ISSN: 2161-1009
Biochemistry & Analytical Biochemistry

OPEN ACCESS Freely available online

Research Article

Microtubule and Adrenaline Interaction: A Key Source to Understand Conscious Balance in a Human Body

Pushpa Sahni*, Sonam

Department of Chemistry, Dayalbagh Educational Institute, Agra, India

ABSTRACT

Microtubules are present in our whole body. Microtubules are regulated by microtubule-associated protein. Microtubules exhibit dynamic instability, an intrinsic behavior characterized by alternating phases of growth, shortening, and pausing. Among the many functions postulated for microtubules, it has frequently been suggested that they play an important role in hormone release. Microtubules are also reported to play an important role in learning, memory and consciousness. The question arises whether a hormone, adrenaline can awake an unconscious person. Adrenaline, also known as epinephrine, is released mainly through the activation of nerves connected to the adrenal glands, which trigger the secretion of adrenaline and thus increase the levels of adrenaline in the blood. There is a relatively small epinephrine neurotransmitter system within the brain. It is also reported that Adrenaline acts on the brain to modulate brain activity and memory. Studies on oxidative stress showed that it has direct link with microtubule assembly and disassembly and it also affects cognitive behaviour. Adrenaline also controls oxidative stress. It becomes interesting and imperative to find out how adrenaline controls oxidative stress and microtubule organization. Oxidative stress decreases microtubule growth. Microtubules play an important role in hormone release. Keeping microtubule a key component, the present study focusses on the docking of adrenaline into Microtubule Associated Proteins (MAPs), alpha and beta tubulin and microtubules. Various computer simulation methods viz. PyMOL, ArgusLab, AutoDock, AutoDock Vina and Discovery Studio Visualizer have been used in the present study to understand the structure, conformation, stability, binding energy and potential energy of protein and its interaction with various ligands. Adrenaline docked successfully into Microtubule Associated Proteins (MAPs), alpha and beta tubulin and microtubules. The present study also led to an interesting observation that Microtubules stability increased when Adrenaline docked into Microtubules. From the present docking study it is hypothesized that Microtubules and Adrenaline together control brain activity and help to maintain the conscious state of the being at physical level.

Keywords: Microtubule; MAPs; Adrenaline; Molecular docking; Alpha and beta tubulin

INTRODUCTION

The development of the Central Nervous System (CNS) and wiring of the brain is an extremely complex process, controlled by the communication and careful coordination of the neuronal cytoskeleton, comprised of Microtubule (MT), actin and intermediate filament networks [1-3]. The dynamic microtubules play pivotal roles in creating cell polarity, as well as aiding in neural migration in order to establish appropriate neural connectivity throughout development. The elaborate MT network is integral to facilitate numerous morphological and functional processes during neurodevelopment, including cell proliferation, differentiation and migration, as well as accurate axon guidance and dendrite arborisation. The organization and remodeling of the MT network is also essential for developing neurons to form axons, dendrites and assembles synapses [4,5].

Microtubules are the Dimers of α- and β-tubulin polymerize to form microtubules, which are composed of 13 protofilaments assembled around a hollow core [6]. Tubulin dimers can depolymerize as well as polymerize, and microtubules can undergo rapid cycles of assembly and disassembly. Both α- and β-tubulin bind GTP,

Correspondence to: Pushpa Sahni, Department of Chemistry, Dayalbagh Educational Institute, Agra, India, E-mail: deipushpasahni@gmail.com

Received: 21-Jun-2024, Manuscript No. BABCR-24-26072; **Editor assigned:** 24-Jun-2024, Pre QC No. BABCR-24-26072 (PQ); **Reviewed:** 10-Jul-2024, QC No. BABCR-24-26072; **Revised:** 17-Jul-2024, Manuscript No. BABCR-24-26072 (R); **Published:** 26-Jul-2024, DOI: 10.35248/2161-1009.24.13.538

Citation: Sahni P., Sonam (2024) Microtubule and Adrenaline interaction: A Key Source to Understand Conscious Balance in a Human Body. Biochem Anal Biochem. 13:538.

which functions analogously to the ATP bound to actin to regulate polymerization. In particular, the GTP bound to β-tubulin (though not that bound to α-tubulin) is hydrolyzed to GDP during or shortly after polymerization. The Microtubule Associated Proteins (MAPs) have been found to have an additional property that has received considerable attention. Walker, et al. studied the dynamic instability of individual microtubules (MAP-tau, MAP-2 and the fractioned heat-stable MAPs) [7]. A model was also proposed to explain how MAP-2 and MAP- tau bind to the microtubule lattice at sites along protofilaments so that the MAPs promote polymerization. Rapid shortening, when it occurs, proceeds primarily by the dissociation of short fragments of protofilaments, which contain the bound MAPs. In the absence of the MAPs, tubulin assembles poorly, if at all, under most *in vitro* conditions. The MAPs dramatically promote the assembly of tubulin into microtubules [8].

Recent research also reports that adrenaline plays a significant role in microtubule organization. Adrenaline is released by the sympathetic nervous system and adrenal medulla and is involved in several physiological functions including regulation of blood pressure, vasoconstriction, cardiac stimulation, and regulation of the blood glucose levels [9,10]. Noradrenaline is mainly produced by neurons within the locus coeruleus and takes part in diverse motor and mental functions including locomotion control, motivation, attention, and cognition and memory formation [11]. It also regulates the differentiation, plasticity, and survival of neurons in both developing and adult brains. In addition it seems that locus coeruleus-noradrenaline system plays a significant role in compensatory mechanisms responding to acute brain injuries, and in defining the progression of neurodegenerative disorders such as Parkinson's and Alzheimer's disease [9,10]. Changes in synaptic strength are believed to underlie learning and memory. Researchers also explored that norepinephrine is an essential modulator of memory through its ability to regulate synaptic mechanisms. Emotional arousal leads to activation of the locus coeruleus with the subsequent release of norepinephrine in the brain, resulting in the enhancement of memory. Norepinephrine activates both pre- and post-synaptic adrenergic receptors at central synapses. A research review also reflects the evidence for noradrenergic modulation of synaptic plasticity with consideration of how this may contribute to the mechanisms of learning and memory.

Recent studies have also shown that microtubule organization also depends upon the conformation of protein [12-14]. The secondary structure of tubulin heterodimer and also the interaction between microtubules and propofol was studied with the help of circular dichroism spectroscopy and time resolved fluorescence spectroscopy which suggested major changes in its overall conformation [13,14]. It is inferred that binding of anesthetics to tubulin protein causes an alteration in secondary structure. Also, kinetics studies are carried out with the help of Eon spectrophotometer to optimize the reaction conditions, which shows that propofol strongly affects the polymerization of tubulin and self-organization of microtubules [13]. Recent research study also focused on among the many functions postulated for microtubules so far, it also plays an important role in hormone release [15]. Research workers in their study have also shown that hormone like epinephrine act on memory [16].

Adrenaline also has an anabolic effect on the enhancement of protein synthesis and inhibition of protein degradation [9,17]. The potential role of neurotransmitters adrenaline and noradrenaline on oxidative stress related processes were investigated considering different aspects of their reactivity, including their peroxyl radical scavenging activity, their Cu (II) sequestering ability, and their possible regeneration [18]. Density functional theory was used to investigate the potential role of neurotransmitters adrenaline and noradrenaline regarding oxidative stress. It is predicted that they can be efficient as free radical scavengers both in lipid and aqueous media, with the main reaction mechanism being the hydrogen transfer and the sequential proton loss electron transfer, respectively. Also, adrenaline and noradrenaline can be considered as both protectors and molecular targets of oxidative stress. From a chemistry point of view oxidative stress is a chemical imbalance between the production and consumption of oxidants, particularly free radicals. Researchers have shown that there is a direct link between oxidative stress and MT dynamics [19]. Under physiological conditions, microtubule growth is directionally biased and the increased production of reactive oxygen species disrupts MT dynamics thereby decreasing K^+ channel trafficking. Besides many health disorder caused by oxidative stress, oxidative stress has also been reported to be involved in several neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, memory loss, and depression [19]. Oxidative stress can be associated with chemical changes in essential biomolecules including lipids, proteins, DNA, enzymes, and neurotransmitters, etc. Thus, the present study is in the continuation of the work done on the effect of propofol (an anesthetic) on microtubules [13,14,20,21]. Protein-ligand docking approach can be used to understand the conformational difference between the unbound and the bound structure [22]. It can become the basis of protein's function in its interaction with other ligands and also the protein's flexible topology. In order to have a visual understanding of the interacting site and binding stability, it is presently focusing on the docking interaction of microtubules, MAPs, alpha and beta tubulin with adrenaline to understand the underlying link between microtubule, Microtubule Associated Proteins (MAPs), Adrenaline and memory.

METHODOLOGY

The present study included protein-ligand interaction and was carried out using ArgusLab, Discovery Studio Visualizer, PyMol, Autogrid and AutoDock vina simulation methods. Standard protocols were followed for the present docking study [23-33].

RESULTS AND DISCUSSION

Microtubules and adrenaline interaction

The 3D structure of Microtubules was visualized with the help of Discovery studio visualizer which shows the presence of alpha and beta-chain (Figure 1a). Adrenaline has been a key component of advanced life support algorithms for many years. With the help of various docking software, docking of Adrenaline with microtubules helped in studying the interaction between them and also helped in analyzing the binding energy and binding site of microtubules when adrenaline docked into microtubules. The 3D-structure of Adrenaline has a benzene ring in which two hydroxyl (OH) groups, a methyl (CH_3) group and an amine group attached to this methyl group (Figure 1b). Docking of Microtubule with ligand (adrenaline) was carried out with AutoDock Vina and Argus Lab. Adrenaline docked into Microtubules successfully with the help of AutoDock Vina. During the docking adrenaline binds with different binding site of Microtubules and change its conformation. AutoDock Vina gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. In the first pose

the binding affinity is -7.5 kcal/mol, whereas in the second pose it is -7.0. -7.5 kcal/mol is lower than the -7.0, it is inferred that it has high stability than -7.0. However, there is small change in energy.

The visualization of docking of adrenaline with microtubules was also done using discovery studio visualizer (Figure 1c). Adrenaline docked into microtubules successfully with the help of AutoDock. During the docking adrenaline bind with different binding sites of microtubules or change its conformation. AutoDock gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. In the first pose the binding affinity is -6.07 kcal/mol, whereas in the second pose it is -5.70 kcal/mol. -6.07 kcal/mol is lower than the -5.70, it is inferred that it has high stability than -5.70 kcal/mol. however there is small change in energy. Lowest Binding energy is -6.07 kcal/mol (Table 1).

Docking of microtubules and adrenaline with Arguslab

Adrenaline docked into Microtubules successfully with the help of Arguslab. During the docking adrenaline bind with different binding site of Microtubules or change its conformation. Arguslab gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. In the first pose the binding affinity is -5.25 kcal/mol, whereas in the second pose it is -5.0 kcal/mol. -5.25 kcal/mol is lower than the -5.0, it is inferred that it has high stability than -5.0 kcla/mol. however there is small change in energy. Adrenaline successfully docked with Microtubule. Below is a snapshot taken from ArgusLab after docking. Binding energy is (-5.25 kcal/mol) (Figure 1d). The best two conformations have been taken into consideration, which showed the change in energy and all energy changes occurred due to change in conformations (Figure 2).

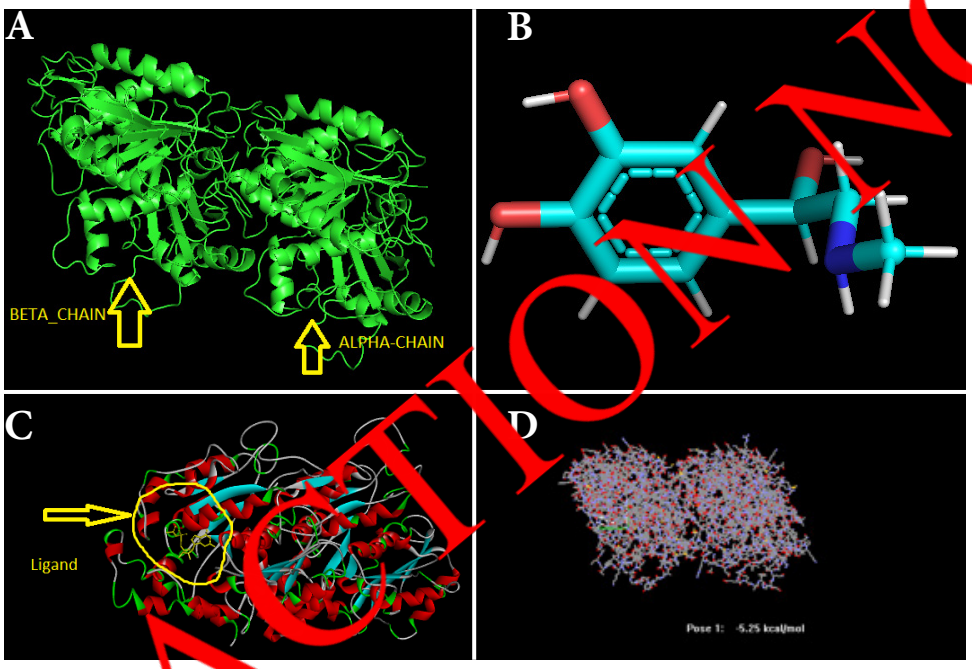
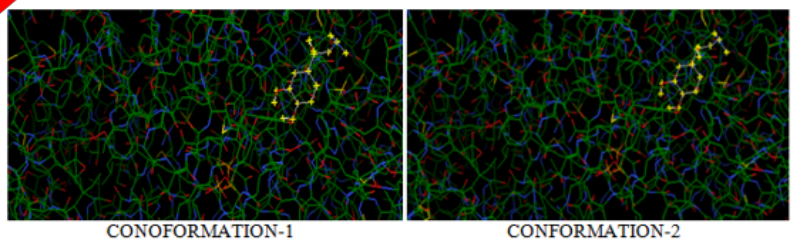


Figure 1: (a) 3D structure of Microtubules; (b) 3D structure of Adrenaline; (c) Interaction analysis using discovery studio visualizer; (d) Adrenaline and Microtubulin docking result using ArgusLab.



CONOFORMATION-1 CONFORMATION-2

Binding Energy	-6.07
kd	35.51 uM
Intermolecular Energy	-7.86
Internal Energy	-0.79
Torsional Energy	1.79
Unbound Extended Energy	-0.79
Cluster RMS	0.0
Ref RMS	80.67

Binding Energy	-4.94
kd	240.9 uM
Intermolecular Energy	-6.73
Internal Energy	-2.1
Torsional Energy	1.79
Unbound Extended Energy	-2.1
Cluster RMS	0.0
Ref RMS	91.1

Figure 2: Conformations after docking with lowest binding energy. **Note:** (a) Energies during first conformation; (b) Energies during second conformation.

Table 1: Adrenaline and microtubulin docking energies using AutoDock Vina.

Rank	Sub-rank	Run	Binding energy	Cluster RMSD	Reference RMSD	Green pattern
1	1	6	-6.07	0.00	80.67	RANKING
1	2	8	-5.70	0.74	80.78	RANKING
2	1	10	-4.94	0.00	91.10	RANKING
3	1	7	-4.93	0.00	59.98	RANKING
4	1	1	-4.76	0.00	88.35	RANKING
4	2	2	-4.56	0.46	88.33	RANKING
5	1	5	-4.73	0.00	98.20	RANKING
6	1	3	-4.44	0.00	96.16	RANKING
7	1	4	-4.14	0.00	54.02	RANKING
8	1	9	-3.44	0.00	82.65	RANKING

Alpha-Tubulin and adrenaline interaction

α/β heterodimers polymerize into microtubules, which are indispensable for cell division and growth. The expression of specific isotypes of tubulin is associated with cancer, but the molecular mechanisms behind this effect are still largely unknown. The figure below (Figure 3a), is the 3-D structure of Alpha-Tubulin visualized with the help of discovery studio.

Arguslab docking result: Adrenaline docked into Alpha-Tubulin at different site successfully with the help of Arguslab. During the docking adrenaline bind with different binding site of Alpha-Tubulin and change its conformation. Arguslab gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. In the first pose the binding affinity is -8.5 kcal/mol, whereas in the second pose it is -7.6 kcal/mol. The first conformation with binding energy -8.5 kcal/mol is stable than the second conformation, however there is small change in energy (Figure 3b).

AutoDock Vina docking result: Adrenaline docked into Alpha-Tubulin successfully with the help of AutoDock Vina. During the docking adrenaline bind with different binding site of Alpha-Tubulin or change its conformation. AutoDock Vina gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. In the first pose the binding affinity is -5.6 kcal/mol, whereas in the second pose it is -5.5 kcal/mol. -5.6 kcal/mol is lower than the- 5.5, it is inferred that it has high stability than -5.5 kcal/mol. However there is very small change in energy. The Figure 3c, below showed the resultant interaction of adrenaline with alpha tubulin and this interaction are visualized using Pymol.

AutoDock docking result: Adrenaline docked into Alpha-Tubulin successfully with the help of AutoDock. During the docking adrenaline bind with different binding site of Alpha-Tubulin or change its conformation. AutoDock gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. In the first pose the binding affinity is -4.27 kcal/mol, whereas in the second pose it is -3.46 kcal/mol. -4.27 kcal/mol is lower than the -3.46 kcal/mol, it is inferred that it has high stability than -3.46 kcal/mol. however there is small change in energy. These are the binding energies of Adrenaline interaction with Alpha-Tubulin using AutoDock (Table 2). The best two conformations have been taken into consideration, which showed the change in energy and showed all changes occurred due to change in conformations (Figure 4).

Beta-Tubulin and adrenaline interaction

βTubulin, the protein to which all clinical agents that disrupt microtubules bind, is encoded by multiple genes and represented by several pseudo genes. At least seven different β-tubulins isotypes (classes I–VII) are differentially expressed in human cells. All drugs that are known to bind to human tubulin bind to β-tubulin. Beta-Tubulin is encoded in vertebrate genomes by a family of six to seven functional genes that produce six different polypeptide isotypes. Figure 5a, is the 3D structure of Beta-Tubulin visualized using Discovery studio visualizer.

AutoDock Vina docking result: Adrenaline docked into Beta-Tubulin successfully with the help of AutoDock Vina. During the docking adrenaline bind with different binding site of beta-Tubulin. AutoDock Vina gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. In the first pose the binding affinity is -6.2 kcal/mol, whereas in the second pose it is -6.1 kcal/mol. -6.2 kcal/mol is lower than the -6.1 kcal/mol, it is inferred that it has high stability than -6.1 kcal/mol. however there is small change in energy.

Arguslab docking result: Adrenaline docked into Beta-Tubulin successfully with the help of Arguslab. During the docking adrenaline bind with different binding site of Beta-Tubulin or change its conformation. Arguslab gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. In the first pose the binding affinity is -7.66 kcal/mol, whereas in the second pose it is -7.59 kcal/mol. -7.66 kcal/mol is lower than the -7.95 kcal/mol, it is inferred that it has high stability than -7.95 kcal/mol. however there is small change in energy (Figure 5b).

AutoDock docking result: Adrenaline docked into Beta-Tubulin successfully with the help of AutoDock. During the docking adrenaline bind with different binding site of Beta-Tubulin or

change its conformation. AutoDock gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. In the first pose the binding affinity is -6.25 kcal/mol, whereas in the second pose it is -5.95 kcal/mol. -6.25 kcal/mol is lower than the -5.95 kcal/mol, it is inferred that it has high stability than -5.95 kcla/mol. however there is small change in energy.

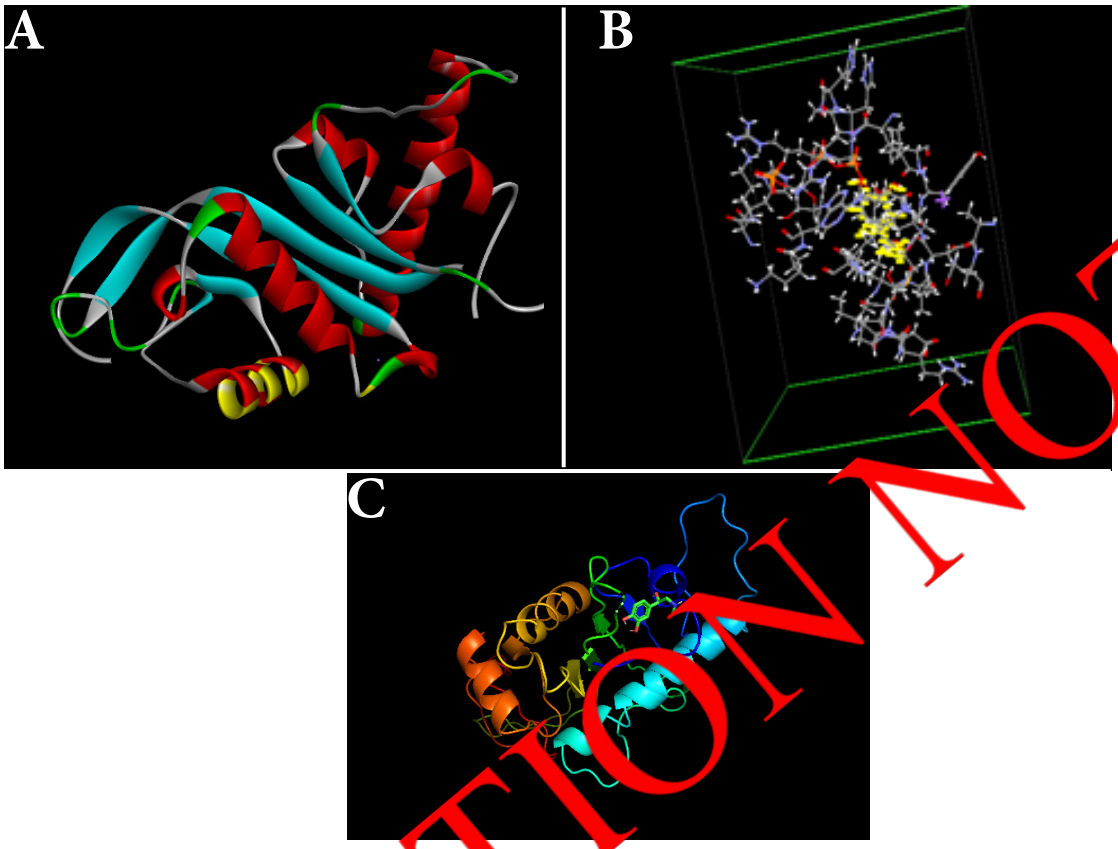
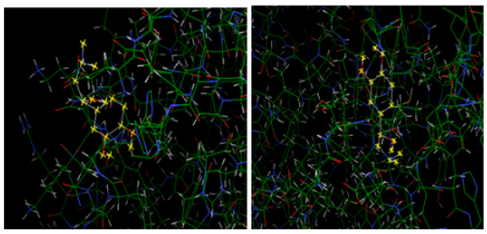


Figure 3: (a) 3-D Structure of alpha-tubulin; (b) Interaction of alpha-tubulin with adrenaline; (c) Interaction of alpha-tubulin with adrenaline.

Table 2: Binding energies of alpha-tubulin interaction with adrenaline.

Rank	Sub-rank	Run	Binding energy	Cluster RMSD	Reference RMSD
1	1	9	-4.27	0.00	18.28
1	2	8	-3.46	1.20	18.28
2	1	5	-4.18	0.00	21.30
3	2	1	-3.72	1.24	21.99
3	1	7	-3.71	0.00	19.43
3	2	3	-3.66	1.15	19.92
3	3	10	-3.53	1.85	20.32
3	4	4	-3.51	0.56	19.44
3	5	2	-3.51	0.68	19.16
4	1	6	-3.33	0.00	17.84



Con.-1

Binding Energy	-4.27
kd	737.21 uM
Intermolecular Energy	-6.06
Internal Energy	-1.6
Torsional Energy	1.79
Unbound Extended Energy	-1.6
Cluster RMS	0.0
Ref RMS	18.28

Con.-2

Binding Energy	-3.46
kd	2.9 mM
Intermolecular Energy	-5.25
Internal Energy	-1.93
Torsional Energy	1.79
Unbound Extended Energy	-1.93
Cluster RMS	1.2
Ref RMS	18.28

Figure 4: Conformations after docking with lowest binding energy. **Note:** (a) Energies during first conformation; (b) Energies during second conformation.

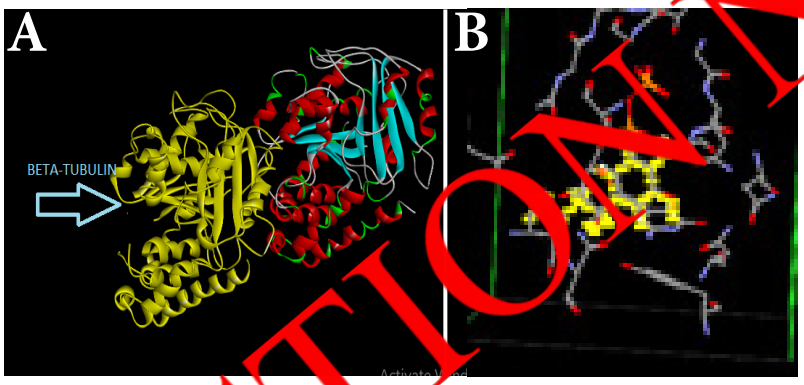


Figure 5: (a) 3D-Structure of beta-tubulin; (b) Interaction of beta-tubulin with adrenaline using Arguslab.

Binding energies of interaction of Beta-Tubulin with adrenaline using AutoDock

The two best conformations have been taken into consideration, which showed the change in energy and showed all changes occurred due to change in conformation (Table 3, Figure 6).

MAP 2 protein and adrenaline interaction

Microtubules are known to play a role in a wide variety of cellular processes. The major component of these structures is tubulin, a globular protein that makes up the microtubule wall. Microtubules contain a number of proteins in addition to tubulin [1-3,34]. These proteins have been referred to by the acronym MAPs, or microtubule-associated proteins [34]. MAP would be any protein that has a specific binding site for microtubules. The MAPs have been found to have an additional property that has received considerable attention. In the absence of the MAPs, tubulin assembles poorly, if at all, under most *in vitro* conditions. The MAPs dramatically promote the assembly of tubulin into micro tubules [2,3].

MAP2 serves to stabilize MT growth by crosslinking MT with intermediate filaments and other MTs. MAP2 isoforms are neuron-specific cytoskeletal proteins enriched in dendrites and perikarya, implicating a role in determining and stabilizing neuronal morphology during neuron development.

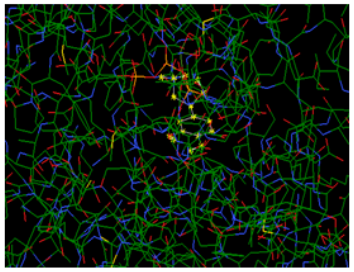
The Figure below (Figure 7a), is the 3D-Structure of MAP2 protein visualized using discovery studio visualizer.

Arguslab docking result: Adrenaline docked into MAP2 successfully with the help of Arguslab. During the docking adrenaline bind with different binding site of MAP2 or change its conformation. Arguslab gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. In the first pose the binding affinity is -6.03 kcal/mol, whereas in the second pose it is -5.97 kcal/mol. -6.03 kcal/mol is lower than the -5.97 kcal/mol, it is inferred that it has high stability than -5.97 kcal/mol. however there is small change in energy (Figure 7b).

AutoDock Vina docking result: Adrenaline docked into MAP2 successfully with the help of AutoDock Vina. During the docking adrenaline bind with different binding site of MAP2 or change its conformation. AutoDock Vina gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. In the first pose the binding affinity is -6.3 kcal/mol, whereas in the second pose it is -5.8 kcal/mol. -6.3 kcal/mol is lower than the -5.8 kcal/mol, it is inferred that it has high stability than -5.8 kcal/mol. However there is small change in energy. In the Figure (Figure 7c), below the resultant interaction MAP2 with Adrenaline was visualized using Pymol.

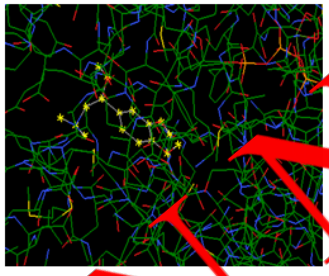
Table 3: Binding energies of interaction of beta-tubulin with adrenaline.

Rank	Sub-rank	Run	Binding energy	Cluster RMSD	Reference RMSD
1	1	2	-6.37	0.00	469.95
1	2	3	-5.80	1.58	469.34
2	1	4	-6.24	0.00	460.95
3	2	8	-5.97	1.62	460.36
3	1	10	-6.22	0.00	458.65
3	2	9	-6.03	1.06	458.88
3	3	1	-5.86	1.25	458.48
4	1	7	-5.68	0.00	459.56
5	1	5	-5.65	0.00	461.62
6	1	6	-5.40	0.00	461.25



CONFORMATION-1

Binding Energy	-6.37
kl	21.28 uM
Intermolecular Energy	-8.16
Internal Energy	-1.11
Torsional Energy	1.79
Unbound Extended Energy	-1.11
Cluster RMS	0.0
Ref RMS	469.95



	-5.8
	55.73 uM
Intermolecular	-7.59
Internal Energy	-1.45
Torsional Energy	1.79
Unbound Extended Energy	-1.45
Cluster RMS	1.58
Ref RMS	469.34

Figure 6: Conformations after docking with lowest binding ener **Note:** (a) Energies during first conformation; (b) Energies during second conformation.

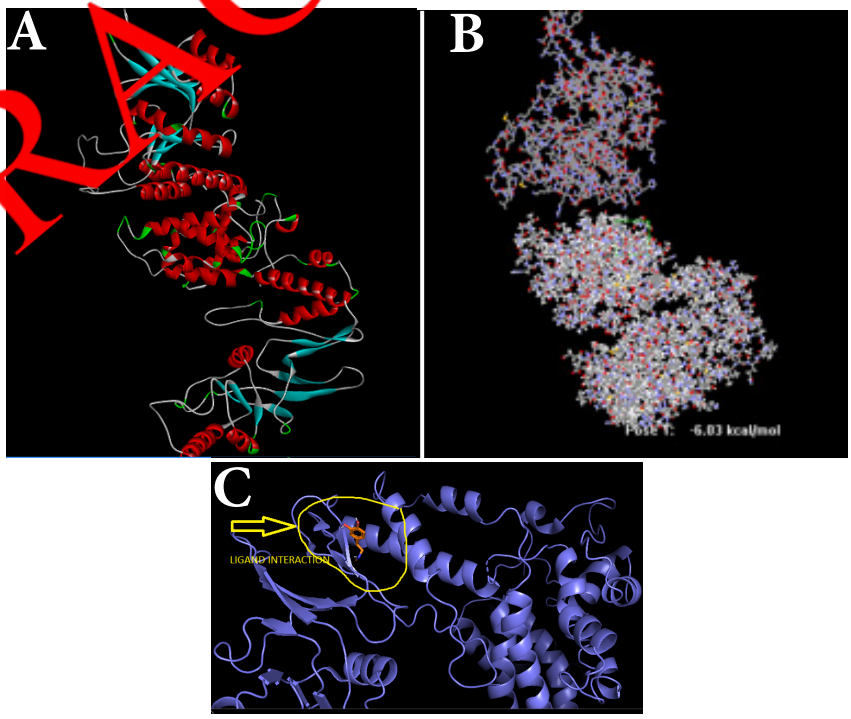


Figure 7: (a) 3-D Structure of MAP2 protein; (b) Binding energy of interaction of MAP2 protein with adrenaline; (c) MAP2 interaction with adrenaline.

AutoDock docking result: Adrenaline docked into MAP2 successfully with the help of AutoDock. During the docking adrenaline bind with different binding site of MAP2 or change its conformation. AutoDock gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. Docking with AutoDock gave the best possible conformations in which the first pose showed the binding affinity -5.66 kcal/mol, whereas in the second pose it is -5.63 kcal/mol. It is inferred that it has high stability than -5.63 kcal/mol. However there is small change in energy. These are the binding energy of interaction of MAP2 protein with Adrenaline using AutoDock (Table 4). The two best conformations have been taken into consideration, which showed the change in energy and showed all changes occurred due to change in conformations (Figure 8).

MAP-TAU protein and adrenaline interaction

The Tau proteins (abbreviated from tubulin associated unit) are a group of six highly soluble protein isoforms produced by alternative splicing from the gene MAPT (microtubule-associated protein tau).

They have roles primarily in maintaining the stability of microtubules in axons and are abundant in the neurons of the central nervous system. Microtubule-Associated Proteins (MAPs) of the MAP2/Tau family include the vertebrate proteins MAP2, MAP4, and Tau and homologs in other animals. All MAP2/Tau family proteins have microtubule-binding repeats near the carboxyl terminus, each containing a conserved KXGS motif that can be phosphorylated [8].

Tau proteins are found more often in neurons than in non-neuronal cells in humans. One of tau's main functions is to modulate the stability of axonal microtubules. Tau is a negative regulator of mRNA translation in both *Drosophila*, mouse, and human brains, through its binding to ribosomes, which results in impaired ribosomal function, reduction of protein synthesis and altered synaptic function. Tau interacts specifically with several ribosomal proteins, including the crucial regulator of translation rpS6.

The Figure below (Figure 9a), is the 3D-structure of MAP-TAU protein visualized using discovery studio visualizer.

Arguslab docking result: Adrenaline docked into MAP-TAU successfully with the help of Arguslab. Adrenaline docked at different site during the docking adrenaline bind with different binding site of MAP-TAU and change its conformation. Arguslab gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. In the first pose the binding affinity is -5.98 kcal/mol, whereas in the second pose it is -5.7 kcal/mol. -5.98 kcal/mol is lower than the -5.7 kcal/mol, it is inferred that it has high stability than -5.7 kcal/mol. However there is small change in energy. Interaction of MAP-TAU protein with adrenaline using Arguslab give the best binding energy -4.55 kcal/mol (Figure 9b).

AutoDock Vina result: Adrenaline docked into MAP-TAU successfully with the help of AutoDock Vina. During the docking adrenaline bind with different binding site of MAP-TAU or change its conformation. AutoDock Vina gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. In the first pose the binding affinity is -4.6 kcal/mol, whereas in the second pose it is -4.5 kcal/mol. -4.6 kcal/mol is lower than the -4.5 kcal/mol, it is inferred that it has high stability than -4.5 kcal/mol. however there is small change in energy. Docking result of Audodock Vina was visualized using PYMOL docking software. It showed the site where adrenaline bind with MAP-TAU protein (Figure 9c).

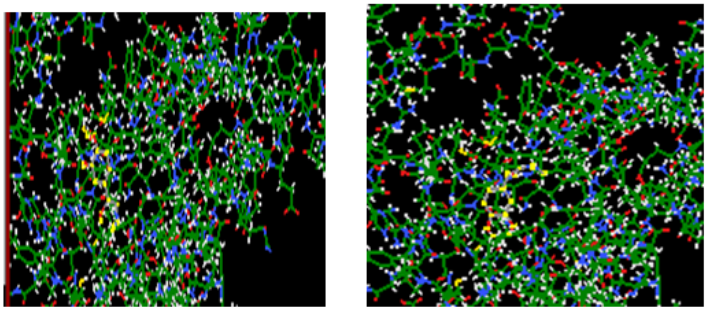
AutoDock result: Adrenaline docked into MAP-TAU successfully with the help of AutoDock. During the docking adrenaline bind with different binding site of MAP-TAU or change its conformation. AutoDock gave the best ten binding poses or conformations which have the lowest binding energy. It is inferred that with the minimum energy/affinity, protein structure is more stable. In the first pose the binding affinity is -4.77 kcal/mol, whereas in the second pose it is -4.74 kcal/mol. -4.77 kcal/mol is lower than the -4.74 kcal/mol, it is inferred that it has high stability than -4.74 kcal/mol. however there is small change in energy. These are the binding energy of interaction of MAP TAU protein with adrenaline using AutoDock (Table 5). The two best conformations have been taken into consideration, which showed the change in energy and showed all changes occurred due to change in conformations (Figure 10).

Above results are summarized into a tabular form with comparison showing different binding energy with different docking software (Table 6).

AutoDock Vina gave the lowest binding energies (great stability) of adrenaline with microtubules. Arguslab gave the lowest binding energies of adrenaline with Alpha-tubulin.

Table 4: Binding energy of interaction of MAP2 protein with adrenaline.

Rank	Sub-rank	Run	Binding energy	Cluster RMSD	Reference RMSD
1	1	3	-5.66	0.00	348.68
2	1	10	-5.63	0.00	349.02
2	2	9	-5.63	0.95	348.90
2	3	8	-5.45	1.23	348.93
2	4	5	-5.40	1.50	348.70
3	1	4	-5.26	0.00	347.31
3	2	6	-4.97	0.65	347.55
4	1	1	-5.24	0.00	348.73
4	2	7	-5.00	0.42	348.76
5	1	2	-5.11	0.00	348.69



CONFORMATION-1

Binding Energy	-5.66
kl	70.43 uM
Intermolecular Energy	-7.45
Internal Energy	-1.37
Torsional Energy	1.79
Unbound Extended Energy	-1.37
Cluster RMS	0.0
Ref RMS	348.68

CONFORMATION-2

Binding Energy	-5.63
kl	75.26 uM
Intermolecular Energy	-7.42
Internal Energy	-1.72
Torsional Energy	1.79
Unbound Extended Energy	-1.72
Cluster RMS	0.0
Ref RMS	349.02

Figure 8: Conformations after docking with lowest binding energy. **Note:** (a) Energies during first conformation; (b) Energies during second conformation.

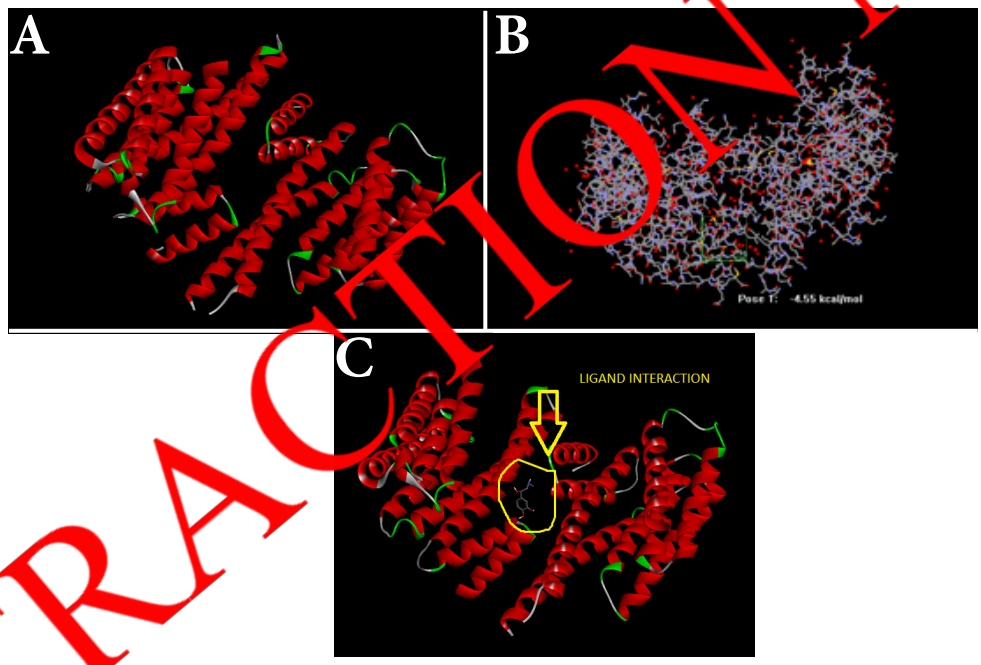
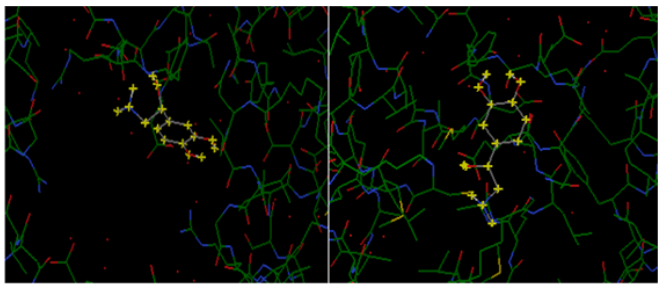


Figure 9: (a) 3D-Structure of MAP-TAU protein; (b) Interaction of MAP-TAU protein with adrenaline; (c) MAP-TAU interaction with adrenaline.

Table Binding energies of Map-Tau interaction with adrenaline.

Rank	Sub-rank	Run	Binding energy	Cluster RMSD	Reference RMSD
1	1	3	-4.77	0.00	76.81
1	2	4	-4.74	0.51	76.85
2	1	10	-4.22	0.00	81.24
3	1	5	-4.12	0.00	77.86
3	2	9	-3.71	1.17	78.62
4	1	6	-4.00	0.00	84.73
5	1	8	-3.92	0.00	82.45
6	1	1	-3.90	0.00	80.29
7	1	7	-3.86	0.00	77.37
8	1	2	-3.81	0.00	88.01



CONFORMATION1

Binding Energy	-4.77
kl	316.63 uM
Intermolecular Energy	-6.56
Internal Energy	-1.37
Torsional Energy	1.79
Unbound Extended Energy	-1.37
Cluster RMS	0.0
Ref RMS	76.81

CONFORMATION-2

Binding Energy	-4.77
kl	336.99 uM
Intermolecular Energy	-6.53
Internal Energy	-1.55
Torsional Energy	1.79
Unbound Extended Energy	-1.55
Cluster RMS	0.51
Ref RMS	76.81

Figure 10: Conformations after docking with lowest binding energy. **Note:** (a) Energies during first conformation; (b) Energies during second conformation.

Table 6: A comparative account of binding energies obtained after molecular docking using different docking software.

S.NO.	Protein+ligand	ArgusLab ("lowest binding energy in kcal/mol")	AutoDock ("lowest binding energy in kcal/mol")	AutoDock Vina ("lowest binding energy in kcal/mol")
1	Microtubules+adrenaline	-5.24	-6.07	-7.5
2	Alpha-tubulin+adrenaline	-8.5	-4.27	-5.6
3	Beta-tubulin+adrenaline	-7.65	-6.31	-6.2
4	MAP2+adrenaline	-6.08	-5.66	-6.3
5	MAP-TAU+adrenaline	-4.55	-4.77	-4.6

CONCLUSION

Microtubules are present in our whole body. Among the many functions postulated for microtubules, it has frequently been suggested that they play an important role in hormone release. Microtubules are also reported to play an important role in learning, memory and consciousness. Oxidative stress has a direct effect on microtubule organization. Adrenaline, also known as epinephrine acts on the brain to modulate brain activity, memory and microtubule organization. Various computer simulation methods *viz.* PyMOL, ArgusLab, AutoDock, AutoDock Vina and Discovery Studio Visualizer have been used in the present study to explore the structure, conformation, binding energy and potential energy of protein and its interaction with various ligands.

From the present study it is inferred that Microtubules stability increases when Adrenaline docked into Microtubules. The study also helped to predict the optimal lowest energy conformation of adrenaline in the target protein (Microtubule, alpha-tubulin, beta-tubulin, MAP 2 and MAP Tau). Docking of adrenaline into different target proteins could change the conformation since it bound at different sites in the target proteins. It is also concluded that with change in conformation of target protein, their topology also changes flexibly but the entire stored information remains intact with the target protein. Microtubules and Adrenaline together control brain activity and help to maintain the conscious state of the being at physical level.

ACKNOWLEDGEMENT

The authors are extremely grateful to Revered Prof. P. S. Satsangi, Chairman, Advisory Committee on Education, Dayalbagh Educational Institutions for incessant research guidance and encouragement. We are also grateful to our DST-FIST funded Department of Chemistry for providing us research facility.

REFERENCES

1. Weisenberg RC. Microtubule formation *in vitro* in solutions containing low calcium concentrations. Science. 1972;177(4054):1104-5.
2. Weingarten MD, Lockwood AH, Hwo SY, Kirschner MW. A protein factor essential for microtubule assembly. Proc Natl Acad Sci U S A. 1975;72(5):1858-62.
3. Borisy GG, Marcum JM, Olmsted JB, Murphy DB, Johnson KA. Purification of tubulin and associated high molecular weight proteins from porcine brain and characterization of microtubule assembly *in vitro*. Ann N Y Acad Sci. 1975;253:107-32.
4. Conde C, Cáceres A. Microtubule assembly, organization and dynamics in axons and dendrites. Nat Rev Neurosci. 2009;10(5):319-32.
5. Mazel T, Biesemann A, Krejczy M, Nowald J, Müller O, Dehmelt L. Direct observation of microtubule pushing by cortical dynein in living cells. Mol Biol Cell. 2014;25(1):95-106.
6. Nogales E, Whittaker M, Milligan RA, Downing KH. High-resolution model of the microtubule. Cell. 1999;96(1):79-88.
7. Walker RA, O'Brien ET, Pryer NK, Soboeiro MF, Voter WA, Erickson HP, et al. Dynamic instability of individual microtubules analyzed by video light microscopy: Rate constants and transition frequencies. J Cell Biol. 1988;107 (4):1437-48.
8. Dehmelt L, Halpain S. The MAP2/Tau family of microtubule-associated proteins. Genome Biol. 2005;6(1):204. (All versions)
9. Umpleby AM, Russell-Jones DL. The hormonal control of protein metabolism. Baillieres Clin Endocrinol Metab. 1996;10(4):551-70. (All versions)

10. Dreborg S, Kim H. The pharmacokinetics of epinephrine/adrenaline autoinjectors. Allergy Asthma Clin Immunol. 2021;17(1):25.

11. Ross JA, Van Bockstaele EJ. The locus Coeruleus- norepinephrine system in stress and arousal: Unraveling historical, current, and future perspectives. Front Psychiatry. 2021;11:601519.

12. Yajima H, Ogura T, Nitta R, Okada Y, Sato C, Hirokawa N. Conformational changes in tubulin in GMPCPP and GDP-taxol microtubules observed by cryoelectron microscopy. J Cell Biol. 2012;198(3):315-22.

13. Sahni P, Bhanupriya, Shreya, Jaya. Tubulin conformation and anaesthetic interaction-an experimental study. Biochem Anal Biochem. 2016;5(1):251.

14. Jessy DP, Sahni P. A study on change in conformation of tubulin on interacting with propofol *via* time of flight mass spectrometry. IJPCBS. 2019;9(3):123-127.

15. Alan P, Cooke P. Microtubules and the adrenal medulla. Ann N Y Acad Sci. 1975;253:653-69.

16. Gold PE, Korol DL, Hormones and memory. Encyclopedia of Behavioral Neuroscience, 2nd edition. 2017;537-544.

17. Källfelt BJ, Waldenström AP, Hjalmarson C. Effects of adrenaline *in vivo* on protein synthesis and sensitivity to ischemia of the perfused rat heart. J Mol Cell Cardiol. 1977;9(5):383-398.

18. Huan L, Qin F, Wu Y. Effects of epinephrine for out-of-hospital cardiac arrest: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2019;98(45):e17502. (All versions)

19. Drum BML, Yuan C, Li L, Liu Q, Wordeman L, Santana LF. Oxidative stress decreases microtubule growth and stability in ventricular myocytes. J Mol Cell Cardiol. 2016;93:32-43.

20. Sahni P, Kumar M, Pachauri R. Mechanism of Propofol's action on MAP rich tubulin and actin-An *in vitro* study. Biochem Anal Biochem. 2017;6:338.

21. Sahni P, Saxena J. Tubulin protein and information processing. J Biochem Int. 2021;8(1):11-23.

22. Vakser IA. Protein-protein docking: From interaction to interactome. Biophys J. 2014;107(8):1785-1793.

23. Chikhi A, Bensegueni A. Docking efficiency comparison of surflex, a commercial package and Argus lab, a Licensable Freeware. Journal of Computer Science and Systems Biology. 2008;81-86.

24. Oda A, Takahashi O. Validation of ArgusLab efficiencies for binding free energy calculations. Chem-Bio Informatics Journal. 2009;9:52-61.

25. Baskaran C, Ramachandran M. Computational molecular docking studies on anticancer drugs. Asian Pac J Trop Biomed. 2012;2:S734-8.

26. Huang SY, Zou X. Advances and challenges in protein-ligand docking. Int J Mol Sci. 2010;11(8):3016-34. (All versions)

27. Eberhardt J, Santos-Martins D, Tillack AF, Forli S. AutoDock Vina 1.2.0: New docking methods, expanded force field, and python bindings. J Chem Inf Model. 2021;61(8):3891-3898.

28. Eswari JS, Dhagat S, Kaser S, Tiwari A. Homology modeling and molecular docking studies of Bacillomycin and Iturin synthetases with novel ligands for the production of therapeutic lipopeptides. Curr Drug Discov Technol. 2018;15(2):132-41.

29. Yuan S, Chan HS, Hu Z. Using PyMOL as a platform for computational drug design. Wiley Interdisciplinary Reviews: Computational Molecular Science. 2017;7(2):e1298.

30. Burak T. Examination of anti-oxidant properties and molecular docking parameters of some compounds in human body. Turkish Computational and Theoretical Chemistry. 2020;4(2):25.

31. Thompson MA. Molecular docking using ArgusLab, an efficient shape-based search algorithm and the AScoring function. ACS meeting Philadelphia 172, CINF 42, PA. 2004.

32. Burgoyne NJ, Jackson RM. Predicting protein interaction sites: Binding hot-spots in protein-protein and protein-ligand interfaces. Bioinformatics. 2006;22(11):1335-42.

33. Tangyuenyongwatana P, Jongkon N. Molecular docking study of tyrosinase inhibitors using ArgusLab 4.0. 1: A comparative study. Thai Journal of Pharmaceutical Sciences (TJPS). 2016;40(1).

34. Sloboda RD, Rudolph SA, Rosenbaum JL, Greengard P. Cyclic AMP-dependent endogenous phosphorylation of a microtubule-associated protein. Proc Natl Acad Sci U S A. 1975;72(1):177-81.