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Original Article

Computational study of Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} binding sites identification on cytokines to predict dental metal allergy: An *in silico* study

[Estudio computacional de Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+} y Hg^{+} e identificación de sitios de unión a citocinas para predecir la alergia dental a metales: Un estudio *in silico*]

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Abstract

Context: Metal allergy is a general term to describe allergic diseases due to the release of metal ion reactions in the body which are mediated by T cells and involve inflammatory cytokines that can cause morbidity and mortality. Molecular docking is an analysis that can be used to assess the interaction of ligand bonds with target proteins that are used to predict metal allergies caused by metal ions that stimulate cytokines.

Aims: To analyze the binding sites of Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} ions on cytokines to predict dental metal allergy through a bioinformatics approach, *in silico*.

Methods: Metal ion particles consisting of Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} were predicted to bind tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin (IL) IL-1β, IL-2, IL-4, IL-10, IL-13, IL-17, IL-23, and IL-33 act as target proteins were examined.

Results: The blind docking simulation succeeded in identifying the comparison of the binding activity of metal ion particles on cytokines target proteins. The docking simulation results show that the metal ion with the most negative binding affinity value binds to the IL-17 protein.

Conclusions: Metal ion particles consisting of Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} have the most negative binding affinity values for binding to IL-17 protein, which can cause allergic reactions predicted by molecular docking, *in silico*.

Keywords: allergy; dentistry; good health and well-being; medicine; orthodontics.

Resumen

Contexto: La alergia a los metales es un término general para describir las enfermedades alérgicas debidas a la liberación de reacciones de iones metálicos en el cuerpo que están mediadas por células T e involucran citocinas inflamatorias que pueden causar morbilidad y mortalidad. El acoplamiento molecular es un análisis que se puede utilizar para evaluar la interacción de los enlaces de ligandos con proteínas diana que se utilizan para predecir alergias a metales causadas por iones metálicos que estimulan las citocinas.

Objetivos: Analizar los sitios de unión de los iones Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, $CrO4^{2-}$, Si^{4+} y Hg^{+} en citocinas para predecir la alergia dental a metales mediante un enfoque bioinformático, *in silico*.

Métodos: Partículas de iones metálicos que consisten en Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+} y Hg^{+} fueron predichas para unirse al factor de necrosis tumoral-α (TNF-α), interferón-γ (IFN-γ), interleucina (IL) Se examinaron IL-1β, IL-2, IL-4, IL-10, IL-13, IL-17, IL-23 e IL-33 que actúan como proteínas diana.

Resultados: La simulación de acoplamiento ciego logró identificar la comparación de la actividad de unión de las partículas de iones metálicos en las proteínas diana de las citocinas. Los resultados de la simulación de acoplamiento muestran que el ion metálico con el valor de afinidad de unión más negativo se une a la proteína IL-17.

Conclusiones: Las partículas de iones metálicos que consisten en Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+} y Hg^{+} tienen los valores de afinidad de unión más negativos para unirse a la proteína IL-17, lo que puede causar reacciones alérgicas predichas por acoplamiento molecular, *in silico.*

Palabras Clave: alergia; buena salud y bienestar; medicamento; odontología; ortodoncia.

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INTRODUCTION

Metal is often applied to the body for restorative or rehabilitative purposes, one of which is applied in the oral cavity as a restorative prosthesis; however, sometimes it can cause allergic reactions. Allergy is a general term to describe allergic diseases due to metal ion release reactions in the body that are mediated by T cells and involve inflammatory cytokines (Itoh et al., 2020; Sitalaksmi et al., 2019). Some metals commonly used in dentistry and often cause allergic reactions are nickel, chromium, mercury, palladium, and cobalt. Allergies to metals are classified as cell-mediated type IV hypersensitivity reactions (Christensen et al., 2017).

In the human body, metal ions Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} act as allergens. In the intraoral, there is a salivary electrolyte solution that can encourage the release of metal electrons, resulting in ionization or the release of metal ions in the oral cavity. The metal ionization process is very influential on the occurrence of allergic reactions because it can bind to proteins and form haptens, which are then recognized by T-cells, so that they can trigger allergic reactions (Chandu et al., 2014).

Metal allergy can cause various manifestations ranging from mild to severe in the skin and mucosa, such as glossitis, glossalgia, cheilitis, gingivitis, stomatitis, oral lichen planus, certain types of dermatitis associated with periodontal disease, palmoplantar pustulosis, dyshidrotic eczema, urticaria, vasculitis, pruritus, and contact dermatitis (Chandu et al., 2014; Christensen et al., 2017; Takaoka et al., 2021). Based on previous studies, the prevalence of metal allergy in the global population is high; about 17% of women and 3% of men are allergic to nickel, and 1-2% of individuals in the global population are allergic to cobalt, chromium, or both. Metal exposure from dental restorations can also predispose patients to metal allergies (Haddad et al., 2019). In the research of Hosoki et al. (2018), metal allergy morbidity in dentistry includes lichen planus by 21.4%, stomatitis, cheilitis, gingivitis by 7.4%, glossitis by 6.7%, and redness of the oral cavity by 0.7%. Metal allergy in dental restorations can cause oral lichen planus, which is a precancerous lesion. Chronic oral lichen planus can develop into oral squamous cell carcinoma, so allergies to dental restorations made of metal can increase the risk of developing oral cancer with a prevalence of 34% (FDA, 2019).

Metal ions can be released through three different mechanisms: mechanical wear, physiochemical corrosion when the metal devices comes into contact with biological fluids like sweat and blood, and cellular-gated mechanisms. Metal ion exposure causes a variety of local and systemic immune responses. Metal ions released can activate the immune system by binding to endogenous proteins to form metal–protein complexes, which T lymphocytes recognize as antigens. T lymphocytes activate macrophages to phagocytose various foreign particles, form foreign body giant cells, and release proinflammatory cytokines such as TNF-α, IL-6, and IL-1α/β. Macrophages also produce chemokines that promote inflammatory cell migration and activation, such as MCP-1 (or CCL2) and CCL3 (MIP-1), which cause allergic reactions (Teo Wendy and Schalock, 2016).

Molecular docking is an analysis to assess the interaction of ligand bonds with target proteins which is used to predict the structure of intermolecular complexes formed, either two or more molecules (Ashraf et al., 2021). In metal allergy, molecular docking analysis was carried out to assess the interaction of metal ion particles such as Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} against the target protein, namely interleukin (IL) IL-1β, IL-6, tumor necrosis factor-α (TNF-α), immunoglobulin E (IgE), inducible nitric oxide synthase (iNOS) and erythroid-derived nuclear factor 2-like 2 (Nrf2) via binding hydrogen and hydrophobic using VinaWizard plugin in PyRx 0.8.1 (Younas et al., 2021). Furthermore, this study was conducted to determine the identification of the binding sites for Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} ions on cytokines to predict dental metal allergy through a bioinformatic approach, an *in silico* study.

MATERIAL AND METHODS

Metal ion particles consisting of Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/). Information such as ion particle name, CID number, formula, physical description, molecular weight, cite, and 2D structure with file structure data format (SDF) was obtained. Pubchem is included in the specific database category because it plays a special role in storing all information about chemical compounds such as natural, synthetic, and substance (Ardani et al., 2022). Target proteins consisting of TNF-α, IFN-γ, IL-1β, IL-2, IL-4, IL-10, IL-13, IL-17, IL-23, and IL-33 were obtained from the Protein Databank (https://www.rcsb.org/). Information consisting of name, visualization method, PDB ID, resolution, molecular weight, sequence length, chain, and 3D structure with protein databank format (PDB) file. The process of sterilization of water molecules and contaminant ligands is carried out on the 3D structure of the protein through PyMol 2.5 version software, then

the process of minimizing and converting the ligand format into a protein databank format (PDB) file is carried out through the OpenBabel plugin on PyRx 0.8.1 version (Susanto et al., 2018). The minimization of ligands plays a role in increasing the flexibility of the molecular structure with a more positive binding energy (Prahasanti et al., 2021).

Simulation of ligand binding to the target protein domain via molecular docking software was determined by auto grid settings in PyRx 0.8.1 version. A grid is a cube whose position has X, Y, Z axes, and can be adjusted according to the research objectives; the position of the grid can direct the binding of ligands to specific domains (Kharisma et al., 2021). This study uses a blind docking method with a grid position that covers the entire protein domain. This method is used to screen for binding affinity produced by ligands when forming complexes with proteins.

Molecular docking aims to identify the binding ability of a ligand to the protein domain and the interaction pattern formed (Nugraha et al., 2021). Metal ion particles consisting of Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} then TNF-α, IFN-γ, IL-1β, IL-2, IL-4, IL-10, IL-13, IL-17, IL-23, and IL-33 act as target proteins. The VinaWizard plugin in PyRx 0.8.1 version software in this study was used for blind docking simulations to determine the interaction of metal ion particles on the target protein activation response.

PyMol 2.5 version software in this study was used to visualize the 3D structure of the protein. The visualization method consisted of staining and structural selection (Rantam et al., 2021) PyMol software works based on the python algorithm to visualize and select stains on specific molecules (Rose et al., 2017). Color selection is used to give specific colors to objects, cartoon structures, transparent surfaces, and shapes are used in this study.

RESULTS

Metal ion particles Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} were obtained from the PubChem database with information, CID number, formula, physical description, molecular weight, cite, and 2D structure (Table 1). Protein samples consisting of TNF-α, IFN-γ, IL-1β, IL-2, IL-4, IL-10, IL-13, IL-17, IL-23, and IL-33 were obtained from the RCSB PDB database with name, visualization method, PDB ID, resolution, molecular weight, sequence length, chain (Table 2). The 3D structure of the target protein is displayed using PyMol 2.5 version software in the form of cartoons, spheres, and transparent surfaces with a selection of coloring based on the type of molecule (Fig. 1). This study uses a blind docking method to screen or identify the activity of metal ion particles with a more negative binding affinity and ignores the functional binding sites in the protein region, then for the grid arrangement, covering all parts of the protein with different center positions and dimensions (Table 3). This study uses a blind docking simulation aimed at identifying the comparison of the binding activity of metal ion particles Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} on target proteins (Fig. 2). The docking simulation results show that the metal ion with the most negative binding affinity value binds to the IL-17 protein (Table 4).

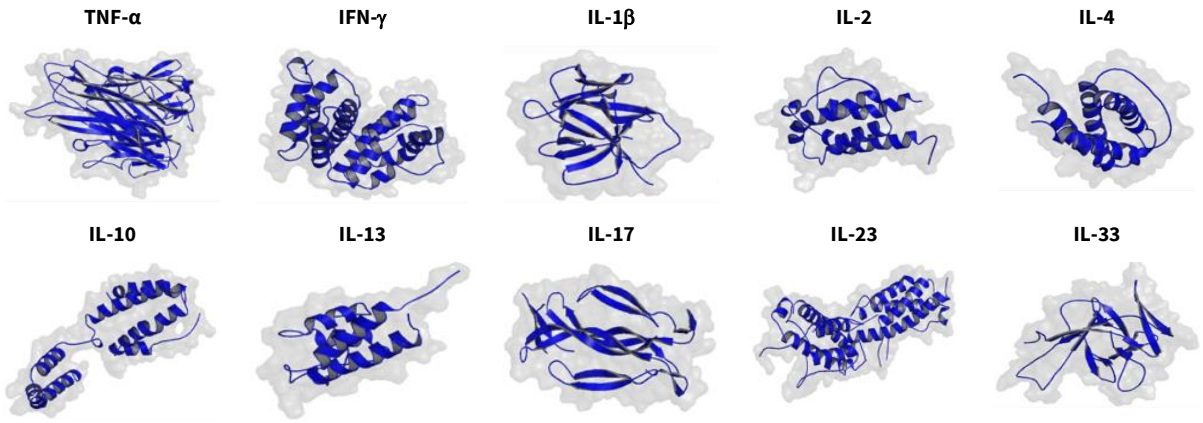

Figure 1. Visualization of the 3D structure of the target protein.
The structure of the target protein is shown with transparent surfaces (grey) and cartoons (blue).

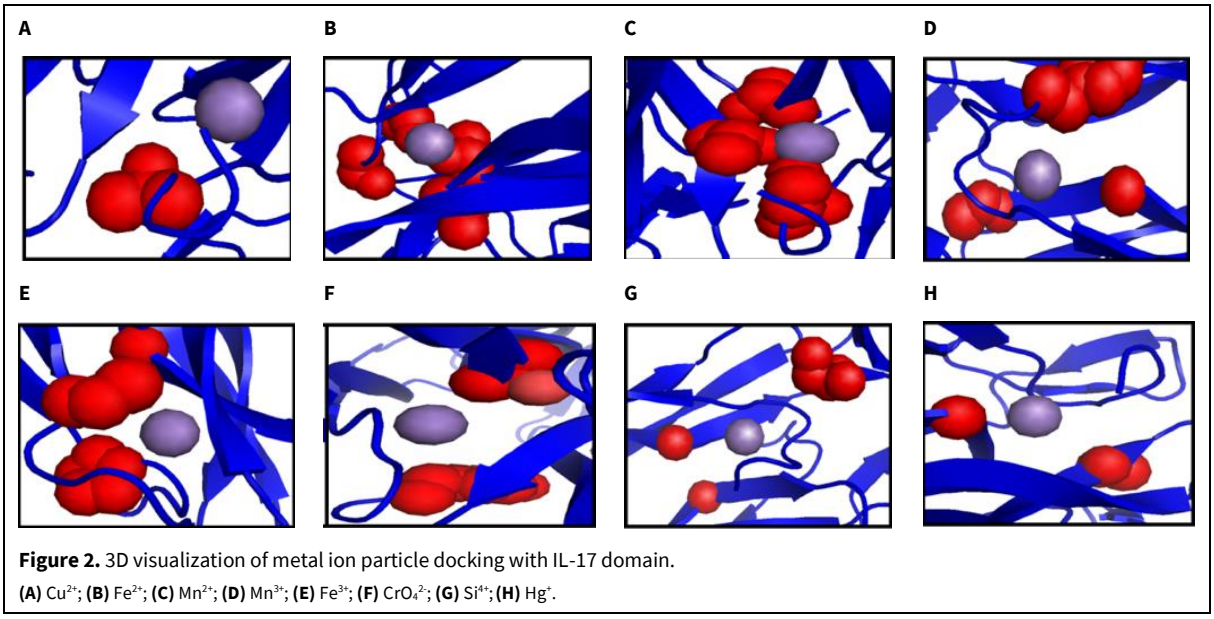

Figure 2. 3D visualization of metal ion particle docking with IL-17 domain.
(A) Cu^{2+}; **(B)** Fe^{2+}; **(C)** Mn^{2+}; **(D)** Mn^{3+}; **(E)** Fe^{3+}; **(F)** CrO_4^{2-}; **(G)** Si^{4+}; **(H)** Hg^{+}.

Table 1. Ligand sample preparation through PubChem.

Name	CID	Formula	Physical description	Weight (g/mol)	Cite
Copper (II)	27099	Cu^{2+}	Solid	63.55	https://pubchem.ncbi.nlm.nih.gov/compound/Cupric-ion
Iron (II)	27284	Fe^{2+}	Solid	55.84	https://pubchem.ncbi.nlm.nih.gov/compound/Ferrous-ion
Manganous (II)	27854	Mn^{2+}	Solid	54.938	https://pubchem.ncbi.nlm.nih.gov/compound/Manganese_2
Manganous (III)	105130	Mn^{3+}	Solid	54.938	https://pubchem.ncbi.nlm.nih.gov/compound/Manganese_3
Iron (III)	29936	Fe^{3+}	Solid	55.84	https://pubchem.ncbi.nlm.nih.gov/compound/Ferric-ion
Chromate	24461	CrO_4^{2-}	-	115.994	https://pubchem.ncbi.nlm.nih.gov/compound/Chromate
Silicon (IV)	4082203	Si^{4+}	Solid	28.085	https://pubchem.ncbi.nlm.nih.gov/compound/Silicon_4
Mercury (I)	105133	Hg^{+}	-	200.59	https://pubchem.ncbi.nlm.nih.gov/compound/Mercury_1

Table 2 Protein sample retrieval from PDB.

Name	Visualization method	PDB ID	Resolution (Å)	Weight (kDa)	Sequence length (mer)	Chain
TNF-α	X-RAY DIFFRACTION	1TNF	2.60	52.11	157	A/B/C
IFN-γ	X-RAY DIFFRACTION	1EKU	2.90	63.02	265	A/B
IL-1β	SOLUTION NMR	2KH2	-	44.79	153	A
IL-2	SOLUTION NMR	1IRL	-	15.36	133	A
IL-4	SOLUTION NMR	1BBN	-	15.39	133	A
IL-10	X-RAY DIFFRACTION	2H24	2.00	18.67	160	A
IL-13	SOLUTION NMR	1GA3	-	12.42	113	A
IL-17	X-RAY DIFFRACTION	4HR9	2.48	28.24	122	A/B
IL-23	X-RAY DIFFRACTION	3D87	2.90	109.29	178	A/C
IL-33	SOLUTION NMR	2KLL	-	18.16	161	A

Table 3. The docking grid positions of proteins.

Protein	Autogrid					
	Center (Å)			Dimensions (Å)		
	X	Y	Z	X	Y	Z
TNF-α	19.967	49.673	39.930	62.728	63.889	61.359
IFN-γ	12.383	36.847	17.154	60.820	48.867	57.976
IL-1β	-22.638	-8.676	0.347	42.583	44.488	37.910
IL-2	-20.586	-36.632	57.530	41.257	53.945	45.511
IL-4	-0.038	0.309	0.008	54.006	41.665	36.190
IL-10	13.264	21.833	5.094	45.746	39.548	75.507
IL-13	-0.911	2.375	0.353	41.540	40.466	31.727
IL-17	11.571	28.929	48.650	56.279	39.811	52.333
IL-23	34.784	32.333	30.075	46.012	72.949	78.274
IL-33	0.154	-0.136	0.152	60.607	43.044	38.753

Table 4. Binding affinity score metal ions particle to cytokines.

Protein	Binding affinity (kcal/mol)							
	Copper (II)	Iron (II)	Manganous (II)	Manganous (III)	Iron (III)	Chromate	Silicon (IV)	Mercury (I)
TNF-α	-1.3	-1.3	-1.3	-1.3	-1.3	-1.2	-1.0	-1.0
IFN-γ	-1.5	-1.5	-1.5	-1.5	-1.5	-1.1	-1.0	-1.2
IL-1β	-1.2	-1.2	-1.2	-1.2	-1.2	-1.0	-1.0	-1.0
IL-2	-1.1	-1.1	-1.1	-1.1	-1.1	-1.0	-0.9	-0.9
IL-4	-1.1	-1.1	-1.1	-1.1	-1.1	-1.0	-1.0	-1.0
IL-10	-1.3	-1.3	-1.3	-1.3	-1.3	-1.2	-0.5	-0.4
IL-13	-1.2	-1.2	-1.2	-1.2	-1.2	-1.1	-0.9	-1.1
IL-17	-1.6	-1.6	-1.6	-1.6	-1.6	-1.6	-1.6	-1.6
IL-23	-1.3	-1.3	-1.3	-1.3	-1.3	-1.2	-1.2	-1.2
IL-33	-1.3	-1.3	-1.3	-1.3	-1.3	-1.2	-1.2	-1.1

DISCUSSION

Molecular docking plays a role in determining the ability of the ligand activity to the target protein when an interaction occurs concerning the binding affinity formed (Kharisma et al., 2020). Binding affinity is the binding energy formed when there is an interaction between protein and ligand. This energy is formed through a reversible reaction at constant temperature and pressure according to the laws of thermodynamics (Ramadhani et al., 2022). Visualization of the docking results of metal ion particles Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} with IL-17, which has the most negative binding energy is shown in Fig. 2, the structure of spheres and cartoons. The interaction between the ligand and the target protein domain results in the formation of weak bonds that play a role in triggering the activation of the protein's biological response (Prahasanti et al., 2021). The results showed that metal ion particles could trigger the activation of IL-17 protein, which allows the inflammatory response to occur because the protein is classified as a proinflammatory agent type.

The cause of allergic reactions to dental metal-based materials in the oral cavity is due to the corrosion process of the metal. Corrosion is an electrochemical reaction in metal that can trigger the release of metal ions. The factors that cause corrosion are low salivary pH, highly reactive metal ions such as halides which can cause oxidation on metal surfaces, and the presence of intraoral bacteria that can aggravate corrosion. The protein content of saliva can affect the release of metal ions through saliva. This is because proteins act as electrolyte media that can trigger elec-

trochemical reactions. An electrochemical reaction is a reaction consisting of an anode (experiencing oxidation) and a cathode (experiencing reduction). Particles of metal ions Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} as anodes and H^{+} ions from electrolyte media as cathodes, thus affecting corrosion and metal ionization such as Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} besides the low salivary pH also increases the metal oxidation process resulting in corrosion, which in turn can lead to intraoral metal allergy (Dundu and Aditya, 2017).

Metallic materials are often used in dentistry, such as copper (Cu^{2+}) used in orthodontic wire and brackets (Agnihotri et al., 2020). Iron (Fe^{2+}, Fe^{3+}) and manganese (Mn^{2+}, Mn^{3+}) can be used as base materials for stainless steel in the manufacture of orthodontic wires, endodontic instruments such as files and reamers, temporary space maintainers, and prefabricated crowns, chromium (CrO_4^{2-}) is often combined with other metals such as nickel and cobalt which can be used as ceramic-metal restorations, and metal frames in removable dentures and are used as alloys for NiCr or COCr metal castings. Silicon (Si^{4+}) is used as a ceramic-metal restorative material. Hg^{+} and Cu^{2+} are used as base materials for amalgam fillings for dental restorations (Jukka, 2018; Sakaguchi and Ferracane, 2019).

Particles of Metal ions Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} can cause allergies with various manifestations of the oral mucosa such as glossitis, cheilitis, dysgeusia, stomatitis, gingivitis, the sensation of discomfort in the oral cavity, glossodynia or painful tongue) and oral lichen planus (Maeno et al., 2021). Metal allergic manifestations can also occur on the skin, such as palmoplantar pustulosis, dermatitis, including atopic dermatitis, and monetary eczema (Kitagawa et al., 2019). When metal ions penetrate the skin and mucosa, metal ions will bind to proteins and form haptens, then T lymphocyte induction occurs. Activated T cells will produce inflammatory cytokines such as TNF-α, IFN-γ, IL-1β, IL-2, IL-5, and IL-10, and inflammatory chemokines that trigger allergic reactions resulting in characteristic lesions at the site of exposure (Pazzini et al., 2016; Saito et al., 2016). Exposure to metal ions in the body can also increase IL-17 secretion through increased ZIP-8 expression (Bonaventura et al., 2017). The IL-17 cytokine is produced as an inflammatory mediator that can increase the inflammatory response. Th17-mediated inflammatory responses with overproduction of the proinflammatory cytokine IL-17 play an important role in the induction of immune dysfunction and the pathogenesis of inflammatory diseases such as rheumatoid arthritis, allergic asthma, and multiple sclerosis (Her and Kavanaugh, 2016; Liu et al., 2020). Previous studies have shown that metal exposure in the body can cause allergic reactions due to the involvement of inflammatory cytokines mediated by T cells (Sitalaksmi et al., 2019). A previous study showed that metal allergy might result from increased expression of inflammatory cytokines such as IFN-γ, IL-4, and IL-10 (Nakasone et al., 2018).

CONCLUSION

The particle of metal Ions Cu^{2+}, Fe^{2+}, Mn^{2+}, Mn^{3+}, Fe^{3+}, CrO_4^{2-}, Si^{4+}, and Hg^{+} can cause allergic reactions that can be predicted through molecular docking (*in silico*), which is indicated by the binding value. The most negative affinity binds to the IL-17 protein. Low salivary pH will increase the metal oxidation process, and an electrochemical reaction triggers the release of metal ions resulting in corrosion, which can then lead to metal allergies in the oral cavity. Further research is needed to examine metal ions against metal-allergic cytokines *in vitro* and *in vivo*.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Berniyati T	Nugraha AP	Hidayati NN	Kharisma VD	Nugraha AP	Tengku NEBTAN
Concepts or ideas	x	x	x	x	x	x
Design	x	x	x	x	x	x
Definition of intellectual content	x	x	x	x	x	x
Literature search	x	x	x	x	x	x
Experimental studies	x	x		x	x	
Data acquisition	x	x	x	x	x	x
Data analysis						
Statistical analysis						
Manuscript preparation	x					
Manuscript editing	x	x	x	x	x	x
Manuscript review	x	x	x	x	x	x

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