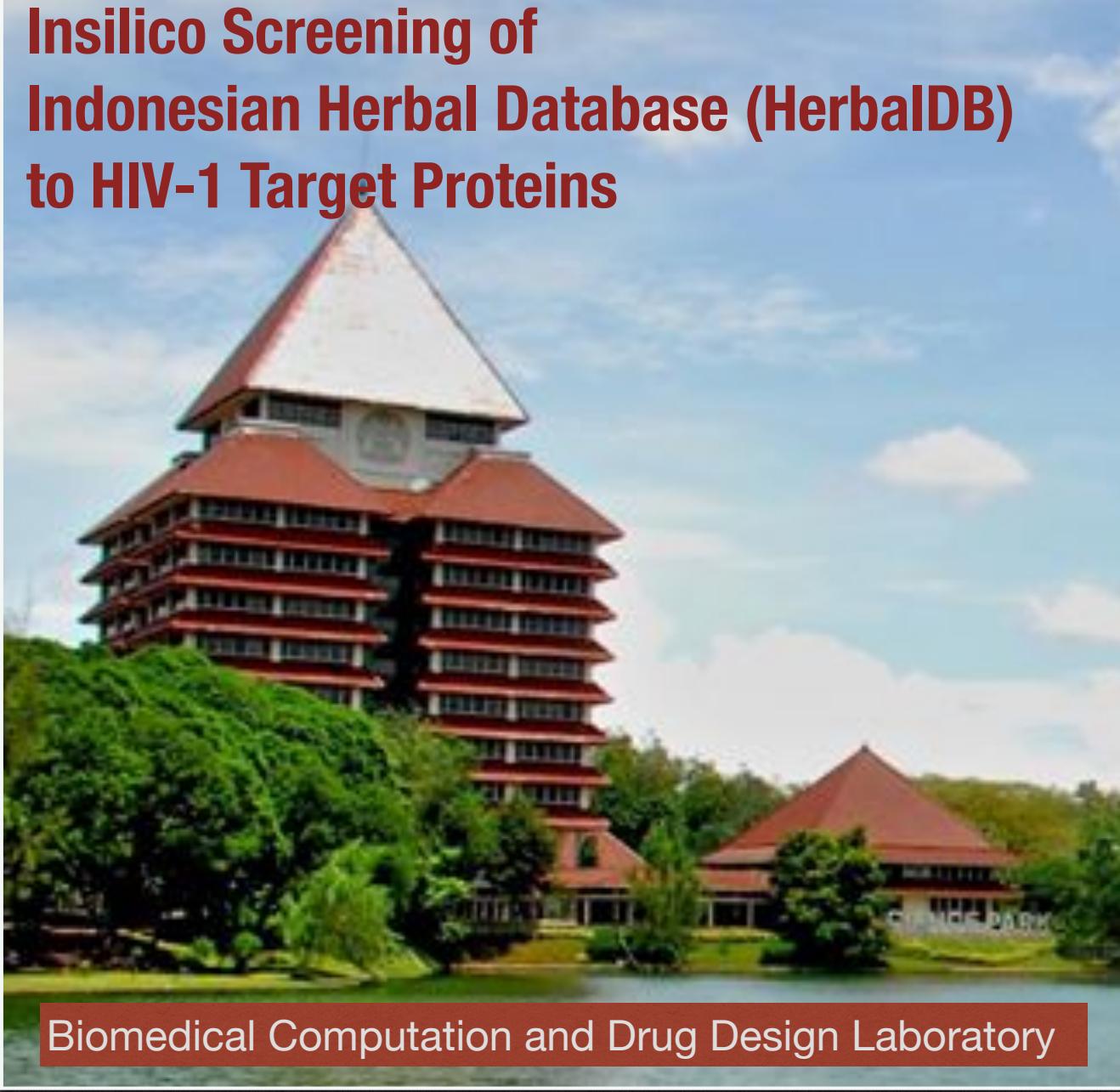


Insilico Screening of Indonesian Herbal Database (HerbalDB) to HIV-1 Target Proteins

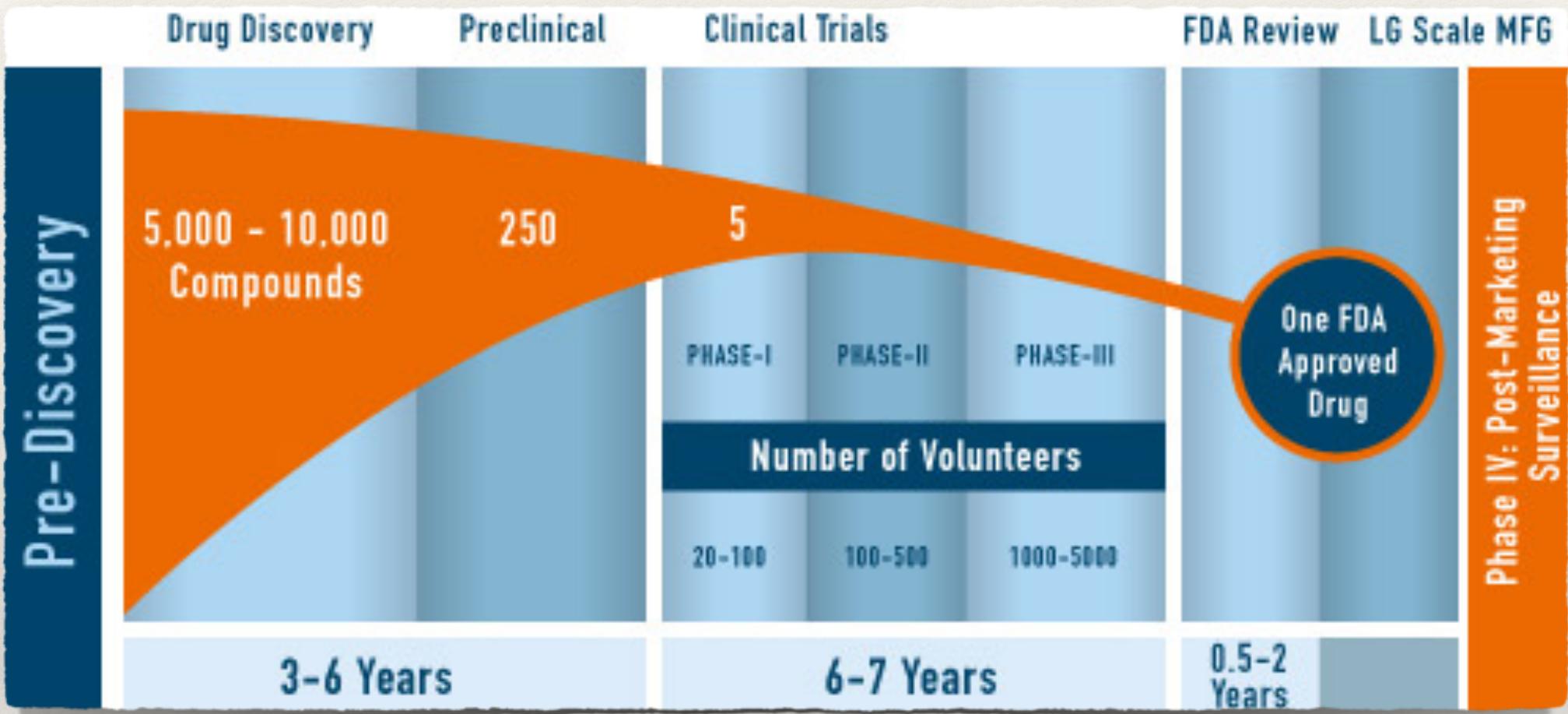


Biomedical Computation and Drug Design Laboratory

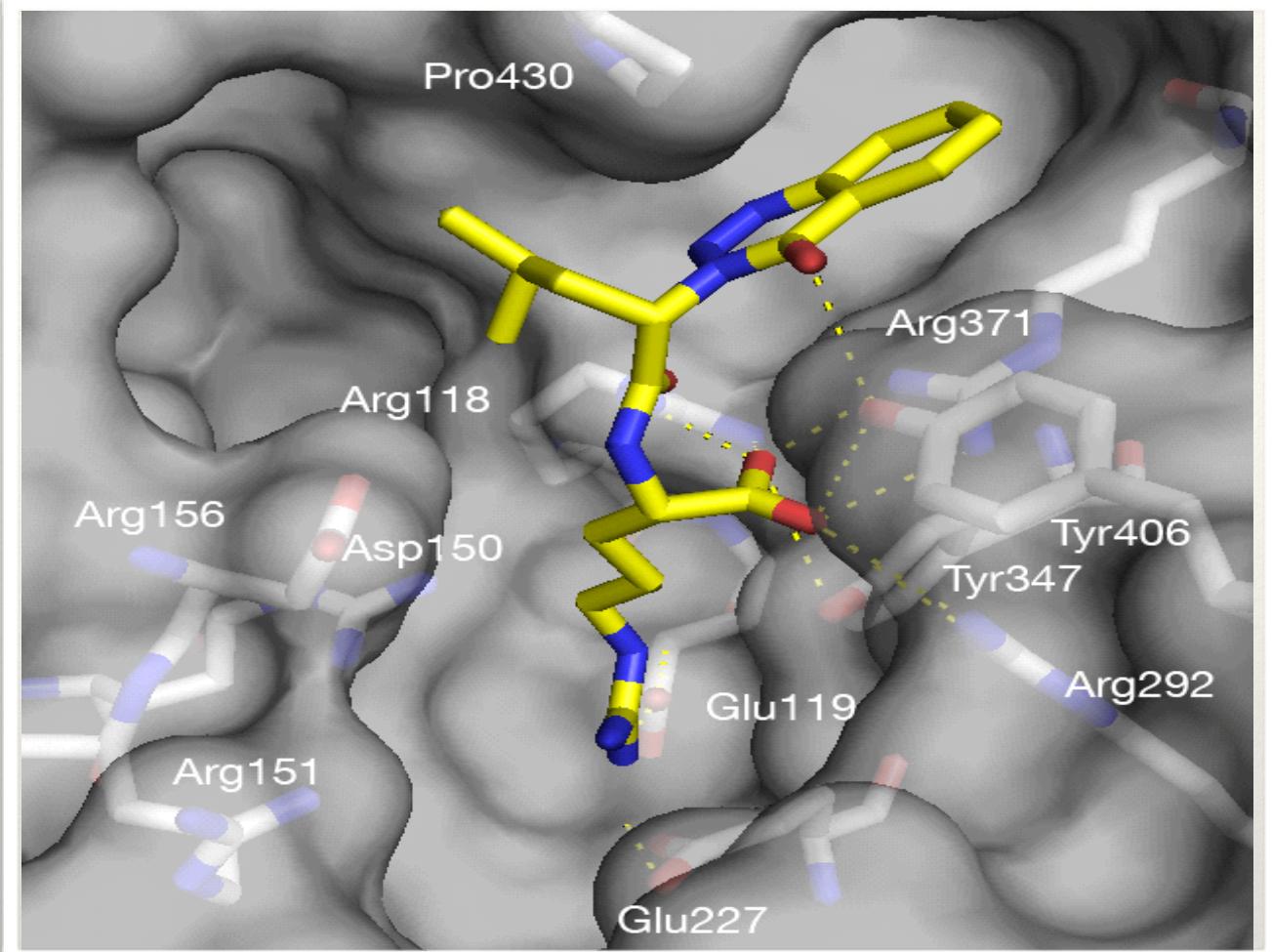


FACULTY OF PHARMACY
UNIVERSITAS INDONESIA

Arry Yanuar



Phases in Drug Discovery



The method used in drug design can be a **structure-based drug design** and **ligand-based drug design**.

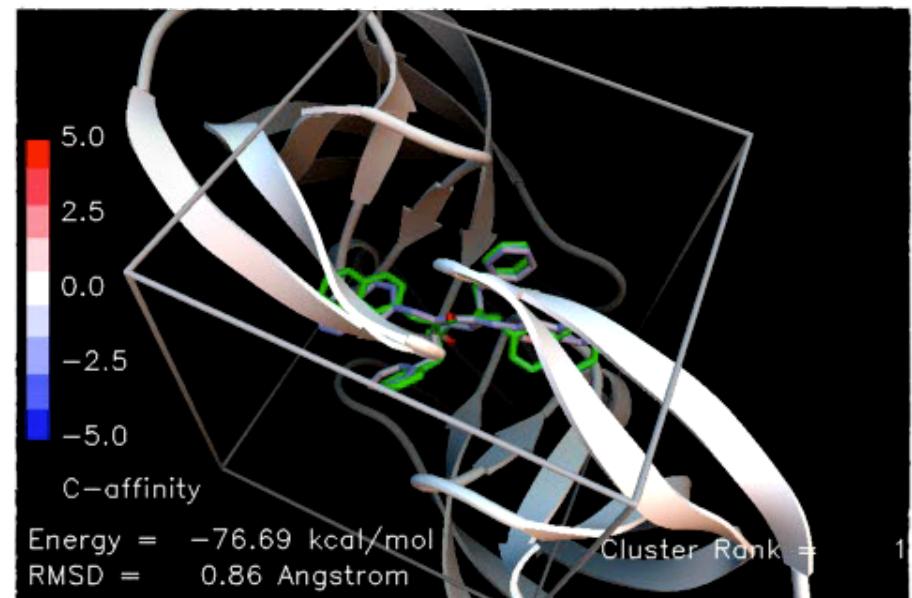
In the field of structure-based drug design, **molecular docking** is a commonly used method.

Docking attempts to find the “best” matching between two molecules, drug/ligand and therapeutic target/protein/receptor

Molecular Docking

- ❖ Posing
- ❖ Scoring
- ❖ Ranking

- ❖ Macromolecule
- ❖ Small Molecule:
 - ❖ Drug
 - ❖ Inhibitor



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Crystal Structure of human Rad GTPase

DOI:[10.2210/pdb2dpx/pdb](https://doi.org/10.2210/pdb2dpx/pdb)

Primary Citation
Biological Assembly 1

Crystal structure of human Rad GTPase of the RGK-family.

Yanuar, A., Sakurai, S., Kitano, K., Hakoshima, T.

Journal: (2006) Genes Cells 11: 961-968

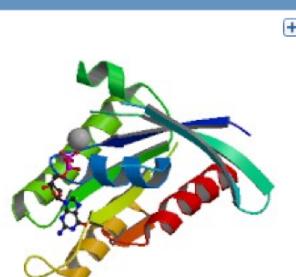
PubMed: [16866878](https://pubmed.ncbi.nlm.nih.gov/16866878/)

DOI: [10.1111/j.1365-2443.2006.00994.x](https://doi.org/10.1111/j.1365-2443.2006.00994.x)

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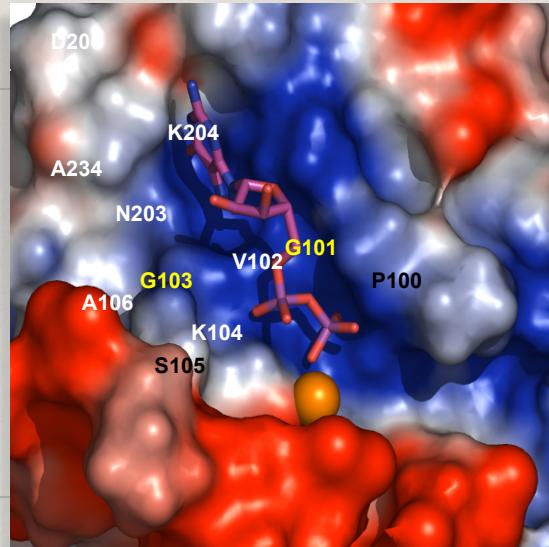
PubMed Abstract:

Rad (Ras associated with diabetes) is an RGK-family small GTPase that is over-expressed in the skeletal muscle of humans with type II diabetes. Unlike other small GTPases, RGK family members including Rad lack several conserved residues in the GTPase domain.... [[Read More & Search PubMed Abstracts](#)]



2DPX

Macromolecule: Protein Data Bank



Small Molecule Database

- ❖ Zinc
- ❖ DrugBank
- ❖ HerbalDB
- ❖ Etc.

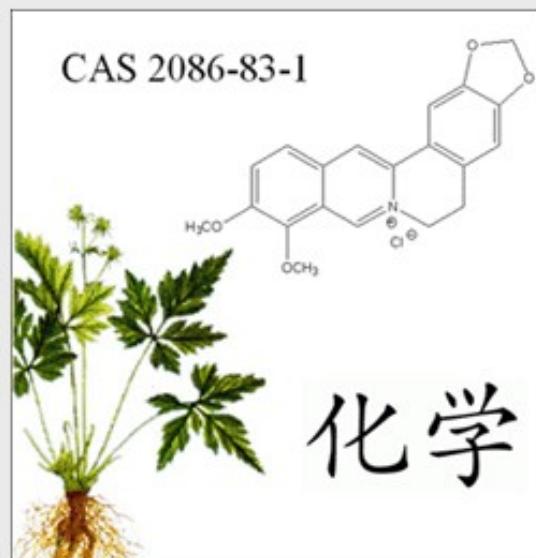


Development of Indonesian Herbal Database (HerbalDB)

CHEM-TCM

Chemical Database of Traditional Chinese Medicine

Chemical Database – Traditional Chinese Medicine



Chem-TCM is the digital database of individual molecules, constituents of plants used in the traditional Chinese herbal medicine. The database consists of four major parts: chemical identification, botanical information, predicted activity against common Western therapeutic targets, and estimated molecular activity according to traditional Chinese herbal medicine categories.

Chem-TCM database is a profound ethnopharmacological study, the culmination of the years of committed research work and modern computational chemistry advancements. It could be the most comprehensive to date attempt to connect Chinese and Western medicine on the molecular level.

The database was developed at King's College London, in the UK, in part with the support of Innovation China-UK. TimTec LLC, a USA based company, is the sole licensee of the database and the commercial partner. Chem-TCM sublicenses are [available for purchase](#) from TimTec.



English | 繁體中文

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Registration

- About TCM Database
- News and Updates
- Basic Search
- Advanced Search
- Calculation Services
- TCM Docking
- Download
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- Video



台灣

Traditional Chinese Medicine Database @ Taiwan



Basic Search

Search the database by choosing "Chinese Medicinal Herb" or "Chemical Composition." The first will return a list of constituents found in the selected medicinal herb; the latter will return a list of medicinal herbs that the selected compound was found.

[read more >](#)



Advanced Search

Search the database by specifying limits on molecular properties.
[read more >](#)

Welcome to TCM Database@Taiwan

The TCM database is currently the world largest and most comprehensive free down small molecular database on traditional Chinese medicine for virtual screening. Users download and use our database or the [iScreen web server](#) should cite this paper when they submit their researches. To cite our papers, please reference:

[TCM Database@Taiwan: The World's Largest Traditional Chinese Medicine Database for Drug Screening *In Silico*. PLoS ONE 6\(1\): e15939. doi:10.1371/journal.pone.0015939.](#)

TCM Database@Taiwan had been reported on [Nature Medicine](#).

Databases aim to bridge the East-West divide of drug discovery, [Nature Medicine](#) 17, 1531 (2011) doi:10.1038/nm1211-1531a.

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TCM Database@Taiwan: The World's Largest Traditional Chinese Medicine Database for Drug Screening *In Silico*

Calvin Yu-Chian Chen^{1,2,3*}

1 School of Chinese Medicine, China Medical University, Taichung, Taiwan, **2** Department of Bioinformatics, Asia University, Taichung, Taiwan, **3** Department of Computational and Systems Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States of America

Abstract

Rapid advancing computational technologies have greatly speeded up the development of computer-aided drug design (CADD). Recently, pharmaceutical companies have increasingly shifted their attentions toward traditional Chinese medicine (TCM) for novel lead compounds. Despite the growing number of studies on TCM, there is no free 3D small molecular structure database of TCM available for virtual screening or molecular simulation. To address this shortcoming, we have constructed TCM Database@Taiwan (<http://tcm.cmu.edu.tw/>) based on information collected from Chinese medical texts and scientific publications. TCM Database@Taiwan is currently the world's largest non-commercial TCM database. This web-based database contains more than 20,000 pure compounds isolated from 453 TCM ingredients. Both cdx (2D) and Tripos mol2 (3D) formats of each pure compound in the database are available for download and virtual screening. The TCM database includes both simple and advanced web-based query options that can specify search clauses, such as molecular properties, substructures, TCM ingredients, and TCM classification, based on intended drug actions. The TCM database can be easily accessed by all researchers conducting CADD. Over the last eight years, numerous volunteers have devoted their time to analyze TCM ingredients from Chinese medical texts as well as to construct structure files for each isolated compound. We believe that TCM Database@Taiwan will be a milestone on the path towards modernizing traditional Chinese medicine.

Citation: Chen CY-C (2011) TCM Database@Taiwan: The World's Largest Traditional Chinese Medicine Database for Drug Screening *In Silico*. PLoS ONE 6(1): e15939. doi:10.1371/journal.pone.0015939

Editor: Andreas Hofmann, Griffith University, Australia

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NATURE MEDICINE | NEWS



Databases aim to bridge the East-West divide of drug discovery

Katharine Sanderson

Nature Medicine **17**, 1531 (2011) | doi:10.1038/nm1211-1531a

Published online 06 December 2011



Citation



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Article metrics

The pharmaceutical industry, like almost every other industry these days, is looking to China for growth. Over the past few years, numerous foreign drug companies, including GlaxoSmithKline, Novartis, Pfizer and Sanofi, have made significant inroads into the country by building manufacturing facilities and forging partnerships with domestic firms. But drug...

HerbalDB Database requirement

- Local name
- Species name, description
- Sample name, how to get the sample / part of plants
- Extract name, Specification/Standard/Identity
- Content /Metabolite / Active Substance
- Activity
- Structure : **2D** (sdf, mol) convert to **3D** (mol2, pdbqt)



KNApSACK
PubChem

OpenBabel

Content	CHEM TCM	TCM Database@Taiwan	HerbalDB
Species			3,826
Species-Local Name			16,247
Species-Compound			12,983
Ingredient/Species	350 herb	453 (herb, animal, mineral)	222 herb
Compound	12.070; 9,500 (*)	>20.000	1.412 (3D)
Data Collection		8 years	2 years

Database Comparison

Thanks to Prof. Kanaya, for providing KNApSack core database to construct HerbalDB.

Medicinal Plants Database and Three Dimensional Structure of the Chemical Compounds from Medicinal Plants in Indonesia

Arry Yanuar^{1*}, Abdul Mun'im¹, Akma Bertha Aprima Lagho¹, Rezi Riadhi Syahdi¹, Marjuqi Rahmat², and Heru Suhartanto²

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Depok, 16424, Indonesia

² Faculty of Computer Sciences, University of Indonesia
Depok, 16424, Indonesia

Hibah Unggulan Universitas Indonesia, 2010

3 Dimensional Structure Database

International Journal of
Computer Science Issue, Vol 8
Issue 5 No 1, Sept 2011

2 Citation from Prof Kanaya
Group Publication.

<http://herbaldb.farmasi.ui.ac.id>

Beranda Daftar Spesies Daftar Senyawa Admin Unggah File Daftar Pengguna FAQs ID

Database Senyawa Aktif Tanaman Obat Indonesia



Temulawak

Saat ini, sebagian besar budidaya temu lawak berada di Indonesia, Malaysia, Thailand, dan Filipina.

2 / 3

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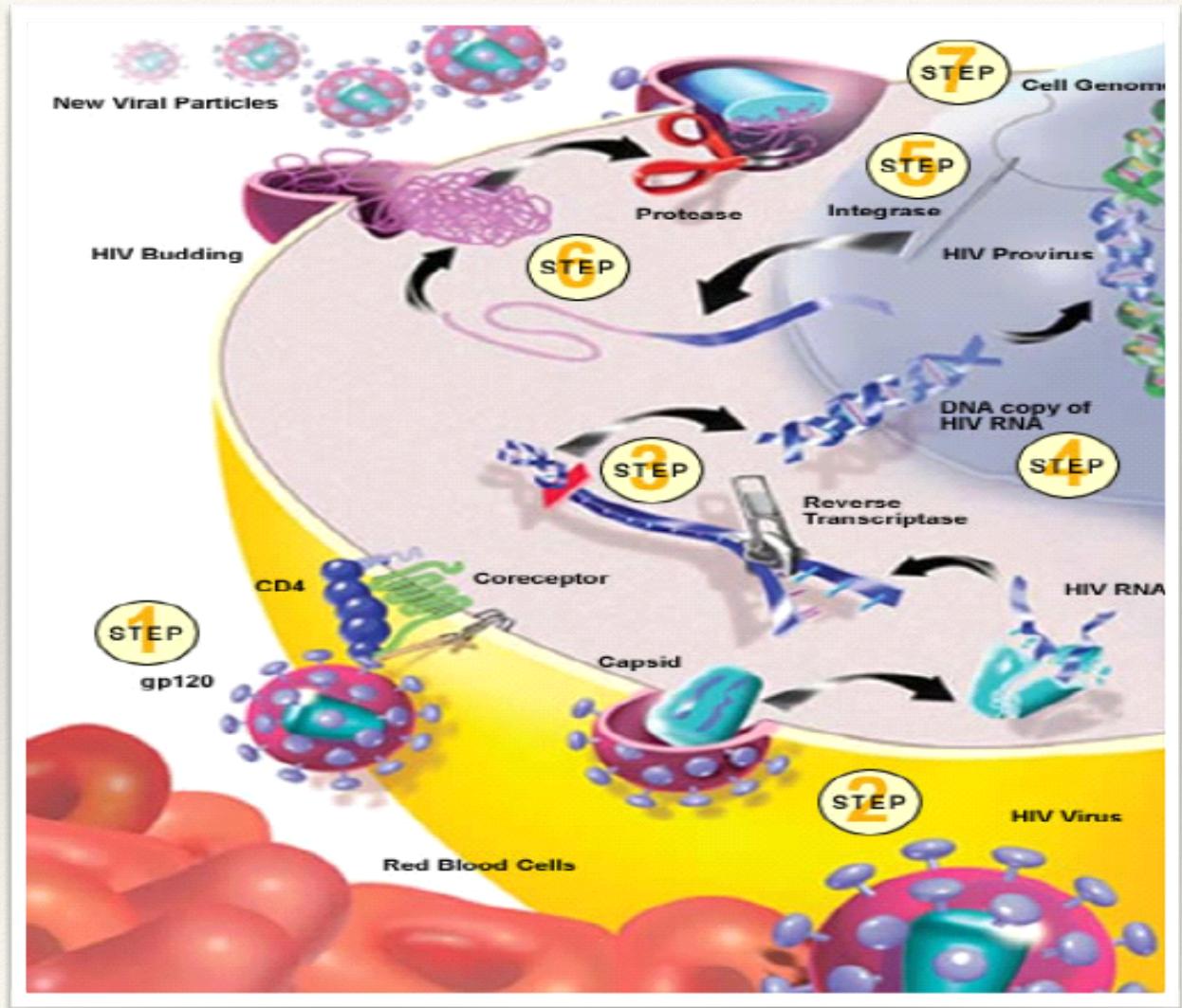
Anda sekarang login sebagai

ADI ASEP SETIAWAN

Use of Indonesian Herbal Database (HerbalDB) in virtual screening of HIV-1 inhibitor

HIV-1 Enzymes Inhibiton

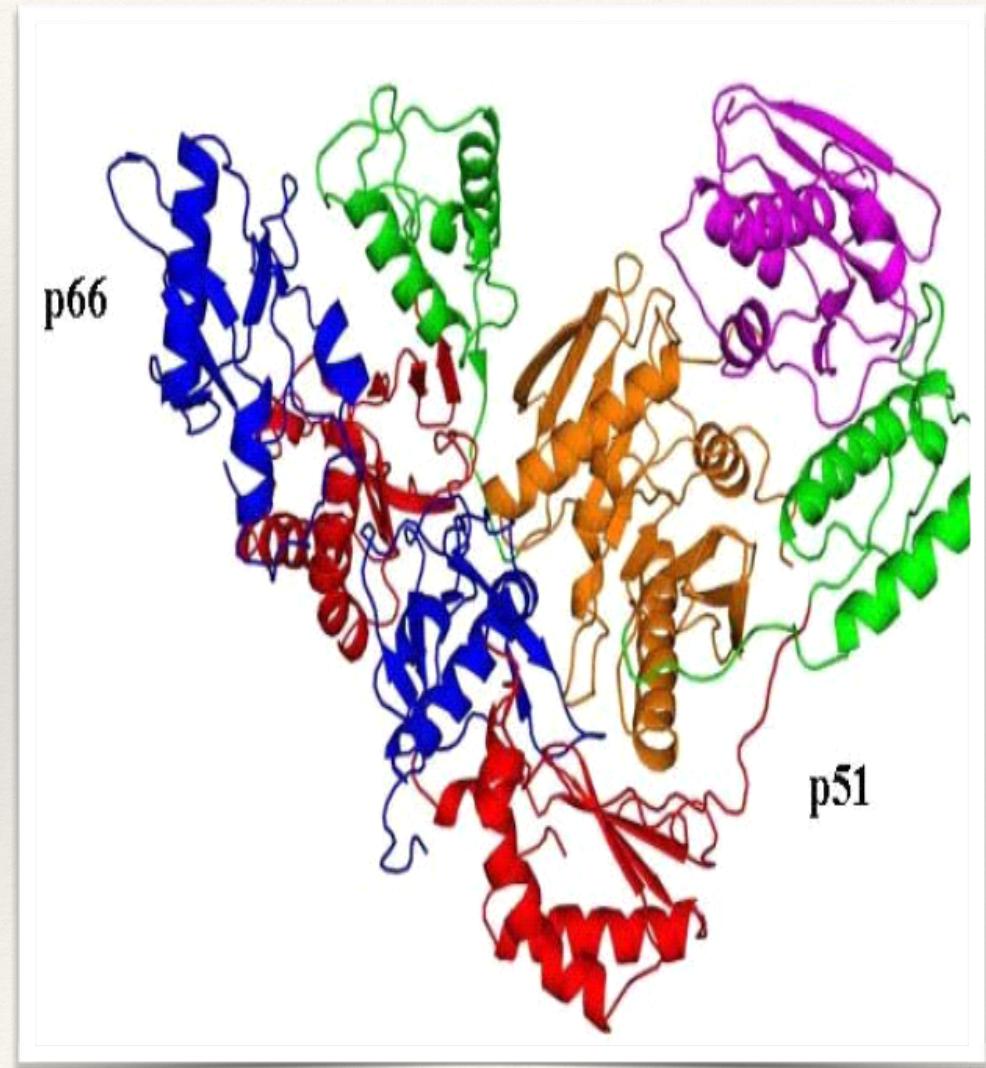
- ❖ HIV-1 Reverse Transcriptase
- ❖ HIV-1 Protease
- ❖ HIV-1 Integrase



HIV-1 Reverse Transcriptase Inhibition

HIV-1 Reverse Transcriptase

- ❖ Four Domain
 - ❖ Finger (blue)
 - ❖ Palm (red)
 - ❖ Tumb (green)
 - ❖ Linker (orange)
- ❖ p66 has open conformation to hold DNA template.
- ❖ Pocket for NRTI complexation in palm subdomain.



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Hypothesis

Volume 8(24)

Virtual screening of Indonesian herbal database as HIV-1 reverse transcriptase inhibitor

Rezi Riadhi Syahdi¹, Abdul Mun'im¹, Heru Suhartanto² & Arry Yanuar^{1*}

¹Faculty of Pharmacy, University of Indonesia, Depok 16424, Indonesia; ²Faculty of Computer Sciences, University of Indonesia, Depok 16424, Indonesia; Arry Yanuar - Email: arry.yanuar@ui.ac.id; *Corresponding author

Hibah Strategis Nasional, DIKTI, Th ke-1, 2012;

Tesis Master Rezi Riadhi Syahdi

HIV-1 RT

Bioinformation, 2012
Vol 8(24)

Rank based on ΔG	Name	ΔG (N = 3) (kcal/mol)	SD (kcal/mol)	CV (%)
1	Etravirine*	-8.82	0.030	0.340
2	Nevirapine*	-7.85	0.010	0.127
3	Rilpivirine*	-7.61	0.221	2.897
4	Efavirenz*	-7.33	0.026	0.361
5	Delavirdine*	-6.72	0.516	7.679
6	Raltegravir**	-4.49	2.328	51.887
7	Amprenavir**	-0.49	2.829	573.403
8	Tipranavir**	5.37	8.278	154.146
9	Darunavir**	6.55	7.410	113.135
10	Nelfinavir**	15.82	14.480	91.528
11	Lopinavir**	83.82	39.737	47.406
12	Saquinavir**	160.33	69.265	43.202
13	Ritonavir**	175.55	82.990	47.273
14	Atazanavir**	294.38	69.715	23.682

Screening Validation

*) **Positive Control** : etavirine, nevirapine, rilpivirine, efavirenz, delavirdine (Member of HIV-1 NNRTI = Nonnucleoside Reverse Transcriptase Inhibitors)

) **Negative Control : raltegravir (Integrase Inhibitor), ampenavir, tipanavir, darunavir, nelvinavir, lopinavir, saquinavir, azatanavir (Protease Inhibitors)

Screening result for HIV-1 RT inhibitor

Table 2: Top ten compounds docked by AutoDock based on its binding energy with HIV-1 RT

Rank	Name	ΔG (kcal/mol)	N	SD (kcal/mol)	CV (%)	Plant(s) source [13, 23]
1	Mulberrin	-11.28	2	0.3041	2.697	<i>Artocarpus fretessi</i> , <i>A. gomezianus</i> Wallich ex Trecul, <i>A. heterophyllus</i> , <i>Morus Alba</i> , <i>M. australis</i> , <i>M. mongolica</i>
2	Plucheoside A	-10.82	4	0.3293	3.044	<i>Pluchea indica</i>
3	Vitexilactone	-10.74	5	0.0438	0.408	<i>Vitex cannabifolia</i> , <i>V. cannabinifolia</i> , <i>V. trifolia</i> , <i>Tinospora rumphii</i>
4	Brucine oxide	N-	5	0.0614	0.574	<i>Strychnos atlantica</i> , <i>S. lucida</i> R. Br., <i>S. spinosa</i> , <i>S. wallichiana</i>
5	Cyanidin arabinoside	3-	-10.66	4	0.1800	<i>Mangifera indica</i> , <i>Acrotriche serrulata</i> , <i>Empetrum nigrum</i> , <i>Epacris gunnii</i> , <i>Gaylussacia spp.</i> , <i>Leucopogon collinus</i> , <i>Rhododendron spp.</i> , <i>Vaccinium padifolium</i> , <i>Sterculia parviflora</i> , <i>Theobroma cacao</i> , <i>Penstemon spp.</i> , <i>Phalaris arundinacea</i> , <i>Polygonum spp.</i> , <i>Aronia melanocarpa</i> , <i>Malus sylvestris</i> , <i>Cinchona ledgeriana</i> , <i>Saxifraga spp.</i> , <i>Camelia japonica</i>
6	Alpha- mangostin	-10.51	4	0.2130	2.028	<i>Allanblackia monticola</i> STANER L.C., <i>Garcinia kowa</i> , <i>G. dulcis</i> , <i>G. echinocarpa</i> , <i>G. fusca</i> , <i>G. Mangostana</i> , <i>G. terpnophylla</i> , <i>Cratoxylum cochinchinense</i>
7	Guaijaverin	-10.49	3	0.1270	1.210	<i>Foeniculum vulgare</i> , <i>Arctostaphylos uva-ursi</i> , <i>Calluna vulgaris</i> , <i>Chamaedaphne calyculata</i> , <i>Richea angustifolia</i> , <i>R. scoparia</i> , <i>Hypericum erectum</i> Thunb., <i>Hibiscus mutabilis</i> , <i>Theobroma cacao</i> L., <i>Eucalyptus cypellocarpa</i> , <i>Psidium guajava</i> , <i>Securidaca diversifolia</i> , <i>Polygonum aviculare</i> , <i>Zanthoxylum bungeanum</i> , <i>Taxodium distichum</i>
8	Erycristagallin	-10.43	3	0.3402	3.261	<i>Erythrina abyssinica</i> , <i>E. crista-galli</i> , <i>E. orientalis</i> , <i>E. subumbans</i> , <i>E. variegata</i>
9	Morusin	-10.43	5	0.3290	3.155	<i>Artocarpus fretessi</i> , <i>Morus alba</i> , <i>M. australis</i> , <i>M. mongolica</i>
10	Sanggenol N	-10.36	4	0.1668	1.611	<i>Morus australis</i>

In vitro HIV-1 RT inhibition assay (update)

Raw Extract

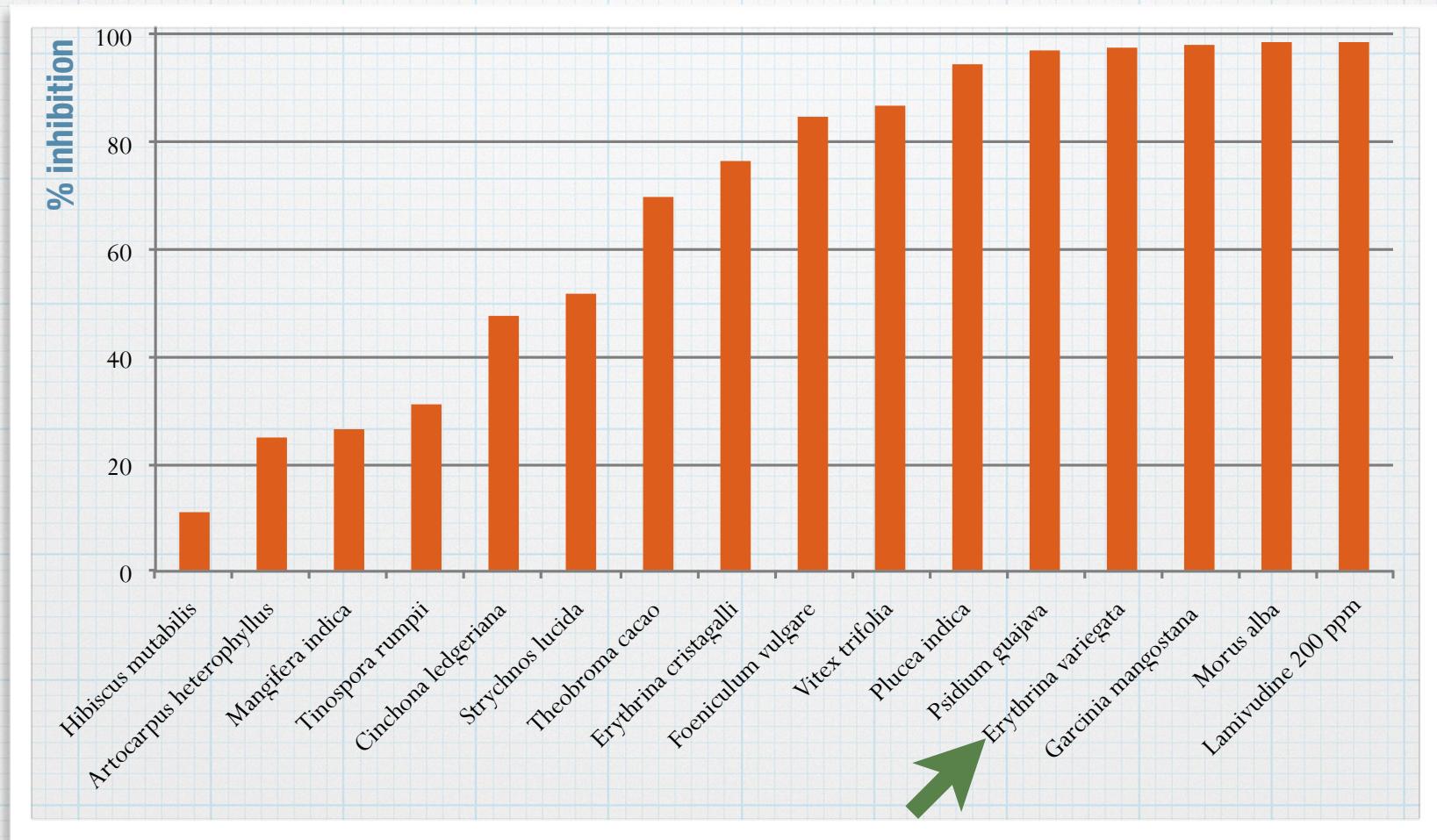


Fraction



Isolate

HIV-1 RT inhibition assay of raw extract



Erythrina variegata

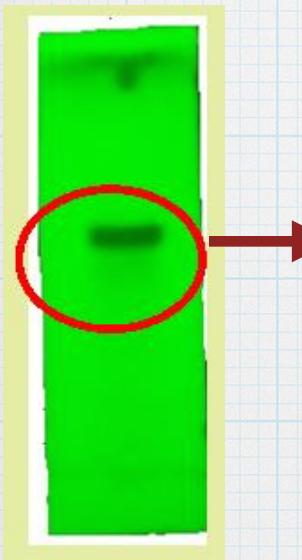


Erythrina variegata
Fabaceae
© G. D. Carr

HIV-1 RT invitro assay

Fraction	% inhibition
n-hexane (5000 ppm)	19.21
	8.2
	18.31
Ethyl acetate (5000 ppm)	59.43
	70.80
	60.08
Lamivudin (200 ppm)	94.29
	93.95
	98.90

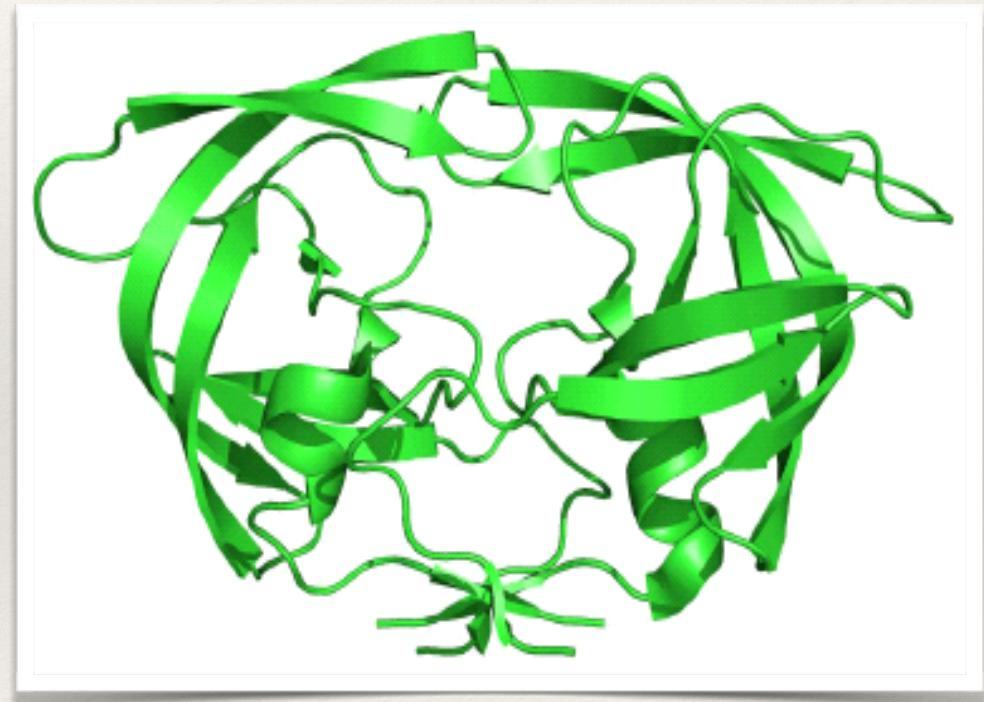
50% Inhibitory Concentration



Fraction (# fraction n-hexane:ethyl acetate)	IC 50 (ug/mL)
Ethyl acetate	348.45
#10 (76:24)	450.47
#11 (76:24)	576.08
#13 (70:30)	233.67
#17 (64:36)	427.54
#19 (54:46)	545.10

HIV-1 Protease

- ❖ Active as homodimer
- ❖ Binding site located between the monomer under the flap



Virtual Screening of Indonesian Herbal Database as HIV-1 Protease Inhibitor

Arry Yanuar^{1*}, Heru Suhartanto², Abdul Mun'im¹, Bram Hik Anugraha¹ & Rezi Riadhi Syahdi¹

¹Faculty of Pharmacy, Universitas Indonesia, Depok 16424, Indonesia; ²Faculty of Computer Sciences, Universitas Indonesia, Depok 16424, Indonesia; Arry Yanuar – Email: arry.yanuar@ui.ac.id; *Corresponding author

Hibah Strategis Nasional, DIKTI, Th ke-2, 2013;

Tesis Master Rezi Riadhi Syahdi;

Skripsi Bram Hik Anugraha

HIV-1 PR

Bioinformation, 2014
Vol 10(2)

Receiver Operator Characteristic (ROC) Curve

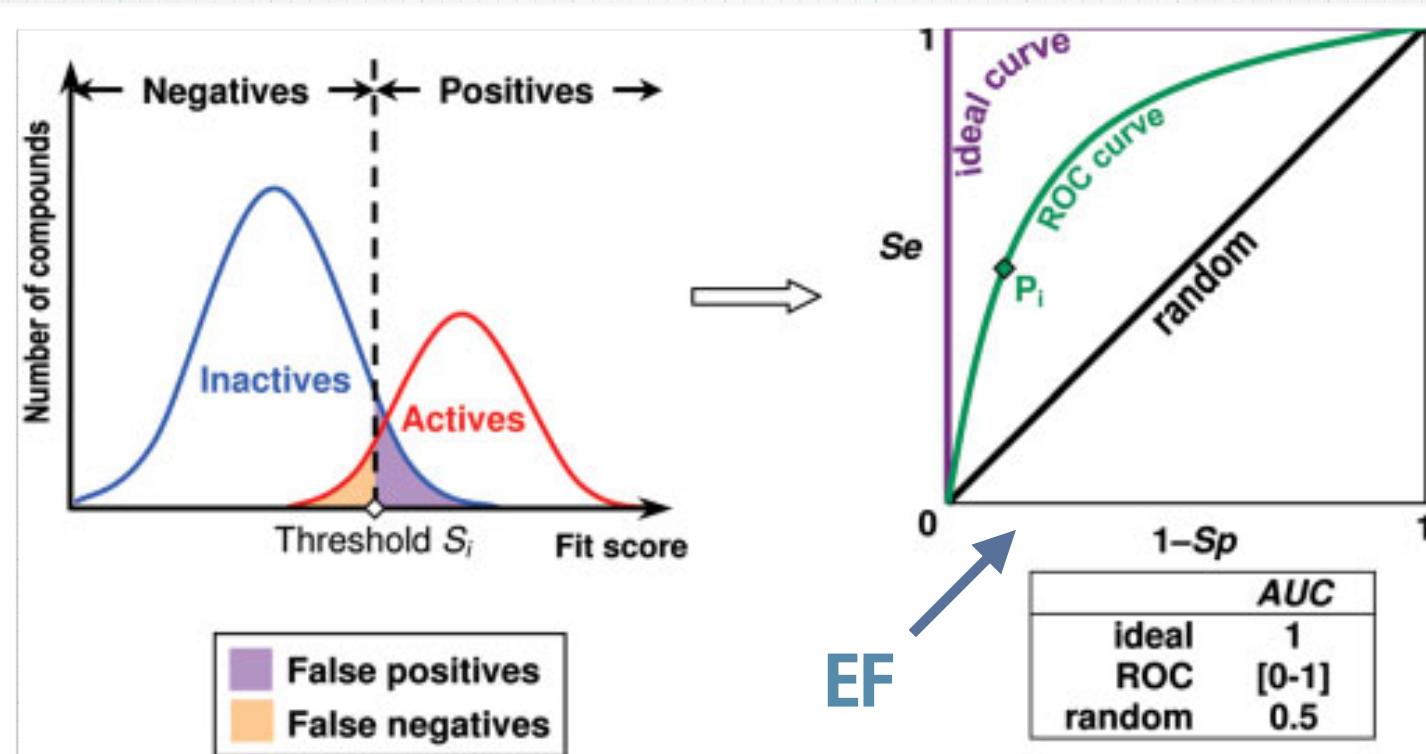


Table 1: Enrichment Factor and Area Under Curve of HIV-1 Protease DUD Database Virtual Screening using AutoDock. The best EF1% and AUC was indicated by bold text.

HIV-1 Protease Condition	Macromolecule	Grid (units)	Box	Maximum Evaluations	Number of Energy	EF 1%	EF 10%	EF 20%	AUC
Without water molecule on binding site	50x50x50			250.000		0	1,45	1,53	0.6551
				1.000.000		6,45	1,77	1,53	0.6152
	60x60x60			250.000		1,61	1,13	0,81	0.4492
				1.000.000		1,61	1,45	1,45	0.5574
Retaining water molecules on binding site	50x50x50			250.000		3,23	2,74	1,61	0.5654
				1.000.000		11,29	3,55	2,34	0.6992
	60x60x60			250.000		1,61	3,23	2,66	0,7275
				1.000.000		1,61	1,13	1,21	0,6055

Validation with DUD

62 ligands
2038 decoys

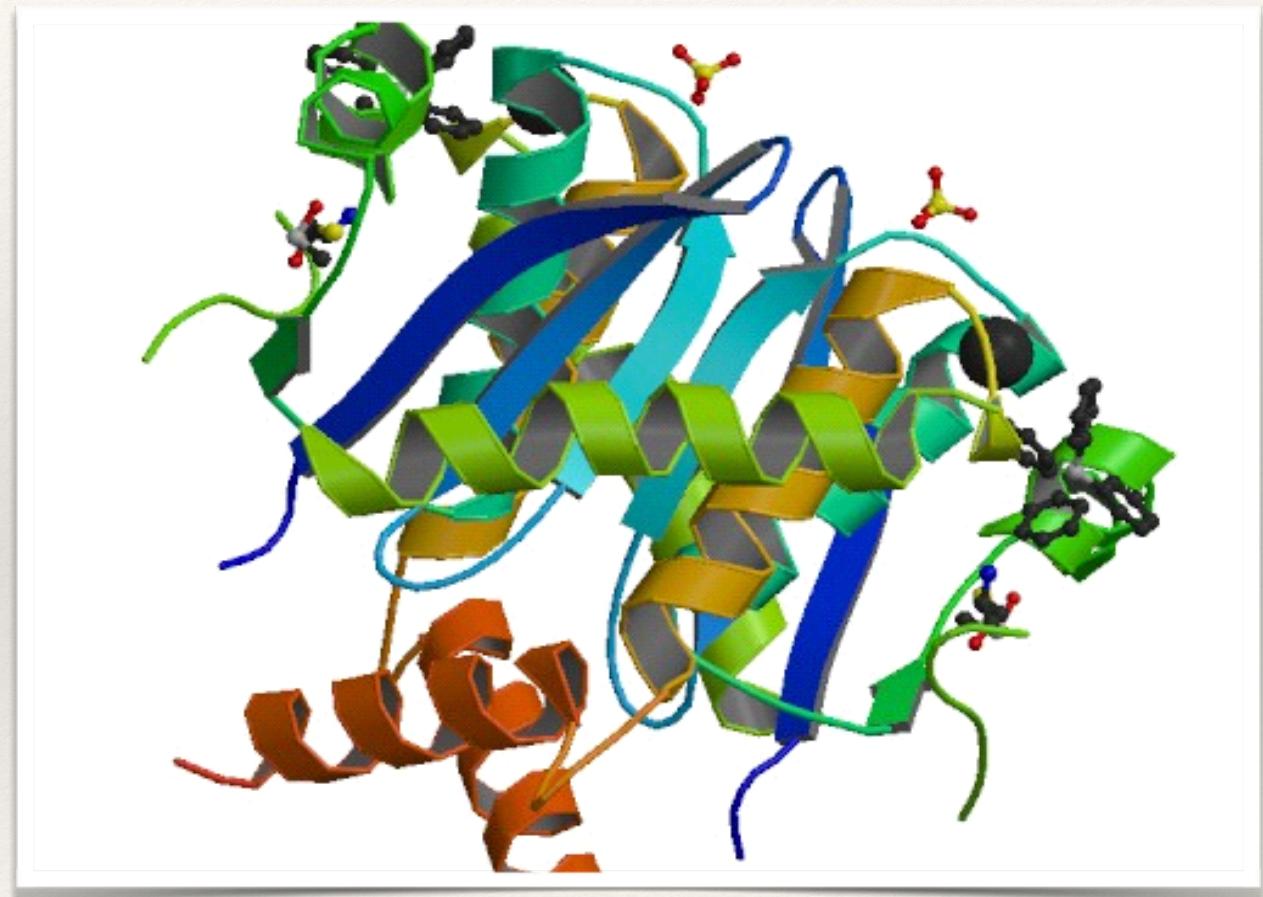
Table 2: Top ten compounds of HIV-1 Protease virtual screening result using AutoDock

Rank	Name		ΔG (kcal/mol)	N	SD	CV (%)	Plant(s) Source
1	8-Hydroxyapigenin (2'',4''-disulfatoglucuronide)	8-	-18,74	5	2,89	15,41	<i>Helicteres isora</i>
2	Isoscutellarein ether 8-(2'',4''-disulfatoglucuronide)	4'-methyl	-17,83	5	1,20	6,72	<i>Helicteres isora</i>
3	Amaranthin		-17,72	5	1,58	8,91	<i>Amaranthus caudatus</i> , <i>Amaranthus tricolor</i> , <i>Celosia argentea</i> var. <i>cristata</i> (L.) Kuntze, <i>Celosia argentea</i> var. <i>plumosa</i> (Burvenich) Voss, <i>Celosia cristata</i> , <i>Atriplex hortensis</i> , <i>Chenopodium amaranticolor</i>
4	Torvanol A		-14,58	5	0,59	4,04	<i>Solanum torvum</i>
5	Ursonic acid		-12,46	5	0,03	0,28	<i>Angelica ursina</i> Maxim, <i>Cordia multispicata</i> , <i>Myrica rubra</i> , <i>Lantana camara</i> LINN.
6	5-Carboxypyranocyanidin 3-O-(6''-O-malonyl-beta-glucopyranoside)		-12,39	4	0,35	2,82	<i>Allium cepa</i>
7	Oleoside		-12,04	5	0,46	3,79	<i>Chionanthus retusus</i> Lindl.& Paxton, <i>Forestiera acuminata</i> (Michx.) Poir., <i>Fraxinus</i> sp., <i>Jasminum</i> sp., <i>Ligustrum</i> sp., <i>Nestegis sandwicensis</i> (Gray) O.& I.Deg.& Johnson, <i>Olea</i> sp., <i>Osmanthus</i> sp., <i>Phillyrea latifolia</i> L.. <i>Picconia excelsa</i> (Aiton) DC., <i>Syringa</i> sp
8	Jacoumaric acid		-11,95	4	0,06	0,47	<i>Jacaranda caucana</i> , <i>Psidium guajava</i>
9	Platanic acid		-11,91	5	0,19	1,56	<i>Platanus occidentalis</i>
10	5-Carboxypyranocyanidin 3-O-beta-glucopyranoside		-11,79	3	0,55	4,63	<i>Allium cepa</i>

HIV-1 Integrase Inhibititon (update)

HIV-1 Integrase

- ❖ Three domains
 - ❖ N-terminal domain
 - ❖ C-Terminal domain
 - ❖ Catalytic core



Validation of Virtual Screening of HIV-1 IN using DUD

Makromolekul	EF 1%	EF 5%	EF 10%
Tanpa Residu Non-standar	1,42	1,79	1,42
Dengan Logam Mg ²⁺ dan 3 Molekul Air	3,93	1,70	1,71

211 ligands
6576 decoys

Makromolekul	Trapezoid	Integral
Tanpa Residu Non-standar	0,6474	0,6475
Dengan Logam Mg ²⁺ dan 3 Molekul Air	0,6936	0,6930

Peringkat	Nama Senyawa	ΔG (kkal/mol)
1	Kasuarinin	-7,7
2	Mirisetin 3-O-(2",6"-di-O- α -ramnosil)- β -glukosida	-7,4
3	5,7,2',4'-Tetrahidroksi-6,3'-diprenilisoflavon 5-O-(4"-ramnosilramnosida)	-7,4
4	Mirisetin 3-robinobiosida	-7,3
5	Sianidin 3-[6-(6-ferulilglukosil)-2-xilosilgalaktosida]	-7,3
6	Mesuein	-7,3
7	Sianidin 7-(3-glukosil-6-malonilglukosida)-4'-glukosida	-7,3
8	Kaemferol 3-[glukosil-(1 \rightarrow 3)-ramnosil-(1 \rightarrow 6)-galaktosida]	-7,2
9	3-O-Galoilepikatekin-(4- β \rightarrow 8)-epikatekin-3-O-galat	-7,2
10	Kuersetin 4'-glukoronida.	-7,2

Hibah Stategis Nasional 2014

Widya Dwi Aryati

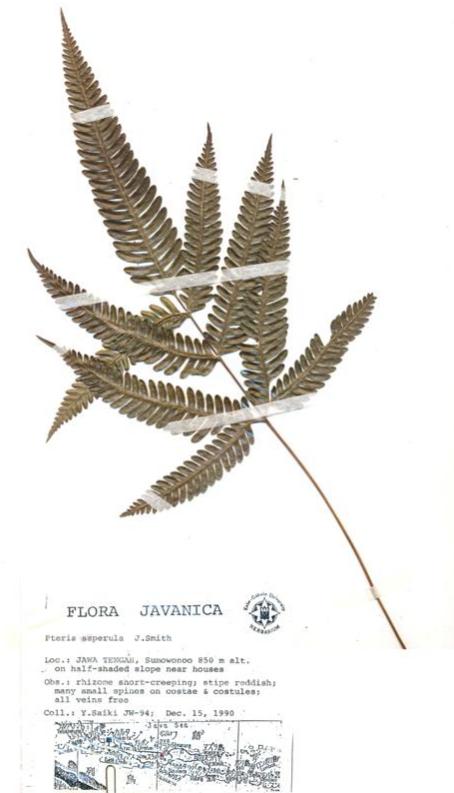
HIV-IN

Validate with 211 ligands and
6576 decoys of DUD with EF
3.93 and ROC AUC 0.69

Future Works and Collaboration

- * Accumulation more data from various literatures for HerbalDB
- * Constructing IndoMarineDB
- * Digitization of Herbarium Collection
- * Invitro assay of HIV-1 RT inhibition
- * Invitro assay of HIV-1 Protease inhibition using FRET
- * Invitro assay of HIV-integrase inhibition
- * MD Simulation of docking (virtual screening) result.
- * Structure modification of active compound and QSAR Study
- * Virtual Screening for various target of diseases such as: Malaria, Diabetes, and Cancer.
- * Develop the usage of HerbalDB for mobile App (M-Herbal App) in social network scheme to collect more data from community.

Sample of Herbarium Digitization



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Thank You

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Bedankt Děkujeme vám

ありがとうございます

Tack