Docking of alpha-terpineol and linalool monoterpene with GABAa in Seizures

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Abstract

Mainly seizures occur due to an increase in excitatory types of neurotransmitters (such as: glutamate) and a decrease in inhibitory neurotransmitters (gamma-aminobutyric acid, GABA) which can cause electrical discharge in brain. Proper and effective treatment is not available in this moment (due to their ineffectiveness or adverse effects like depression and ataxia). Linalool and terpineol are alcoholic monoterpenes which can be found in some herbs. GABA is an inhibitory neurotransmitter. It lessens a nerve cell's ability to receive, create or send chemical messages to other nerve cells. Linalool and terpineols such as alpha-terpineol have many roles from antidepression to anti-inflammatory and anticonvulsant. Studies have indicated that some monoterpenoids have positive modulatory effects on insect GABA receptors. After getting PDB format of GABA-A (PDB ID: 7PDB) and preparing our ligands (Linalool and α-Terpineol, PubChem CID: 6549, 17100; respectively) we use pyrx software for molecular docking. For getting the 2D and 3D structure of our complex and its interaction we used DISCOVERY STUDIO software. Terpineol and linalool didn't violate Lipinski rule of 5 and they have high gastrointestinal (GI) absorption (data was achieved from swiss-adme). In our chosen conformer ΔG of interaction between terpineol and linalool with GABAa is -6.2 and -5.1, respectively. Based on our study linalool and terpineol have shown proper interaction and ΔG, but further investigation is needed.

Keywords: Monoterpene, Terpineol, seizure, *In silico* investigation, Molecular docking, GABAa.

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Ticlopidine inhibits FapC fibrillation and biofilm formation: Potential antibiotic properties

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Abstract

As bacteria become increasingly resistant to antibiotics and persistent infections are attributed to biofilms, there is an urgent need to develop new antibiotics to combat these problems. We investigated ticlopidine (TP), an anti-platelet drug, for its antibacterial and antibiofilm properties. TP demonstrated prolonged efficacy against both Gram-positive (MRSA) and Gram-negative (E. coli and P. aeruginosa) bacteria. It significantly reduced the survival of Gram-negative bacteria in human blood, while its effect on Gram-positive bacteria was lower. TP induced the death of MRSA by inhibiting staphyloxanthin pigment synthesis, causing oxidative stress and leading to bacterial death. Scanning electron microscopy revealed membrane damage and lysis in Gram-negative bacteria. TP exhibited strong anti-biofilm activity against P. aeruginosa and MRSA, with superior biofilm degradation in P. aeruginosa. Thioflavin T fluorescence revealed that TP inhibited amyloid formation in biofilms, which was confirmed by assays with the P. aeruginosa protein FapC. TP prolonged the lag phase of aggregation and reduced subsequent growth rates, providing sufficient time for its antibacterial effect. In conclusion, TP acts as an antibiotic against both Gram-positive and Gram-negative bacteria, targeting various bacterial processes, cellular structures and the biofilm matrix.

Keywords: Ticlopidine, Antibacterial, Bacterial biofilm, FapC, Amyloid fibrillation

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Kaempferol could suppress MMP1, a hub protein and prognostic biomarker in pancreatic adenocarcinoma identified by a bioinformatic study

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Abstract

Pancreatic adenocarcinoma (PA) is fatal with a 5-year survival rate of 8% and a median survival of 6 months. Also, the management of PA has evolved but surgical resection remains the only potential cure. Many studies have shown that kaempferol, a kind of flavonoid, has significant anticancer effects. Therefore, there is an emerging emphasis on identifying key genes, and prognostic biomarkers and performing target therapy. The top 200 significant differentially expressed genes in PA were extracted from the OncoDB database and protein-protein interaction (PPI) was analyzed via String database. Hub genes were determined using the CytoHubba plugin in Cytoscape. InteractiVenn web tool, GEPIA, and KEGG databases were used respectively for common gene, prognostic value, and pathway analysis. The docking procedure was done using the Chimera and PyRx software. The interaction of A and B chains with kaempferol, an anticancer flavonoid, was investigated. Among 24 common hub genes, KRT17, KRT19, and MMP1 are recognized as a prognostic marker. MMP1 (Hazard Ratio = 1.6, p-value = 0.03, logFC = 7) was chosen due to its role in carcinogenesis based on KEGG pathway analysis. The best models provided by PyRx revealed that the binding affinity of Kaempferol to the A and B chains of MMP1 was -5.5 kcal/mol and -5.9 kcal/mol, respectively. MMP1 was identified as a hub gene and prognostic biomarker which is upregulated significantly in pancreatic adenocarcinoma. Kaempferol could suppress carcinogenesis caused by MMP1 by effectively binding to the B chain of MMP1.

Keywords: Bioinformatics, Docking, Hub Gene, MMP1, Pancreatic adenocarcinoma, Protein-protein interaction network.

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A Molecular Dynamics Study on the Peptide-Drug Interactions in the Modified Carbon Nanotube-Based Drug Delivery System

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Abstract

Despite many achievements in cancer treatment techniques, effective therapeutic strategies with low side effects urgently required. Toward this aim, the usage of nanostructures such as carbon nanotubes have attracted growing interest. These materials often act as nanovectors (NVs) to transport anticancer agents, preventing from degradation, hydrolysis or undesirable reactions. On the other hand, peptides are versatile compounds for the development of NVs. So that conjugation of them to NVs improve their bioavailability, targeting and cell penetration. Therefore, peptide-based therapeutic strategies, coupling of good safely and adaptive functionalities have been paid attention in drug delivery. Herein, we designed the carboxylated single-walled carbon nanotube wrapped by a compatible octa-peptide named PW3 containing tryptophan (Trp), valine (Val) and lysine (Lys) amino acids for the more efficient delivery of doxorubicin (DOX) anticancer drug which has been followed using molecular dynamics (MD) simulations. MD results showed the more effective loading of DOX molecules on the nanocarrier containing PW3 chains compared to the pure one. Focusing on the drug-peptide interactions highlighted the importance of Trp residues in the PW3 peptide structure, causing DOX stably adsorption on the nanovector through π-π stacking interactions between the planar tricyclic moiety of drug and Trp indole ring. Moreover, numerous functional groups of the peptide contributed in H-bonds formation process between DOX molecules and PW3 chains which was well investigated by microscopic structural analysis. Hopefully, this research can open a new avenue for more investigations on the peptide nanovector modification for this drug, leading to the most efficient delivery system.

Keywords: Drug Delivery, Nano vectors, Carbon Nanotubes, PW3 Peptide, Doxorubicin, Molecular Dynamics Simulation

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Microscopic Interactions of Lysozyme with Aqueous Choline Based Ionic Liquids Using Molecular Dynamics Simulations

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Abstract

Due to the importance of proteins in catalysts, food, and biomedicine, many efforts have been made to preserve the protein structure for a long time without freezing. A promising way to stabilize proteins is to add aqueous solutions of ionic liquids (ILs) that stabilize proteins and do not disrupt their secondary and tertiary structures and maintain their native state [1, 2]. The properties of ILs can be adjusted by changing the type of ions or adding cosolvents. In particular, the biocompatible choline family of ILs mixed with water has shown protein-stabilizing effects [3-5]. A layer of ILs that surrounds every protein molecule in an aqueous solution plays a central role in the structure, dynamics, and function of the protein. ILs can bind to proteins by interactions such as hydrogen bonds, van der Waals, electrostatic interactions, and hydrophobic effects. They also interact with the hydrated layer water molecules. In this molecular dynamics (MD) simulation study, we intend to investigate the effect of three choline based ILs with glycinate, hydroxide, and dihydrogen phosphate anions on the intermolecular protein-IL interactions, microscopic structure, and the stability of lysozyme protein at the atomic level. Comparatively, the higher and lower protein stability is obtained in the presence of choline ILs with dihydrogen phosphate and hydroxide anions.

Keywords: Protein, Ionic Liquids, Choline Cation, Solvation Layer, Stability, Molecular Dynamics Simulation

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Detection of amyloid fibril from the other forms of protein with the help of new synthesized compounds as amyloid detector

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Abstract

Alzheimer's disease is a neurodegenerative disease that causes a great social and economic burden. The main problem in the current treatments is that they cannot stop the progress of dementia, so recent treatment approaches are changing to early intervention with the aim of stopping the neurodegeneration, as a result, early detection methods become necessary. Curcumin, a polyphenolic compound commonly known as turmeric, has shown good anti-inflammatory, anti-cancer, neuroprotective and diagnostic properties. In this research, curcumin derivatives were used to distinguish amyloid fibrils from other protein forms (amorphous aggregate and native). The results of protein morphology studies, including scanning electron microscope (SEM), analysis of Congo Red standard markers and thioflavin-T (ThT) fluorescent probe confirmed the formation of ovalbumin protein amyloid fibrils (as a model protein). The results of the fluorescence analysis showed that the L13 probe has the ability to specifically detect amyloid fibrils, but its diagnostic power is lower than the standard thioflavin-T probe and it shows a lower emission intensity. Also, the results of docking studies showed that the L13 probe has a lower binding tendency to beta amyloid (lower binding energy), which confirms the experimental data. Although the diagnostic power of the L13 probe is lower than ThT, it does not have permanent positive charge like that and because it is curcumin based, it may have anti-amyloid properties. Also, the results showed that this probe has better function in lower concentrations (10 μM), so, it can be a good candidate as a diagnostic probe for amyloid fibrils.

Keywords: Protein aggregation, Amyloid fibril detection, Ovalbumin, Bovine serum albumin, Curcumin derivatives.

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In silico and in vitro effect of bacterial derived antibiotics on aggregation of proteins

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Abstract

Amyloid proteins are widely recognized as the etiological factors behind many neurological disorders. This study was conducted to investigate the possible inhibitory effects of antibiotics derived from microorganisms on the process of protein fibrillation. To achieve this goal, a combination of computational and biological screenings was used, using human lysozyme as a representative model of amyloid. Using computational methods, the interaction of antibiotics with human lysozyme was investigated spatially, and then the inhibitory effects of antibiotics on amyloid fibrillation of human lysozyme were shown using turbidimetric evaluation and thioflavin T (ThT) fluorescence analysis. For further investigations, the antibiotics erythromycin and vancomycin, which had anti-aggregation activity in the previous tests, were confirmed in 8-anilino-1-naphthalene sulfonic acid (ANS) and dynamic light scattering (DLS) assays. It was shown that the erythromycin and vancomycin has the potential to reduce the fibrillation of human amyloid lysozyme by30% and 70% reduction in ANS assay and 99.8% and 99.5% reduction in lysozyme fibrillation in DLS assay, respectively. Furthermore, both erythromycin and vancomycin predicted to make interaction with the active site of the lysozyme and form a stable complex mainly by hydrogen bonding, van der Waals forces, and hydrophobic contacts. Thus, erythromycin and vancomycin are suggested as candidate compounds for reducing the accumulations of amyloid-beta for drug repurposing purpose.

Keywords: Neurodegeneration, Amyloid, Human lysozyme, Antibiotics, Molecular docking.

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Finding Myxobacterial compounds modulating bone differentiation targets of ALP and RUNX 2 by in silico prediction

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Abstract

The condition of osteoporosis (OP) characterized by decreased bone mass, increased fragility, and decreased bone microstructure requires new medications for treatment. The first step was to collect in the scientific literature commercially available compounds from myxobacteria. Alkaline phosphatase (ALP) and Runt-Related Transcription Factor 2 (RUNX2), both activated during osteoblast differentiation and maturation, were targets of osteogenic-promoting agents in this study. Through docking studies, specific interactions between myxobacteria compounds and crucial targets were verified and compounds activating ALP and RUNX 2 were screened according to their affinity for receptor-binding pockets. The gene targets of Epothilone A, Myxothiazol, and Ratjadon were intersected with known osteoporosis targets, and key genes were explored with the Metascape tool using GO enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. A gene list enrichment was performed in the TRRUST ontology category with a p-value < 0.05, a minimum count of 3, and an enrichment factor > 1.5, among which several terms are related to osteoblast differentiation and regulation: STAT3, RUNX2, SP3, HDAC1, and HIF1A signaling pathways. According to the results, compounds from myxobacteria were found to reduce osteoporosis by improving signaling pathways involved in osteogenesis. It is possible that bone disorders can be effectively treated with promising compounds targeting bone-promoting pathways.

Keywords: Differentiation osteoblast, Myxobacterial compounds, Molecular docking, Alkaline phosphatase, Runt-related transcription factor 2.

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A Bioinformatic Study on The Effect of Amino Acid Content and/or Sequence on Protein Aggregation and Protein Liquid-Liquid Phase Separation

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Abstract

Studies on neurodegenerative diseases indicate that there exist a strong casual relation between protein aggregation and occurrence of these diseases. Protein aggregation and folding are two manifestations of amino acid sequence and content which if understood would become instrumental in development of effective therapies against these lethal and drastic diseases. In recent years it was also became clear that formation of aggregate species from monomeric molecules of peptides and proteins needs to pass a stage of liquid-liquid phase separation in the cytosolic and/or extracellular space to make membrane less organelles in the former or simply an assembly in the latter. In this work we have tried to investigate common features in amino acid sequence and/or content of peptides and proteins such as beta amyloid peptide (Aβ42), tau protein, alpha synuclein, … that cause them firstly produce a separate phase and then become aggregated, through bioinformatic methodologies such molecular ducking and molecular dynamics by coarse modeling (e.g., GROMACS) and by all-atom approach. We have understood that the presence of amino acids such as glycine, arginine, tyrosine, tryptophan, and serine, and formation of motifs such as RGG is a crucial factor in phase separation and aggregation and seen commonly in proteins.

Keywords: Bioinformatics, phase separation, aggregation, amino acid sequence, motif.

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A Comparative Study on the Effect of Protein Aggregates on the Induction of Apoptosis in Human Neuroblastoma Cells (SH-SY5Y) and Human Adipose Mesenchymal Stem Cells

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Abstract

Alzheimer's disease (AD) is the most common form of neurodegenerative disease that causes gradual loss of memory, learning and cognition. The death of neurons occurs as the main pathological event which is mainly due to the aggregation of extracellular amyloid beta protein and intracellular tau protein and subsequent formation of neurofibrillary tangles. Stem cell therapy, to alleviate neuronal death, is proposed as potentially good approach to construct a treatment regimen for AD. This approach could be considered if the appropriate and candidate stem cell itself be tolerant against the toxic effects of proteinaceous aerates. In this regard, we investigated the interactions between human adipose mesenchymal stem cells (AMSC) and human neuroblastoma cells (SH-SY5Y) with human lysozyme protein aggregates. The aggregates of lysozyme were formed and then the viability of the above-mentioned cells was investigated upon their presence in the culture media. Morphological and viability tests presented dual characteristics of both apoptosis and necroptosis cell death. Due to these observations, more precise tests on the type of cell death were executed to rule out various cell death hypothesis and manifest a single one. Therefore, cell cycle arrest, apoptosis assay via Anexin-PI, phosphorylation of MLKL and more precise examinations on morphological changes via TEM microscopy were studied, after cell exposure to aggregated lysozyme. The results showed the aggregates of lysozyme caused cell apoptosis in old AMSC and SH-SY5Y cell line but not in young AMSC, which was very promising in the future usage of stem cells in AD therapy.

Keywords: protein aggregation, lysozyme, human adipose mesenchymal stem cells (AMSC), human neuroblastoma cells (SH-SY5Y), stem cell therapy, apoptosis, necroptosis.

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A molecular docking study on the interactions between lysozyme, insulin and amyloid beta peptide with melatonin as their ligand

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Abstract

Protein aggregation is associated with a wide range of human diseases, including neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease. Protein aggregation exerts its pathogenic effect by depositing aggregates in certain tissues such as brain. AD is one of the types of diseases that destroy the nervous system and is known as the most common type of dementia, and many people around the world suffer from this disease and the number of patients is increasing rapidly. One of the main causes of Alzheimer's disease is misfolding and then the formation of amyloid-beta aggregation outside the nerve cells and tau protein inside the cells, which eventually causes the death of brain neurons. Inhibiting the formation and development of these protein aggregates using aggregation inhibitory molecules is proposed as one of the therapeutic targets of Alzheimer's disease. In this study, the effect and interaction of melatonin, which has a wide range of properties, such as antioxidant, anti-apoptotic, and anti-amyloid properties, with three proteins, lysozyme, insulin, and amyloid beta, has been studied by docking method. The aim of the study is to compare the specific or general inhibitory effect of melatonin on the aggregation of these proteins. Docking studies show that the negative binding affinity of melatonin with lysozyme, insulin and amyloid beta proteins is -6.4, -4.5 and -5.3, respectively, which can be the basis for further in vitro studies and investigating the inhibitory effect of melatonin on these proteins.

Keywords: Protein aggregation, Alzheimer's disease, melatonin, beta amyloid, molecular docking, neurodegenerative diseases.

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A study on Measuring the Inhibitory Effect of Two Types of Synthesized Porphyrin on Lysozyme Protein Aggregation

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Abstract

Amyloid aggregation is associated with many degenerative diseases of the human nervous system, such as Parkinson's disease, Huntington's disease, and Alzheimer's disease, which are caused by the loss of neurons and glia in the brain or spinal cord. Aggregation of proteins involved in this kind of diseases causes toxicity. Therefore, targeting the aggregation of proteins and peptides in degenerative diseases of the nervous system is used as a potential treatment function. By using compounds and small molecules such as tetrapyrroles, the aggregation of involved proteins and peptides can be targeted. This implies the fact that a significant contribution to the inhibition of amyloid formation is made by the cumulative interaction between the aromatic moieties of the inhibitors and the aromatic amino acid residues of peptides and proteins. In this study, tetrapyrrole compounds were used in order to inhibit aggregation at different levels. Lysozyme was used in this study as an aggregation model protein and the effect of a number of synthetic tetrapyrrole compounds were studied on its aggregation. Lysozyme monomer showed typical sigmoidal growth curves with three different lag phases, logarithmic phase and saturation phase. Incubation of MC1PP and TC4PP with lysozyme at a molar ratio of 1:50 showed ThT fluorescence at 440-485 nm, which indicated that MC1PP and TC4PP could inhibit the fibrillization of lysozyme by approximately 50%.

Keywords: Degenerative diseases of the nervous system, Lysozyme, Porphyrin, Porphyrin derivatives, Amyloid aggregation.

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An investigation on the effect of mutation in cancer cell on binding of mitoxantrone to G-quadruplex DNA by spectroscopic and electrophoresis techniques

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Abstract

G-quadruplex structure detected especially in Nuclease Hypersensitive Element (NHE III1) upon the promoter of c-Myc gene that roles as gene silencer. c-Myc gene have many roles on cellular function and malfunction of this gene expression causes cancers. The rate of mutation increases in cancer cells due to high rate of proliferation, for example G to A single mutation in NHE III1 region of c-Myc gene increase its expression. Mitoxantrone is a chemotherapeutic drug used for treatment of different types of cancer. In this investigation, the effect of single nucleotide mutation in the middle G-tetrad of the c-MYC promoter was evaluated on binding of mitoxantrone to G-quadruplex structure of c-MYC promoter sequence in vitro. In this investigation, absorption spectroscopy, fluorescence emission spectroscopy and Poly Acrylamide Gel Electrophoresis (PAGE) were used. The spectroscopic results indicated that mitoxantrone influences on folding of the both sequences that labeled with fluorophore and quencher; it brings the two ends of G-quadruplex structures together. Mitoxantrone binds externally to the wild and mutated types and end stacks on the G-tetrad planes of them. Analysis the spectra implied that binding affinity of the drug changes upon G to A transition in the middle G-tetrad. In addition, the electrophoresis indicated that the transition influence on the conformation of G-quadruplex structure and electrophoretic mobility of the two types of structure in the Gel. In conclusion, it can be said that the mutation of DNA in cancer cell probably influences on the binding of DNA-binding anticancer drug to DNA sequences.

Keywords: G-quadruplex, G to A transition, Mitoxantrone, c-Myc, Promoter

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The effect of transition from guanine to adenine at the end G-tetrad planes on the interaction of doxorubicin with c-MYC promoter G-quadruplex

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Abstract

G-quadruplex (G4) is a structure that is formed in guanine-rich regions by creating guanine tetrad sheets. c-MYC promoter is a 27-nucleotide region rich in guanine base that forms G4. This gene regulates cell growth and proliferation, so the c-MYC promoter is considered a target for designing chemotherapy drugs. Guanine to adenine mutations are nucleotide mutations that occur in the c-MYC promoter of cancer cells. Doxorubicin is anthracycline chemotherapeutic agents. Here, we investigated the interaction of doxorubicin with G4 in c-MYC gene promoter and two mutated one with a single G to A transition at 5'-end and 3'-end tetrad planes. Fluorescence and absorption spectroscopy and gel electrophoresis were used to evaluate the interaction. The results of spectroscopic techniques indicated that the G to A transitions have no influence on the mode of binding and doxorubicin bind externally to grooves, loops and/or end tetrads of wild and the both mutated types of G4. Based on Scatchard plots, the drug binds in a negative cooperative manner to the all types of G4. Analysis the spectra demonstrated that the mutations lead to increase binding and Stern-Volmer constant values indicating G to A transition at the end tetrads increase binding affinity of doxorubicin to the G-quadruplex DNA. Gel electrophoresis indicated a meaningful retardation in mobility of the G4 structures upon binding to the drug. Consequently, G to A transition at the end tetrad planes influence on the binding affinity, but not on the mode of binding of doxorubicin to c-MYC promoter G-quadruplex.

Keywords: Doxorubicin, c-MYC Promoter, Mutation, Interaction, G-quadruplex.

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Detection and monitoring of amyloid fibrils using oxazolidine compounds

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Abstract

Protein misfolding leading to formation of amyloid fibrils is a key feature of a wide range of neurodegenerative diseases, including Alzheimer's diseases, Parkinson's disease, and type II diabetes [1,2]. Therefore, efficient detection and monitoring of amyloid fibrils can significantly advance early diagnosis and therapy relating to these diseases. The most common existing fluorescent probe for detection of amyloid fibrils is Thioflavin T [3,4,5]. But drawbacks such as interfering with fibrillation process and quenching of its fluorescence upon entrance into cell have significantly restricted its application as an efficient probe for cellular studies. Herein, we present two molecular probes Oxazolidine 1 and 2 with the potential to detect amyloid fibrils. Both probes were able to monitor the nucleation-dependent kinetic of human insulin and α-synuclein amyloid fibrillation in vitro. This ability was further confirmed using fluorescence microscopy. Moreover, co-localization of FITC-labeled human insulin with oxazolidines further confirmed the binding of these compounds to the amyloid fibrils, but not monomers, of protein. Our preliminary data indicated the uptake of these compounds by SH-SY5Y cells suggesting their potential to use as molecular probes for detection of intracellular aggregates.

Keywords: α-synuclein, human insulin, fibril, Thioflavin T, Oxazolidine.

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AtPEPR1 receptor can perceive the nanomlar ratio of AtPep1 ligand and activate the immune system in the genetic model Arabidopsis thaliana

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Abstract

In innate immunity, the pattern recognition receptors (PRRs) recognize microbial and danger defense signal components known as microbe-associated molecular patterns (MAMPs) and damage-associated molecular patterns (DAMPs) known as host-derived danger signals. As the consequence of ligand perception, the immune system is activated. AtPEPs ligands are small peptides that are regarded as endogenous peptide signals in the model plant A. thaliana. They are considered as DAMPs because they play a critical role in defense signaling, but they may also be involved in development. Specific perception by the AtPEPRs, like perception of microbe-associated molecular patterns by the corresponding PRRs, leads to the activation of downstream defense cascades including ion fluxes across the plasma membrane such as increase in Ca2+ influx and activation of specific transcription factors that have important role in the transcription of defense marker genes. In the current study, we have investigated several molarity ratios of AtPep1 including 10 micro-molar, 1 micro-molar, 10 nono-molar and 1 nano-molar to evaluate the sensitivity of ligand perception by specific receptor AtPEPR1. In our sensitive gene expression system, we found that even at the one nano-molar ratio, AtPep1 can perceive by its specific receptor and expression of the transcription factor of the important defense marker gene including WRKY40 is dramatically increased 30 minutes after ligand perception. This finding clearly showed the high specificity of AtPep1 as the very sensitive ligand signal in innate immunity. This is the first report of high sensitivity of AtPep1 as the very specific ligand signal.

Keywords: Receptor, AtPEPR1, ligand, signal, immune system.

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Structural Properties of β-catenin Destruction Complex; Computational Approach

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Abstract

In the 19th century, it was discovered that lithium could inhibit glycogen synthase kinase 3 beta (GSK3β) and improve symptoms related to Bipolar Disorders (BD). Previous studies have focused on the effect of GSK3β inhibition, and this research uses computational tools to investigate the role of the Wnt pathway in neurological disorders at protein-protein β interaction level. The study examines the effect of APC protein mutations attributed to schizophrenia (SCZ) on the stability of β-catenin destruction complex, as a complex affected upon Wnt pathway, as well as the presence of GSK3β (the most important proten in BD). To achieve this, we employed molecular docking methods and utilized the HADDOCK tool to generate four states of the four-protein complex (GSK3β-2, APC, β-catenin and AXIN) in the presence of the water molecules. The affinity of these four sets was determined by calculating GB/SA scores, and the results showed a significant increase in binding affinity and GB/SA score. According to the results, the Wnt pathway may be disrupted by APC protein mutations that increase the binding affinity of β-catenin destruction complex, despite its natural tendency to inhibit the β-catenin destruction complex assembly. In conclusion, this probably causes a malfunction in the Wnt signaling pathway.

Keywords: GSK3β, APC, β-catenin destruction complex, molecular docking, complex assembly, Binding affinity.

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Binding of doxorubicin to wild and single nucleotide-mutated NHE III1 region of c-Myc promoter

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Abstract

G-quadruplexes are four-stranded DNA arrangements that occur in guanine-rich sequences. They play a regulatory role in proto-oncogene expression like c-MYC gene. Doxorubicin, a potent anthracycline anticancer drug, leads to the inhibition of DNA and RNA synthesis. It has been reported that G to A mutation in NHE III1 region of c-Myc promoter influences on the expression of this gene. This study aims to investigate binding of doxorubicin to wild and single nucleotide-mutated NHE III1 region of c-Myc promoter that form G-quadruplex structure in vivo. The mutated nucleotide is in the middle of G-tetrad plane. Spectroscopic techniques including absorption spectroscopy and fluorescence emission spectroscopy and poly acrylamide gel electrophoresis (PAGE) were used to evaluate interaction between the G-quadruplex structures and doxorubicin. The spectroscopic results indicated that doxorubicin influences on folding of the wild and mutated sequences in a different manner; it brings the fluorophore and quencher labeled ends of the mutated structure closer together at the low concentration, but increases the two ends distance at the higher concentration, while the distance between the two ends of wild DNA increase upon binding to the drug at the all concentrations. In addition, the mutation changes binding affinity of doxorubicin to the G-quadruplex structure. The electrophoresis indicated that the locations and intensity of the DNA bands are influenced by the mutation indicating change in the conformation of G-quadruplex structure. It can be concluded that the mutations in the cancer cells should be considered in examining the drug effects.

Keywords: G-quadruplex, Doxorubicin, Mutation, Interaction, Ligand-binding.

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Efficient Inhibition of Amyloid Fibrillation Human Insulin Using Biosynthesized Silver Nanoparticles Decorated by Polyphenols of Echium Amoenum

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Abstract

Neurodegenerative diseases include a wide range of human diseases resulting from the misfolding and aggregation of amyloidogenic proteins into soluble oligomers and eventually mature fibrils Accordingly, most remedial strategies are mostly based on developing drugs that inhibit amyloid fibrillation. Among large variety of compounds screened to identify molecules effective in inhibition of amyloid fibrillation, use of naturally-occurring molecules, especially certain dietary polyphenols extensively found in foods and herbal remedies, has attracted a great attention. Borage (Echium Amoenum) is an ancient herbal plant with a diverse chemical composition, including anthocyanins, various flavonoids, and alkaloids, and exhibits anti-inflammatory, antianxiety, antidepression, and antioxidant properties. In the present study, the extraction of polyphenolic fraction of Borage petals (PFBP) was confirmed using spectroscopic assays. Using a range of methods for amyloid detection, including Thioflavin T fluorescence assay and Congo red binding measurement, we showed the potency of PFBP in preventing the amyloid fibrillation of human insulin in a dose-dependent fashion. Further experiments are needed to elucidate the mechanism involving anti-amyloidogenic properties of PFBP.

Keywords: Amyloid fibril; Human insulin; Thioflavin T; Borage; Polyphenol.

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Binding of Some curcumin degradation products to Bovine Insulin and their effect on the protein fibrillation

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Abstract

Amyloid fibrils are stable structures that form when peptides and proteins misfold due to genetic factors and environmental stresses. These fibrils cause diseases such as Alzheimer's, Parkinson's, and Huntington's. Polyphenols have the potential to prevent amyloid fibril formation. Curcumin is a polyphenol from Curcuma longa that is unstable and prone to degradation in the physiologic condition. There are many investigations on the biological effect of curcumin, but not its degradation products. This investigation aimed to evaluate the interaction of vanillin and ferulic acid as two degradation products of curcumin with bovine insulin as well as their effect on their effect on the amyloid formation of the protein. In addition, curcumin was degraded at the alkaline pH and then the inhibitory effect of the degraded curcumin was evaluated on the amyloid fibrillation. The experiments were carried out by fluorescence spectroscopy, fluorescence microscopy, and atomic force microscopy. The results of fibrillation of bovine insulin demonstrated that not only curcumin but also the products of curcumin after degradation inhibit fibrillation. In addition, both vanillin and ferulic acid affect the protein. Consequently, it can be concluded that curcumin after degradation still has the potential to inhibit amyloid formation.

Keywords: Bovine Insulin, Fibril formation, Degradation, Curcumin, Vanillin and Ferulic acid.

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A study on the propensity of proteins for binding to Azole compounds using embedded information in protein primary structure

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Abstract

The exploration of protein-ligand binding sites is an important aspect of studying biological activities. Prediction of ligand binding sites was based on sequence and structure; however, some methods combined these two approaches. Azole compounds play a critical role as antimicrobial and antifungal. In this study, we employ a novel method to Predict protein-ligand binding sites using protein sequence and structure. we identified the residues which participate in interactions between azoles and proteins. The Specific sequences of proteins that were involved in binding to the azole ring were extracted. residues of ligand binding sites were collected into a library. we used Multiple sequence alignments to create blocks, and then a consensus sequence was generated. this sequence was scanned against the Protein Data Bank to generate a Position-Specific Scoring Matrix (PSSM) using PSI-BLAST. The results of the PSSM search against the database show proteins that specifically have an azole ring but, this approach has a high false positive rate because of an imbalanced database and results show that our method achieves Matthew correlation coefficient (MCC)=0.0516, Accuracy (ACC)=9.86% and Sensitivity (SN)=4.65%, therefore to improve the accuracy of our method after increasing the size of the control negative database we employed receiver operating characteristic (ROC) analysis to adjust an E-value threshold for the PSSM matrix generated. Finally, we achieved results with an AUC=93.2%, ACC=90.4%, SN =88.38% and MCC of 0.7740 in the optimized Threshold. however, these results show that, other approaches can also perform on this proposed method to improve results beside our analysis.

Keywords: protein, ligand binding site, azole compounds, Position-Specific Scoring Matrix, sequence.

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Inhibition of amyloid fibrillation of human insulin using porphyrin derivatives and baicalein

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Abstract

Aberrant folding and aggregation of peptides/proteins are associated with various neurodegenerative diseases, including Alzheimer's and Parkinson's diseases, characterized by the formation and precipitation of fibrillar structures known as amyloid fibrils. Protein aggregation into amyloid fibrils appears to be initiated by destabilization of their native conformation that may result in formation of partially unfolded intermediates. This may suggest that inhibition of amyloid formation and/or clearance of fibrillar structures may provide an effective therapeutic approach for treatment of amyloid-related diseases, leading to extensive research for discovering compounds with anti-amyloidogenic properties. So far, many compounds have been studied to inhibit the formation of amyloid fibrils. Among these inhibitors are polyphenols with antioxidant properties. Porphyrin and its derivatives are among other compounds that have the ability to bind to proteins and inhibit their self-assembly. In this study, the potency of two porphyrin derivatives, including 5,10,15,20-tetrakis(4-carboxyphenyl) porphin (TCPP) and 5-mono-4carboxyphenyl(10,15,20-triphenyl) porphin (MCTPP), and Baicalein polyphenol in modulating the fibrillation process of human insulin was investigated using a range of techniques, including oxazolidine fluorescence assay and intrinsic fluorescence measurement. The obtained results showed that all tested compounds were able to effectively inhibit the fibrillogenesis of human insulin even at protein: compound ratio as low as 100:1. In addition, TCPP showed a higher inhibitory effect. For samples incubated with baicalein, however, we did not observe any significant inhibition.

Keywords: Amyloid fibril, Human insulin, Baicalein, MCTPP, TCPP, Oxazolidine.

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Identification and investigation of some genes coding for receptors involved in immune response for human and Arabidopsis thaliana models: A bioinformatics study

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Abstract

Eukaryotic cells have developed intricate defense mechanisms to confront microbial challenges and safeguard the overall integrity of the organism. Both plants and animals possess a conserved innate immune system, which is effective in neutralizing pathogens and constraining infections. In this study, we investigated the genes encoding common membrane receptors that are involved in the immune response in humans and Arabidopsis. First, we extracted the sequence of human TXK tyrosine kinase and EFNB1 receptors and FLS2, CRK1 and DRD1 genes of Arabidopsis in the Uniprot database. Then we examined their homologs in Arabidopsis and humans. The Protparam server was used to check the physicochemical properties of genes. The domains of the genes were checked with the Interpro server. Also, the gene network for each gene was checked with the STRING server. The protein structure of candidate genes was checked with PDB server and drawn with I-TASSER. The phylogeny relationship with the data of proteins FASTA format was checked with Mega software. Our results showed that human TXK gene has high similarity with STY, human EFNB1 Receptor gene with GRP14 in Arabidopsis. Human FLS2, CRK1 and DRD1 genes showed a high similarity percentage with LRRC39, IRAK4 and ABCG2 genes, respectively. By examining the obtained gene network, all these genes are involved in the path of immune responses both in humans and in Arabidopsis. Also, the results of physicochemical characteristics of homologous genes showed a positive relationship. The results of the phylogeny tree showed the relationship of the genes.

Keywords: innate immune system, TXK, EFNB1, FLS2, CRK1.

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Investigation of the interaction of some small molecules with native and fibrillar forms of human insulin: an in silico molecular docking study

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Abstract

Amyloids are fibrillar, non-branching structures of proteins resulting from protein self-assembly. The appearance of these structures is associated with a wide variety of human diseases such as Alzheimer's and Parkinson's diseases and type II diabetes. Human insulin is prone to form amyloid fibrils, which may pose a significant challenge during storage and when subcutaneously injected into patients with diabetes. By reducing the time and cost associated with experimental screening, bioinformatics-based approaches such as molecular docking are emerged as effective tools in drug discovery. In this study, we employed molecular docking to identify possible binding modes of baicalein and two porphyrin derivatives, including 5,10,15,20-tetrakis(4-carboxyphenyl) porphin (TCPP) and 5-mono-4carboxyphenyl(10,15,20-triphenyl) porphin (MCTPP) with native (PDB ID:3I40) and fibrillar forms of human insulin derived from B-chain residue 12-17 segment of insulin (PDB ID:2OMQ). The blind docking was performed for three ligands to be flexible and the protein to be rigid. All tested ligands were able to interact with significant residues in chain B of insulin, which plays a crucial role in the process of insulin fibrillation. The interactions between the ligands and human insulin residues promotes mainly through pi-alkyl, pi-pi stacking, and hydrogen bonding. Among the three ligands, MCTPP exhibited the highest binding energy, followed by TCPP and baicalein showing poor binding energy. Based on these results, we may suggest that these ligands could prevent amyloid fibrillation of human insulin.

Keywords: Amyloid, Human Insulin, Molecular docking, baicalein, porphyrin derivatives.

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Bovine serum albumin facilitates the adequate ligand perception by its corresponding receptor AtPEPR1 and trigger the robust innate immunity response in Arabidopsis thaliana

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Abstract

Microbe-associated molecular patterns (MAMPs) are highly specific and conserved molecules from microbes that as a ligand specifically bound by host pattern recognition receptors (PRRs) to trigger immune responses. PRRs are receptor-like kinases that mediates the recognition and perception of invading signals and subsequently activate the adequate defense responses. PRRs can sense the signals from bacteria, fungi and viruses. More recently it is observed that damage-associated molecular patterns (DAMPs) known as host-derived danger signals can trigger the defense response same as the invading agents. Among the several classes of DAMP endogenous signals that have been identified so far, the importance of AtPep1 in higher plants needs more investigation. The downstream signaling mechanisms should be understood and proper ligand perception needs to be evaluated. In the current study, we have evaluated the innate immunity response in the model plant Arabidopsis thaliana and monitored the expression of the pathogenesis-elated gene 1 (PR1) as an important defense marker gene and the expression of the transcription factor WRKY40 with and without Bovine serum albumin (BSA). We observed that in compared to the control, the presence of BSA can facilitate the full ligand perception and dramatically activate the expression of PR1 and WRKY40 genes. We observed that BSA diminish nonspecific binding sites and increases the full ligand perception. We found that the BSA enhance the sensitivity of the adequate ligand perception by its corresponding receptor AtPEPR1. This finding clearly showed the importance of BSA for proper perception of AtPep1 as an important ligand in innate immunity in Arabidopsis.

Keywords: BSA, Receptor, AtPEPR1, ligand, signal, innate immunity.

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A potent conductive EGCG-GO grafted cellulosic scaffold for enhanced neural differentiation: Unveiling the potential of a hybrid platform for neural development

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Abstract

Combining natural compounds with nanomaterials to mimic healthy tissue microenvironments offers a novel approach for human tissue engineering. Epigallocatechin gallate (EGCG) is one of effective polyphenols with neuro-inductive capability but current delivery approaches are still nonefficient for clinical applications. On the other hand, coating graphene oxide (GO) offers a solution for EGCG manipulation as well as improving conductivity of obtained matrices. This study assessed the in-silico interactions between EGCG, graphene oxide and herbal-derived cellulose scaffolds and evaluated the impact of EGCG-GO-cellulose scaffolds on induction of neural differentiation. First, in-silico studies, molecular docking with AutoDock4 conducted to evaluate the interactions between EGCG and GO as well as the binding affinity of the conjugates to the cellulose scaffolds. This computational approach provided valuable insights into the effectiveness of our material design at the molecular level. In order to prepare scaffolds, first decellularized Phoenix dactylifera by using detergent-based protocol, after freeze-drying and plasma treatment, the scaffolds were immersed in a GO adhesion to the cellulose matrix. Following this, the GO-treated scaffolds were then soaked in EGCG. Molecular docking revealed a high-affinity interaction between EGCG-GO and the cellulose scaffold. The EGCG-GO grafted cellulose scaffolds showed hopeful results in promoting neural stem cell viability, and differentiation which confirm their potential for neural tissue repair applications. This approach combines the advantages of GO's conductivity, EGCG's neuroprotective properties, and cellulose's biocompatibility, offering a promising platform for future regenerative medicine strategies.

Keywords: Neural differentiation, Graphene oxide, Molecular docking, Tissue engineering, Regenerative medicine.

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Evolutionary Study of a Complex of Four Proteins Involved in The Wnt Signaling Pathway

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ABSTRACT

The Wnt signaling pathway is a key pathway involved in cancer cell proliferation and invasion. The major regulatory complex in this pathway consists of glycogen synthase kinase 3 beta (GSK-3beta), adenomatous polyposis coli (APC), axin2, and beta-catenin. To study the evolution of the protein complex, species from four different groups of vertebrates including homo sapiens (human), gallus gallus (grey hen), xenopus laevis (African clawed frog), and danio rerio (zebra fish) were selected. Homology modelling was performed on the FASTA sequences of the four proteins. Dimer (GSK-3beta/beta-catenin), trimer (GSK-3beta/beta-catenin/axin2), and tetramer (GSK-3beta/beta-catenin/axin2/APC) complexes were formed by a step-wise docking. After an energy minimization step, the dimer, trimer, and tetramer complexes with minimum energies were determined. Several energetic parameters were compared among GSK-3beta, beta-catenin, and the obtained complexes. It was the electrostatic force that maintained the stability of the studied complexes. The enhancement of 'mers' reduced the ruining effect of the Van der Waals energy during evolution. It seemed that in the lower organisms the dimer was more stable than the trimer complex while in the higher ones like human beings the trimer complex was more stable than the dimer. In the case of the bird neither the dimer nor the trimer was stable. There, the tetramer complex is suggested to be able to overcome the problem. In conclusion, the formation of the GSK-3beta/beta-catenin/axin2 complex was more favorable in higher vertebrates than in lower ones and this happened mainly through increased electrostatic and decreased Van der Waals energies.

Keywords: Network evolution, Protein-protein interaction, GSK-3beta, Beta-catenin, axin2, Wnt signaling.

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Investigating The Inhibitory Effect of Some New Triazole Compounds on Mushroom Tyrosinase Activity

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Abstract

Tyrosinase is an important enzyme in melanin biosynthesis and physiological functions in various organisms. increased tyrosinase activity leads to disorders such as hyperpigmentation, freckles, age spots, melasma, as well as enzymatic browning of freshly cut or damaged fruits and vegetables during harvest. therefore, the ability of tyrosinase is very high. in this study, for the first time, the effect of two triazole compounds on the activity of diphenolase of mushroom tyrosinase was investigated. the interaction of the ligands with the enzyme was done through molecular docking (theoretical) by the autodock 4.2 program and the results were analyzed by discovery stoudio and ligaplot. (experimental) fluorescence quenching studies the reduction of tyrosinase emission due to binding with both ligands was investigated by fluorescence spectroscopy. the results of fluorescence quenching showed a decrease in the intensity of enzyme release in the presence of both compounds (1-(3-(3-1-venyl-1h-imidazol-3-iom-1-yl)propyl)-1h-1,2,3- triazol-5-yl)methyl)-1,4-diazabicyclo[2.2.2]octan-1-iome bromide and 2-((1-benzyl-1h-1,2,3-triazol-4-)yl)methyl) showed isoindoline-1,3-dione and the quench is of static type. the molecular docking results showed the binding of ligand 1 and 3 to tyrosinase with ΔG -6.41 and -4.17, respectively. the molecular docking results confirm the fluorescence quenching results.

Keywords: tyrosinase, melanin, triazole, molecular docking, fluorescence quenching.

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Binding of H2T(2-N-MePy) P and H2T(3-N-MePy) P to human telomere G-quadruplex DNA

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Abstract

Human telomeric region has tandem repeats of TTAGGG. Telomeres protect chromosome ends from degradation, rearrangement, and end joining. The non-coding repetitive single stranded sequences in the telomere have a potential to form G-quadruplex (G4) structure in the physiological condition. G4 structures are promising targets for treatment of cancer, therefore the ligands that bind and stabilize these structures are candidate for cancer therapy. Porphyrins are aromatic tetracyclic compounds with a wide Ї€ planar structure and large cationic groups that bind to different forms of DNA structure, so these compounds are investigated as candidates for chemotherapy. In this study, the interaction of H2T(2-N-MePy) P and H2T(3-N-MePy) P with human telomeric G-quadruplex DNA was evaluated by absorption spectroscopy, fluorescence spectroscopy, circular dichroism and electrophoresis. Circular dichroisom indicated that the both porphyrins decrease the structural compactness. A little decrease in the intensity and 2 nm red shift of absorption spectra concomitant with quenching of the fluorescence spectrum of H2T(2-NMePy) P demonstrated that this porphyrin binds to the grooves and/or the loops of the G-quadruplex DNA. Binding of the other porphyrin leads to 10 nm red shift and 67% hypochromisity of the absorption spectra and a remarkable decrease in intensity of the fluorescence spectra indicating H2T(3-N-MePy) P binds between the G-tetrads. Retardation in the electrophoretic mobility of the G4 structure was observed in the presence of H2T(3-N-MePy)P and the other porphyrin has no such effect. Consequently, the results demonstrated that position of the methyl group in the porphyrins has remarkable influence in their binding mode to the G-quadruplex DNA.

Keywords: H2T(2-N-MePy) P, H2T(3-N-MePy) P, Telomere, Binding, G-quadruplex.

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Binding of H2T(4-N-MePy) P to human telomeres with (TTAGGG)n and (CTAGGG)n repeats

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Abstract

Inhibition of telomerase enzyme is an approach to treat cancer. G-quadruplex binding ligands have potential to inhibit the telomerase activity. TTAGGG repeats form the telomere repeat arrays of all vertebrate telomere, but one particular repeats type, (CTAGGG)n, has been identified that causes telomere instability. In spite of many reports on the interaction of porphyrins with human telomeric DNA, little is known about their interaction with sequence-variant telomere repeats. Here, we have investigated the binding of H2T(4-N-MePy) P to human telomeres bearing (TTAGGG)n and (CTAGGG)n repeats with spectroscopic and gel electrophoresis techniques. The results of circular dichroism indicated that the both repeats can form G-quadruplex structure, but compactness of CTAGGG repeats is different from that of the TTAGGG repeats. binding of H2T(4-N-MePy) P to the G-quadruplex structures decreased the intensity of circular dichroism. The Soret band of H2T(4-N-MePy) P showed a 9 and 15 nm shift to longer wavelengths with a concomitant 63% and 67% decrease in the intensity of the band upon binding to TTAGGG and CTAGGG repeats, respectively. Emission of the porphyrin has been quenched in presence of the both telomere repeats. The porphyrin retarded the mobility of the G-quadruplex forms of DNA significantly. These results indicated that H2T(4-N-MePy) P can bind to the G-tetrad planes in the G-quadruplexes and decreases compactness of their structures. However, there are some differences between the binding mode of H2T(4-N-MePy) P to (TTAGGG)n and (CTAGGG)n repeats. Also, the binding affinities and structural effects were not the same. Consequently, the change in the sequence of telomere can affect the binding of ligands to this region of chromosome.

Keywords: H2T(4-N-MePy) P, (CTAGGG)n repeats, (TTAGGG)n repeat, Binding, Telomer.

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Binding of H2T(2-N-MePy) P, H2T(3-N-MePy) and H2T(4-N-MePy) P to c-MYC promoter G-quadruplex

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Abstract

G-quadruplex DNA is more likely to be formed in the regions rich in guanine such as telomeres and promoters of oncogenes such as c-MYC promoter containing G-rich sequence with a potential to form G-quadruplex structure. Targeting DNA secondary structures by ligands is an approach for the development of anticancer ligands. We investigated the binding of three porphyrins including meso-tetrakis(N-2-methylpyridyl) porphyrin, meso-tetrakis(3-N-methylpyridyl) porphyrin and meso-tetrakis(4-N-methylpyridyl) porphyrin to c-MYC G-quadruplex DNA. Fluorescence and absorption spectroscopy were used to evaluate binding of the ligands to c-MYC G-quadruplex structure. Red shift and hypochromicity in the absorption bands of the porphyrins indicated that H2T(2-N-MePy) P binds externally to the G-quadruplex structure, but H2T(3-N-MePy) and H2T(4-N-MePy) P bind through intercalation and/or end-stacking. A concave-up Scatchard plot indicated negative cooperativity of H2T(3-N-MePy) P and H2T(4-N-MePy) P binding to the DNA structure. Furthermore, the binding constant of the latter porphyrins was greater than that of H2T(2-N-MePy) P. Consequently, the mode of binding, affinity of the ligands and probably their biological effect are influenced by the position of methyl group in the porphyrin structure.

Keywords: G-quadruplex, Binding, c-MYC promoter, Meso-tetrakis(N-methylpyridyl) porphyrin, Spectroscopy.

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Thymol is new drugs API

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Abstract

The use of plants and their essential oils and extracts in the treatment of bacterial diseases has a history as old as human history. Due to the progress made and the acquisition of new tools to investigate how compounds interact with different parts of microorganisms, various studies have been conducted in this field. Thymol (isopropyl-5-methylphenol-2) is a phenolic compound found in many plants and the antimicrobial, antiviral and anti-inflammatory properties of this compound have been proven. Thymol can be used as a new therapeutic method to treat Helicobacter pylori or inhibit Staphylococcus aureus. In addition, docking studies show the strong effect of thymol on SARS-COV-2 virus. Exposure to thymol induced marked changes in membrane fatty acid composition in S. aureus cell membranes, which may reduce cell viability. In addition, docking studies showed that thymol binds to the minor groove of DNA, which causes a slight destabilization of the DNA secondary structure and aggregates DNA molecules. According to the results, it can be seen that aromatic medicinal plants that contain these volatile compounds have less side effects than synthetic drugs, and these compounds can be used as Active Pharmaceutical Ingredient (API) in the pharmaceutical industry.

Keywords: Active Pharmaceutical Ingredient, Thymol, docking.

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