Turkish Journal of Science & Technology
18(1), 177-182, 2023

Research Paper
https://doi.org/10.55525/tjst.1224871

Molecular Docking Study on Interaction of Polyvinyl Alcohol (PVA) with Group IA Bacteriocin

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(Geliş/Received: 26/12/2023; Kabul/Accepted: 11/03/2023)

Abstract: PVA with the molecular formula $(C_2H_4O)n$ is a polymer prepared from polyvinyl acetates by replacing acetate groups with hydroxyl groups. It is a synthetic polymer with low surface tension, flexible and soft, water-soluble and cross-linkable thanks to the hydroxyl groups in its structure, biodegradable and non-toxic due to the carbon bonds in its chain. Bacteriocins are compounds of a protein nature that are ribosomally synthesized by bacteria and suitable for use as a filler in polymer matrices, especially in food packaging systems, and drug design because they are natural antimicrobial compounds sensitive to various enzymes and do not disrupt the physicochemical structure of foods while inhibiting pathogenic microorganisms. Considering their biochemical properties, they are generally divided into 4 different classes. The fact that Nisin and PVA have a structure that can serve a common purpose and have superior properties made us wonder about the interaction and bonding modes between these two. Molecular docking work is important because it prevents time, energy, and economic consumption and prepares the ground for the synthesis of new and advanced materials that are likely to be obtained in the laboratory environment. Therefore, in this study, Nisin bacteriocin (in Group IA) was chosen as the target, and a single monomer of the PVA polymer was chosen as the ligand, and the interaction between them was simulated by molecular docking method. A rational depiction of ligand-protein binding interactions was made.
Key words: Polyvinyl alcohol, molecular docking, nisin.

Polivinil Alkolün (PVA) Grup IA Bakteriyosiniyle Etkileşimi Üzerine Moleküler Docking Çalışması

Öz: $(C_2H_4O)n$ moleküler formülüne sahip PVA, asetat gruplarının hidroksil gruplarıyla değiştirilmesiyle polivinil asetatlardan hazırlanan bir polimerdir. Düşük yüzey gerilimli, esnek ve yumuşak, yapısındaki hidroksil grupları sayesinde suda çözünür ve çapraz bağlanabilir, zincirindeki karbon bağları sayesinde biyolojik olarak parçalanabilen ve toksik olmayan sentetik bir polimerdir. Bakteriyosinler, bakteriler tarafından ribozomal olarak sentezlenen, çeşitli enzimlere duyarlı doğal antimikrobiyal bileşikler olmaları ve patojenik mikroorganizmaları inhibe ederken gıdaların fizikokimyasal yapısını bozmamaları nedeniyle özellikle gıda paketleme sistemlerinde ve ilaç tasarımında polimer matrislerde dolgu maddesi olarak kullanıma uygun, protein niteliğindeki bileşiklerdir. Biyokimyasal özelliklerine göre genel olarak 4 farklı sınıfa ayrılırlar. Nisin ve PVA'nın ortak bir amaca hizmet edebilecek yapıya ve üstün özelliklere sahip olmaları, bu ikisi arasındaki etkileşim ve bağlanma modlarını merak etmemize neden oldu. Moleküler yerleştirme çalışması, zaman, enerji ve ekonomik tüketimin önüne geçmesi ve laboratuvar ortamında elde edilmesi muhtemel yeni ve ileri malzemelerin sentezine zemin hazırlaması nedeniyle önemlidir. Bu nedenle bu çalışmada hedef olarak Nisin bakteriyosini (Grup IA'da), ligand olarak da PVA polimerinin tek bir monomeri seçilmiş ve aralarındaki etkileşim moleküler yerleştirme yöntemi ile simüle edilmiştir. Ligand-protein bağlanma etkileşimlerinin rasyonel bir tasviri yapılmıştır.
Anahtar kelimeler: Polivinil alkol, moleküler yerleştirme, nisin.

1. Introduction

Access to food is decreasing day by day due to reasons such as global warming, the gradual decrease of arable land and the increasing human population. When microbial factors such as aflatoxins and food spoilage that threaten human and animal health as a result of not keeping the harvested agricultural products under proper storage conditions are added to all these problems, the result is more frightening. Therefore, importance is given to the production of antibacterial packaging in order to prevent food loss and to prevent packaging wastes that pose a danger to nature. For this reason, manufacturers have turned to advantageous packaging materials with barrier and protective properties to meet the need for fresh and minimally processed food. For this reason,

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Bacteriocins are natural antimicrobial compounds synthesized by the same or different bacterial groups, in protein structure, and sensitive to various enzymes [1]. While bacteriocins inhibit pathogenic and spoilage microorganisms, they do not disrupt the physicochemical structure of foods [2]. Bacteriocins, also called antimicrobial peptides or proteins, vary in molecular mass, disulfide and monosulfide (lanthionine) bonds, the spectrum of action, genetic origin, and biochemical properties. The most well-studied group of peptides are bacteriocins produced by lactic acid bacteria (LAB) due to their potential for use in food preservation. Klaenhammer classified these bacteriocins into 4 groups based on their molecular weight, heat sensitivity, enzymatic sensitivity, presence of post-translationally modified amino acids, and mechanism of effect [3, 4]. These are given in Table 1.

Table 1. Classification of bacteriocins [3, 4].

BACTERIOCINS			
Group I	Group II	Group III	Group IV
Group IA; *Nisin, Lactocin S,…*	Group IIA; *Pediocin PA-1, Sakacin A,…*	*Helveticin J, Lacticin A,…*	*Plantaricin S, Leuconocin S,…*
Group IB; *Cinnamycin, Duramycin,…*	Group IIB; *Lactacin F, Lactococcin G,…*		
	Group IIC; *Acidocin B, Enterocin P,…*		

Group IA bacteriocins are hydrophobic polypeptides that have a net positive charge [5]. Nisin, one of the important bacteriocins in this group, is produced by a group of Gram-positive bacteria belonging to Lactococcus and Streptococcus species. Nisin is known as a lantibiotic synthesized from mRNA and the translated peptide contains several unusual amino acids due to post-translational modifications [6]. Among the lantibiotics, nisin has the unique function of being used as a food preservative because it is non-toxic. Since it is in a polypeptide structure, the residues left in the food are digested. Many natural and genetically modified variants of Nisin have been identified and studied for their unique antimicrobial properties. Nisin is FDA (the Food and Drug Administration) approved and is generally considered a safe peptide with recognized potential for clinical use. Recently, the application of Nisin has spread to biomedical fields [7]. Nisin has been reported to have additional biological activities beyond its antimicrobial activities. For example, Nisin has beneficial properties in biomedical applications including bacterial infections, cancer, oral diseases, and more [8, 9].

Antimicrobial properties are given to plastic packaging by various modifications of the respective natural-based substances. Recently, bacteriocins and other biologically derived antimicrobials are among the highly interesting materials in packaging systems. Of particular interest is its use in packaging materials. Nisin, which inhibits Gram-positive foodborne pathogens and spoilage microbes, is one of the bacteriocins suitable for use in reliable packaging systems. Among the widely studied bacteriocins, Nisin is the only protein generally recognized as safe and approved by the US Food and Drug Administration [10, 11]. For this reason, some commercially produced Nisin species are often added to food products as preservatives. However, since the use of Nisin is limited by its structural instability resulting from loss of activity due to interactions with food and cell matrices, its incorporation into polymers is more advantageous to overcome this instability.

Polymers are high molecular weight substances or macromolecules that are formed as a result of the combination of simple molecules called monomers with chemical bonds. Polyvinyl alcohol, whose structural formula is given in Fig.1, is a highly used polymer in medical applications due to its biocompatibility, biodegradability, non-toxicity, good mechanical properties, and adhesiveness. In this respect, PVA has proven to be a promising candidate for medical applications such as biomedicine and pharmaceuticals. Commercially

available synthetic polymer poly(vinyl alcohol) (PVA) is also frequently used in packaging applications for food, cosmetics, and pharmaceutical products due to its superior properties [12, 13].

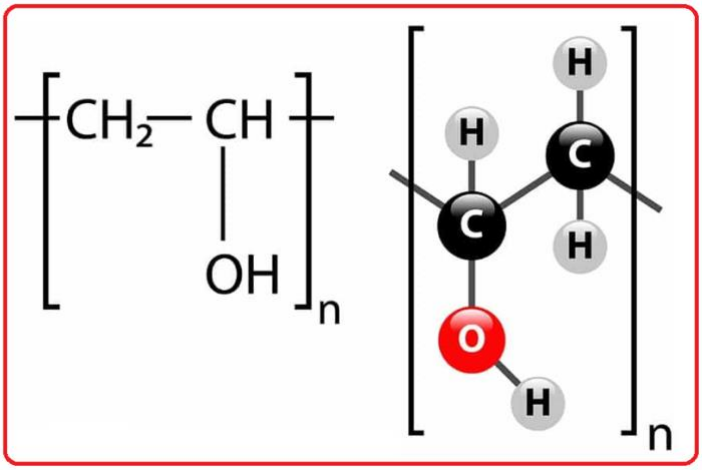

Figure 1. The structural formula of PVA [14].

To our knowledge, there has not been a study examining PVA-Nisin interactions before. Since both substances are suitable for use in similar applications, we examined the interactions between them in this study. The interaction of a monomer of PVA polymer as a ligand and Nisin bacteriocin as a protein was investigated by the Molecular Docking method. The placement of the PVA monomer in certain regions of the protein structure was simulated with certain score algorithms, taking into account many factors such as the electro negativities of the atoms, their position to each other, and the conformation of the molecule. This work lays the groundwork for the modification of the structure with the correct estimation of the binding modes and creates a strategic infrastructure for the synthesis of materials that are likely to be more effective.

2. Materials and Methods

Nisin's (PDB ID: 1WCO) structure was obtained from The Protein Data Bank (PDB, https://www.rcsb.org/). The pdb file of the 2DDE protein was prepared using chain A and transferred to AutoDockTools (ADT ver.1.5.6). Water molecules of the structures were removed and the pdbqt files of the proteins were saved. The chemical structure of the PVA (PubChem CID: 11199) ligand was obtained from the National Library of Medicine (https://www.ncbi.nlm.nih.gov/). Torsions of the ligand were examined and then the files of the ligand were saved as pdbqt format by AutodockTools (ADT ver.1.5.6).

The molecular docking study was performed using Autodock 4.1 [15]. Each docking was performed according to standard Autodock steps [16]. The most suitable possible binding modes obtained as a result of the Molecular Docking processes were determined with Autodock 4.1, and their analyzes and visuals were obtained with the Biovia Discovery Studio Visualizer 2021 program.

3. Results and Discussion

The molecular docking analysis was performed and evaluated following the literature as described in the material method [17]. Molecular docking results on Nisin a polycyclic antibacterial peptide, and monomer of PVA are shown in Table 2. The most stable structures of the ligand with Nisin were determined according to the binding energy and the interaction of the molecule with the active site. Considering the binding energy, it can be said that the studied compound showed significant binding affinity to Nisin.

Table 2. Molecular docking analysis of Nisin and the monomer of PVA.

Protein	Ligand	Binding Energy/ΔG (kcal/mol)	Inhibition Constant/Ki (mM)	Bonds	Length (Å)
Nisin	C_2H_4O	-1.46	59.34	LYS-12−O	4.01
				LYS-12−C	4.19
				MET-17−C	5.42
				MET-21−C	5.13

The hydrogen bonds at the most suitable binding site analyzed are given in Fig.2. In the figure, it is shown in 2D that the amino acid Lysine (LYS-12) forms a conventional hydrogen bond with the oxygen element. Alkyl bonds are formed between the carbon element and the amino acids Lysine (LYS-12), Methionine (MET-21), and MET-17. In addition, the van der Waals bond, which is a weak interaction between the Asparagine (ASN-20) and Cysteine (CYS-19) amino acids of the Nisin protein and the ligand, formed.

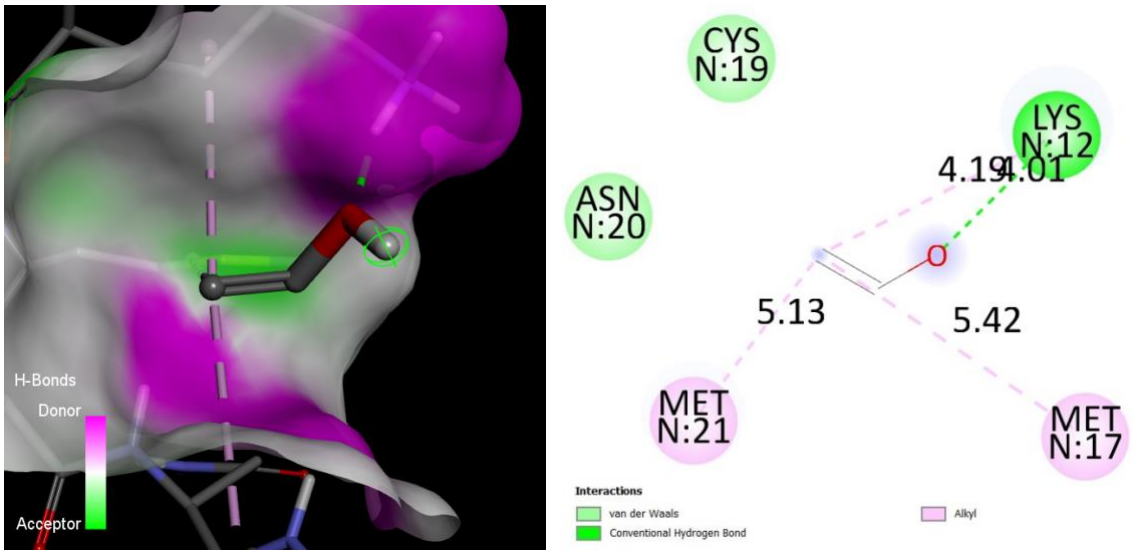

Figure 2. 2D interaction of the ligand with the amino acids of the Nisin binding site.

In Fig.3, the binding sites in the protein pocket are simulated. Shown in red is oxygen, dark gray is carbon, light gray is hydrogen, yellow is sulfur, and blue is nitrogen. As can be seen in the figure, the ligand is located in the surface space of the Nisin receptor with good complementarity.

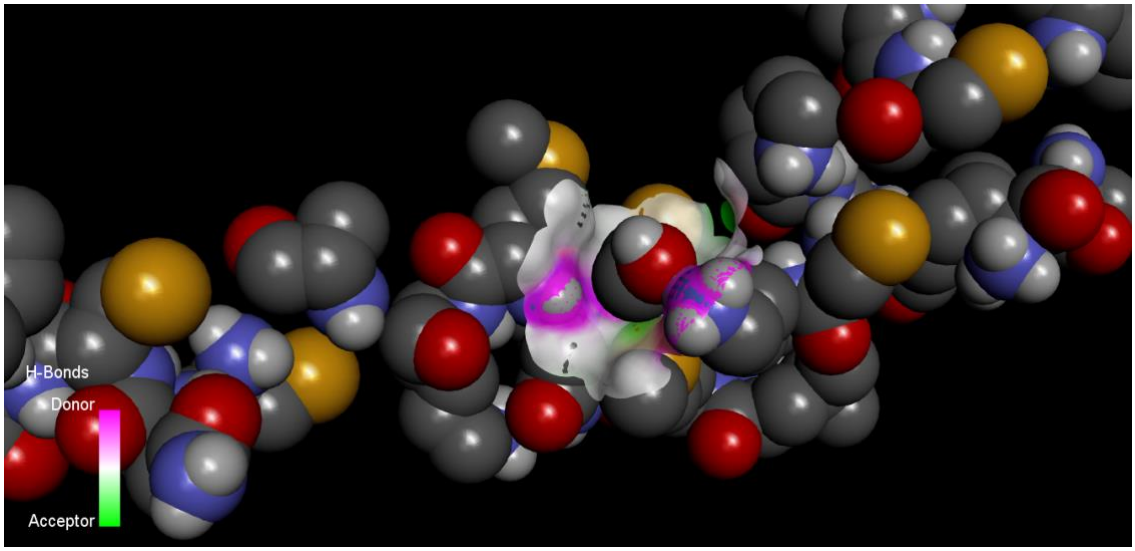

Figure 3. The binding sites in the pocket of protein (1WCO).

4. Conclusion

Nisin, a polycyclic antibacterial peptide produced by *Lactococcus lactis* bacteria, is suitable for use as a food preservative [18]. On the other hand, PVA is a synthetic polymer preferred in many fields such as pharmacology, biomedicine, biotechnology, and food chemistry, thanks to its superior properties such as its chemical structure, thermal stability in a wide temperature range, non-toxicity, and compatibility with living tissue [19, 20]. The fact that the usage areas of Nisin and PVA are compatible with each other and that there has not been a study examining the interaction between these two as a result of our research has led us to this study. As a result of our molecular docking study, the presence of binding energy of -1.46 kcal/mol was determined between the C_2H_4O monomer of PVA selected as the ligand and the Nisin protein selected as the receptor. Considering the hydrogen bonds formed between the amino acids LYS-12, MET-17, and MET-21 of Nisin, which has 34 amino acid residues, and the PVA monomer, it can be mentioned that there is an interaction between them [21]. As a result, this study can serve as a template for materials to be produced for use in appropriate fields, especially in the food industry.

Acknowledgment

This work was presented at the MSNG2022 Conference, Gazi University, Ankara, Turkey, Sep 22-24, 2022.

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