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An Investigation on the Inhibitory Effects of Essential Oils, Extracted from Aerial Parts of Salvia officinalis, on Protein Aggregation

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ABSTRACT

Amyloid fibril formation serves as a key pathological feature of several different human degenerative diseases. Evidences suggest that inhibition of amyloid fibril formation could be considered as a promising approach toward treatment of these diseases. Investigation of amyloid fibril formation by using hen egg white lysozyme (HEWL), as a model protein, can aid in understanding possible inhibition strategies for tackling amyloid aggregation. Making use of different parts of plants and/or their extracts and essences has been used traditionally in the treatment process of diseases including neurodegenerative diseases. The purpose of this Investigates was to elucidate if essential oils extracted from aerial parts of Salvia officinalis (a local aromatic sage growing in zanjan province) could show any inhibitory effect on the aggregation of HEWL or not. Upon investigation of the chemical composition of the essential oil by the use of GC-MS it was determined that the Salvia officinalis essential oil contained 31 different organic compounds, major of which we Œ±-thujone (24.57%), Œ≤-thujone (5.45%), camphor (13.13%). Then, different volumes of Salvia officinalis essential oil (140, 70, 35, 17, 9 and 5 ¬µl) were incubated with acidic solutions of HEWL (20 mg/ml in phosphate buffer solution at pH 2 and the temperature set to 60ÀöC) for different time periods (24, 48, 72, 96 hour). The aggregate contents of the resulting samples at the end of incubation times were measured by thioflavin (ThT) fluorescence spectroscopy. ThT fluorescence results showed that Salvia officinalis essential oil had inhibitory effect of on aggregation process of HEWL in a volume-dependent manner. The morphology and relative sizes of aggregates, in the presence and absence of Salvia officinalis essential oil, were investigated by atomic force microscopy (AMF) and SDS-PAGE, respectively, and both showed the presence of larger aggregate assemblies in the absence of Salvia officinalis essential oil.

Keywords: Salvia officinalis, Hen egg white lysozyme, Protein aggregation

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Structural Effects of Diamonds Nanoparticles on the Histone H3 Structure

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ABSTRACT

In the nucleosome of eukaryotic cells, DNA is wrapped around histone octamer proteins and these proteins help DNA to condense into chromatin. It is well-proven that histones shield DNA from external damage. All classes of this family of proteins (H1, H2A, H2B, H3, and H4) consist of numerous subtypes except histone H4. Histone H3 contains a main globular domain and a long N-terminal tail. Nanodiamonds (NDs) are carbon nanotube (CNT) that has carbon-carbon covalent link. NDs are called the 21st century biomaterials and can be applied both in vivo and in vitro conditions. Since histone H3 is an essential protein in the field of epigenetics, we investigated the effects of NDs on histone H3 structure with fluorescence and UV-Vis spectroscopy. The UV-Visible spectroscopy and steady-state fluorescence spectroscopy results showed that NDs could form a complex with HSA. The binding constant (KA) and the number of binding sites (n) were also determined. Furthermore, the value of the standard Gibbs free energy change revealed that NDs interact with HSA spontaneously. The results obtained from this study can help in identifying the biomedical properties of NDs.

Keywords: Protein structure, Nanodiamonds, Histone H3, Spectroscopy, Gibbs free energy

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A Study on Inhibition of Aggregation: Inhibition of Amyloid Beta Peptide and Lysozyme Aggregation by Sumoylation and Thymus daenensis Essence, Respectively

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ABSTRACT

Proteins and peptides can be accumulated under various factors. These aggregates deposit in the different tissues of the human body and cause pathogenesis. If these insoluble aggregates deposit in the brain and nervous system, they are associated with the development of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, which have adverse effects on the human life and mortality. Therefore, obtaining effective therapeutic approaches and finding a way to inhibition of these protein aggregates for treatment of this amyloidogenic diseases is very important. Recently noticed to the use of benefit natural products as effective anti-aggregation compounds. In this study we investigated the effects of sumoylation process and Thymus daenensis essential oils on the aggregation of beta amyloid peptide (AŒ≤) and Hen Egg White Lysozyme. We in the first step induced the aggregation of lysozyme and AŒ≤ in in vitro condition. Then in the next step included SUMO and Thymus daenensis essence in the experimental reaction mixtures. The aggregates were detected and characterized by the use of techniques such as fluorescence spectroscopy, atomic force microscopy, electrophoresis and cell culture. The results showed that binding or presence of SUMO protein had no significant effect on amyloid beta peptide aggregation, but thyme essential oils could significantly reduce lysozyme protein aggregation. The study of the viability of lysozyme aggregation showed the inhibitory effect of Thyme essential oils on the toxicity of lysozyme accumulations on SH-SY5Y cells.

Keywords: Beta amyloid peptide (AŒ≤), Protein aggregation, Lysozyme, Sumoylation, Thymus daenensis, Essential oils

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Atorvastatin Potential to Ameliorate the Aggregation of Amyloid-beta Peptide

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ABSTRACT

Alzheimer‚Äôs disease is characterized by the presence of characteristic amyloid plaques in the brain of patients. It is proven that the plaques, in the extracellular space, are mainly composed of the beta-sheet-rich aggregated form of the amyloid-beta peptide. To ameliorate the peptide aggregation, many small molecules, synthetic and natural, from different families, have been introduced. One of the families are those molecules that contain a fluorine group, to increase their bioavailability, and an amide group, to could bind to bio-macromolecules with a higher affinity, in their structures. As an amide-containing fluorinated compound, Atorvastatin is a known drug that can lower cholesterol in the blood. Based on our studies, at the University of Tehran with a collaboration with the Max Planck Institute for Biophysical Chemistry, we showed that Atorvastatin can inhibit the amyloid-beta (1-42) aggregation to a large extent as well. To reach the result, we have employed various 1D and 2D NMR experiments such as monomer consumption assay and 1H-13C /1H-15N

HSQC, and other methods including CD spectroscopy, Thioflavin-T fluorescence assay, and Transmission Electron Microscopy.

Keywords: Alzheimer, Äôs disease, amyloid-beta, aggregation, atorvastatin, monomer consumption assay, NMR

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Inhibition of Amyloid Fibrillation and Remodeling of Preformed Fibrils of Human Insulin by Silymarin Nanoparticles

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ABSTRACT

Among existing strategies for inhibition of amyloid fibril formation and/or promoting clearance of preformed fibrils, use of naturally occurring polyphenols attracted a growing body of attention. Silymarin, the extract of milk thistle (Silybum marianum), has been shown to possess a broad spectrum of biological activities, such as antiviral, anticancer, anti-inflammatory, anticancer, antioxidant, as well as anti-aggregation properties. Relating to amyloid-related diseases, silymarin is one of the most widely used flavonoids in relation to Alzheimer and Parkinson diseases. In the present study, direct oxidative pyrolysis was employed to produce pure nanoparticles. Then, the efficacy of silymarin nanoparticles to inhibit amyloid fibrillation of human insulin was investigated using a range of amyloid-specific techniques including thioflavin T (ThT) and Nile red fluorescence assays and fluorescence microscopy. Obtained results showed higher capacity of silymarin nanoparticle, in comparison with silymarin, for fibrillation inhibition as well as clearance of preformed fibrils of human insulin. Based on ThT results, prolongation of nucleation phase through interaction with and stabilizing monomeric species appears to be the mechanism by which silymarin nanoparticles inhibit human insulin amyloid fibrillation. Increased aqueous solubility and enhanced surface area upon nanonization, may provide some explanations for improved anti-aggregation properties of silymarin in the form of nanoparticle.

Keywords: Silymarin, nanoparticle, amyloid fibril, human insulin

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A Comparative Study on the Effect of Polyphenolic Fraction of Propolis, in the Free and Nanosheet Forms, on the Amyloid Fibrillation and Remodeling of Preformed Fibrils of α-Synuclein

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ABSTRACT

Among common strategies for amyloid fibrillation inhibition, use of naturally occurring polyphenols as an efficient therapeutic approach, has been attracted a growing body of attention. However, low aqueous solubility and bioavailability of these compounds have greatly restricted their clinical application relating to amyloid-related diseases. Thus, different types of formulations have been developed to overcome these limitation, among them, nanonization appears to be one of the most notable approaches. In the present study, possible effects of polyphenolic fraction of propolis (PFP), in the free and nanosheet forms, on the amyloid fibrillation of α-synuclein have been investigated. Direct oxidative pyrolysis was employed to self-polymerize PFP monomers for the construction of pure nanosheets (nano-PFPs). Obtained results showed higher capacity of nano-PFPs, in comparison of PFPs, for fibrillation inhibition as well as clearance of preformed fibrils of α-synuclein. This increased efficiency of nano-PFPs may attributed to increased aqueous solubility and enhanced surface area provided by nanonization, which can lead to a strong

binding with and trapping of protein at the surface of the nanoparticle and consequently effective amyloid fibrillation inhibition. We suggest that nanonization of natural small molecules can be considered as a powerful approach to improve their antiamyloidogenic properties and overcome obstacles originate from poor water solubility and low bioavailability of drug candidates relating to neurodegenerative diseases.

Keywords: Propolis, polyphenol, nanoparticle, amyloid fibril, α-synuclein

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Efficient Amyloid Fibrillation Inhibition and Remodeling of Preformed Fibrils of HEWL by Pomegranate Seed Polyphenols-Based Nanosheets

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ABSTRACT

Major obstacles for development and clinical application of polyphenolic compounds in relation to neurodegenerative disease are their poor water solubility and bioavailability. To dominate these limitations, various methods have been proposed, among them nanoformulation is considered as a promising approach. Herein, we have compared the potency of polyphenolic fraction of Pomegranate seeds (PFPS), in the free and nanosheet forms, on the amyloid fibrillation of hen egg white lysozyme (HEWL). Direct oxidative pyrolysis was employed to self-polymerize PFPS monomers for the construction of pure nanosheets. Obtained results showed that PFPS, in the form of nanosheet (PFPS nanosheet), exhibits improved capacity for amyloid fibrillation inhibition as well as clearance of preformed fibrils of HEWL. It appears that increased aqueous solubility and surface-to-volume ratio are involved in improved anti-aggregation activity of PFPS nanosheets. Based on Thioflavin T results, it seems that elongation of the nucleation stage, through binding to and stabilizing of monomeric species, is the mechanism by which PFPS nanosheets modulate fibrillation process of HEWL. Taken together, we suggest that nanonization of polyphenolic compounds can be a powerful approach to overcome poor-water solubility and low bioavailability of these compounds and improve their anti-amyloidogenic properties in relation to neurodegenerative diseases.

Keywords: Pomegranate seed polyphenols, nanosheet, amyloid fibril, HEWL

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Molecular Docking Studies of the Newly Synthetized Triazole Derivatives with Hsp90

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ABSTRACT

Molecular chaperons are responsible for the folding, function and stability of the variety of their client proteins. Heat shock proteins 90 (Hsp90) have recently emerged as a target for cancer drugs due to their role in the regulation and stabilization of oncogenic proteins. Hsp90 is an ATP-dependent chaperon and its ATP binding site has a unique feature that only exists in the GHKL family. Inhibition of the Hsp90 and its ATPase activity leads to proteasome degradation of oncogenic proteins and ultimately kills cancer cells. Finding new and safe Hsp90 inhibitors have become a promising therapeutic strategy for the development of new effective drugs against cancer. One way to find new inhibitors is in silico studies such as molecular docking. In an effort to find new Hsp90

inhibitors, we investigated the interactions of newly synthetized triazole derivatives and Hsp90 using the flexible docking by AutoDock Vina software. In this way the N-domain of Hsp90 is targeted molecular docking of a triazole derivatives to the ATP binding site of Hsp90. Based on the results, these compounds are located at the ATP binding site and interact with key residues such as Asn51, Ala55, Asp93, Met98, and Thr184. In addition, the binding energy of these compounds is lower than that of many previous inhibitors.

Keywords: Hsp90, inhibitor, Molecular docking, Cancer, Triazole derivatives, AutoDock Vina

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Molecular Interaction of Chemotherapeutic Drug of 5-Fluorouracil and Fe3O4 Nanoparticles with Milk Carrier Protein of Bovine α-Casein

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ABSTRACT

In the present study, the interaction and side effects of a chemotherapeutic anti-cancer drug of 5-Fluorouracil and Fe3O4 nanoparticles (NPs) with the milk carrier protein of α-casein was investigated using spectroscopic method of fluorescence at three temperatures of 25, 37 and 42℃. The analysis data of intrinsic fluorescence spectra of protein indicated that the incubation of the 5-Fluorouracil to α-casein solution followed titration by NPs, and also incubation of NPs then addition of 5-FU conversely led to a significant decreasing in the intrinsic fluorescence spectra of the protein due to quenching of the fluorescence intensity. Values of the number of binding sites and the binding constants of two ligands simultaneously on the protein were calculated at different temperatures according the quenching method. Analysis of Stern-Volmer curve of protein showed that the dynamic quenching mechanism has a major role. Moreover, binding results analysis have represented that there is one binding sites on α-casein for binding of ligands at all three temperatures. Finally, we found the chief roles are the Van der Waals forces and H-bonding interactions.

Keywords: α-casein, 5-Fluorouracil, Fe3O4 nanoparticles, Fluorescence, Quenching, Binding site

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Screening of Peptides with High Affinity to α-Synuclein Oligomers Rather Than Monomers Using Celluspots Peptide Array Technique

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ABSTRACT

α-synuclein (α-syn) is one of the presynaptic intrinsically disordered proteins. However, the change in environmental factors (such as pH, ionic strength, severe shaking) induces the formation of α-syn aggregations and amyloid fibrils in vitro. Lewy bodies are aggregates of protein that are seen in Parkinson's patients. The main component of the Lewy bodies are the amyloid fibers of α-syn. The exact function of this protein and the mechanisms that cause toxicity and cell death are still not well defined. Inhibition α-syn aggregations may be an approach to preventing and treating Parkinson's disease. A number of polyphenol antioxidants have been discovered that inhibit α-syn fibers. However, their effects are non-specific. Generally, protein-protein interactions are highly specific

and well-regulated. Here, celluspots peptide arrays have been applied to measure the interaction between α-syn monomers and oligomers with different unique peptide sequences on the arrays. Peptide sequences with high specificity and affinity for α-syn oligomers rather than α-syn monomers can be selected and synthesized. Then its interaction with vesicle membrane and toxicity of the obtained protein species are investigated by different methods.

Keywords: Celluspots peptide array, Parkinson, Äôs disease, Lewy body, Amyloid fibers, α-Synuclein, Peptide

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Developing a Stable Breast Tumor Model Using Three-Dimensional Co-culture of MDA-MB-231 and Hu02-KP Cell Lines

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ABSTRACT

Introduction: Three-dimensional (3D) cell culture to develop tumor models is one of the most effective methods in cancer researches. The MDA-MB-231 cell line is a breast cancer cell line used for metastatic studies due to its aggressive behavior. In this study, we attempt to develop a metastatic breast cancer tumor model using 3D co-culture of MDA-MB-231 and human fibroblast cells and examine its growth kinetics and molecular properties.
Methods: The different ratios of Hu02-KP and MDA_MB231 cell lines were cultured in the non-adherent plates containing specific media. Incubation was performed for two weeks with daily change of culture media. Their ability to produce mammospheres and their morphology were studied by daily imaging. Moreover, the growth kinetics of generated mammospheres were assessed. In addition, flow-cytometry analysis was performed to determine the molecular phenotype of cells generating the mammospheres.
Results: The results showed that MDA-MB-23 cells do not produce a mammosphere, lonely. However, in the presence of fibroblast cells, they achieve this ability. In addition, seeding the equivalent number of these two types of cells led to the best kinetic growth curve. Furthermore, CD-marker analysis of mammospheres demonstrates they dominantly consist of cells with CD24+/CD44+ and CD24-/CD44+ phenotypes.
Discussion & Conclusion: MDA-MB-231 cells due to their metastatic subpopulation (CD24-/CD44+) are not capable to produce the mammosphere. The presence of fibroblast cells in 3D co-culture mediates cell to cell adhesion and efficiently help to generate the mammospheres.

Keywords: Breast cancer, Tumor model, 3D cell culture, Mammosphere, Mda-mb-231, co -culture

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Preparation and Characterization of Nisin Containing Alginate-Fibrinogen Hydrogel

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ABSTRACT

Today, wound healing is a great concern in the medical field and hydrogels are one of the popular dressings in this field. Since fibrinogen presents a coagulating activity it can play a significant role in wound healing. Furthermore, alginate is a biopolymer used in a variety of biomedical applications due to its favorable properties, such as biocompatibility and non-toxicity. On the other hand, widespread presence of bacteria in the wound causes

infections and increases the tissue damage and bad smell. Hence, a desired dressing should have an antibacterial property. In our study, we designed a hydrogel using fibrinogen, the antibiotic nisin and alginate to be applied in a hydrogel based wound dressing. The properties of prepared hydrogel including profile of nisin release, antibacterial activity and swelling were assessed. According to our results, the prepared hydrogel released a remarkable amount of the loaded nisin during 10 h. In other words, nisin was released steadily and slowly from the hydrogel. Interestingly, the in vitro study confirmed that the prepared hydrogel could considerably inhibit the growth of bacteria at the wound site, which was revealed by appearance of a growth inhibition zone. The hydrogel also could absorb water up to 500 times its original mass. As a result, this dressing was suitable and effective for skin wound healing.

Keywords: Tissue engineering; Wound healing; Hydrogel; Alginate; Fibrinogen; Nisin

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Neuroprotective Effect of Propolis Polyphenols Based-Nanosheets Against Rotenone Induced Neurotoxicity in Human Neuroblastoma SH-SY5Y Cells

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ABSTRACT

Parkinson disease (PD) is a neurodegenerative disorder characterized by progressive loss of dopaminergic neurons in substantia nigra part compacta. Oxidative stress and mitochondrial dysfunction may underlie this process. Therefore, using free radical scavenging molecules is one of the strategies considered in relation to neurodegenerative diseases including PD. However, low aqueous solubility and bioavailability of these compounds have greatly restricted their clinical application regarding amyloid-related diseases. Thus, different types of formulations have been developed to overcome these limitation, among them, nanonization appears to be one of the most notable approaches. Propolis is a natural remedy with a highly variable chemical composition (mainly polyphenols), possessing various biological activities such as anticancer, anti-viral, anti-inflammatory, antioxidant, and immunomodulatory properties. Herein, we aimed to investigate the neuroprotective effects of polyphenolic fraction of propolis (PFP), in the free and nanosheet forms, against rotenone-induced neurotoxicity in human neuroblastoma SH-SY5Y cells. Direct oxidative pyrolysis was employed to self-polymerize PFP monomers for the construction of pure nanosheets (PFP nanosheets). Preliminary MTT experiments showed increased cell viability of human neuroblastoma cells pretreated with PFP or PFP nanosheets for 2h prior to rotenone. Then, lactate dehydrogenase release as a marker for integrity of plasma membrane was investigated, where PFP nanosheets were more effective in maintaining membrane integrity. Clearly, further studies are needed to confirm our findings and present a mechanistic explanation for our observations.

Keywords: Propolis, Nanosheet, Neuroprotection, Neurotoxicity, SH-SY5Y, Rotenone

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Preparation and Kinetic Study of a Single Wall Carbon Nanotube Decorated by Fe3O4@ROL Nanobiocatalyst

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ABSTRACT

Nowadays, nano biomaterials are used in many industrial applications, and immobilized lipase enzymes as valuable biocatalysts are suitable candidates for many practical/industrial applications. Hence, their immobilization on nano substrates can lead to their improved thermal and pH stability, storage time and reusability. Lipases are being used in pharmaceutical industry and production of fine chemicals and even biofuel. Employing lipases requires a full recycling of these enzymes to optimize economic benefits and minimize waste disposal for industrial purposes, which could be accomplished using magnetic nanoparticles as immobilization substrates. Therefore, the aim of this work was to prepare suitable magnetic substrates to immobilize Rhyzopus Orizaei lipase (ROL) to make a more effective nanobicatalyst and study the kinetic parameters of this nanobiocatalyst to find how its enzymatic reaction changes comparing to the free ROL. For this purpose, at first, Single Wall Nanotubes (SWCNT) nanoparticles were magnetized with Fe3O4 magnetic nanoparticles, using a co-precipitation method. Afterwards, the ROL was directly immobilized onto the magnetic SWCNT through a covalent interaction. Enzyme activity was assessed by measuring catalytic hydrolysis of p-nitrophenyl butyrate. The kinetic parameters, catalytic constant and catalytic efficiency, were improved after immobilization.

Keywords: Rhyzopus Orizaei Lipase, SWCNT, Fe3O4, nanobiocatalyst, kinetic, immobilization

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Metal Ions Can Alter Alpha Synuclein Function on Microtubules

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ABSTRACT

Alpha-Synuclein (Syn) is a natural disorder protein, which is abundant in brain tissue specifically in the pre-synaptic region. Despite a number of studies on its pathology, physiology of Syn remained unclear. Recently, its effect on microtubule (MT) polymerization has been suggested as a possible physiological functional route for Syn. Although there is a controversy about the effect of Syn on MT polymerization, it seems that Syn has MT dynamase activity. Along with this, it is demonstrated that metal ions interact with Syn and accelerate its fibrillation. In this study, Syn was pre-incubated with three metal ions including Ca, Zn and Mg and its effect on MT polymerization was assessed at 37¬∞C. Incubated of Syn with each of these ions, the protein was found to have different impact on MT polymerization kinetics compared to Syn alone. These findings propose metal ions as effective ligands able to change Syn function.

Keywords: Alpha-Synuclein, Microtubule, Tubulin, Metal Ions, Alpha Synuclein function

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Evaluation and Molecular Docking Analysis of Some New Synthetic Compounds as A New Class of Mushroom Tyrosinase Inhibitors

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ABSTRACT

Tyrosinase (EC 1.14.18.1) is widely distributed in nature and plays an essential role in melanogenesis. Excess production of melanin can be a reason of hyperpigmentation skin disorders in mammals and enzymatic browning in plant-derived foods. So inhibition of the enzyme activity leads to some advantages such as skin whitening.

In an effort to find new safe and efficient tyrosinase inhibitors we evaluated the inhibitory effects of some novel pyridine derivatives on the mushroom tyrosinase activity.

According to the results, when L-Dopa was used as the substrate, one of the tested compounds (compound B)

showed strong inhibitory effect against the activity of the enzyme (%78 inhibition). The results of molecular docking analysis showed that the compound well binds to the enzyme active site and is coordinated by some important residues.

Keywords: Tyrosinase, Diphenolase activity, Inhibition kinetics, Melanin, Molecular docking

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Sweetness Intensity and Different Patterns of Atomic Interactions between Sweeteners and Sweet Taste Receptor

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ABSTRACT

Previous studies on the sweet taste receptor and 316 small sweet molecules had shown a 60% correlation between sweetness intensity and ligand affinity. The current study was designed to get insight about atomic interactions of the sweeteners with different sweetness intensities or affinities. Four previously docked small sweet molecules, Aspartame derivatives (Asp-209, Asp-199), leucrose, and xylose were simulated for 300 ns (3*100 ns), in physiologic condition. YASARA suit 2019 was used for the whole procedure. Trajectory analyses included carbon-alpha RMSD, and total energy of the receptor with/without the ligands, ligands movements and conformations fluctuations, hydrogen bonds (HBonds) and other non-covalent interactions of the ligands during simulations, total energy of ligand-receptor/water HBonds, and dynamic cross-correlation matrix (DCCM) of all the residues. Xylose (low sweetness/low affinity) left the binding pocket after almost 30 ns and was excluded from further analyses. Presence of the ligands slightly increased total energy of the receptor, however significantly decreased the fluctuation of energy, which was consistent with CA-RMSDs. Correlations were observed between ligand-receptor/water total HBonds energies, and affinity or sweetness intensity. Also, DCCM analyses showed different patterns for highly sweet molecules Asp-209 and Asp-199 and low sweetness leucrose. Ligand movement patterns were different for high affinity Asp-209 and leucrose, in contrary to Asp-199 with low affinity.
In conclusion, observed correlations brought up possibilities that atomic interaction patterns of the sweeteners with both solvent and the receptor may lead to displacements of some residues in the receptor which affects the sweetness intensity.

Keywords: Sweetness, MD simulation, Aspartame, Asp-209, Asp-199, Xylose, Leucrose

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Studying The Effect of Electric Field at 100 and 400 kHz On the Conformation of Bovine Serum Albumin

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ABSTRACT

Today, due to the application of the electric field in the treatment of tumor cells, research for identification of the mechanism of its effect has become important. The aim of this study was to investigate the effect of alternating electric field at two frequencies of 100 and 400 kHz on the protein behavior. For this purpose, in order to design the electric field application chamber, Comsol Mutiphysics simulation was performed. According to the obtained results, the physical and structural characteristics of the field application chamber were determined by considering a barrier layer between the metal electrode and the protein

solution. Bovine serum albumin (BSA) was exposed to the mentioned electric field as a model protein followed by studying its conformation using fluorescence and circular dichroism spectroscopies. The results of intrinsic fluorescence showed an irreversible decrease in emission over time dependent on the intensity and frequency of the alternating electric field. The level of changes in the secondary structure of the protein was minor and associated with a slight decrease in the alpha helix content along with a slight increase in the content of random coil. According to the results, BSA adopted a loose conformation when exposed to the alternative electric field.

Keywords: Electric field, 100 kHz, 400 kHz, Fluorescence, Circular dichroism, Bovine serum albumin (BSA)

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A Predictive Model for Discriminating Toxic and Non-Toxic Anti-Microbial Peptides Based on Their Physico-Chemical Properties

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ABSTRACT

Antimicrobial peptides (AMPs) are promising tools to fight against ever-growing antibiotic resistance. However, despite many advantages, their toxicity to mammalian cells is a critical obstacle in clinical applications. Here, by using an up-to-date dataset, a machine learning classification model has been trained successfully to distinguish between toxic and non-toxic AMPs based on a comprehensive set of physico-chemical properties extracted from AMPs. Multiple machine learning algorithms were implemented and optimized to achieve highest F1 score in discriminating toxic and non-toxic AMPs. This model can be used as a tool for extracting AMPs with low toxicity from AMP libraries.

Keywords: Antimicrobial peptides, peptide toxicity, Machine learning, Physico-chemical properties, classification model

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Preparation and Characterization of a Novel Wound Dressing Hydrogel Based on Chitosan

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ABSTRACT

Hydrogels are hydrophilic polymers with a high ability to absorb water and a network structure composed of numerous pores, which can be applied to load drugs. Furthermore, Chitosan polymer is widely used in wound healing due to its biocompatibility, optimal water absorption and antibacterial properties. The aim of this study was to prepare a chitosan hydrogel containing the antibiotic nisin to heal skin wounds. For this purpose, a hydrogel composed of chitosan and loaded with nisin was prepared. The results of scanning electron microscopy showed that the hydrogel uniformly has high porosity and is endowed with enough space to load the drug. The data obtained from the swelling test showed that the prepared hydrogel swells up to 400 times its volume and has the ability to absorb a considerable amount of water to provide a moist environment for wound healing. Cytotoxicity test data also showed that the hydrogel was nontoxic to skin epithelial cells, indicating its biocompatibility. Antimicrobial data also revealed the hydrogel,Äôs antibacterial activity. As a result, the prepared hydrogel presented favorable swelling, sufficient porosity,

biocompatibility and antimicrobial activity and can be a desirable dressing for healing infectious wounds.

Keywords: Chitosan, Hydrogel, Cytotoxicity, Swelling, Wound, Biocompatible

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The Role of Copper Ion Concentrations on The γ-Crystallin

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ABSTRACT

γ-crystallin is a member of the small heat shock protein family (sHSP) with chaperone ability and structural properties. This protein along with γ-crystallin plays a protective role in the eye lens and preserve transparency and individually indicates a protective function in the other tissues especially in the nervous system. The interaction of copper ion with this protein is very important both in the ocular tissues and in other tissues which its high concentration has a great relationship with cataract and degenerative diseases by ROS generation mechanisms. This is happening while the presence of this ion is necessary at low concentrations and its reduction leads to disorders. In the current report, the structural properties of human γ-crystallin were assessed incubating with the range of copper concentrations (1 to 30 ratio of copper to the protein) via spectroscopic methods. In the presence of copper ions, γ-crystallin exhibited important structural alteration. From 2:1 to 30:1 ratio of copper ion to the γ-crystallin concentration, the increase of protein size was observed. These conformational changes are associated with reduced hydrophobicity and tryptophan emissions. Binding data show that the protein has two sites for the binding of copper ions. That is important to note this variation of copper ion concentrations upon interaction with γ-crystallin induced the role in cataract formation.

Keywords: γ-crystallin; copper ion, Binding site, Hydrophobicity, Cataract interpretation

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A Study about The Interaction of Some Azole-Like Molecules and Prolyl Hydroxylase Domain-Containing Protein 2 (PHD2) by Docking Approach

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ABSTRACT

Prolyl hydroxylase domain-containing protein 2 (PHD2) is one of the major regulators of the angiogenic pathway, which controls the cytosolic level of Hypoxia-inducible factor 1-alpha (HIF-1α) and inhibits angiogenesis in the normoxic conditions. Cancer cells invade and metastasize in the hypoxic conditions, which increases the HIF-1α and enters the cell nucleus. HIF-1α increases transcription of genes involved in angiogenesis to adaption to hypoxic conditions. Azole compounds have antitumor effects in inhibiting this invasion. Inhibition of the angiogenic process is one of the new ideas in the treatment of tumor cells. The aim of this project is to study the interaction of a number of similar azole compounds as ligands with PHD2 protein. These interactions have been investigated by computational molecular docking methods with Rosetta software. The three-dimensional structure of PHD2 protein with 3OUJ code was provided from the protein database. Docking process revealed that studied ligands, Amlexanox had the most stable state to be in the PHD2 protein binding site with the minimum of the binding energy.

Keywords: PHD2, HIF-1α, Angiogenesis, Hypoxia, Molecular docking, Rosetta software

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A Designed and Synthesized Hydrophobic Nano-Inhibitors for Transthyretin Aggregation

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ABSTRACT

Transthyretin is a homotetramer plasma protein that transfers retinol and T4 hormone through the blood. Transthyretin is triggered for aggregation and may deposit into fibrils in nervous and cardio muscular cell causing disease such as familial amyloidosis polyneuropathy (FAP). This situation occurs as a result of mutation or aging process. Inhibiting of protein aggregation by ligand is a promising strategy and important field of recent studies. Thus, we tried to interfere in transthyretin aggregation via designed and synthesized hydrophobic nano-ligands in order to inhibit the process.

In this study, a mutant of transthyretin that is not able to assemble and maintain tetramer structure (mTTR) was utilized. Transthyretin aggregation was studied in the presence and the absence of hydrophobic ligands and kinetics parameters were obtained by ThT fluorescence and also structural evaluations were performed using intrinsic fluorescence and circular dichroism.

mTTR aggregation in a variety of conditions including pH and temperature was investigated and the ligands were introduced to the reaction in order to interfere with the aggregation process. The results indicated that the designed ligands significantly inhibited mTTR aggregation by maintaining the tertiary structure and excluding the triggered conformation. It was revealed that the hydrophobic nano-ligand scored the most inhibition of mTTR aggregation.

Keywords: Transthyretin, Protein aggregation, hydrophobicity, ThT fluorescence and circular dichroism

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Signaling Mechanism for Structural Dynamics in α-Glucosidase

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ABSTRACT

How would the structural analysis dependent on the conformational dynamics of non-competitive regulation in a protein, as like α-glucosidase, enrich the existed experimental data? α-glucosidase, as an enzyme for carbohydrate digestion in the small intestinal epithelium, considered as a potential target for the treatment of type II diabetes. So as the goal of study about the mechanism of non-competitive inhibition, two long molecular dynamics simulations of α-glucosidase MAL12 conducted as apo (i.e., unbound structures) and holo type (i.e., the complex structure reached by docking a formative of indolyl xanthene inhibitor, in predicted allosteric site).

The structural post-simulation analyses of the Cartesian coordinates used such as RMSD, RMSF and principal component analysis (PCA) as a dimension reduction method. Also, the estimation of free energy landscape (FEL) created by analysis in the probability distribution functions (PDFs) of two subspaces crossed by PC1 and PC2, to depict intermediate conformations. Analysis of side chain torsion angles and consequently hotspot residues distance probability distributions were calculated.

As the outcomes, the key residues reported, which play more critical roles in streaming between the active site and an allosteric site in this protein inhibition mechanism. Also, the gate residues introduced on the active site catalytic zone

as the door guard, which converge and closing the gate of the active site regarding ligand binding.
Furthermore, since the proteins as like α-glucosidase MAL12, does not have X-ray crystallography or NMR spectroscopy, so these types of studies can clarify the structures of this protein and used to extract functional-related information from the simulation data and manifest significant conformational changes as by the effects of diverse drugs.

Keywords: Non-competitive Inhibition, αGlucosidase Inhibition, Molecular Dynamics Simulation (MD), Sidechain Torsion Angles, Hotspot Residues, Allostery

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Assessing Binding of HSA Fibrils to Copper and Zinc Ions

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ABSTRACT

Zinc (Zn+2) and Copper (Cu+2) ions have been specially involved in disease pathogenesis of amyloid-related to metal ions. Metal ions are enriched in the β-amyloid aggregates typically found in patients with Alzheimer, Parkinson, and CreutzfeldtJakob. β-amyloids implicate in a primary pathogenic factor in Alzheimer disease that especially links metal ions, specifically copper, to the formation and structure of β-amyloid assemblies which are the signature of this disease. Human Serum Albumin (HSA), a preferred drug-carrier molecule, can also aggregates in-vitro. This study reports the surface of HSA molecules in the presence of ions by fluorescence microscopic assay that they are more densely packed. Moreover, HSA strands in the presence of ions compared to absence of them are more uniformed in the length. The HSA-Cu+2 strands have more monotonic shape than HSA-Zn+2 strands. HSA strands may fold more in the presence of Cu and Zn ions. HSA with large inter-strand sepration illustrates that there is not hydrogen binding between adjacent strands. Comprehension of β-amyloid microscopic structural specifications and it‚Äôs variation interacts with itself or other elements can open the door to studies of β-amyloid aggregates in the tissues environment.

Keywords: Zinc ion; Copper ion, Fluorescence microscopy, Human Serum Albumin (HSA), Amyloid, interaction

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Interaction of Human Serum Albumin (HSA) with Quercetin in The Absence and Presence of A Magnetic Field

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ABSTRACT

The objective of this work is to study the interaction of the quercetin (QUE) with human serum albumin (HSA) in the absence and presence of magnetic field making use of UV-Vis spectroscopy and molecular modeling. The absorbance spectra of protein, ligands and protein-ligand show complex conformation between ligands and HSA. The results showed that the binding parameters are different in the absence and presence of the magnetic field. The analysis of absorption data in the binary systems showed that decrease the binding parameters between QUE and HSA in the presence of magnetic field. Prediction of the best binding sites of each ligand in binary systems in molecular modeling approach was performed using the value of Gibbs free energy.

Keywords*:* Human serum albumin, Flavonoid, Quercetin, Magnetic field, UV-Vis spectroscopy, Molecular modeling

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Investigation of Amyloid Beta-42 Peptide Aggregation in The Presence of Insulin and Amylin Peptides (IAPP)

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ABSTRACT

Aggregation of proteins and formation of amyloids are among the main causes of diseases such as diabetes mellitus (T2D), Alzheimer's (AD) in which the aggregation of a specific protein or peptide is significantly involved. Since there are considerable amounts of evidences about relationships between the occurrence of T2D and AD and also some casual relationships between these two diseases, in this study we tried to investigate the aggregation of amyloid beta peptide (Abeta 42) in the presence of insulin and amylin (IAPP), to see if there might be a molecular link between AD and T2D. Appearance of aggregated species were detected by thioflavin-T (ThT) fluorescence spectroscopy and atomic force microscopy (AFM) and the toxicity of aggregated species were investigated by the use of trypan blue staining of SH-SY5Y cells. We investigated the binary (Abeta 42 + insulin, Abeta 42 + IAPP and insulin + IAPP) and ternary (Abeta 42 + insulin + IAPP) combinations and we understood that they were aggregated significantly more than those in which only one polypeptide was present in reaction mixtures. We found that aggregated species showed toxic effects on SH-SY5Y cells but the toxicity of ternary mixtures was higher than single species. It is hoped that this study would help to understand better association between AD and T2D, particularly when aggregation of Abeta 42 is to be considered in the presence of IAPP, where it caused less Abeta 42 aggregation, the result that might help to build a novel therapeutic approach to AD.

Keywords*:* Alzheimer's Disease, Protein Aggregation, Amyloid Beta Peptide, Insulin, Amylin

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De novo Antimicrobial Peptide Design Using a Hybrid Model of Transformer Neural Networks and Docking/MD

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ABSTRACT

There are approximately 700,000 death cases annually caused by antimicrobial-resistant bacterial strains. It is anticipated that this resistance could affect 24 million people in the next decade. The inefficiency of the current antibiotics from one side and the ever-decreasing number of active researches on the discovery of the antibiotics from the other has promoted the utilization of Antimicrobial Peptides (AMPs) in recent years. AMPs are often naturally derived and are either not selective, unstable, or have MICs only in the high micromolar range. Here, we present a generative hybrid model of transformer networks and molecular dynamics for combinatorial de novo antimicrobial peptide design. Originally the transformer networks are designed to process sequential data and are widely used and proven to be effective in natural language processing (NLP) tasks like generative language modeling. The problem of designing de novo AMPs can be reduced to generating new AMP sequences whose higher-level structure can carry out antimicrobial functionality. Transformer networks are a perfect match in the process of generating new antimicrobial peptides as they can grasp a general grammar among all the known sequences. The performance evaluation of generated de novo sequences is calculated by first computing the tertiary structure of the sequence using ab-initio protocols and then passing it through a docking/MD pipeline against its target. We trained the transformer network on pattern recognition and modeling of AMPs and used the resulting model for generating de novo AMP sequences. Among generated sequences, 89.6% showed significant activity against membrane structures, and 80% of them were predicted to have membranolytic activity compared to 38% of the randomly sampled collection of sequences drawn from the same amino acid distribution as the training set. We

showed that the Transformer networks in a hybrid form with physics-based modeling could generalize well to the task of constructing new AMP amino acid sequences with a given functionality in mind. This approach can be further tailored to be applicable in other domains such as anticancer peptides design without the need for passively exhausting large libraries.

Keywords*:* De novo peptide design, Peptide design, Transformer networks

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Seeking the Mesenchymal-Epithelial Transition of Leukemic Cells Mediated by Differentiation Therapy

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ABSTRACT

The epithelial-mesenchymal transition (EMT) process is well-known through its role in progressing metastasis, invasion and resistance against chemotherapeutics in solid and non-solid tumors. Inversely, mesenchymal cells can convert to epithelial cells with restored function, called mesenchymal-epithelial transition (MET). Herein, we evaluate the MET mediated by inducible caspase-9 (iC9) gene transfection and ATRA treatment in NB4 cells as a model of Acute Promyelocytic Leukemia. With this aim, the invasion and drug response of cells treated by iC9 and ATRA were investigated by performing invasion assay, gelatinase assay to study the activity of matrix metallopeptidase-9 & matrix metallopeptidase 2, and immunocytochemistry of CD44 and MMP9. Results demonstrate, in consequence of gene transfection and ATRA treatment, the invasive features of the cells decreased compared to the control sample, although the expression of CD44 and MMP-9 remained unchanged. Also, MMP-2 activity in the gene-treated and differentiation cells has increased. Furthermore, the drug response has increased in the treated cells. Altogether, it can be concluded that the applied therapeutics such as caspase-9 (iC9) gene transfection and ATRA treatment were successful in driving MET of leukemic cells.

Keywords*:* Epithelial-mesenchymal transition (EMT), Mesenchymal-epithelial transition (MET), Invasion, Differentiation therapy, inducible caspase-9 (iC9), Acute promyelocytic leukemia (APL)

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Developing a Structural Model Based on Electrospun Nanofibers to Mimic Ductal Carcinoma Breast Cancer

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ABSTRACT

One of the major challenges in cancer studies is the necessity of developing an appropriate in vitro model to mimic complex tissue microenvironments. Modeling of the tumor microenvironment requires three-dimensional cell-cell and cell-extracellular matrix interactions. Herein, we attempt to develop a model of non-invasive ductal carcinoma of breast cancer using a fibrous scaffold made by emulsion electrospinning method, that fibrous scaffold is considered as an artificial extracellular matrix. Primarily, to construct the scaffold, different ratios of gelatin/polylactic acid (PLA) were applied in aqueous inner phase and continuous organic phase, respectively. The manufactured scaffolds were characterized by FTIR, thermogravimetric analysis, scanning electron microscopy and mechanical test. Then, the MCF-7 cells were seeded on the scaffolds composed of different ratios of gelatin/PLA. Cell viability was measured by MTT assay showed that 16.9% by weight of gelatin has the highest cell viability. The best ratio was chosen and again the cells were injected to the chosen duct. Five days after incubation, the cells

cultured within the duct were evaluated by SEM images. The images verified the attachment and growth of the cells inside and outside of the duct. Hence, the constructed model is suitable for furtherer studies related to cancer treatment.

Keywords: Ductal Carcinoma Breast Cancer, Emulsion electrospinning, Polylactic Acid/Gelatin Emulsion, Fibrous scaffold, Cell viability

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The Physico-Chemical Study on Hemoglobin upon Interaction with 2-hydroxy-1, 4-naphthoquinone

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ABSTRACT

2-hydroxy-1, 4-naphthoquinone is a color phyto-chemical component taken from Henna. It can make an impact on hemoglobin structure certainly change hemoglobin functions. In some of in vivo study formation of hemichrome and Heinz body has been seen and these effects will lead to kidney, spleen and liver toxicity by increase their weight, iron sediment and hemolytic anemia. In this report. The interaction of hemoglobin with 2-hydroxy-1, 4-naphthoquinone induced the change of hydrophobic pocket area (aromatic amino acids) conformation. The incubation of hemoglobin with 2-hydroxy-1, 4-naphthoquinone at 37 °C at 24 hours occurred left shift that indicates deformation of hemoglobin and formation of hemichrome then Heinz bodies.

Keywords: Hemoglobin alteration, Phyto-component, Protein structure and function relationship

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Virtual Screening of Matrix Metalloproteinase 2 Enzyme Inhibitors as Potential Drug for Multiple Sclerosis Disease

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ABSTRACT

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system. Matrix metalloproteinase 2 (MMP-2) plays an important role in inflammation and immunity and causes BBB disruption, which facilitates immune cells transmigration into the CNS, fragmentation of the MBP (myelin based protein), demyelination, and axonal injury. Metalloproteinase inhibitors are a powerful therapeutic strategy for the treatment of central nervous system disorder. Virtual screening emerged as an important tool in our quest to access the novel drug-like compound. At first, we found 165 ligands for all matrix metalloproteinase enzymes. Then, we docked these ligands into matrix metalloproteinase 2 protein using AutoDock Vina and Molegro Virtual Docker software and the best 30 ligands were chosen. Then using the infinite software 5000 similar ligands were obtained. Again, we docked them into MMP-2 protein and the best 526 ligands were obtained from this step. According to their interaction with the enzyme active site residues, the best 56 ligands were selected. According to the Lipinski role of five and ADME properties using the SwissADME online server, nine ligands were screened from this step. Finally, we performed MD simulation using the GROMACS software. MD simulation results and binding free energy showed three ligands (figure 1) are the best inhibitors for matrix metalloproteinase 2.

Keywords: Matrix metalloproteinase, Docking, Virtual screening, MD simulation, Inhibitor

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A Bioinformatics Investigation on The Relationship between Aggregation Propensity of Peptides and Proteins and Their Amino Acid Sequence, Extent of Beta Structure and Intrinsically Disordered Regions in Their Structures

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ABSTRACT

In recent years, protein aggregation has become a hot topic of research due to its importance in medical and biotechnology research. Protein aggregation and the formation of protein amyloid are major causes of common disease such as Alzheimer's, Parkinson's and Diabetes. Today, our understanding of aggregation is at the molecular level. Along with this advanced, various computing softwares have been developed to predict and evaluate protein aggregation that serve as a tool to guide and assist experimental research. In this study, the data obtained from AGGRESCAN and TANGO software, two softwares that are used as efficient and widely used software in predicting protein aggregation on aggregating proteins of the nervous and systemic system as well as non-aggregating proteins, have been studied. The software output data were analyzed with X-ray crystallographic data from the PDB database. The comparisons had a high overlap of the software data with the crystallographic structure. According to the results, the overlap of the prediction data in short-length proteins with crystallographic structure is greater, and the longer proteins, the overlap of the data reaches very different values. Also to understand the aggregation basis of each protein, the software output data were compared with the output data of DISOPRED3 software, which predicts intrinsically disorder region and structures. Aggregating proteins, especially aggregating proteins of the nervous system, are due to their high aggregation due to the presence of intrinsically disordered structures, but the aggregation of proteins in which the percentage of intrinsically disordered regions is low, such as superoxide dismutase, is due to mutation in the gene.

Keywords: Protein Aggregation, Protein Aggregation Prediction, Computational Biology, Alzheimer's Disease

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Investigation of The Interaction of Apigenin and Urease Enzyme

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ABSTRACT

Helicobacter pylori infection of the stomach is one of the causes of gastric and duodenal ulcers, which sometimes show resistance to antibiotics. The urease of helicobacter pylori cleaves urea into ammonia and carbamate, which is essential for regulation of pH and survival of the bacterium. The importance of finding natural substances with antibiotic properties and less side effects has always been a matter of concern. The aim of this study was to investigate the influence of apigenin, one of the natural flavonoids in chamomile, on the structural properties of urease enzyme. The interaction of apigenin and urease was investigated using fluorescence and Circular Dichroism spectroscopy methods. Excitation wavelength was 280 nm and the fluorescence emission spectra verified in the wavelength range of 290-550 nm. The fluorescence and far UV CD (190-260 nm) spectra obtained at room temperature. The results showed that in the presence of apigenin, the emission of intrinsic fluorescence of urease decrease. The quenching process seems to be static which results from binding of apigenin to urease and formation of a complex. Although CD results showed that binding of apigenin does not change the secondary structure of urease significantly. Apigenin binding can alter the conformation of the urease

without changing its secondary structure and alter its activity. This study provides understanding of the binding and interaction of apigenin with urease. It may be possible to use apigenin and plants containing this flavonoid as a natural inhibitor of the urease enzyme in herbal medicines as well as a beneficial diet.

Keywords: Urease, Apigenin, protein conformation, Enzyme inhibition

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Design of The Uniform Device to Study of Catalase Inactivation through Static Magnetic Field

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ABSTRACT

Studies indicate that exposure to the magnetic fields due to high permeability, according to Faraday's law, causes disease risk. Cell phones and BST antennas have a magnetic flux density around 0.2 µTesla, whereas ordinary distribution pillars, power substations, and shoplifting alarms have a magnetic flux density near one µTesla. Catalase is a significant enzyme in protecting the cell from oxidative damage by reactive oxygen species (ROS). It contains Fe3+ atoms with paramagnetic properties; therefore, its performance and structure are expected to be affected by exposure to a magnetic field. In order to study the catalase activity in terms of exposure to the magnetic fields, a device was designed. This electromagnetic system has two iron cores placed in a steel frame with an adjustable distance. There is a pulley on them, and copper coils with a certain number of turns are wound on the pulleys. Two iron cores become magnets after connecting to the DC power supply. This device can generate a magnetic field in the range of 1µTesla up to 1.5 Tesla without a time limit and for any material (cell, proteins, enzyme, etc.). In this case, the desired material can be poured into the cuvette and placed between two iron cores. A platform shaker ensures that all materials inside the cuvette are subjected to a uniform magnetic field. The ambient temperature is measured with a temperature sensor. To cool the system, the device is placed in a cold room with a temperature of 4 °C. Therefore, we place the catalase in the magnetic field at different time periods and study the structure and function of catalase via spectroscopy techniques.

Keywords: Catalase, Magnetic field, Fe3+, Enzyme activation, Iron core, Uniform magnetic field

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Macromolecular Crowding Effects on The Activity and Conformational Structure of Catalase

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ABSTRACT

Crowding is due to the short-range repulsive barrier of interaction potentials with macromolecules in the cell. The effects of inert polymers with different molecular sizes and weights are known as crowding agents on the thermodynamic stability and the conformational state of the catalase enzyme were analyzed in order to understand the molecular mechanism whereby the macromolecular crowding governs the enzyme structure and activity. Bovine Liver Catalase was selected as the very important enzyme because it is used in several biotechnological processes and its metabolic importance. The activity of catalase was studied in presence of different crowding conditions using spectrometric and Molecular Dynamics methods. It can be assumed that catalase molecules in the solutions with high crowding, must stay far from each other and from substrate molecules; caused by short-range repulsion, which is ultimately due to the Pauli exclusion of atomic electrons on a length scale of about 0.1 nm. This effect also restricts enzyme spatial freedom and exerts

enthalpic weight on the system. Molecular Dynamics simulations also can be used as an approach to help with understanding the mechanism of structural change in Catalase. The crowding effect can be reasonably explained by the exclusion mechanism of crowding agents which decreases the accessible area around them.

Keywords: Macromolecular crowding, Catalase, Protein stability, Enzyme activity

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The Effect of Cadmium and Nickel Heavy Metals on The Stability of Horseradish Peroxidase

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ABSTRACT

Heavy metals are common environmental pollutants that are considered to have a high degree of toxicity. Cadmium and nickel are among the most commonly found heavy metals in wastewater which have high risks for human health and the environment. Heavy metals as environmental stress cause to oxidative damage to plants and the role of antioxidant enzymes for overcoming the stress is well known. Peroxidase induction is a general response of higher plants to the uptake of phytotoxic amounts of heavy metals like Cd and Ni. Peroxidases are heme-containing enzymes that oxidize various organic and inorganic substrates using hydrogen peroxide. In this investigation, the activity and thermal stability of horseradish peroxidase were measured in the presence of cadmium and nickel salts in order to evaluate the effect of the heavy metals on the tolerance of the peroxidase enzyme to the stress conditions. The enzyme activity was measured using ABTS substrate by the colorimetric method. The results indicated that Cd and Ni cause to decrease in the peroxidase activity and thermal stability. The remaining activity of horseradish peroxidase reduces upon the addition of both metals on the enzyme solution and the half lifetime decreases remarkably. In addition, Tm for the enzyme remaining activity reduces about 10°C. Accordingly, it can be concluded that the heavy metals influence on the peroxidase enzyme stability and cause to decrease its tolerance on the stress conditions.

Keywords: Cadmium, Nickel, Peroxidase, Thermal stability, Heavy metal, Activity

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The Effect of Substitution of Guanine with Oxoguanine and Adenine in C-Myc Quadruplex DNA on Its Interaction with Mitoxantrone

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ABSTRACT

The G-quadruplex structural motif of DNA has emerged as a novel target for anticancer drug discovery. G4 formation occurs during replication, transcription, and recombination when double-stranded DNA temporarily becomes single-stranded. Guanine rich sequences are found to occur throughout the genomes of most organisms and are prevalent in the promoter regions of a variety of genes and oncogenes, as well as at the telomeric ends of chromosomes. Small molecules that selectively target the G- quadruplex structure may serve as potential therapeutic agents and have garnered significant interest in the recent years. Several types of antitumor agents, such as anthracyclines and mitoxantrone hydrochloride, bind to DNA polymers in tumor or cancer cells, thereby inhibiting cell growth or even necrosis. It is reported that oxidative DNA base damage is presumed to play an important role in the carcinogenesis. 8-Oxoguanine is a major oxidized base lesion formed by reactive oxygen species. In this investigation, the interaction of mitoxantrone hydrochloride with 27-nt G-rich strand of c-myc proto-oncogene and its 8-oxoguanine oxidized and G to A mutated forms was evaluated by absorption and

fluorescence spectroscopic techniques. UV-visible absorption titration experiments showed that the binding of mitoxantrone to the three forms of the G-quadruplex DNA results in a red shift of 11-12 nm and 35-42% hypochromicity. The intensity of mitoxantrone emission decreases and its emission spectra shift to the longer wavelengths due to the interaction with the different forms G-quadruplex DNA. Accordingly, it can be suggested that mitoxantrone binds to the mentioned G-quadruplex DNA via intercalation.

Keywords: G-quadruplex, c-myc, Mitoxantrone, Spectroscopy, Interaction, Oxidative damage

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The Effect of Guanine Oxidation on The Ligand Binding and Folding of c-myc G-quadruplex DNA

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ABSTRACT

Overexpression of the c-myc proto-oncogene causes different types of human cancer such as colon, breast and prostate cancers. The NHE III1 region of the c-myc promoter forms a parallel-stranded G-quadruplex structure in K+ solution. Oxidative damage of DNA caused by various endogenous and exogenous agents increases the risk of cancer and aging-related diseases. Guanine is the most easily oxidized nucleotide therefore G-quadruplexes are hot-spots for DNA oxidation. Oxidation of guanine causes G:C-T:A transversions during DNA replication. Guanine converts to 8-Oxoguanine due to oxidation and only two Hoogsteen hydrogen bonds form between guanines affecting G-quadruplex structure and therefore c-myc proto-oncogene expression. Here, folding of 27-nt G-rich strand of c-myc proto-oncogene and its 8-oxoguanine oxidized and G to A mutated forms was investigated using the dual-labeled (5' HEX and 3' BHQ) G-rich oligonucleotides. In addition, the interaction between the three forms of DNA and the two fluorophore dyes was evaluated by fluorescence spectroscopy. The results indicate that when potassium ion is added to the DNA solution for stabilization of the G-quadruplex structures, folding of the oxidized and mutated forms occurs more slowly than the wild type one in the lower concentrations of potassium ion. Furthermore, there is difference among the thermal unfolding of the three forms of DNA. Interaction of hoechst with the all forms of DNA is similar, but this is not the case for thiazole orange. Consequently, oxidation and subsequent mutation influence the folding of c-myc G-quadruplex DNA and its interaction with the intercalative and outside binding ligands.

Keywords: c-myc, G-qudruplex, Oxidation of Guanine, Folding, Binding, G to A mutation

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Effect of Naringenin on Radiosensitivity of MDA-MB-231 Breast Cancer Cell Line

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ABSTRACT

Breast cancer is the most common malignancy with more than one million occurrences, worldwide. Among different cancer therapies, radiotherapy is still an important option for treatment. The application of radiosensitizers can improve the effectiveness of radiation. Former studies proved the anticancer effect of naringenin. We conducted the study on this flavonoid to investigate its effect on radiosensitivity. After performing growth curve assay and calculating the doubling time of MDA-MB-231 cell line, MTT assay was carried out. As concentration increased, the

viability decreased. In the next step, colonogenic assay was conducted and naringenin had little effect on clonogenicity of MDA-MB-231 cells. For the following assays accompanied by irradiation, cells were treated with 20 µM naringenin for 72 h, and also treated with 1000 times diluted DMSO as control for drug. Cells were then exposed to 2, 4, 6, and 8 Gy radiations. 0 Gy was also considered as the control for radiation. Colonies were counted and plating efficiencies and surviving fractions were calculated. The results indicated that, treatment of cells with 20 µM naringenin for 72 hours before radiation could not induce radiosensitivity in MDA-MB-231 breast cancer cell line.

Keywords: Naringenin, Radiotherapy, Radiosensitization, Breast cancer, MDA-MB-231 cell line, Clonogenic assay

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Eugenol Enhances Radiosensitivity of MDA-MB-231 Breast Cancer Cell Line

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ABSTRACT

Breast cancer is the most common and deadly cancer among women. Radiotherapy is one of the most common treatments for this and many other types of cancer. This type of treatment affects both cancer cells and healthy irradiated cells. Therefore, it is imperative to use a strategy that makes tumor cells more sensitive to radiation. Radiosensitizers are used for this purpose. Eugenol is a phenylpropanoid that has been shown to have anticancer effects in cancers such as skin, breast, colon, bone, lung, prostate, cervical, stomach and blood cancers. Given the widespread anticancer effect of Eugenol and similarity of its mechanism of action with radiosensitizers' action, as well as the effect of some phenylpropanoids as radiosensitizers in various cancers, this study aimed to investigate the effect of Eugenol as a radiosensitizer on the MDA-MB-231 cell line. In this study, Trypan Blue staining assay was used to measure the Viability, MTT assay for metabolic response and viability, and colony assay for cell survival. Due to the growth curve of these cells, the second day was selected as the appropriate time for drug treatment, and on this day, cells were treated with 0 to 1000 µM Eugenol for 72 h. Colonogenic assay data showed that pretreatment of MDA-MB-231 cell line with Eugenol resulted in a decrease in colonization rate in this cell line. Combined treatment with Eugenol (20 µM concentration) and radiation showed the evident role of this phenylpropanoid as a radiosensitizer.

Keywords: Eugenol, Combination Therapy, Radiosensitization, Breast cancer, MDA-MB-231 cell line, Clonogenic assay

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Curcumin Versatility on Protein and Life Sciences

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ABSTRACT

Curcumin, a natural polyphenolic product, exhibits therapeutic activity against several diseases, attributed mainly to its chemical structure and unique physical, chemical, and biological properties. The o-methoxyphenol group and methylenic hydrogen of curcumin are responsible for the antioxidant activity. Curcumin interacts with proteins through non-covalent and covalent bonding. Curcumin could bind directly to numerous signaling molecules, like inflammatory molecules, cell survival proteins, protein kinases, protein reductases, histone acetyltransferase, histone deacetylase, xanthine oxidase. The α-diketo group forms chelates with transition metals, thereby reducing the metal-induced toxicity. Curcumin could not show anticancer activity without OH in the

phenolic group. Our results demonstrated curcumin decreases protein fibrillation and ROS generation. However, its low bioavailability due to low solubility and low stability in physiological conditions is a significant challenge in the field of its efficient and effective utilization in medicinal purposes. We attempt to increase the bioavailability of curcumin that encapsulated in camel Beta-Casein increased the solubility of curcumin at least 2500-fold and curcumin encapsulation with gum Arabic and whey protein nanofibrils improved antioxidant activity. Today, the antiviral potential of curcumin has received a lot of attention. Our published review paper in this field showed that curcumin has the antiviral activity against the virus of of HIV, HBV, HPV, HSV1, HCV, HuNoV, MERS- coronavirus and SARS-Cov2 through the direct interaction with viral replication machinery or activation and suppression of signaling pathway that essential for viral replication.

Keywords: Curcumin, Functional groups, Protein fibrillation, Bioavailability, Antiviral activity

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Application of Dendrimer-Modified Graphene Oxide Nanoparticles to Doxorubicin Delivery

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ABSTRACT

Doxorubicin is an anticancer drug known for a variety of cancers. As a targeted drug, it is loaded onto branched graphene oxide nanoparticles (GONPs). In this research, polymeric coatings containing vinyl alcohol bonded of the fifth generation of dendrimers containing methyl methacrylate (MMA) and ethylenediamine (EDA) groups act as a responsive polymer.
The precursors are polymerized to form the dendrimer coating as the last carrier on the graphene oxide surface. Then polyvinyl alcohol (pH-sensitive polymer) coating is used on the surface of branched graphene oxide. When the nanoparticles carry the drug, they are not recognized by the immune system. The amount of drug release is increased. The average size of the final product is 30 nm. It is characterized by FTIR, TGA, XRD, and SEM-EDX to investigate different adsorption properties. Some of the physical parameters of the adsorption process, such as pH, time, and temperature for doxorubicin are investigated using the final adsorbent. The drug release by the adsorbent coated with pH-sensitive polymer is more than when the polymer coating was not applied on the nanoparticle. Drug release tests showed pH sensitivity behavior of graphene oxide/dendrimer/polyvinyl alcohol (GO/dendrimer/PVA), with %99.7 drug release at acidic (pH = 5.6) and %59 at neutral (pH = 7.4) conditions, that`s means in the pH of a tumorous cell and the blood pH level, respectively.

Keywords: Drug Delivery, Graphene Oxide, pH-Sensitive Polymer, Dendrimer Nanoparticles, Doxorubicin

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Volatile Compounds of Lavender as Antagonists of NR2B Subunit of NMDA Receptor: A Molecular Docking and Experimental Methods

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ABSTRACT

Lavender is one of the most important herbs in the world that has many applications in the pharmaceutical and cosmetic industries. The objective of study is to determine the chemical components of essential oil from the lavender (Lavandula angustifolia Miller) and assess their antagonist effect on N-methyl-D-aspartate (NMDA) receptors in the brain using gas chromatography coupled with mass spectrometry (GC-MS) and computational approaches. The essential oil was isolated by water distillation using Clevenger apparatus from flowering top, and GC-MS were used to analysis of chemical volatile components. Molecular docking and the evaluation of the molecular structures were carried out on the twenty components that showed the higher frequency during the experimental parts. Autodock vina version 4.0 of Pyrx software was used to perform the molecular docking of 20 ligands with NMDAR. SwissADME web tool was applied to investigate molecular descriptor values. In GC-MS analyze of essential oil samples, 41 active components were detected representing 95.5% of the total volatile compounds of cultivated lavender plant. The highest oil component of lavender was trans-carveol, isopulegol, 1,3,8, para-menthatriene and isoborneol, respectively. In silico studies showed that the first-three best binding results include trans-carveol, isopulegol and 1,3,8, para-menthatriene which demonstrated the higher affinity to active site of the NMDAR. Ifenprodil as a known antagonist shared common binding sites with Camphor, Thymol, alpha Phellandrene, Limonene, gamma-3-Carene, beta-Thujone, trans-Carveol, beta-Caryophyllene. Camphor, Thymol, beta-Thujone and trans-Carveol were the most GI absorption and trans-Carveol had the lowest binding energy with NMDAR. Camphor, Thymol, beta-Thujone and trans-Carveol could be chosen as a potential lead target to inhibit NMDAR, improve learning and memory in neurodegenerative diseases.

Keywords: Alzheimer,Äôs Disease, Volatile compounds, Lavender, Molecular docking simulation, NMDA receptor antagonist.

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Antioxidant Effects Assessment of L-Lysine and Lysulin in Streptozotocin-Induced Diabetic Rats

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ABSTRACT

Diabetes mellitus can be considered as a significant risk factor for atherosclerosis, and coronary heart disease, as well, is currently the most common cause of mortality in diabetic patients. The imbalance between pro-oxidants and antioxidants lead to oxidative stress (OS), which is one of the pathogenic mechanisms for this increased risk. Hyperglycemia induces none-enzymatic glycation, and monocyte dysfunction, resulting in soaring production of free radicals and oxidative damage of biomacromolecules like DNA, lipids and proteins. We previously elucidated the L-lysine's effects on diabetes complications, especially oxidative stress in diabetic rats, in some cell lines and in test tube. Regarding the antioxidant activities of vitamin C and zinc, it is worthy to assess the practical effects of combination of them with Lys (Lysulin) and investigating its effect on diabetic rats. The streptozotocin (50 mg/kg body weight) was injected intraperitoneally into Wistar rats to induce diabetes. Then, they were randomly divided into six groups (# 6 in each group) of normal or diabetic rats. They were treated with L-lysine, Lysulin dissolved in water, or nothing. The data showed that both Lysine and Lysulin refined oxidative stress markers, including Advanced Oxidation Protein Products (AOPP) and Advanced Glycated End Products (AGE), along with enhancing the antioxidant capacity, which was measured by Ferric Reducing Antioxidant Power (FRAP) in rats. Lysulin showed the protective effect against oxidative stress induced by diabetes in rats, much better than L-lysine alone.

Keywords: Streptozotocin, Adult Rats, Diabetic Complications, AGEs

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Investigation on The Effect of Tartrazine Industrial Dye on Structural Changes in Human Hemoglobin

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ABSTRACT

Along with changing lifestyles and increasing people's approach to the use of ready-to-eat foods, the usage of dyes are increasing day by day in food and medicine for beautifying, shape uniforming, and sometimes hiding and making imperfections and defects in food and medicine products. But the usage of these dyes is accompanied with toxic and even carcinogenic effects in humans. Hemoglobin, with its vital multifunction and oxygenation index, is one of the body's vital proteins that is targeted for such changes. In the present study, the effect of tartrazine as a dye on the structural changes of hemoglobin protein was investigated. For this purpose, after hemoglobin purifying from human blood sample and its treating with tartrazine in different time interval, fluorescence spectroscopy was used to detect changes in the hemoglobin's third structure and superficial changes. The results showed a clear effect of dye on hemoglobin structure, especially on its porphyrin ring. It can be due to opening of hemoglobin structure especially accompanied with increasing treatment intervals. Regards to direct relationship between protein structure and function, the native hemoglobin function can be disturbed by its structural changes via tartrazine. Therefore, this dye has destructive effects on the human body and should not be used. So, deep attention of different kind of industries to these destructive effects will be very important.

Keywords: Hemoglobin, Tartrazine, Structural changes, Oxidative stress

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The Inhibitorv Effect of Thvmol as A Natural Antioxidant on The Destruction of Human Hemoglobin Third Structure

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ABSTRACT

The pathology of many different diseases takes place due to oxidative stress and cellular components destruction. Many oxidative factors play an important role in the occurrence of these events. Among them, the industrial dyes with wide application in various industries have raised serious concerns. The usage of plant antioxidants has been considered as an important method for cellular oxidative stress inhibition. Among the plants, thyme or thymus from the genus Mint and the genus oregano, has powerful antioxidant properties. The phenolic antioxidants in thyme (lutein, zeaxanthin and thymonin) can neutralize and eliminate free radicals in the body. Thymol as potent active and phenolic antioxidant ingredient in thyme has anti-diabetic and antimicrobial properties which can strengthen the immune system. The present study was performed to investigate the inhibitory effect of thymol on human hemoglobin tertiary structure changes due to AZO industrial dye. For this purpose, after purifying hemoglobin from human blood sample, hemoglobin was treated with dye alone or with thymol antioxidant. The treated samples were chosen at regular time intervals and the fluorescence spectroscopy was used to track changes in hemoglobin third structure. The results showed a significant effect of industrial dye on hemoglobin tertiary structural. Our results also showed that thymol affected on hemoglobin-dye complex and prevented the

structure from opening. Its phenolic content and steric hindrance can be the reasons of thymol influence. This treatment limited the destructive effect of dye on hemoglobin structure and caused hemoglobin resistance increment.

Keywords: Antioxidant, Thymol, Hemoglobin, Oxidative stress, Structural changes

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