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Original Article

A bioinformatic approach of hydroxyapatite and polymethylmethacrylate composite exploration as dental implant biomaterial

[Un enfoque bioinformático de la exploración con compuestos de hidroxiapatita y polimetilmetacrilato como biomaterial de implantes dentales]

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Abstract

Context: The most common biomaterial used for dental implants is titanium. However, the release of metal ions and the risk of allergic reactions to metals that may occur in some patients cannot be avoided. Hydroxyapatite-polymethylmethacrylate (HA-PMMA) composite biomaterials are proposed to have potential as dental implant biomaterials due to their mechanical, chemical, and biological properties. HA-PMMA may induce osseointegration, biocompatible, less allergic reactions, and no metal ions released. In addition, HA-PMMA can be obtained from Indonesia's abundant natural resources.

Aims: To explore HA-PMMA composites through molecular docking as a biomaterial candidate for dental implants *in silico*.

Methods: Structure data format (sdf), molecular weight, and identity number (CID) of HA-PMMA ligand samples were obtained from PubChem database and minimized through OpenBabel. 3D structure, selection method, resolution, atom count, weight, sequence length, and ID protein BMP2, BMP4, BMP7, alkaline phosphatase (AP), osteonectin, osteopontin, and osteocalcin on RCSB-PDB native ligand and water sterilization on PyMol were carried out with the aim of to maximize the formation of binding affinity during molecular docking simulations.

Results: HA-PMMA composites can enhance the activity of proteins associated with osseointegration such as BMP-2/4/7, AP, osteocalcin, osteonectin, and osteopontin *in silico*. HA-PMMA composites have the strongest binding to osteonectin and are predicted to enhance the AP activity *in silico*.

Conclusions: HA-PMMA composites are potential candidates for dental implant biomaterials with the osteointegration ability through binding with BMP-2/4/7, AP, osteocalcin, osteonectin, and osteopontin *in silico*.

Keywords: biomaterials; composite; human well-being; hydroxyapatite-polymethylmethacrylate; *in silico*; osseointegration.

Resumen

Contexto: El biomaterial más común utilizado para implantes dentales es el titanio. Con este no se evita la liberación de iones metálicos y el riesgo de reacciones alérgicas a los metales que pueden ocurrir en algunos pacientes. Se propone que los biomateriales compuestos de hidroxiapatita-polimetilmetacrilato (HA-PMMA) tienen un potencial como biomateriales de implantes dentales debido a sus propiedades mecánicas, químicas y biológicas. HA-PMMA puede inducir osteointegración, reacciones biocompatibles, menos alérgicas y sin liberación de iones metálicos.

Objetivos: Explorar los implantes HA-PMMA a través del acoplamiento molecular como biomaterial candidato para implante dental *in silico*.

Métodos: Formato de datos de estructura (sdf), peso molecular y número de identidad (CID) de muestras de ligando HA-PMMA se obtuvieron de PubChem y se minimizaron a través de OpenBabel. Estructura 3D, método de selección, resolución, recuento de átomos, peso, longitud de secuencia e identificación de proteínas BMP2, BMP4, BMP7, fosfatasa alcalina (AP), osteonectina, ostepontina y osteocalcina en ligando nativo RCSB-PDB y esterilización de agua en PyMol fueron desarrollados con el objetivo de maximizar la formación de afinidad de unión durante las simulaciones de acoplamiento molecular.

Resultados: Los implantes de HA-PMMA pueden potenciar la actividad de proteínas asociadas con la osteointegración como BMP-2/4/7, AP, osteocalcina, osteonectina y osteopontina *in silico*. Los implantes de HA-PMMA se unen fuertemente a la osteonectina y podrían mejorar la actividad AP *in silico*.

Conclusiones: Los implantes de HA-PMMA son candidatos potenciales para implantes dentales con capacidad de osteointegración por la unión con BMP-2/4/7, AP, osteocalcina, osteonectina y osteopontina *in silico*.

Palabras Clave: bienestar humano; biomateriales; hidroxiapatita-polimetilmetacrilato; implante; *in silico*; osteointegración.

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INTRODUCTION

The lack of dental and oral health knowledge in Indonesian society may increase caries and periodontal diseases in Indonesia (Chen et al., 2019; Renjana et al., 2020; Rosalien et al., 2019). Meanwhile, periodontitis can increase the level of malondialdehyde, cathepsin C, and C-reactive protein that may enhance the risk factor of cardiovascular disease (Ramadhani et al., 2020a; 2020b). Poverty in some low-middle-income countries such as Indonesia is associated with untreated or neglected dental caries and periodontal diseases (Folayan et al., 2020). Neglected caries and untreated periodontal diseases increase root surface caries and tooth loss cases (Hariyani et al., 2018). Furthermore, neglected dental caries and periodontal diseases contribute to tooth loss in the Javanese population (Timmerman et al., 1998; van der Velden, 2015). Any severe tooth loss may lead to the disturbance of stomatognathic function such as chewing, speaking, eating, temporomandibular disorders (Sipilä et al., 2013). Moreover, it can decrease the patient's quality of life-related to oral health (Gerritsen et al., 2010; Kassebaum et al., 2014; Haag et al., 2017).

The rehabilitation of stomatognathic function is necessary to improve the patient's quality of life with tooth loss. Stomatognathic function due to tooth loss can be rehabilitated by applying dental prosthetics, such as complete or partial denture, removable or permanent denture, one of which is a dental implant (Hirai and Koshino, 2006; da Silva et al., 2012; Alves et al., 2018; Tabitha et al., 2021).

A dental implant is the most chosen option because they are more functional, adaptive, strong, and durable (Eposito et al., 2012; Clark and Levin 2019). Currently, the most commonly used dental implant biomaterial is titanium. Titanium for dental implant biomaterial has excellent mechanical properties. However, the release of metal ions, corrosion, the risk of allergic and hypersensitivity reactions to metals in some patients is inevitable (Sicilia et al., 2008; Siddiqi et al., 2011; Bilhan et al., 2013; Delgado-Ruiz and Romanos, 2018; Ottria et al., 2018; Hanawa, 2020). Moreover, the prices of titanium dental implants are relatively high in Indonesia. Therefore, any exploration of dental implant biomaterials with mechanical, chemical, and biological properties that are biocompatible and can induce osseointegration characterized by the increased biological markers in periodontal tissue is necessary (Alghamdi and Jansen, 2020).

Hydroxyapatite-polymethylmethacrylate (HA-PMMA) composite biomaterials are recognized to have potential as the new dental implant biomaterials because they have mechanical, chemical, and biological properties. HA-PMMA may induce osseointegration, be biocompatible, less allergic and hypersensitivity reactions, noncorrosive, and no metal ions released (Deb, 1998; Giavaresi, 2004; Kang et al., 2012). HA can be obtained from Limestone in Padalarang, Indonesia, as natural resources. Thus, it is expected to reduce production costs, replace the imported materials, and be economically profitable. HA isolated from Padalarang Limestone has hydroxyl and phosphate groups, crystal particles, the composition of O, Ca, and P with a Ca/P ratio of 1.64, and non-toxic umbilical cord mesenchymal stem cell, which meets the requirements of a biocompatible biomaterial candidate (Pridanti et al., 2020).

The successfulness of dental implants to rehabilitate stomatognathic function disturbance due to tooth loss is strongly determined by the osseointegration between dental implants and periodontium (Albrektsson and Wennerberg, 2019; Pellegrini et al., 2018; Goo and Goh, 2020). Osseointegration of dental implant it can be predicted by increasing the expression or secretion of osteogenic related protein marker in periodontium such as bone morphogenic protein (BMP)-2, BMP4, BMP7, alkaline phosphatase (AP), osteonectin, osteopontin, and osteocalcin (Nugraha et al., 2018a; 2018b; 2019; Prahasanti et al., 2020; Saskianti et al., 2020).

The investigation and exploration of HA-PMMA composite biomaterials can be performed by applying molecular docking using software and databases through a bioinformatic approach or *in silico* studies (Kharisma et al., 2020a; 2020b). The bioinformatics approach can predict the bind-

ing HA-PMMA composites, which qualifies for enhancing or not the osseointegration-related molecular marker proteins before the *in vitro* and *in vivo* study is conducted. Therefore, this study aims to explore HA-PMMA composites through molecular docking as a biomaterial candidate for a dental implant *in silico*.

MATERIAL AND METHODS

Sample preparation

The 3D structure in the structure data format (sdf), molecular weight, and identity number (CID) of the ligand samples consisting of PMMA and HA were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in which both ligands were minimized through OpenBabel. 3D structure, selection method, resolution, atom count, weight, sequence length, and protein ID BMP2, BMP4, BMP7, AP, osteonectin, osteopontin, osteocalcin were acquired on RCSB PDB (https://www.rcsb.org/). The 3D protein structure obtained underwent native ligand and water sterilization on PyMol version 2.5, which aimed to maximize the formation of binding affinity during the molecular docking simulation process (Kharisma et al., 2021).

Molecular binding

PyRx version 0.8 software (https://pyrx.sourceforge.io/home) with Windows operating system was utilized for molecular docking simulation. Tethering aimed to decide the level of ligand activity when it bound to the target protein. The ligands in this study were the HA-PMMA complex and the target proteins of BMP2, BMP4, BMP7, AP, osteonectin, osteopontin, and osteocalcin. The blind and random docking method was applied in this study to determine the activity of the HA-PMMA complex against the target based on bond affinity regardless of the functional side (Kharsima et al., 2020b).

Protein-ligand interactions

Molecular interactions on the molecular complexes of docking simulation results were analyzed through the Discovery Studio software version 16. 1. 0 to shape the types of chemical bonds formed. Several types of chemical bonds such as hydrogen, hydrophobic, Pi-Alkyl, Van der Waals, and electrostatic are shown in 2D structures (Kharsima et al., 2020a; 2020b).

Visualization of 3D structures

The complex 3D structure of the mooring simulation results was displayed through PyMol software for structural selection and coloring. The structure displayed through the software consisted of sticks, cartoons, ribbons, spheres, and surfaces. Then, for staining, the target domain could be distinguished from the ligands (Kharisma et al., 2021).

RESULTS AND DISCUSSION

The ligands obtained from PubChem consisted of PMMA CID: 6658 molecular with the weight of 100.12 g/mol and HA CID: 18986957 molecular with 192.13g/mol weight. A total of seven target proteins were obtained from the PDB database. All samples were similar through visualization in the laboratory using the X-ray method, and then the protein had A/B chains were sequenced with a maximum length of 484-mer and a minimum of 49-mer, for each target protein. The samples had a PDB ID (4UI1, 1REU, 1LX5, 2GLQ, 1BMO, 1MOY, and 1Q8H), a maximum number of atoms (4289) and a minimum (353), and the highest resolution (3.30) and the lowest (1.55) (Table 1).

Meanwhile, the protein resolution *in silico* describes the clarity of the atomic distance in amino acid residues when it is displayed in the software, the higher the value, the clearer the molecular visualization (Qian et al., 2007). Based on the results of target preparation, the 3D protein structure was obtained from a tertiary type of database because it was a secondary formation that had folds and consisted of one or more chains (Rehman et al., 2020). The seven protein structures were sterilized with water, and the original ligands in the PyMol software was to obtain the maximum binding energy value when simulating the docking of molecules (Baran et al., 2017).

Table 1. The results of target protein sample preparation from RCSB-PDB.

Name	PDB ID	Visualization	Resolution (Å)	Atom Counts	Weight (kDa)	Chain	Sequence length (mer)
BMP2	4UI1	X-ray	2.35	353	51.34	A/B	114
BMP4	1REU	X-ray	2.65	833	11.73	A	103
BMP7	1LX5	X-ray	3.30	1695	29.23	A	139
AP	2GLQ	X-ray	1.60	4289	53.57	A	484
Osteonectin	1BMO	X-ray	3.10	3854	55.23	A/B	233
Ostepontin	1MOY	X-ray	1.55	1066	13.80	A	130
Osteocalcin	1Q8H	X-ray	2.00	378	5.85	A	49

RCSB-PDB: native ligand; BMP-2, BMP-4, BMP-7: bone morphogenic proteins associated with osseointegration; AP: alkaline phosphatase; PDB ID: Protein Data Bank Identification.

The molecular docking simulation aims to shape the ligand-binding activity of the target receptor by observing the affinity level of the bonds formed (Meng et al., 2011). Meanwhile, bond affinity is the binding energy generated when a ligand interacts with a target, through which the affinity value obtained can be used to regulate the binding activity of the ligand (Luqman et al., 2020). The working principle of bond affinity is under the laws of thermodynamics. If it gets negative, it can affect the response activity of the target protein (Pantsar and Poso, 2018). The blind type molecular docking method was used in this study, and it aimed to screen the binding energy produced by the HA-PMMA ligand complex when it is bound to the seven targets to control the target activation response activity's ability HA-PMMA binding.

The simulation results of molecular docking showed three bond affinity scores formed through three modes, this study used mode 0, which was the best binding location compared to other modes (Table 2). The 3D structure of the molecular docking simulation results is displayed through PyMol software. It presents the structure of the cartoons on the target protein, while the spheres and sticks are for ligands, letters are signed to the image based on the molecular complex (Fig. 1). E molecule complex, which is the binding of the HA-PMMA ligand with osteonectin protein, shows a more negative bond affinity value than other complexes. It allows HA-PMMA to increase osteonectin activity compared to other proteins through direct contact mechanisms.

The entire molecular complex resulting from molecular docking was then analyzed for ligand-protein interactions through the Discovery Studio software to determine the position, type, and the number of bonds formed. Molecular interactions consisting of hydrogen, Van der Waals, alkyl, hydrophobic, and electrostatic interactions play an important role in initiating protein biological response, namely the activation and inhibition (Li et al., 2016). Furthermore, the molecular interaction analysis (Table 2) shows different types of interactions produced by ligands consisting of Van der Waals, pi-alkyl, and hydrogen. However, E molecular complex has a total number of interactions more than others, making it possible to initiate a response to an increase in target activity because it has more molecular interactions. Visualization of the molecular interaction identification results in molecular complex E through the Discovery Studio software is displayed in a representative display (Fig. 2).

HA-PMMA can enhance osseointegration between dental implant and periodontium through the osteogenic pathways, such as BMP-2, BMP-4, BMP-7. BMP is a strong regulator protein in osteogenic pathways. BMP-2 can enhance cell mineralization *in vitro* and osseointegration *in vivo* (Teng et

al., 2016). BMP-2, BMP-4, and BMP-7 are expressed and produced abundantly in mesenchymal stem cells and progenitor cells that possess a pivotal role during osteogenesis and osseointegration of dental implants (Waris et al., 2010; Prahasanti et al., 2020). The stimulation of BMP-7 has advantages to bone and tendon regeneration *in vitro* through the elevation expression of osteogenic and fibroblast transdifferentiation, which is the key factor during successful osseointegration (Schwarting et al., 2015).

Osteogenic-related proteins like AP, osteocalcin, osteopontin, and osteonectin expression and secretion can predict the bone repair process during osseointegration (Palin et al., 2018). Those osteogenic related proteins are also expressed in the gingival mesenchymal stem cells with a role during osteogenic differentiation (Nugraha et al., 2018a; 2018b; 2019). The surface modification with the addition of HA in the dental implant may improve the osteogenic-related protein that enhances the osseointegration of dental implant (Sirin et al., 2016; Hu et al., 2017).

Table 2. The binding energy results from the simulation of molecular docking.

Molecular complex	Ligand	Protein	Docking grid		Mode	Binding affinity (kcal/mol)
			Centre (Å)	Dimension (Å)		
A	HA-PMMA	BMP2	X: 21.772	X: 39.081	0	-3.1
			Y: 9.256	Y: 45.617	1	-2.9
			Z: 9.271	Z: 55.099	2	-2.9
B	HA-PMMA	BMP4	X: -18.049	X: 35.286	0	-3.1
			Y: -21.892	Y: 56.805	1	-3.0
			Z: -40.965	Z: 38.239	2	-3.0
C	HA-PMMA	BMP7	X: 79.198	X: 54.126	0	-3.5
			Y: 35.787	Y: 36.155	1	-3.5
			Z: 45.693	Z: 43.192	2	-3.5
D	HA-PMMA	AP	X: 43.872	X: 64.911	0	-3.7
			Y: 23.205	Y: 70.704	1	-3.6
			Z: 9.204	Z: 66.173	2	-3.6
E	HA-PMMA	Osteonectin	X: 38.335	X: 88.374	0	-4.2
			Y: 17.716	Y: 72.496	1	-4.2
			Z: 19.753	Z: 93.243	2	-3.9
F	HA-PMMA	Ostepontin	X: -13.074	X: 38.151	0	-3.5
			Y: 8.026	Y: 42.830	1	-3.5
			Z: -26.463	Z: 73.905	2	-3.4
G	HA-PMMA	Osteocalcin	X: 8.069	X: 25.000	0	-3.3
			Y: 25.299	Y: 25.000	1	-3.2
			Z: 22.859	Z: 25.000	2	-3.1

HA-PMMA: hydroxyapatite-polymethylmethacrylate; BMP2, BMP4, BMP7: bone morphogenic proteins associated with osseointegration; AP: alkaline phosphatase.

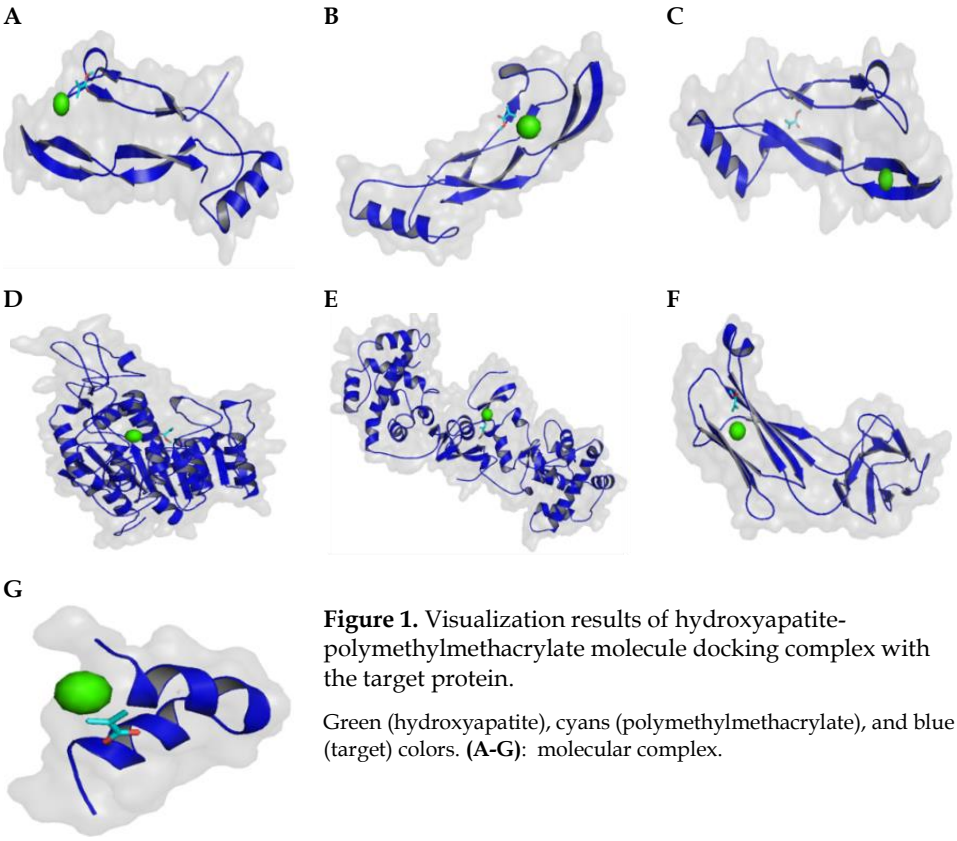

Figure 1. Visualization results of hydroxyapatite-polymethylmethacrylate molecule docking complex with the target protein.

Green (hydroxyapatite), cyans (polymethylmethacrylate), and blue (target) colors. **(A-G)**: molecular complex.

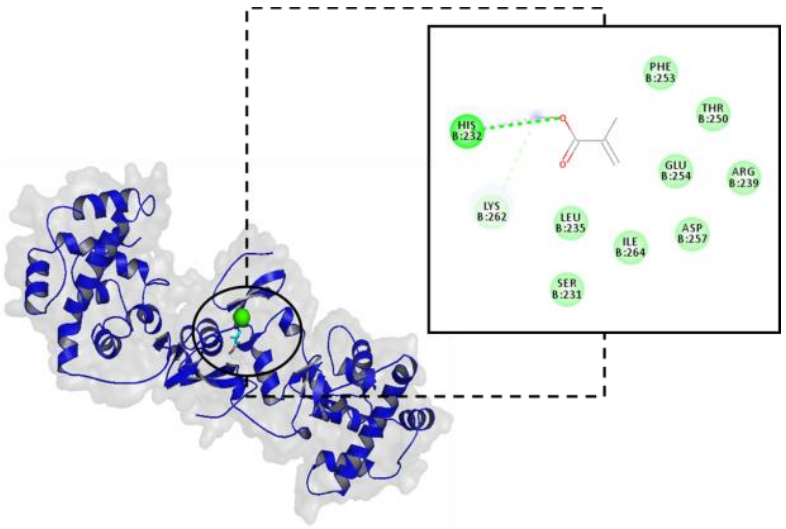

Figure 2. 2D molecular interaction on molecule E complex visualization.

CONCLUSIONS

The E molecule complex consisting of hydroxyapatite-polymethylmethacrylate binding with osteonectin is predicted to influence the increase of alkaline phosphatase activity because it has more negative bond affinity values. Hydroxyapatite-polymethylmethacrylate interacts through the binding domains of His232, Lys262, Leu235, Ser231, Ile264, Asp257, Glu254, Arg239, Thr250, Phe253

through the interaction of Van der Waals, hydrogen, and Pi alkyl, and produces a total number of interactions more than other complexes. Thus, hydroxyapatite-polymethylmethacrylate binding can increase osteonectin activity, as proven *in silico*. However, further analysis must be carried out *in vitro* and *in vivo*.

CONFLICT OF INTEREST

The authors declare no conflicts of interests.

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REFERENCES

Albrektsson T, Wennerberg A (2019) On osseointegration in relation to implant surfaces. Clin Implant Dent Relat Res 21(Suppl 1): 4–7.

Alghamdi HS, Jansen JA (2020) The development and future of dental implants. Dent Mater J 39(2): 167–172.

Alves AC, Cavalcanti RV, Calderon PS, Pernambuco L, Alchieri JC (2018) Quality of life related to complete denture. Acta Odontol Latinoam 31(2): 91–96.

Baran D, Pszolla MG, Lapidoth GD, Norn C, Dym O, Unger T, Albeck S, Tyka MD, Fleishman SJ (2017) Principles for computational design of binding antibodies. Proc Natl Acad Sci U S A 114(41): 10900–10905.

Bilhan H, Bural C, Geckili O (2013) Titanium hypersensitivity. A hidden threat for dental implant patients? N Y State Dent J 79(4): 38–43.

Chen KJ, Gao SS, Duangthip D, Lo ECM, Chu CH (2019) Prevalence of early childhood caries among 5-year-old children: A systematic review. J Investig Clin Dent 10(1): e12376.

Clark D, Levin L (2019) In the dental implant era, why do we still bother saving teeth? Dent Traumatol. 35(6): 368–375.

Da Silva GR, Roscoe MG, Ribeiro CP, da Mota AS, Martins LR, Soares CJ (2012) Impact of rehabilitation with metal-ceramic restorations on oral health-related quality of life. Braz Dent J 23(4): 403-408.

Deb S (1998) Polymers in dentistry. Proc Inst Mech Eng H 212(6): 453–464.

Delgado-Ruiz R, Romanos G (2018) Potential causes of titanium particle and ion release in implant dentistry: a systematic review. Int J Mol Sci 19(11): 3585.

Esposito M, Maghaireh H, Grusovin MG, Ziounas I, Worthington HV (2012) Interventions for replacing missing teeth: management of soft tissues for dental implants. Cochrane Database Syst Rev 2012(2): CD006697.

Folayan MO, El Tantawi M, Aly NM, Al-Batayneh OB, Schroth RJ, Castillo JL, Virtanen JI, Gaffar BO, Amalia R, Kemoli A, Vulkovic A, Feldens CA; ECCAG (2020) Association between early childhood caries and poverty in low and middle-income countries. BMC Oral Health 20(1): 8.

Gerritsen AE, Allen PF, Witter DJ, Bronkhorst EM, Creugers NH (2010) Tooth loss and oral health-related quality of life: a systematic review and meta-analysis. Health Qual Life Outcomes 8: 126.

Giavaresi G (2004) Poly(2-hydroxyethyl methacrylate) biomimetic coating to improve osseointegration of a PMMA/HA/glass composite implant: In vivo mechanical and histomorphometric assessments. Int J Artif 27: 674–680.

Goo CL, Goh V (2020) Beyond osseointegration: dealing with late dental implant complications. J Oral Implantol 46(6): 602–611.

Haag DG, Peres KG, Balasubramanian M, Brennan DS (2017) Oral conditions and health-related quality of life: a systematic review. J Dent Res 96(8): 864–874.

Hanawa T (2020) Zirconia versus titanium in dentistry: a review. Dent Mater J 39(1): 24–36.

Hariyani N, Spencer AJ, Luzzi L, Do LG (2018) Root surface caries among older Australians. Community Dent Oral Epidemiol 46(6): 535–544.

Hirai T, Koshino H (2006) Expectations for prosthetic dentistry as a health science [Japanese]. Nihon Hotetsu Shika Gakkai Zasshi 50(3): 353–362.

Hu MH, Lee PY, Chen WC, Hu JJ (2017) Incorporation of collagen in calcium phosphate cements for controlling osseointegration. Materials (Basel) 10(8): 910.

Kang BH, Ryu SC, Park HC (2012) A study of the use of a hydroxyapatite and poly (methyl methacrylate) composite as a material for implants. J Ceram Process Res 13(6): 791–796.

Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJ, Marcenes W (2014) Global burden of severe tooth loss: a systematic review and meta-analysis. J Dent Res 93(7 Suppl): 20S–28S.

Kharisma VD, Ansori ANM, Nugraha AP (2020a) Computational study of ginger (*Zingiber officinale*) as E6 inhibitor in human papillomavirus type 16 (HPV-16) infection. Biochem Cell Arch 20(Suppl. 1): 3155–3159.

Kharisma VD, Ansori ANM, Widyananda MH, Utami SL, Nugraha AP (2020b) Molecular simulation: the potency of conserved region on E6 HPV-16 as a binding target of black tea compounds against cervical cancer. Biochem Cell Arch 20: 2795–2802.

Kharisma VD, Widyananda MH, Ansori ANM, Nege AS, Naw SW, Nugraha AP (2021) Tea catechin as antiviral agent via apoptosis agonist and triple inhibitor mechanism against HIV-1 infection: a bioinformatics approach. J Pharm Pharmacogn Res 9(4): 435–445.

Li Y, Wang Z, Wei Q, Luo M, Huang G, Sumer BD, Gao J (2016) Non-covalent interactions in controlling pH-

responsive behaviors of self-assembled nanosystems. Polym Chem 7(38): 5949–5956.

Luqman A, Kharisma VD, Ruiz RA, Götz F (2020) *In silico* and *in vitro* study of trace amines (TA) and dopamine (DOP) interaction with human alpha1-adrenergic receptor and the bacterial adrenergic receptor QseC. Cell Physiol Biochem 54: 888–898.

Meng XY, Zhang HX, Mezei M, Cui M (2011) Molecular docking: a powerful approach for structure-based drug discovery. Curr Comput Aided Drug Des 7(2): 146–157.

Nugraha AP, Narmada IB, Ernawati DS, Dinaryanti A, Hendrianto E, Ihsan IS, Riawan W, Rantam FA (2018a) *In vitro* bone sialoprotein-I expression in combined gingival stromal progenitor cells and platelet rich fibrin during osteogenic differentiation. Trop J Pharm Res 17(12): 2341–2345.

Nugraha AP, Narmada IB, Ernawati DS, Dinaryanti A, Hendrianto E, Riawan W, Rantam FA (2018b) Bone alkaline phosphatase and osteocalcin expression of rat's gingival mesenchymal stem cells cultured in platelet-rich fibrin for bone remodeling (*in vitro* study). Eur J Dent 12: 566–573.

Nugraha AP, Narmada IB, Ernawati DS, Dinaryanti A, Susilowati H, Hendrianto E, Ihsan IS, Riawan W, Rantam FA (2019) Somatic cells acceleration by platelet rich fibrin. Indian Vet J 96(4): 30–34.

Ottria L, Lauritano D, Andreasi Bassi M, Palmieri A, Candotto V, Tagliabue A, Tettamanti L (2018) Mechanical, chemical and biological aspects of titanium and titanium alloys in implant dentistry. J Biol Regul Homeost Agents 32(2 Suppl. 1): 81–90.

Palin LP, Polo TOB, Batista FRS, Gomes-Ferreira PHS, Garcia Junior IR, Rossi AC, Freire A, Faverani LP, Sumida DH, Okamoto R (2018) Daily melatonin administration improves osseointegration in pinealectomized rats. J Appl Oral Sci 26: e20170470.

Pantsar T, Poso A (2018) Binding affinity via docking: fact and fiction. Molecules 23(8): 1899.

Pellegrini G, Francetti L, Barbaro B, Del Fabbro M (2018) Novel surfaces and osseointegration in implant dentistry. J Investig Clin Dent 9(4): e12349.

Prahasanti C, Nugraha Ap, Saskianti T, Suardita K, Riawan W, Ernawati DS (2020) Exfoliated human deciduous tooth stem cells incorporating carbonate apatite scaffold enhance BMP-2, BMP-7 and attenuate MMP-8 expression during initial alveolar bone remodeling in Wistar rats (*Rattus norvegicus*). Clin Cosmet Investig Dent 12: 79–85.

Pridanti KA, Cahyareni F, Harijanto E, Soebagijo, Rianti D, Kristanto W, Damayanti H, Putri TS, Dinaryanti A, Karsari D, Yuliati A (2020) Characteristics and cytotoxicity of hydroxyapatite from Padalarang–Cirebon limestone as bone grafting candidate. Biochem Cell Arch 20(2): 4727–4731.

Qian B, Raman S, Das R, Bradley P, McCoy AJ, Read RJ, Baker D (2007). High-resolution structure prediction and the crystallographic phase problem. Nature 450(7167): 259–264.

Ramadhani NF, Nugraha AP, Gofur NRP, Hakiki D, Ridwan RD (2020b) Elevation of C-reactive protein in chronic periodontitis patient as cardiovascular disease risk factor. Biochem Cell Arch 20: 2875–2878.

Ramadhani NF, Nugraha AP, Putra Gofur NR, Permatasari RI, Ridwan RD (2020a) Increased levels of malondialdehyde and cathepsin C by *Aggregatibacter actinomycetemcomitans* in saliva as aggressive periodontitis biomarkers: A review. Biochem Cell Arch 20: 2895–2901.

Rehman I, Kerndt CC, Botelho S (2020). Biochemistry, Tertiary Protein Structure. In StatPearls. StatPearls Publishing.

Renjana AR, Pratomo H, Arminsih R (2020) Factors associated with the dental health status of health promotion students in the Faculty of Public Health, Universitas Indonesia: A cross-sectional study. J Int Oral Health 12: 236–240.

Rosalien R, Saragih FAI, Agustanti A, Setiawati F, Maharani DA (2019) Validity of self-perceived and clinically diagnosed gingival status among 12-15-year-old children in Indonesia. Asian Pac Isl Nurs J 4(2): 72–76.

Saskianti T, Nugraha AP, Prahasanti C, Ernawati DS, Suardita K, Riawan W (2020) Immunohistochemical analysis of stem cells from human exfoliated deciduous teeth seeded in carbonate apatite scaffold for the alveolar bone defect in Wistar rats (*Rattus novergicus*). F1000Res 22(9): 1164.

Schwarting T, Benölken M, Ruchholtz S, Frink M, Lechler P (2015) Bone morphogenetic protein-7 enhances bone-tendon integration in a murine *in vitro* co-culture model. Int Orthop 39(4): 799–805.

Sicilia A, Cuesta S, Coma G, Arregui I, Guisasola C, Ruiz E, Maestro A (2008) Titanium allergy in dental implant patients: a clinical study on 1500 consecutive patients. Clin Oral Implants Res 19(8): 823–835.

Siddiqi A, Payne AGT, De Silva RK, Duncan WJ (2011) Titanium allergy: could it affect dental implant integration? Clin Oral Implants Res 22(7): 673–680.

Sipilä K, Näpänkangas R, Könönen M, Alanen P, Suominen AL (2013) The role of dental loss and denture status on clinical signs of temporomandibular disorders. J Oral Rehabil 40(1): 15–23.

Sirin HT, Vargel I, Kutsal T, Korkusuz P, Piskin E (2016) Ti implants with nanostructured and HA-coated surfaces for improved osseointegration. Artif Cells Nanomed Biotechnol 44(3): 1023–1030.

Tabitha SA, Bennis MA, Mani G (2021) Oral health-related quality of life among implant-supported full-mouth rehabilitation patients treated in a University Dental Hospital - a retrospective study. J Long Term Eff Med Implants 31(1): 65–71.

Teng FY, Chen WC, Wang YL, Hung CC, Tseng CC (2016) Effects of osseointegration by bone morphogenetic protein-2 on titanium implants *in vitro* and *in vivo*. Bioinorg Chem Appl 2016: 3837679.

Timmerman MF, Van der Weijden GA, Armand S, Abbas F, Winkel EG, Van Winkelhoff AJ, Van der Velden U (1998) Untreated periodontal disease in Indonesian adolescents.

Clinical and microbiological baseline data. J Clin Periodontol 25(3): 215–224.

Van der Velden U, Amaliya A, Loos BG, Timmerman MF, van der Weijden FA, Winkel EG, Abbas F (2015) Java project on periodontal diseases: causes of tooth loss in a cohort of untreated individuals. J Clin Periodontol 42(9): 824–831.

Waris V, Waris E, Sillat T, Konttinen YT (2010) BMPs in periprosthetic tissues around aseptically loosened total hip implants. Acta Orthop 81(4): 420–426.

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Contribution	Prahasanti C	Nugraha AP	Kharisma VD	Ansori ANM	Ridwan RD	Putri TPS	Narmada IB	Ardani IGAW	Ramadhani NF	Noor TNEBA
Concepts or ideas		x	x		x		x		x	
Design	x	x	x	x			x		x	
Definition of intellectual content		x	x		x	x	x	x	x	x
Literature search	x	x	x	x				x	x	
Experimental studies	x	x		x	x	x	x			
Data acquisition	x	x	x	x						
Data analysis		x	x	x	x	x				
Statistical analysis		x								
Manuscript preparation	x	x	x	x	x	x	x	x	x	x
Manuscript editing	x	x	x	x	x	x	x	x	x	x
Manuscript review	x	x	x	x	x	x	x	x	x	x

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