Advances in Health Sciences Research (AHSR), volume 2
Health Science International Conference (HSIC 2017)

Toxicity on Class of Antibiotic Agents Using Toxtree Software and Its Interaction with Its Receptors Using Molecular Virtual Docker Software

Sovia Aprina Basuki*, Neva Melinda Maulanasari and Engrid Juni Astuti

Department of Pharmacy, Faculty of Health Science, University of Muhammadiyah Malang, Indonesia
Jalan Bendungan Sutami 188A, Kota Malang, Jawa Timur, 65145
**Corresponding author: soviaaprina@gmail.com*

ABSTRACT

Background *Antibiotics is a drug used to treat infections caused by bacteria that are often used in the practice of pharmacy. In addition to the therapeutic effect of antibiotics also have side effects. The most common side effects of diarrhea, but it also can cause serious effects if there are toxicophore groups in the antibiotic drug.* ***Objective:*** *So the purpose of this study was to determine the drug class of antibiotics that are carcinogenic and mutagenic along with the group predicted to cause potential carcinogenic and mutagenic characteristics are based Toxtree, then know interaction group of carcinogenic and mutagenic antibiotics with receptor based MVD.* ***Method:*** *used in silico that is antibiotic drug toxicity predicted with Toxtree and their interaction with the receptor is predicted with MVD. the result form this study that is from 131 antibiotic drug tested, there were 65 drug detected has a cluster of potentially carcinogenic and mutagenic. Then analysis related to the type of group causes carcinogenic and mutagenic showed that there were 10 toxicophor group with genotoxic mechanism and 4 toxicophor group with non-genotoxic mechanism.* ***Result:*** *After testing the docking of 65 drugs there were 36 drug with their toxicophore group including farmacophore group that bind to amino acid receptors that kind of bond hydrogen bonds.* ***Conclusion:*** *of this study are 36 antibiotics potentially carcinogenic and mutagenic characteristics on the human body.*

Keyword : Antibiotic, Carcinogenicity, Mutagenicity, Toxtree, Molegro Virtual Docker

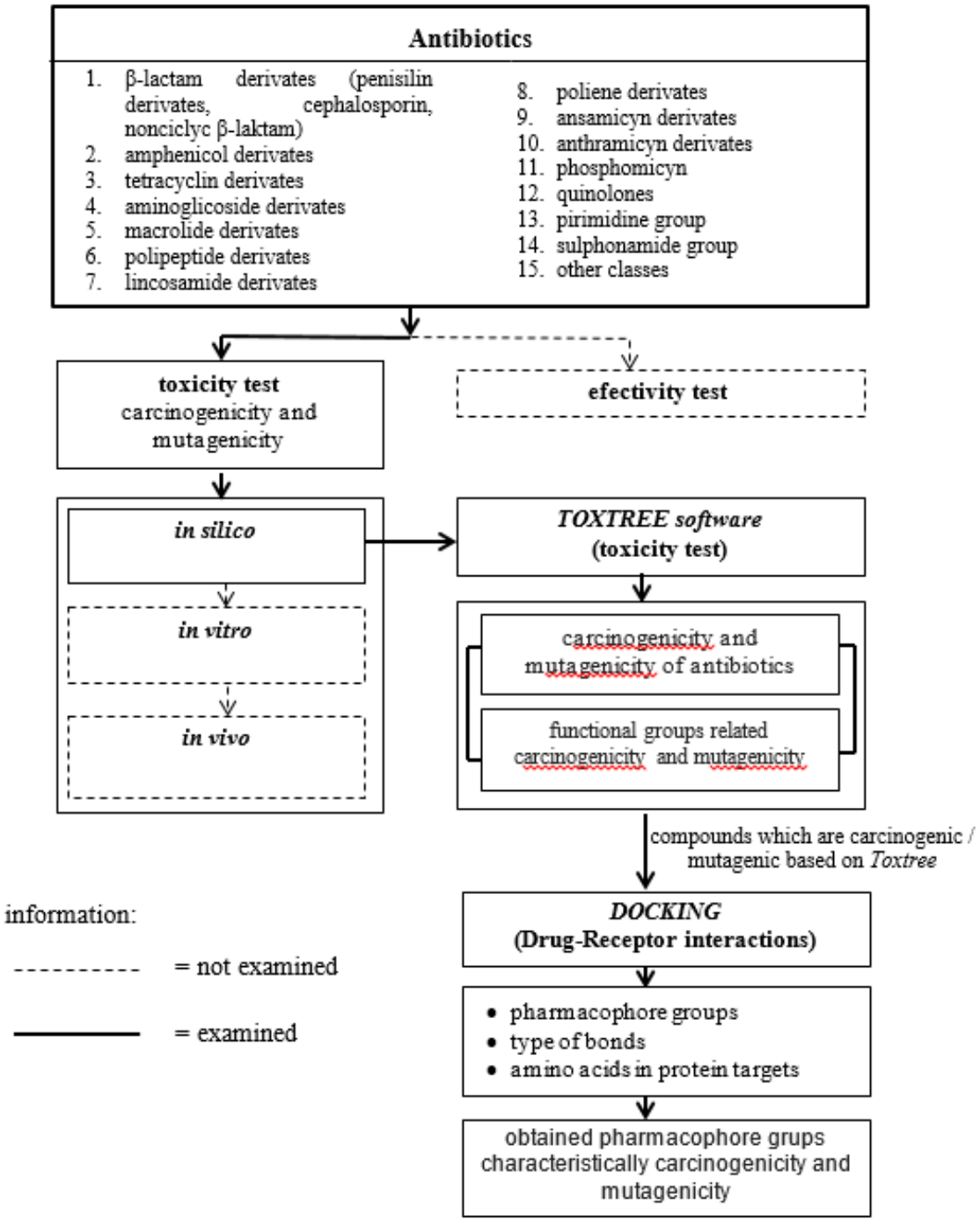
INTRODUCTION

Antibiotics are drugs used to treat infections caused by bacteria. However, antibiotics also have side effects which is varied depend on antibiotic, its dose, and individual condition as well. The most common side effect is diarrhea, but it can be possible causing serious effects notably the compound which contain toxicophore groups. A toxicophore is a chemical structure or a portion of a structure (e.g., a functional group) that is related to the toxic properties of a chemical.

This research will be conducted toxicity tests on antibiotic compounds. Toxicity test consists of 3 types of in silico, in vitro, and in vivo. All three methods have advantages and disadvantages of each, but all three can be mutually supportive. the test of carcinogenic and mutagenic toxicity in vitro is used methods Cell Transformation Assays (CTA) and Gap Junction intercellular Communication (GJIC) (Eisenbrand, 2002). In vivo test is appliedlong-term rodent carcinogenicity bioassays method which is usually for two years (Fielden and Kolaja, 2008). Whereas the carcinogenic and mutagenic toxicity tests in silico utilize predictive models over the computationally. The purpose of predictive in

silico including as a preliminary test, for screening test compounds that many before proceed to the stage of in vitro and in vivo, for predicting the toxicity of a compound, and in case compoundswhich are not posible to be studied using in vitro and in vivo methods (Ekins et al., 2007).

The purpose of this research was to know carcinocity and mutagenicity of antibiotics along predicted groups which is responsible to these toxicities based on Toxtree. Those functional groups were called toxicophores. Further those toxicophores were observed their interaction with its each protein targets using Molegro Virtual Docker software.



METHOD

Softwareswere used in this study were:

1. Toxtree v2.6.13
   Toxtree is a software developed by Ideaconsult Ltd. (Sofia, Bulgaria) under the terms of the contract JRC. The software is freely accessible as a service for scientific researchers and anyone with an interest in the application of computer-based estimation methods in the assessment of chemical toxicity (Toxtree, 2015)
2. Molegro Virtual Docker v5.0
   Molegro Virtual Docker v5.0 is a major tool in structural molecular biology with the aid of computer models to predict the ligand binding to the target protein region in 3D structure. Docking in this study is used to rapidly and flexibly to study and predict the orientation and binding affinity of antibiotics by using Molegro Virtual Docker (Molegro, 2011).
3. ChemDraw
   ChemDraw is one of the application program Ultra Chem Office 2010 v12, for drawing 2D and 3D structures in the fields of chemistry, especially organic chemistry, biochemistry, and polymers. In this study ChemDraw used to support SMILES Toxtree in providing data and the method of docking with the software Molegro Virtual Docker is used to draw the structure of 2D, 3D, optimize energy, and save the file in the form of SYBYL MOL2 (SYBYL2).
4. PubChem
   PubChem is designed to provide information about the biological activities of small molecules, generally those with a molecular weight of less than 500 dalton. Merging PubChem with NCBI Entrez retrieval system provides sub / structures, structures with similarities, bioactivity of data as well as links to information in the biological properties and Sources Protein PubMed NCBI 3D structure. In this study PubChem used to support Toxtree in providing data SMILES.
5. PDB (Protein Data Bank)
   Protein Data Bank is the only provision of storing information in the form of 3D structures of proteins, nucleic acids, and complex structures RCSB GDP can be accessed at http://sg.pdb.org. In this study, the GDP is used to support the method of docking with the software Molegro Virtual Docker in providing data PDB ID.

RESULT AND DISCUSSION

In this study conducted toxicity tests on 131 antibiotic compounds. Toxicity tests with the software Toxtree v.2.6.13 by using two methods: carcinogenicity (genotoxic and mutagenicity) rule-based ISS and mutagenicity in vitro by the rules of the ISS. Thereafter, compounds which were carcinogenic or mutagenic based Toxtree was docked using Virtual Docker Molegro v.5.0software. These software was aimed to determine antibiotic drug interactions with receptors based on several points, such as farmakofor groups, amino acids in the receptors, and type of bonds. Before docking testing, internal validations were first done. Parameters of internal validation is the value of RMSD < 2.0 (table 1).

Table 1 The recapitulation of antibiotic compounds were toxic and farmakofor

No	Antibiotics	Total Antibiotics (Compounds)	Antibiotics Contained Toxicophores (Compounds)	Pharmacophores Contained Toxicophores (Compounds)
1	β-lactam	53	17	13
2	amphenicol	4	4	-
3	tetracyclin	10	10	10
4	aminoglikoside	13	-	-
5	makrolide	7	2	-
6	polipeptide	4	-	-
7	linkosamide	5	2	-
8	poliene	3	1	-
9	ansamycin	1	1	1
10	anthracyclin	4	3	2
11	phosphomycin	4	1	1
12	quinolone	13	13	1
13	pirimidine	1	1	-
14	sulphonamide	6	6	5
15	other classes	6	5	3

The results showed that from 131 tested antibiotics compounds, there were 65 drugs detected had potential carcinogenic and mutagenic effect. Then those 65 compounds were analyzed the type of bonds which caused carcinogenic and mutagenic using MDV showed that there were 10 toxicophore groups with genotoxic mechanism and 4 toxicophore groups with nongenotoksik mechanism. Besides, 36 toxicophores were contained in pharmacophores via hydrogen bonds (table 2).

Table 2 Docking Analysis Results Using Software Virtual Docker Molegro

No	Class of Antibiotic	Carcinogenic and mutagenic Drug	Group		Type of Bond
			Toxicophore	Including Pharmacophore	
1	**β Laktam Antibiotic**	**Penicillin Derivate**			
		Kloksasilin natrium	Halogenated Benzene	-	-
		Prokain Penisilin	Primary aromatic amine	√	Hydrogen Bond
		Cephalosporin 2 generation			
		Cefuroxim	Alkil Karbamat	√	Hydrogen Bond
		Cefotetan	α,β unsaturated carbonyls	-	-
		Cephalosporin 3 generation			
		Ceftibuten	1. α,β unsaturated carbonyls 2. Primary aromatic amine	√	Hydrogen Bond
		Ceftizoxime		√	Hydrogen Bond
		Cefotiam		√	Hydrogen Bond
		Cefetamet		√	Hydrogen Bond
		Ceftriaxone	Primary aromatic amine	-	-
		Cefpodoxime		√	Hydrogen Bond
		Cefixime		-	-
		Cefdinir		-	-
		Ceftazidime		√	Hydrogen Bond
		Cephalosporin 4 generation			
		Cefepime	Primary aromatic amine	√	Hydrogen Bond
		Cefpirome		√	Hydrogen Bond
		β Laktam Non cyclic			
		Carbapenem			
		Acparenomycine A		√	Hydrogen Bond
		β Laktam Monocyclic Derivate			
		Astreonam	Primary aromatic amine	√	Hydrogen Bond

Table 2 Docking Analysis Results Using Software Virtual Docker Molegro (continued)

2	**Amphenicol Derivate**	Azidamphenicol	1. Azide group 2. Nitro Aromatic	-	-
		Cloramphenicol	1. Aliphatic Halogen 2. Nitro aromatic	-	-
		Cetophenicol	Aliphatic halogen	-	-
		Tiamphenicol		-	-
3	**Tetracyclin Derivate**	Tetracyclin	α,β unsaturated carbonyls	√	Hydrogen Bond
		Oxitetracyclin		√	Hydrogen Bond
		Clortetracyclin		√	Hydrogen Bond
		Demeclocyclin HCl		√	Hydrogen Bond
		Doxicyclin		√	Hydrogen Bond
		Tetracyclin HCl		√	Hydrogen Bond
		Doxicyclin HCl		√	Hydrogen Bond
		Minocyclin	1. α,β unsaturated carbonyls 2. ethyl aromatic amine	√	Hydrogen Bond
		Minocyclin HCl		√	Hydrogen Bond
		Tigecyclin		√	Hydrogen Bond
4	**Macrolida Derivate**	Oleandomicin	Epoxide	-	-
5	**Lincosamide Derivate**	Clindamycin HCl	Aliphatic Halogen	-	-
		Clindamycin		-	-
6	**Ansamicin Derivate**	Rifampicin	1. Hydrazine 2. Subtituted n-alkylcarboxylic acid (non genotoxic mecanism) 3. α,β unsaturated carbonyls	√	Hydrogen Bond
7	**Antracyclin Derivate**	Daunorubicine HCl	Quinones	-	-
		Doxorubicine HCl	1. Quinones 2. Anthrone	√	Hydrogen Bond
		Epirubicine		√	Hydrogen Bond
8	**Fosfomycin**		Epoxides	√	Hidrogen Bond
9	**Quinolones**	Ciprofloxacin	α,β unsaturated carbonyls	√	Hydrogen Bond
		Norfloxacin		-	-
		Gemifloxacin		-	-
		Levofloxacin		-	-
		Gatifloxacin		-	-
		Ofloxasin		-	-
		Moxifloxacin		-	-
		Ciprofloxacin HCl		-	-
		Levofloxacin hemihydrate		-	-
		Perfloxacin mesilat dihidrat		-	-
		Grepafloxacin		-	-
		Trovafloxacin		-	-
		Sparfloxacin		-	-
10	**Pyrimidine**	Trimethoprim	Primary aromatic amine	-	-
11	**Sulfonamide**	Sulfasitin	1. Primary aromatic amine 2. Benzensulfonat ether (mechanism nongenotoxic)	√	Hydrogen Bond
		Sulfisoksazole		√	Hydrogen Bond
		Sulfadiazine		√	Hydrogen Bond
		Sulfamethoksazole		√	Hydrogen Bond
		Sulfapiridin		√	Hydrogen Bond
		Sulfadoxine		-	-
12	**Others**	Co-trimoksazole	1. Primary aromatic amine 2. Benzensulfonat ether (mechanism of nongenotoxic)	√	Hydrogen Bond
12	**Others**	Metronidazole	Nitro aromatic	√	Hydrogen Bond
		Metronidazole benzoate		-	-
		Vancomycin HCl	1. Halogenated Benzene (nongenotoxic mechanism) 2. o-phenylphenol (nongenotoxic mechanism)	√	Hydrogen Bond

Information :
(√) : toxicophores include pharmacophores
(-) : there is no toxicophores include pharmacophores

CONCLUSION

There were 36 drugs in the class of antibiotics that were potentially carcinogenic and mutagenic properties on the human body because it contains toxicophores that was included in pharmacophores binding to its protein target through hydrogen bonds. It can be used as supporting data for the structure modification of the drug in order to drug discovery.

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