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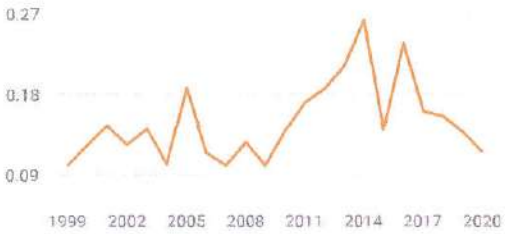

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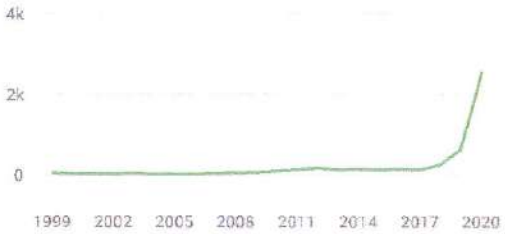

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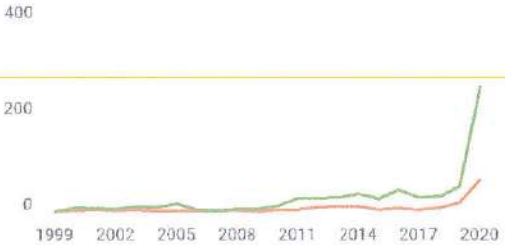

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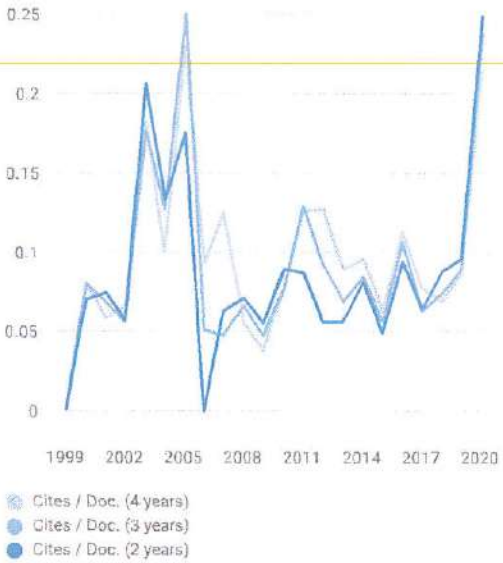

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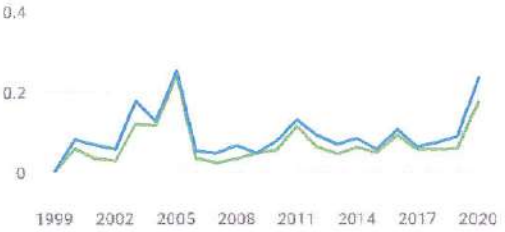

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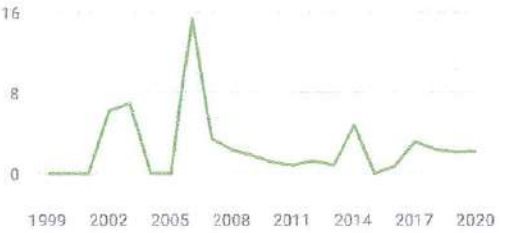

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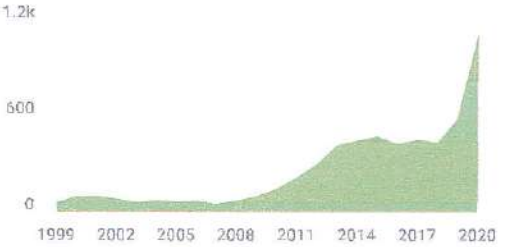

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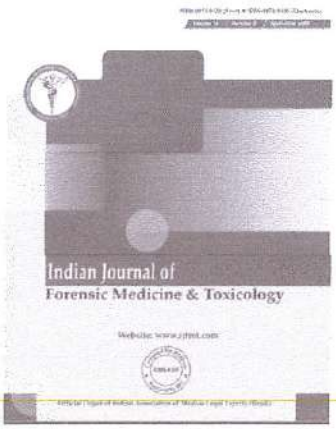

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Articles

Current Issue

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Molecular Docking, Pharmacokinetics, and Toxicity Prediction of Epigallocatechin-3-Gallate (EGCG) on IKK Receptor in Photoaging Prevention

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Abstract

Photoaging is skin aging, caused by chronic exposure of ultraviolet radiation. Photoaging decreases patients' quality of life because the skin was the outer organ seen by others. Ultraviolet radiation causes oxidative stress, that activated inhibitory kappa B kinase (IKK), increased nuclear factor kappa B (NF-kB), matrix metalloproteinase (MMP), and degradation of collagen. Epigallocatechin-3-gallate (EGCG) was the main green tea polyphenol and the main source of biologic activity of green tea. This study was an in silico study, aimed to obtain the effectiveness of EGCG component through molecular docking on IKK receptor (PDB ID: 5EBZ). The bioinformatics tools based on reverse docking used in this study, were Protein Data Bank, ChemDraw, Chem3D, and Molegro Virtual Docker software. Docking and binding site analysis showed, that EGCG was able to interact with IKK receptor. Rerank score of interaction between EGCG and IKK receptor was higher than that of arbutin and 5TL_701[A]. It showed that EGCG has higher potential in photoaging prevention than arbutin, as one of the agents in photoaging prevention. Pharmacokinetics and toxicity (ADMET) prediction in this in silico study were conducted using pkCSM On Line tool. The pkCSM results showed EGCG was predicted having good pharmacokinetics profile without toxicity effect.

Keywords: *photoaging, EGCG, IKK, docking, pharmacokinetics, toxicity, ADMET.*

Introduction

Photoaging is extrinsic skin aging, caused by ultraviolet radiation. Photoaging plays role in 80-90% of skin aging procession. Geriatric population in developed and developing countries were increased.[1,2,3,4] Geriatric population in the United States in 2000 was 13 % (35 million people), and predicted it would be 30% in 2030. Increasing life expectancy will increase the aging problems, especially skin aging because the skin is the outer layer of human organ seen by others. Photoaging decreases patients' self-esteem and quality of life.[1,5]

Inhibitory kappa B kinase (IKK) plays an important role in photoaging pathogenesis, and are an attractive target for photoaging prevention. The IKK receptor can be used as a target in photoaging prevention and can be applied in molecular modeling and structure-activity relationship based drug design.[6,7,8,9] The biggest problems in photoaging prevention are drug effectivity and drug efficiency. The discovery of new drugs with the effective target, that was started with research on drug design, is needed in photoaging prevention.[10]

The drug discovery and development are complicated processions. These processions need a long duration of time and expensive cost. The methods of drug discovery and development are divided into 2 methods, high throughput screening (HTS) dan virtual

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screening. High throughput screening (HTS) consist of chemical compound synthesis and screening based on the protein. Synthesis of a chemical compound, in vitro study, and low hit rate were performed in all pharmacy company, but the high cost in these processions are always the biggest problem.[11,12]

Drug discovery and development term become drug design, so the knowledge about biochemical procession and protein that play role in the pathogenesis of diseases, and drug design in modulating this protein are needed. In silico study, in vitro study, and in vivo study are completing each other in drug design procession.[11,13]

In vitro study of EGCG for photoaging prevention has already done. It can prevent photoaging by inhibiting cJun terminal kinase (JNK) and p38-mitogen-activated protein kinase (p38 MAPK) pathway.[14] This study was an in silico study, aimed to obtain the effectiveness of EGCG component through molecular docking on IKK receptor (PDB ID: 5EBZ).

In silico study in drug development is based on protein-drug interaction, by docking procession. The reactivity of protein is based on protein structure and chemical bond (hydrogen bond, van der Waals bond, covalent bond, and ionic bond). Computer-aided drug delivery (CADD) is able to show computational analysis of protein reactivity, by evaluating protein structure, chemical bond, and protein-drug interaction.[15]

Material and Method

The molecular structure of IKK receptor was downloaded from protein data bank (PDB), and PDB ID: 5EBZ was selected. The structure of ligands was drawn using ChemDraw software application, version 11 and copied into Chem 3D software application, version 11 to create the 3D structure and measure its minimum energy using Molegro Virtual Docker, version 5.5. The validation of the docking study was performed by re-docking the ligand reference into an appropriate protein cavity. Re-docking is accepted if the root mean square value (RMSD) < 2.0 A°.

The docking study of EGCG on the IKK receptor (PDB ID: 5EBZ) was conducted using Molegro Virtual Docker, version 5.0 (processor: Intel (R) Pentium (R) CPU N4200 @1.10GHz; installed RAM: 4.00 GB; system type: 64-bit-operating system). The best docking results were detected visually by comparing the structure of the docked molecules with the structure of reference ligand (5TL_701[A] or 6'-amino-5'-(amino(hydroxy) methyl)-1,2,3,6- tetrahydro-[1,1':3',1"-terpenyl]-4-sulfonamide) in the binding site. The MolDock and ReRank scores have presented the energy needed in receptor-ligand bond (Table 1). The lowest energy visualized the best binding pose between the ligand and amino acid residue of the protein (Figure 1-3).[16]

Pharmacokinetics prediction (absorption, distribution, metabolism, excretion) and toxicity prediction of EGCG, arbutin, and reference ligand were performed using pkCSM On-Line Tool. The molecular structure of EGCG, arbutin, and reference ligand were drawn as 2D molecular structures with ChemDraw software, copied into Chem3D software to create 3D structure, and stored as a .sdf file. The .sdf format of EGCG, arbutin, and reference ligand were translated into SMILE format using SMILE Translator Online Help. The SMILE format was processed using the pkCSM Online Tool to predict the pharmacokinetics and toxicity of compounds.[16,17,18,19]

Findings

Molecular docking was performed to evaluate the mode of binding between the compound and IKK receptor (PDB ID: 5EBZ). The result of molecular docking 3D structure between candidate ligand (EGCG), control ligand (arbutin), and reference ligand (5TL_701[A]) in IKK cavity showed, that the ligands were able to interact with IKK receptor as the target protein (PDB ID: 5EBZ) on the same binding site (Figure 1).

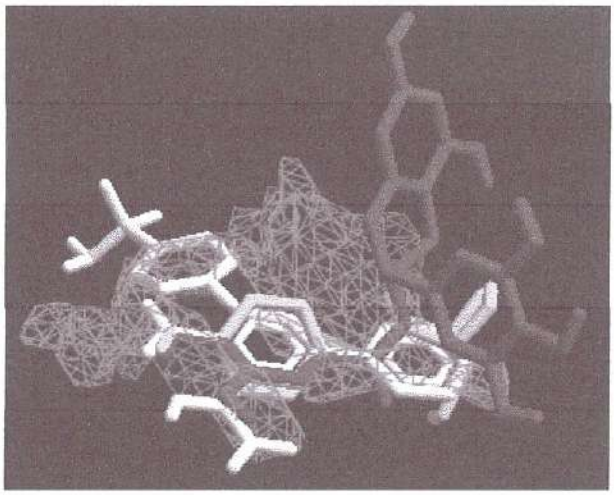

Figure 1 The result of molecular docking 3D structure between candidate ligand (EGCG), control ligand (arbutin), and reference ligand (5TL_701[A]) in IKK cavity. Description: green (IKK cavity), red (EGCG), yellow (arbutin), white (5TL_701[A]).

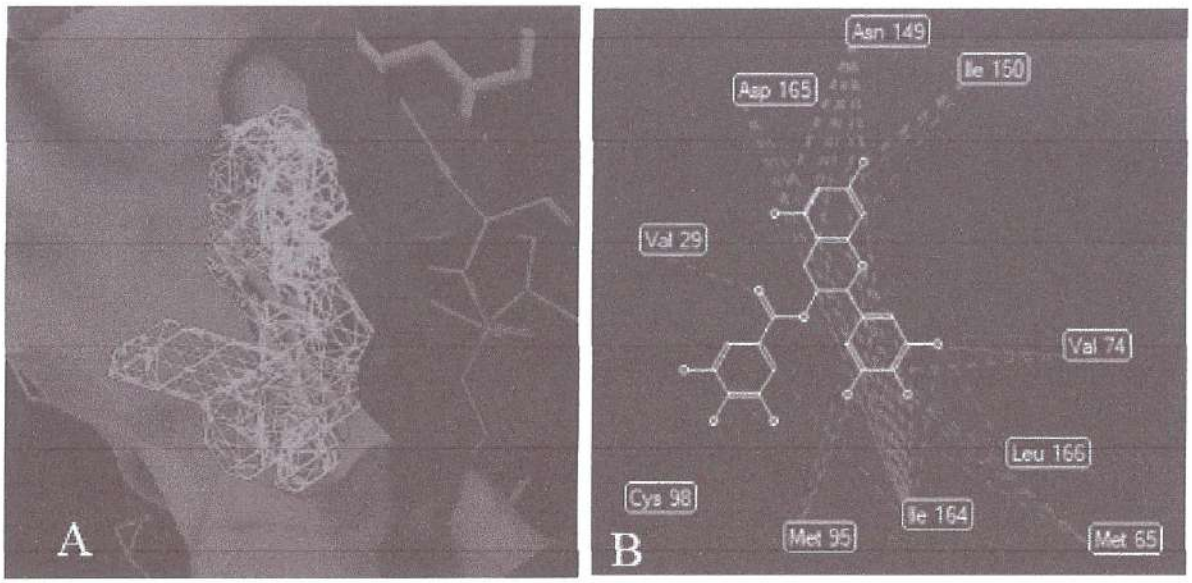

Figure 2 (A) Hydrophobicity view of the interaction between EGCG in IKK cavity using Molegro Virtual Docker software. EGCG (red) was bound to target protein (5EBZ). (B) Hydrogen and steric bound between EGCG and target protein (5EBZ).

The best docking position in the 3D structure molecules of EGCG to IKK receptor (PDB ID: 5EBZ) can be seen in Figure 2A. The docking was carried out at cavity 5, vol. 86.016; surface: 296.96. The bond location of the ligand binding site and target protein showed, that EGCG interacted with IKK receptor through 54 number of bonds. Hydrogen and steric bond from 10 amino acids (Asp 165, Asn 149, Ile 150, Val 74, Leu 166, Met 65, Ile 164, Met 95, Val 29, and Cys 98) were showed at Figure 2B. The Mol Dock score and Rerank score of interaction between EGCG and 5EBZ in IKK cavity were shown in Table 1.

Table 1: Moldock Score And Rerank Score Of Interaction Between 5EBZ Protein And Compounds

Compounds	MolDock Score (kcal/mol)	Rerank Score (kcal/mol)
EGCG	-154.7±7.80	-115.8±2.96
Arbutin	-84.52±0.03	-79.05±0.85
5TL_701[A] as ligand	-128.31±2.24	-84.46±0.75

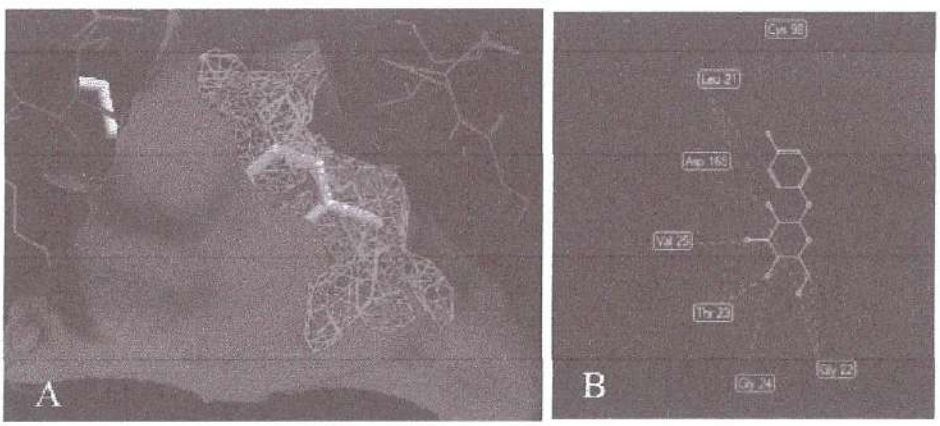

Figure 3 (A) Hydrophobicity view of the interaction between arbutin in IKK cavity using Molegro Virtual Docker software.

Arbutin (yellow) was bound to target protein (5EBZ). (B) Hydrogen and steric bound between arbutin and target protein (5EBZ).

Arbutin is a topical agent that is used in photoaging prevention. The best docking position in the 3D structure molecules of arbutin to IKK receptor (PDB ID: 5EBZ) can be seen in Figure 3A. The docking was carried out at 5, vol. 86.016; surface: 296.96. The bond location of the ligand binding site and target protein showed, that control ligand (arbutin) interacted with IKK receptor through 36 number of bonds. Hydrogen and steric bonds from 7 amino acids (Cys 98, Gly 22, Gly 24, Thr 23, Val 29, Asp 165, and Leu 21) were showed in Figure 3B. The Mol Dock score and Rerank score of interaction between arbutin and 5EBZ in IKK cavity were shown in Table 1.

The result of molecular docking between IKK receptor (PDB ID: 5EBZ) with a candidate ligand (EGCG), a control ligand (arbutin, as one of topical agent in photoaging prevention), and a reference ligand (5TL_701[A]) using Molegro Virtual Docker software, showed that the binding affinity of IKK receptor with EGCG to be higher than that of arbutin. Based on Table 1, the average Mol Dock and Rerank score of interaction between IKK receptor and EGCG were -154.7±7.80 kcal/mol and -115.8±2.96 kcal/mol; between IKK receptor and arbutin were -84.52±0.03 kcal/mol and -79.05±0.85 kcal/mol; and between IKK receptor and 5TL_701[A] were -128.31±2.24 kcal/mol and -84.46±0.75 kcal/mol.

Based on the in silico study of the physicochemical properties of EGCG, the molecular weight value was 458.375 (<500), and the value of the log of octanol/water partition coefficient (log P) was 2.2332. The result of pharmacokinetic prediction of EGCG can be seen in Table 2.

The absorption of a compound is very important because it determines the action of the compound. The pkCSM intestinal absorption prediction is based on the proportion of compounds that were absorbed via the human small intestine. If the pkCSM intestinal absorption prediction value is less than 30%, it is considered to be poorly absorbed.[17,18] Table 2 showed that the value of human intestinal absorption of EGCG was 48%, higher than arbutin. Therefore, it can be predicted that EGCG has moderate intestinal absorption.

The skin permeability is an important consideration in the administration of the topical formulation. Skin permeability reflected transdermal drug delivery. The pkCSM was expressed as constant log Kp (cm/h). Low skin permeability was expressed as log Kp more than -2.5 cm/h.[17,18] The value of skin permeability of EGCG was -2.735 (Table 2). Therefore, it can be predicted that EGCG has good skin permeability.

Table 2: Pharmacokinetics properties of EGCG, arbutin, and 5TL_701[A]

Pharmacokinetics properties	Model name	Predicted value (EGCG)	Predicted value (Arbutin)	Predicted value (5TL_701[A])	Unit
Absorption	Intestinal absorption (human)	48.191	42.175	73.943	% Absorbed (Numeric)
	Skin Permeability	-2.735	-2.743	-2.737	Log Kp (Numeric)
Distribution	BBB permeability	-2.091	-0.865	-0.924	Log BB (Numeric)

Cont... **Table 2: Pharmacokinetics properties of EGCG, arbutin, and 5TL_701[A]**

Metabolism	CYP2D6 substrate	No	No	No	Yes/No (Categorical)
	CYP3A4 substrate	No	No	Yes	Yes/No (Categorical)
	CYP1A2 inhibitior	No	No	No	Yes/No (Categorical)
	CYP2C19 inhibitior	No	No	No	Yes/No (Categorical)
	CYP2C9 inhibitior	No	No	No	Yes/No (Categorical)
	CYP2D6 inhibitior	No	No	No	Yes/No (Categorical)
	CYP3A4 inhibitior	Yes	No	No	Yes/No (Categorical)
Excretion	Total Clearance	0.406	0.595	0.672	Log ml/min/kg (Numeric)
Toxicity	AMES toxicity	No	No	Yes	Yes/No (Categorical)
	Hepato-toxicity	No	No	Yes	Yes/No (Categorical)
	Skin Sensitisation	No	No	No	Yes/No (Categorical)

Discussion

The potentially interactive target protein with EGCG was IKK receptor. The IKK receptor plays role in inhibition of kappa B kinase, which activated NFkB. Nuclear factor kappa B (NFkB) plays role in photoaging pathogenesis, by activating matrix metalloproteinase (MMP) and increasing collagen degradation.[5,19,20] It was predicted, that inhibition of IKK receptor by EGCG would be able to prevent photoaging.

The binding affinity of EGCG to IKK receptor was higher than that of arbutin and reference ligand (5TL_701[A]), and it showed that EGCG has higher potential than arbutin and reference ligand (5TL_701[A]) to be an alternative agent in photoaging prevention.

The blood-brain barrier (BBB) protects the brain from the exogenous compound. If the logBB is more than 0.3, it is considered that the compound is able to across blood-brain barrier and enter to the brain, while the logBB less than -1 showed that the compound is poorly across blood-brain barrier and enter to the brain.[17,18] The BBB permeability of EGCG was -2.091 (Table 2), lower than arbutin and reference ligand. Therefore, it can be predicted that EGCG is poorly distributed to the brain. It can also be predicted EGCG gives minimal side effect and toxicity into the brain.

The most important detoxification enzyme in the body in liver is cytochrome P450. Cytochrome P450 deactivated some drugs, and it can also activated several drugs. The drug metabolism are mainly regulated by two isoforms (CYP2D6 and CYP3A4 substrates). These two main isoforms will predict whether a molecule can be metabolized by cytochrome P450. Inhibition of cytochrome P450 may disturb the drug metabolism. The different isoforms of cytochrome P450 (CYP1A2/ CYP2C19/ CYP2C9/ CYP2D6/ CYP3A4) were built.

These different isoforms were able to inhibit cytochrome P450. The predictors in pkCSM can predict whether a molecule was an inhibitor of cytochrome P450 or whether a molecule metabolised by cytochrome P450.[17,18] Table 2 showed that EGCG is not likely to be metabolized by cytochrome P450 and does not inhibit CYP1A2, CYP2C19, CYP2C9, CYP2D6, but inhibits CYP3A4. Therefore, it can be predicted that EGCG is unable to metabolize by cytochrome P450 and EGCG is not likely going to be a cytochrome P450 inhibitor.

Total clearance of the drug is measured by proportionally constant CL tot, and it is a combination of hepatic and kidney clearance. Total clearance is related to the bioavailability of a molecule. The total clearance predictors is given in log(ml/min/kg).[17,18] Table 2 showed that the prediction of total clearance of EGCG was 0.406 log ml/min/kg.

Toxicity of compound can be predicted from AMES toxicity, hepatotoxicity, and skin sensitization. The mutagenic potential of the compounds can be predicted from the AMES test. A positive AMES toxicity test indicates that a compound is mutagenic and may become a carcinogen agent. The important safety consideration for new drug development is drug-induced liver injury. The drug-induced liver injury may also cause drug attrition. The hepatotoxicity predictors in pkCSM may predict whether a molecule may disturb the function of the liver. The most potential adverse effect from topical drug application is skin sensitization. The most important safety consideration of topical drug is the evaluation of whether a compound can induce allergic contact dermatitis.[17,18] It was predicted from pkCSM that EGCG does not induce mutagenic effect, hepatotoxicity, and skin sensitization.

Conclusion

This in silico study showed, that EGCG has potential in photoaging prevention, by interacting with IKK receptor (PDB ID: 5EBZ). EGCG was predicted having good pharmacokinetics profile and no toxicity effect to be an alternative agent in photoaging prevention.

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Ethical Clearance: Taken from Ethical Committee in Faculty of Veterinary Medicine, Airlangga University, Surabaya, Indonesia.

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