Conference Paper

Eicosapentaenoic Acid (EPA) from Fish Oil and Margarine as Bioactive Compound for Anti-inflammation in Occupational Dermatitis

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Abstract

Occupational dermatitis (OCD) is a skin inflammatory disease caused by allergens and irritant agents in the workplace. The disease is related to hypersensitivity reaction, which is correlated with an immunological mechanism (allergic contact dermatitis) and a nonimmunological mechanism (irritant contact dermatitis). Patients with atopic history (rhinitis allergy, asthma, and atopic dermatitis) have a higher risk of contracting OCD. Atopic individuals suffer from barrier skin damage that increases the risk of allergen and irritant penetration. Inflammatory reaction involves T-helper 1 (Th1), which produces cytokine tumor necrosis factor alpha (TNF-α) and interferon-γ (INF-γ), while T-helper 2 (Th2) produces interleukin (IL-4, IL-6, IL-8, IL-10). Eicosapentaenoic acid (EPA) is an omega-3 substance from polyunsaturated free fatty acids (PUFAs) that has been shown to have an anti-inflammatory effect and the ability to decrease macrophage accumulation. In the inflammatory process, EPA inhibits IL-6, IL-8, and TNF-α, which are mediated by the free fatty acid-binding proteins (FABPs). The aim of this study was to determine the bioactivity compound of EPA for anti-inflammatory agents and its target, based on *in silico* screening. The bioinformatic tools based on reverse docking used in this study were the PubChem compound database, the protein target prediction database, PharmMapper, SwissTargetPrediction, molecular docking software PyRx 0.8, ligand docking, and binding site analysis using PyMOL

software. Docking and binding site analysis showed that EPA was able to interact with FABPs, with the binding affinity of EPA with FABP 4 higher (–4.2 kcal/mol) than that of hydrocortisone with FABP 4 (–7.4 kcal/mol). EPA has the same binding site and relative bonding power as the FABPs; thus, it has potential as an alternative anti-inflammatory medicine in OCD.

Keywords: occupational dermatitis, eicosapentaenoic acid (EPA), free fatty acid binding proteins (FABPs), reverse docking

1. Introduction

The National Institute of Occupational Safety and Health (NIOSH) has included dermatologic disorders among the top 10 work-related diseases and injuries in the United States. The most common injuries are caused by lacerations, punctures, abrasions, and burns. Occupational contact dermatitis (OCD) is a skin inflammatory disease caused by allergens and irritant agents at the workplace. The disease is related to hypersensitivity reaction, which is correlated with an immunological mechanism (allergic contact dermatitis) and a nonimmunological mechanism (irritant contact dermatitis) [1]. Contact dermatitis accounts for 90 percent of occupational skin diseases. Among host-related factors, atopic dermatitis has been the most investigated risk factor in the development of occupationally induced skin diseases, particularly adult atopic hand dermatitis. Individual atopic dermatitis has a reduced threshold for developing irritant contact dermatitis from soap, detergents, solvents, and chemical irritants [1, 2].

Patients with atopic history (rhinitis allergy, asthma, and atopic dermatitis) have a higher risk of contracting OCD. Atopic individuals suffer from barrier skin damage that increases the risk of allergen and irritant penetration. The inflammatory reaction involves T-helper 1 (Th1), which produces tumor necrosis factor alpha (TNF-α) and interferon-γ (INF-γ), while T-helper 2 (Th2) produces interleukin (IL-4, IL-6, IL-8, IL-10). The worldwide prevalence of AD has increased in the past three decades. It often begins during early childhood, and adult patients frequently suffer from chronic diseases.The etiology of atopic dermatitis is unknown, but most individuals who are affected are diagnosed with allergic manifestations (e.g., asthma, food allergies, seasonal allergies), and there is no definitive treatment for AD [1–3].

Polyunsaturated free fatty acids (PUFAs) such as eicosapentaenoic acid (EPA) have a major impact on human health, for example, causing motor and cognitive development

disorders, mental health and psychiatric disorders, and cardiovascular disorders as well as immunologic and inflammatory responses [4]. EPA cannot be produced by human bodies; it is primarily found in dietary fish oils and can also be derived from plant products such as margarine [4, 5]. EPA has been shown to have anti-inflammatory effects, and its biological effects are mediated by the production of pre-resolving mediators, which have been proposed to modulate and likely resolve inflammatory responses[5, 6]. This study aims to discover the natural bioactivity compounds of eicosapentaenoic acid (EPA) derived from fish oils and margarine for the treatment of occupational contact dermatitis, based on *in silico* screening.

2. Methods

2.1. Ligand preparation

The 3D chemical structure and simplified molecular-input line-entry system (SMILES) of EPA were obtained from the PubChem compounds database (https://pubchem.ncbi.nlm.nih.gov/) with ID number: CID 446284.

2.2. Target selection

The target protein for EPA was obtained by entering SMILES into multiple servers, for example, SwissTargetPrediction (*http://www.swisstargetprediction.ch/*) and PharmMapper (http://59.78.96.61/pharmmapper/submit_file.php). The servers provided lists of predicted target proteins for EPA; these were compared, and target proteins with the most potential as ligands (EPA) were selected.

2.3. Molecular docking

Molecular docking for EPA, the target proteins, and the compound control was performed using the PyRx 0.8 software.

2.4. Molecular visualization and intermolecular interaction

Interaction between EPA, the target proteins, and the control compounds was visualized and analyzed using PyMOL and LigPlus as well as the BIOVIA Discovery Studio 2016 Client.

3. Results

The results of the target selection using PharmMapper (job ID: 17091218418) and SwissTargetPrediction (SMILES: CCC=CCC=CCC=CCC=CCC=CCCCC(=O)O) were obtained. The potentially interactive target protein with EPA was fatty acid-binding protein 4 (FABP 4). FABP 4 belongs to a family of cytosol proteins with a small molecular weight (15 kDa) that is bound in high affinity to unsaturated long-chain fatty acids. FABP 4 plays a role in the active regulation of lipid trafficking and inflammatory activities and is clearly expressed in almost all tissues with high rates of fatty acid uptake and lipid metabolism [7, 8]. Fatty acids shift to long-chain fatty acids that are transported by FABPs to various tissues, where they are metabolized, stored, or utilized [8]. Fatty acids such as EPA can be metabolized into a large, diverse family of bioactive lipid mediators called eicosanoids, which may function as anti-inflammatory mediators [9–11].

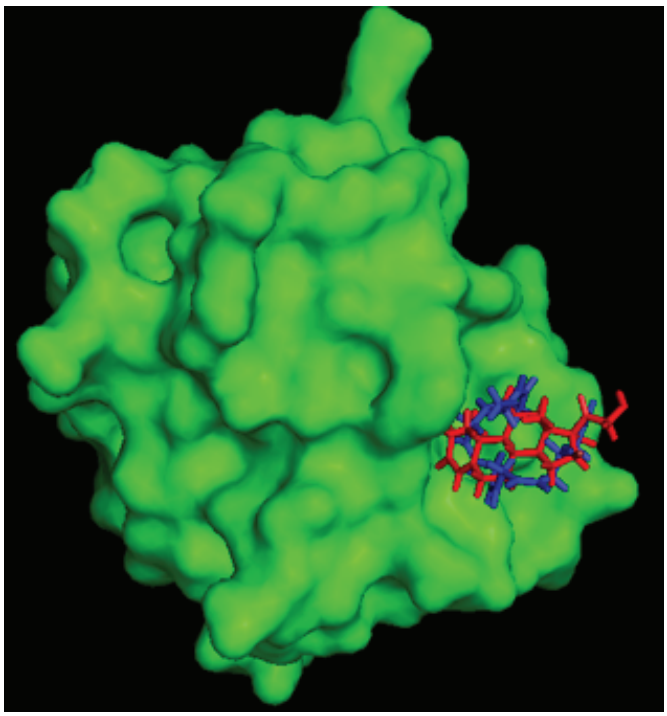
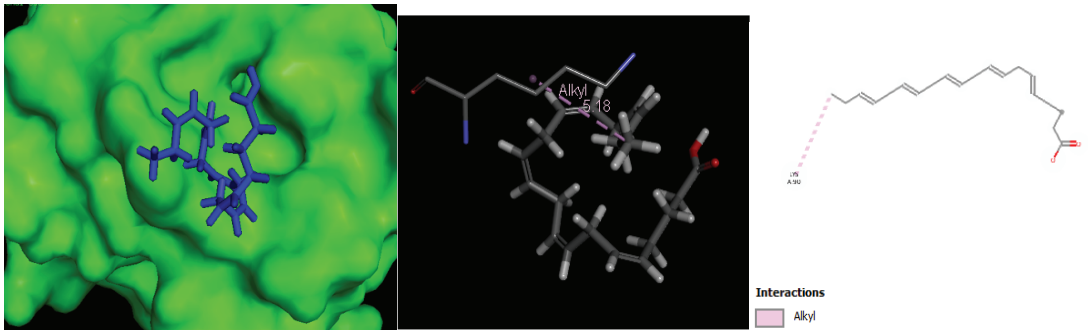
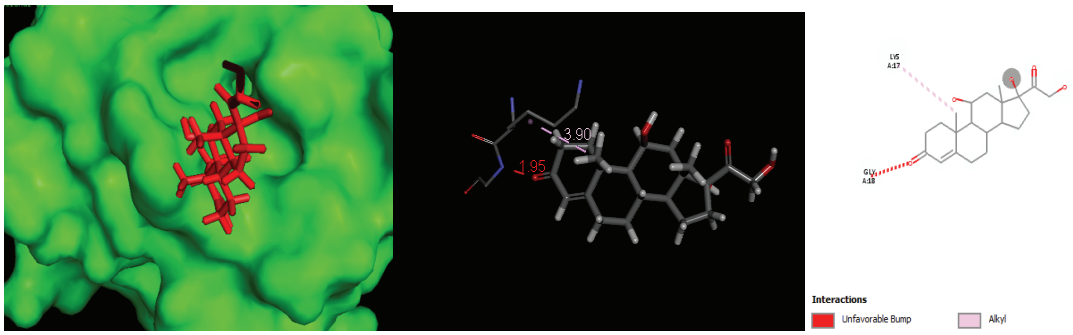


Figure 1: Results of molecular docking 3D structure between target proteins (fatty acid-binding protein 4), candidate ligand (eicosapentaenoic acid), and control ligand (hydrocortisone), which indicate that the ligands are capable of interacting with target proteins on the same binding site. Description: green (FABP 4), blue (EPA), red (hydrocortisone).



(a) (b) (c)

Figure 2: Visualization of the interaction between eicosapentaenoic acid (EPA) and fatty acid-binding protein 4 (FABP 4) using Discovery Studio Client BIOVIA, 2016. (a) EPA (blue) is bound to target proteins (FABP 4); (b) the distance of the type of interaction or bonding between EPA and FABP 4; (c) the types of interactions between the amino acids of EPA and FABP 4.



(a) (b) (c)

Figure 3: Visualization of the interaction between hydrocortisone and fatty acid-binding protein 4 (FABP 4) using Discovery Studio Client BIOVIA, 2016. (a) Hydrocortisone (red) is bound to target proteins (FABP 4); (b) the distance of the type of interaction or bonding between hydrocortisone and FABP 4; (c) the types of interaction between the amino acids of hydrocortisone and FABP 4.

4. Discussion

Reverse docking is a computing-based method that can be used to search for patterns of interaction involving molecular docking (drug/ligand) on a potential binding site on a set of clinically relevant macromolecule targets. The results of reverse docking between fatty acid-binding protein 4 (PDB ID: 3P6H) resolutions of 1:41 Å, with a candidate ligand (EPA) and a control ligand (hydrocortisone), using the software PyRx 0.8, showed the binding affinity of EPA with FABP 4 to be higher (–4.2 kcal/mol) than that of hydrocortisone with FABP 4 (–7.4 kcal/mol). Then the docking results visualized using the software PyMOL indicated that the candidate ligand (EPA) and the control ligand (hydrocortisone) were able to interact with the FABP 4 on the same binding site (Figure 1).

The bond and location of the ligand binding site on a target protein were visualized with the BIOVIA Discovery Studio 2016 Client. The results of the visualization showed that EPA interacts with FABP 4 through the alkyl bond from amino acid Leu 90 (5.18 Å) of FABP 4 (Figure 2). Hydrocortisone interacts with FABP 4 through an alkyl bond of amino acid Lys 17 (3.90 Å) and a bond unfavorable bump of amino acid Gly 18 (1.95 Å) (Figure 3).

5. Conclusion

This study proves that EPA has potential as an anti-inflammatory agent in OCD by interacting with fatty acid-binding protein 4 (FABP 4), which activates anti-inflammatory effects. EPA and hydrocortisone are able to interact with the FABP 4 on the same binding site. When the binding affinity of EPA has a higher bond than that of hydrocortisone, it has the potential to be an alternative anti-inflammatory medicine in OCD cases.

Conflict of Interest

The authors have no conflict of interest to declare.

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