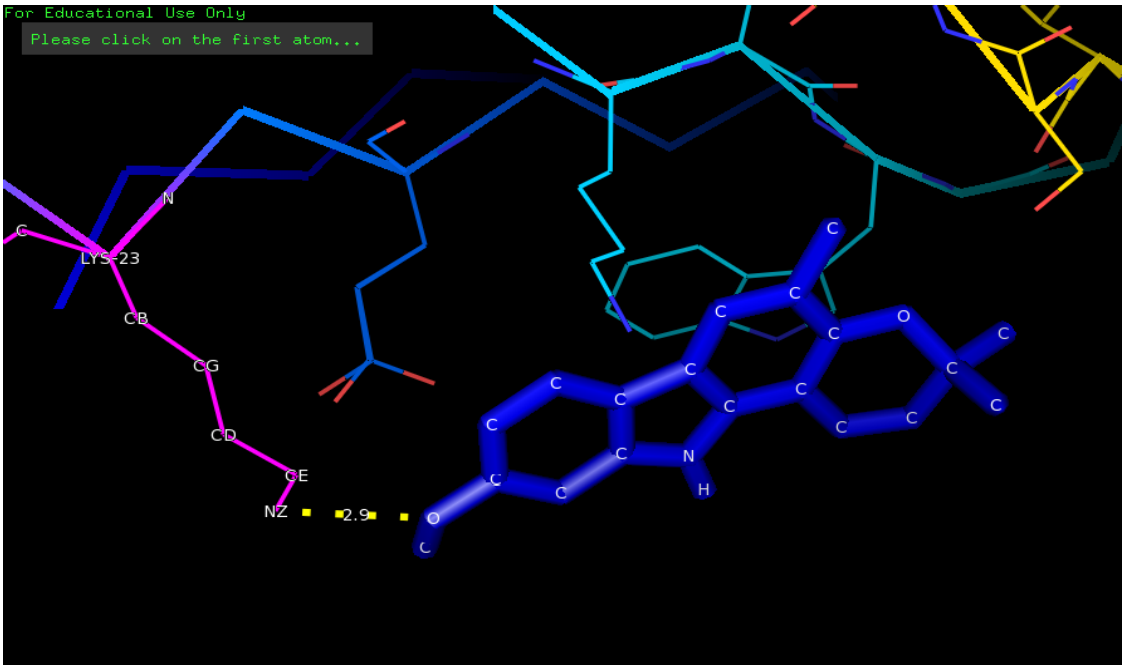
(c)

Fig.6 Docking of 2xjk with O-methylmurrayamine A (a)Binding energy score(b)Interaction between SOD1 and O-methylmurrayamine is visualized using AutoDock (c)Hydrogen bond interactionsbetween SOD1 and O-methylmurrayamine is visualized using PyMol.The protein shown in magenta color is represented using wireframe model and ligand molecule shown in blue color is represented using stick model. The hydrogen bond interaction is mentioned as yellow dotted line.



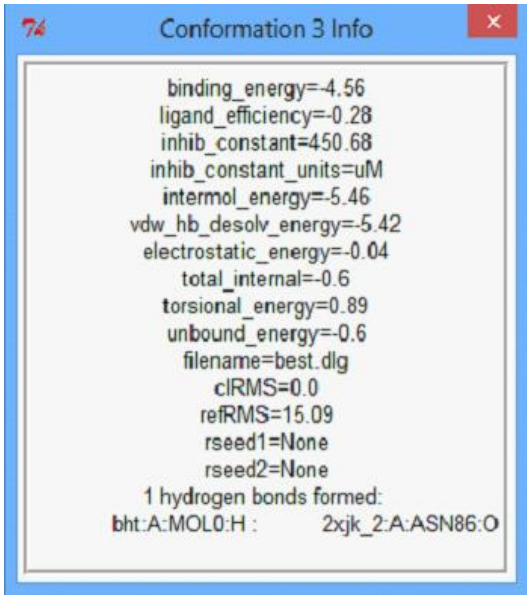


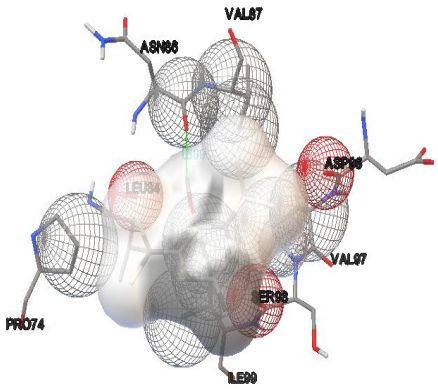
(a) **(b)**



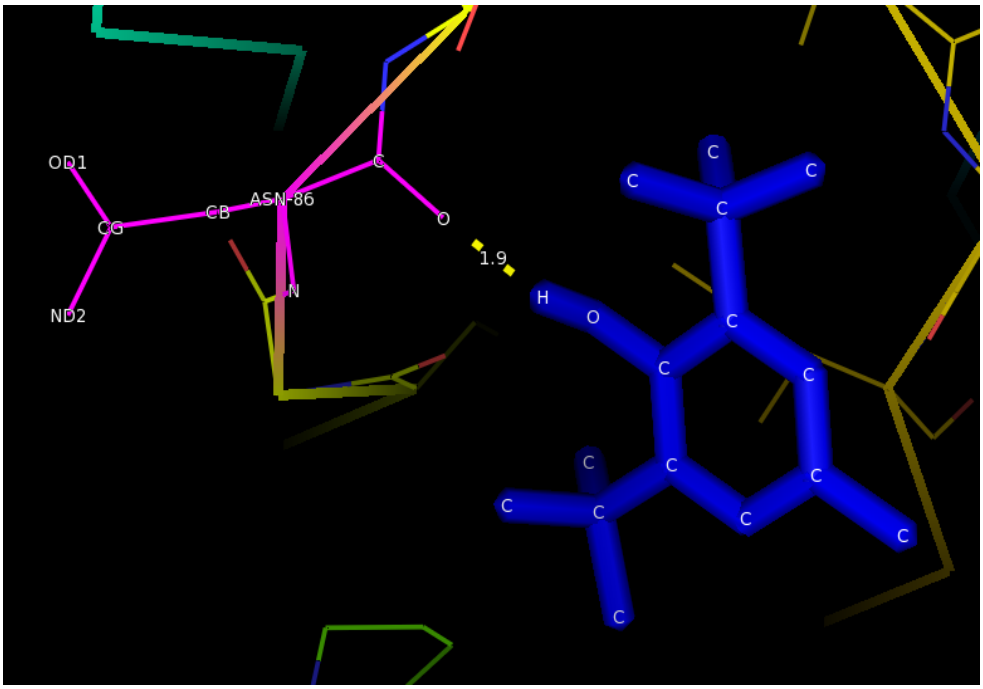
(c)

Fig.7 Docking of 2xjk with butylatedhydroxytoluene (a)Binding energy score(b)Interaction between SOD1 and butylatedhydroxytoluene is visualized using AutoDock (c)Hydrogen bond interactionsbetween SOD1 and butylatedhydroxytoluene is visualized using PyMol. The protein shown in magenta color is represented using wireframe model and ligand molecule shown in blue color is represented using stick model. The hydrogen bond interaction is mentioned as yellow dotted line.





(a) **(b)**



(c)

SOD1, the macromolecule and the natural antioxidant ligands from *Murrayakoenigii* (O-methylmahanine and O-methylmurrayamine A) and synthetic antioxidant ligand molecule (butylated-hydroxytoluene) were docked using AutoDock 4.2. Thebinding energy of compounds with the SOD1 during docking along with ten conformations was generated. Hydrogen bond interactions and the distance between the donors and acceptors were measured for the best conformers (Archana *et al*., 2010). The Binding energy is correlated with the probability of affinity and stable bound between ligand and its receptor. Binding energy values may also predict the bioactivity value for a ligand to the corresponding receptor (Kartasasmita *et al*., 2009). O-methylmahanine(-6.61Kcal/Mol), O-methylmurrayamine A (-6.69Kcal/Mol), and butylated-hydroxytoluene (-4.56Kcal/Mol). The mode of binding interactions of the ligands with the Superoxide dismutase 1 in relation to its crystal structure was explained in table 8.

From this study, we conclude that the activity of superoxide dismutase 1 is enhanced by both natural antioxidant compounds from *Murrayakoenigii* (O-methylmurrayamine A & O-methyl-mahanine) and synthetic antioxidant compounds (butylatedhydroxytoluene) through their binding to the allosteric site of the SOD1. This binding interaction was calculated by using the AutoDock software. Insilco docking studies of both natural antioxidants such as O-methylmurrayamine A & O-methylmahanine and synthetic antioxidant, namelybutylatedhydroxytoluene (BHT) was performed. The results indicated that in o-methylmurrayamine and O-methylmahanine the binding energies and hydrogen bond formation were stronger than in the synthetic antioxidant Butylated-Hydroxytoluene (BHT). Thus, we conclude that natural antioxidants such as o-methylmurrayamine A and O-methylmahanine could be used as potent natural therapeutic agents to combat oxidative stress.

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How to cite this article:

Victoriya Salomi M., R. Aishwarya and Saranya N. 2016. Comparative In-Silico Docking Analysis of SOD1 against Natural Synthetic Antioxidant. *Int.J.Curr.Res.Aca.Rev.* Special Issue-3: 134-147.