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Molecular Docking of Sodium Fluoride to Biomarkers of Osteogenesis, Osteoclastogenesis, and Inflammation in Ortodhontic Tooth Movement

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Abstract

The alveolar bone remodeling system can increase the apposition process and reduce excessive alveolar bone resorption, which is a material containing Fluorine. Based on the in vivo research that has been conducted by adding Sodium Fluoride topical administration at a dose of 11.75 ppm, it can affect the expression of TGF β, RUNX 2, SOX 2, ALP, Collagen type 1, OPG, RANKL, IL-10, IL-1β, TNF α on Orthodontic tooth movement. However, to see the interaction between the Sodium Fluoride compound and the above biomarkers, namely Osteogenesis (TGF β, RUNX 2, SOX 2, ALP, Collagen type), Osteoclastogenesis (OPG, RANKL), and inflammation (IL-10, IL-1β, TNF α) has not been done. One of the ways to analyze the interaction is by using in silico testing, especially using molecular docking. Purpose: The purpose of the study is to analyze the Molecular Docking of Sodium Fluoride to Biomarkers of Osteogenesis, Osteoclastogenesis, and inflammation in Orthodontic Tooth Movement. Material and methods: This study is a non-experimental analytical descriptive study based on chemical computation using computer devices through an in silico test, especially using molecular docking. Ligand preparation begins with making a two-dimensional (2D) structure using the Chem Draw Ultra 8.0 program in the Chem Office 8.0 program package, followed by a three-dimensional (3D) ligand structure made using Chem3D 8.0 in the Chem Office 8.0 program package and saved in a file format. The 3D crystal structures of TGF β, RUNX 2, SOX 2, ALP, Collagen type β, OPG, RANKL, IL-10, IL-1β, and TNF α were obtained from the RCSB Protein Data Bank (PDB). Conclusion: Molecular docking analysis showed that sodium fluoride had low binding affinity (–1.3 to –1.8 kcal/mol) to all target proteins, suggesting weak molecular interactions.

Keywords: Molecular docking; In silico test; Binding affinity; Osteogenesis; Osteoclastogenesis

1. Introduction

Teeth that are moved orthodontically will experience a process called bone remodeling, which is a system to maintain the balance of tooth-supporting tissue, which aims to maintain bone thickness and maintain the relationship between teeth and alveolar bone so that it is relatively constant [1]. One of the materials that can affect the alveolar bone remodeling system, namely, it can increase the apposition process and can reduce excessive alveolar bone resorption, is a material containing Fluoride. In in vivo research, Sodium Fluoride, according to research conducted by Sutjiati, concluded that topical administration of Sodium Fluoride at a dose of 11.75 ppm can increase the expression of TGF β,

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RUNX 2, SOX 2, ALP, collagen type 1, OPG, RANKL, IL-10, IL-1β, TNF α in orthodontic tooth movement [2]. However, the relationship between Sodium Fluoride compounds and these biomarkers has not been explored. One way to analyze the relationship of the interaction is by using the in silico test, especially using molecular docking. In general, the term in silico is used to describe experiments conducted with the help of a computer. This in silico test can be used to determine the interaction between a compound and a target molecule, one of which is a receptor. The interaction can be seen in the form and strength of the bond through molecular docking. The interaction of compounds with receptors can be visualized using computational methods and can be used to determine the pharmacophore of a compound.

Based on the description above, the formulation of the problem is how the molecular docking of Sodium Fluoride affects biomarkers of osteogenesis, osteoclastogenesis, and inflammation in orthodontic tooth movement. The benefits of the study are to provide basic scientific information about the molecular docking of Sodium Fluoride to biomarkers of osteogenesis, osteoclastogenesis, and inflammation in orthodontic tooth movement.

2. Material and methods

This study is a non-experimental analytical descriptive study based on chemical computation using computer devices through in silico tests. Ligand preparation begins with creating a two-dimensional (2D) structure using the Chem Draw Ultra 8.0 program in the Chem Office 8.0 program package, followed by a three-dimensional (3D) structure saved in a file format. The 3D crystal structures of TGF β, RUNX 2, SOX 2, ALP, Collagen type, OPG, RANKL, IL-10, IL-1β, and TNF α were obtained from the RCSB Protein Data Bank (PDB). Each new compound can be predicted based on the similarity of functional groups of other compounds that have known potential. Prediction of target protein, compounds whose structure and potential are known, can be predicted to target proteins in cells. Then molecular docking was performed. Data analysis results from molecular docking in the form of binding affinity and visualization.

3. Results

In this study, Sodium Fluoride was used as a ligand, and molecular docking was performed with the target proteins TGF β, RUNX 2, SOX 2, ALP, collagen type 1, OPG, RANKL, IL-10, IL-1β, and TNF α. Molecular docking was performed using Pymol and Pyrx. Before docking, a grid box consisting of a grid center and molecular docking dimensions was created for each protein. The grid box was created to cover the ligand-receptor binding as a validation of the docking. The grid box creation data consisted of spacing in angstrom units (x, y, and z) and grid box center values (x, y, and z). In molecular docking, the parameters analyzed included binding affinity and visualization.

Binding affinity is a value that indicates the ability of a ligand to bind to a receptor. The higher the binding affinity value, the lower the ability of the ligand to bind to the receptor, while a more negative binding affinity value means that the ligand and protein bind very strongly without requiring a large amount of energy (Al Huda et al., 2020).

Table 1 Binding affinity molecular docking

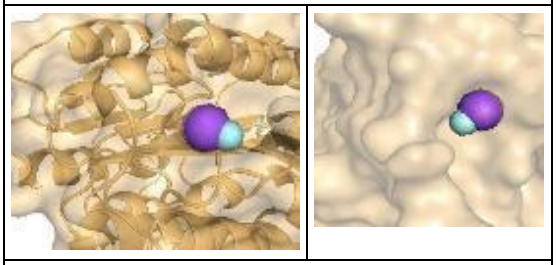
Protein	Ligand	Binding Affinity
TGF-β (1PY5)	4-(3-pyridin-2-yl-1h-pyrazol-4-yl)	-9.6
	Sodium Fluoride	-1.5
RUNX 2 (6VGE)	Dexamethasone	-7.9
	Sodium Fluoride	-1.7
SOX 2 (6WX8)	Sulindac	-7.7
	Sodium Fluoride	-1.6
ALP (1ZED)	Dexamethasone	-7.6
	Sodium Fluoride	-1.5
KOLAGEN TIPE 1 (6LOS)	Tranilast	-6.1
	Sodium Fluoride	-1.4

OPG (3URF)	Raloxifene	-8.4
	Sodium Fluoride	-1.6
RANKL (5BNQ)	Resveratrol	-7.1
	Sodium Fluoride	-1.3
RANKL (3URF)	Resveratrol	-6.3
	Sodium Fluoride	-1.6
IL-10 (6X93)	Rocaglamide	-6.3
	Sodium Fluoride	-1.4
IL-1β (1ITB)	Resveratrol	-7.7
	Sodium Fluoride	-1.8
IL-1R (1GOY)	Resveratrol	-7.2
	Sodium Fluoride	-1.6
TNF-α (TNFR1) (1EXT)	Resveratrol	-6.9
	Sodium Fluoride	-1.6

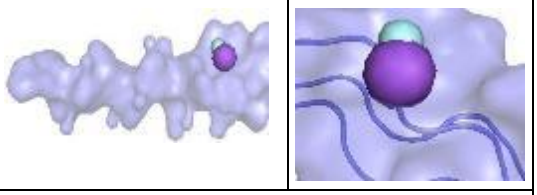
Based on the molecular docking results between Sodium Fluoride and various proteins involved in osteogenesis and inflammation, it was found that Sodium Fluoride exhibits relatively weak binding affinity compared to other reference ligands. In general, the binding energy of Sodium Fluoride against all target proteins ranged from –1.3 to –1.8 kcal/mol, indicating weak interactions between sodium fluoride and the target proteins.

On the other hand, control ligands such as dexamethasone, resveratrol, sulindac, raloxifene, and others showed stronger (more negative) binding affinities. Dexamethasone exhibited strong interactions with RUNX2 (–7.9 kcal/mol) and ALP (–7.6 kcal/mol); resveratrol demonstrated high affinity for IL-1β (–7.7 kcal/mol), IL-1R (–7.2 kcal/mol), and RANKL (–7.1 kcal/mol); while sulindac showed strong interaction with SOX2 (–7.7 kcal/mol). Notably, TGF-β exhibited the strongest interaction with the ligand 4-(3-pyridin-2-yl-1H-pyrazol-4-yl), with a binding affinity of –9.6 kcal/mol, making it the strongest interaction recorded.

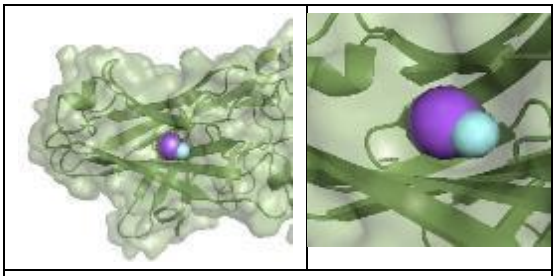
ALP – Sodium Fluoride



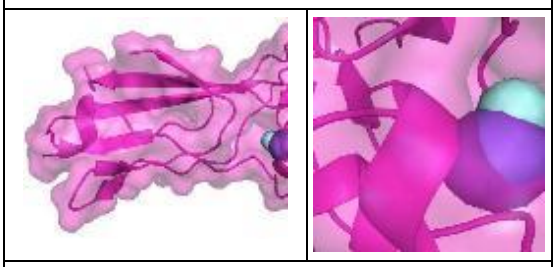
Kolagenase 1 – Sodium Fluoride



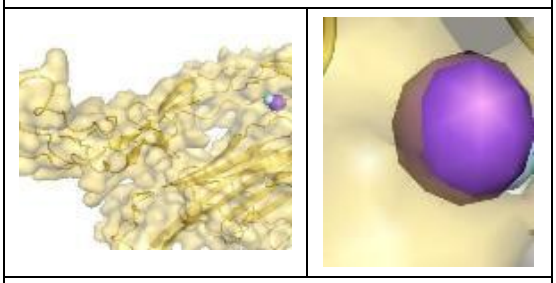
IL-1B – Sodium Fluoride



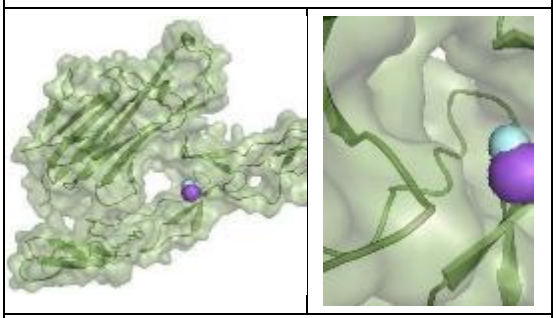
IL10 – Sodium Fluoride



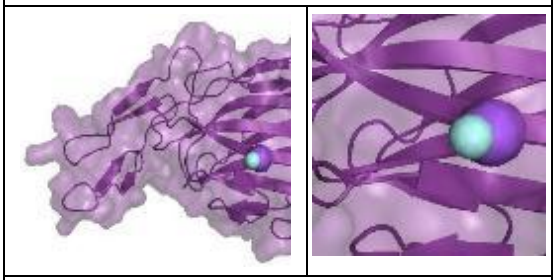
OPG – Sodium Fluoride



RANKL – Sodium Fluoride



RANK – Sodium Fluoride



RUNX2 – Sodium Fluoride

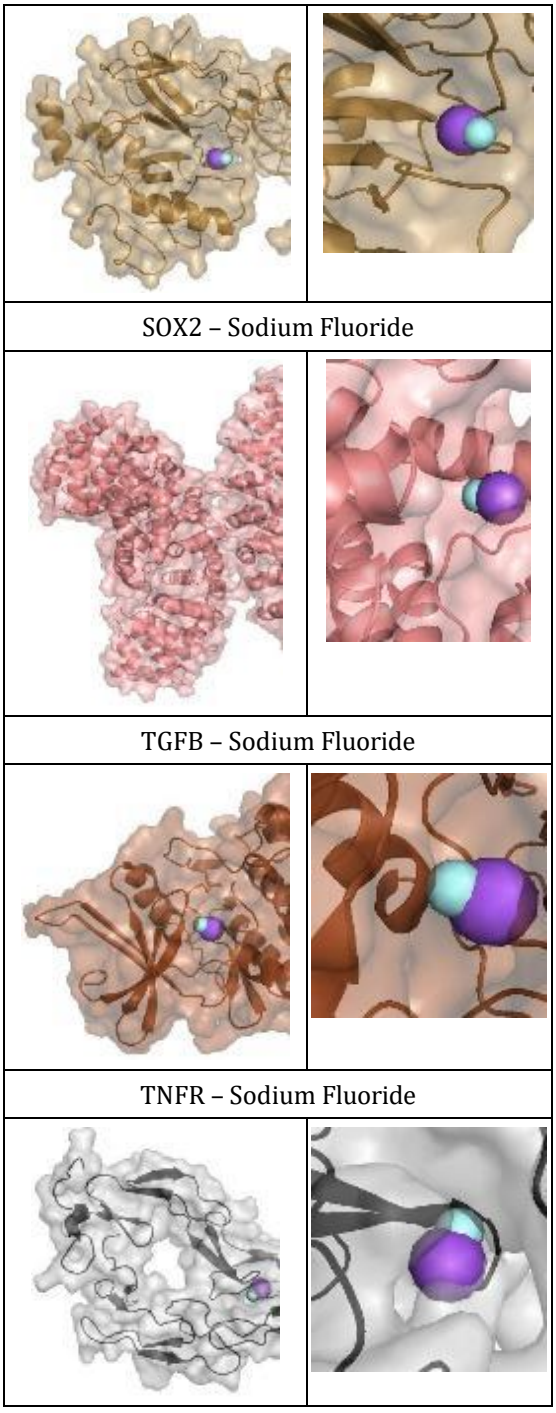


Figure 1 Visualization molecular docking between Sodium Fluoride ligands and target protein receptors TGF β, RUNX 2, SOX 2, ALP, Collagen type 1, OPG, RANKL, IL-10, IL-1β, TNF α

4. Discussion

Molecular docking analysis revealed that Sodium Fluoride exhibits relatively low binding affinity toward all target proteins, ranging from −1.3 to −1.8 kcal/mol, indicating weak interactions. In contrast, control ligands such as dexamethasone, resveratrol, sulindac, and raloxifene demonstrated significantly stronger affinities (more negative values). For instance, dexamethasone showed strong binding to RUNX2 (−7.9 kcal/mol) and ALP (−7.6 kcal/mol), while resveratrol exhibited high affinity toward IL-1β (−7.7 kcal/mol), IL-1R (−7.2 kcal/mol), and RANKL (−7.1 kcal/mol). The strongest interaction was observed between TGF-β and the ligand 4-(3-pyridin-2-yl-1H-pyrazol-4-yl) with a binding

energy of –9.6 kcal/mol. These findings align with previous studies showing that ligands such as resveratrol can strongly bind to inflammatory and osteogenic proteins, such as RANKL (–6.9 to –7.6 kcal/mol) and IL-1β (–7.7 kcal/mol), as reported in molecular docking and experimental studies [3]. Additionally, another study by Patil (2024) supports that resveratrol forms strong hydrogen bonds with TNF-α, underpinning its potential as an anti-inflammatory and osteoprotective agent [4]. These results suggest that the direct interaction between Sodium Fluoride and the target proteins is likely to be molecularly insignificant, whereas control ligands with stronger binding affinities may possess greater potential for modulating biological activities. This supports the hypothesis that the biological mechanism of Sodium Fluoride may occur indirectly or through secondary signaling pathways, in contrast to ligands like dexamethasone or resveratrol, which show potential as biocompatible and osteoprotective agents.

Based on the results of molecular docking, supported by previous research stating that Sakallioğlu proved that high dose Fluoride administration can cause an increase in TGF-β 1 and TIMP/MMP and an average of TIMP/TGF-β 1 [5, 6]. The molecular biological mechanism in mechanical pressure received by teeth in orthodontic treatment is characterized by the presence of an inflammatory process in the periodontal tissue. Orthodontic treatment is done by applying pressure to the teeth, which causes tooth movement in the alveolar bone around the teeth. Alveolar bone remodeling is very important because it is a process of maintaining the balance of the tooth support tissue. The remodeling process is used to maintain bone thickness and maintain the relationship between the tooth and the alveolar bone so that it is relatively constant [7, 8]. One way to prevent relapse is by retention. Retention is maintaining the movement of new teeth in that position long enough to stabilize the correction [9]. Pressure on the tooth crown will be transmitted through the tooth root to the alveolar bone and periodontal ligament. The surface of the alveolar bone that is under pressure will undergo a resorption process, and the opposite side will experience a pulling or apposition process [2]. Inflammatory mediators will trigger biological processes related to alveolar bone resorption and apposition. The biological mechanism that stimulates alveolar bone resorption is physiologically related to cytokines.

Cytokines are a group of mediators of tissue damage and play a role in orthodontic tooth movement [10, 11]. Mechanical pressure also activates inflammatory cells, especially macrophages and neutrophils, to produce various chemical mediators, including: Prostaglandin, Interleukin-1, Interleukin-6, tumor necrosis factor-alpha, and osteoclast differentiation by nuclear factor kappa B ligand activator receptor and osteoprotegerin, which can be identified in gingival crevicular fluid examination. Furthermore, mechanical pressure stimulates alveolar bone resorption [12, 13]. Bone resorption is characterized by increased osteoclast activity controlled by cytokines, namely IL-1, IL-6, and TNF-λ, which stimulate osteoclastogenesis in bone resorption through NF-kβ ligand activator receptor (RANKL), NF-kβ RANK), and osteoprotegerin (OPG) [14, 15]. Recent studies have shown that OPG is a RANKL inhibitor and inhibits the binding between RANKL and RANK, osteoclastogenesis. Factors that influence the occurrence of relapse are bone resorption, which experiences the initial tooth movement nine times greater than the appositional bone, allowing for greater relapse [16, 17]. To improve the apposition process by increasing osteoblast cell proliferation, Fluoride is given.

5. Conclusion

Molecular docking on TGF β, RUNX 2, SOX 2, ALP, Collagen type 1, OPG, RANKL, IL-10, IL-1β, and TNF α proteins shows the attachment of Sodium Fluoride to the active side of the protein.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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