PROPOSAL PENELITIAN 2019

ID Proposal: 7680fe2c-d219-4698-9cf2-00b5df9e218b
Rencana Pelaksanaan Penelitian: tahun 2020 s.d. tahun 2022

1. JUDUL PENELITIAN

Thai_Indonesian_Czech Team for Antimicrobial Compounds

Bidang Fokus RIRN / Bidang Unggulan Perguruan Tinggi	Tema	Topik (jika ada)	Rumpun Bidang Ilmu
Kesehatan	Teknologi kemandirian bahan baku obat	Bahan baku obat kimia	Farmakologi dan Farmasi Klinik

Kategori (Kompetitif Nasional/ Desentralisasi/ Penugasan)	Skema Penelitian	Strata (Dasar/ Terapan/ Pengembangan)	SBK (Dasar, Terapan, Pengembangan)	Target Akhir TKT	Lama Penelitian (Tahun)
Penelitian Kompetitif Nasional	Penelitian Terapan	SBK Riset Terapan	SBK Riset Terapan	5	3

2. IDENTITAS PENGUSUL

Nama, Peran	Perguruan Tinggi/ Institusi	Program Studi/ Bagian	Bidang Tugas	ID Sinta	H-Index
DACHRIYANUS Ketua Pengusul	Universitas Andalas	Farmasi		259368	9
DIRA S.Farm, M.Sc. Anggota Pengusul 2	Universitas Andalas	Farmasi	isolasi dari bahan alam	6725787	0
Abdi Wira Septama, Ph.D. Anggota Pengusul 1	Pusat Penelitian Kimia, LIPI	-	Isolasi dan Bioasay	0	0

3. MITRA KERJASAMA PENELITIAN (JIKA ADA)

Pelaksanaan penelitian dapat melibatkan mitra kerjasama, yaitu mitra kerjasama dalam melaksanakan penelitian, mitra sebagai calon pengguna hasil penelitian, atau mitra investor

Mitra	Nama Mitra

Mitra Pelaksana Penelitian	Ing. Jiri Janata
Mitra Pelaksana Penelitian	Dr. Amit Jaisi
Mitra Pelaksana Penelitian	Eldiza Puji Rahmi, M.Sc, Apt
Mitra Calon Pengguna	HONESTI BASYIR

4. LUARAN DAN TARGET CAPAIAN

Luaran Wajib

Tahun Luaran	Jenis Luaran	Status target capaian (*accepted, published, terdaftar atau granted, atau status lainnya*)	Keterangan (*url dan nama jurnal, penerbit, url paten, keterangan sejenis lainnya*)
1	Dokumen pendaftaran paten proses	Terbit nomor pendaftaran paten	
2	Dokumen hasil uji substansi	Ada/tersedia	Paten Metoda
3	Dokumen hasil uji substansi	Ada/tersedia	Paten Metoda

Luaran Tambahan

Tahun Luaran	Jenis Luaran	Status target capaian (*accepted, published, terdaftar atau granted, atau status lainnya*)	Keterangan (*url dan nama jurnal, penerbit, url paten, keterangan sejenis lainnya*)
2	Artikel di Jurnal Internasional Terindeks di Pengindeks Bereputasi	Accepted	Industrial crops and product

5. ANGGARAN

Rencana anggaran biaya penelitian mengacu pada PMK yang berlaku dengan besaran minimum dan maksimum sebagaimana diatur pada buku Panduan Penelitian dan Pengabdian kepada Masyarakat Edisi 12.

Total RAB 3 Tahun Rp. 1,274,850,000

Tahun 1 Total Rp. 419,950,000

Jenis Pembelanjaan	Komponen	Item	Satuan	Vol.	Biaya Satuan	Total
Bahan	Bahan Penelitian (Habis Pakai)	Consumable, solvents, media, biological kit, several items for isolation of compounds, HPLC preparative coloums (C18, C8 and Hilic 1 each with a size range from 50-100 mg extract size)	set	1	201,576,000	201,576,000
Pengumpulan Data	FGD persiapan penelitian	expenses of the indo team to do exploration sample (plant)	set	1	36,955,600	36,955,600

Jenis Pembelanjaan	Komponen	Item	Satuan	Vol.	Biaya Satuan	Total
		in several location in Indonesia (we plan to explore 5 location to collect plants material)				
Pengumpulan Data	HR Pembantu Peneliti	personal cost PhD student who will work in partner lab in Czech	month	6	13,438,400	80,630,400
Pengumpulan Data	HR Sekretariat/Administrasi Peneliti	reportsand DHL service if necessary for material exchange among all participating countries	set	1	33,596,000	33,596,000
Pengumpulan Data	Transport	expenses of the Ino team members (travel costs, living expenses, visa if applicable) for traveling to the first common meeting held in October 2020 in Prague (4 days of meeting plus 2 days for transpost	person	3	16,798,000	50,394,000
Pengumpulan Data	Tiket	the expenses (flight economy class and visa cost)	set	1	16,798,000	16,798,000

Tahun 2 Total Rp. 419,950,000

Jenis Pembelanjaan	Komponen	Item	Satuan	Vol.	Biaya Satuan	Total
Bahan	Bahan Penelitian (Habis Pakai)	equipment and consumable cost for research activity (kit for bioassay, media culture, consumable, animals, protein targeteds, DNA, glassware, solvents) and for sample collection and	set	1	201,576,000	201,576,000

Jenis Pembelanjaan	Komponen	Item	Satuan	Vol.	Biaya Satuan	Total
		identification				
Pengumpulan Data	HR Pembantu Peneliti	personal cost PhD student who will work in partner lab in Czech	month	6	13,438,400	80,630,400
Pengumpulan Data	HR Pembantu Peneliti	personal cost for research who will work in Thai partner	month	6	5,039,400	30,236,400
Pengumpulan Data	HR Sekretariat/Administrasi Peneliti	reportsand DHL service if necessary for material exchange among all participating countries and maintenence	set	1	47,034,400	47,034,400
Pengumpulan Data	Transport	travel expenses for exchange visiting student to Czech/Indonesia	person	2	13,438,400	26,876,800
Pengumpulan Data	Transport	travel expenses for exchange visiting student to thai	person	2	3,359,600	6,719,200
Pengumpulan Data	Transport	travel expenses for second year mid term progress report visits to Prague	person	2	13,438,400	26,876,800

Tahun 3 Total Rp. 434,950,000

Jenis Pembelanjaan	Komponen	Item	Satuan	Vol.	Biaya Satuan	Total
Bahan	Bahan Penelitian (Habis Pakai)	equipment and consumable, solvents, media, biological kits, animals (normal and infected animals) standard drugs, HPLC and LCMS solvents, glassware and other research items	set	1	201,576,000	201,576,000
Pengumpulan Data	HR Pembantu Peneliti	personal cost PhD student who will work in partner lab in Czech	month	6	13,438,400	80,630,400
Pengumpulan Data	HR Pembantu Peneliti	personal costs for researcher who will work in Thai partner	month	6	5,039,400	30,236,400

Jenis Pembelanjaan	Komponen	Item	Satuan	Vol.	Biaya Satuan	Total
Pengumpulan Data	Transport	cover expenses of the team members meeting progress report and symposium in Jakarta	set	1	98,990,000	98,990,000
Pelaporan, Luaran Wajib, dan Luaran Tambahan	Luaran KI (paten, hak cipta dll)	cost such as reports, patent services and open access publication fee	set	1	23,517,200	23,517,200

Ringkasan penelitian tidak lebih dari 500 kata yang berisi latarbelakang penelitian, tujuan dan tahapan metode penelitian, luaran yang ditargetkan, serta uraian TKT penelitian yang diusulkan.

RINGKASAN

The current antibiotic crisis represents a global problem of fundamental importance. Humankind faces the threat that infectious diseases will once again become the leading cause of death worldwide within one generation. The overall motivation of the project is to combat infections including those caused by multi-drug resistant (MDR) species to last-resort drugs (antibiotics and antiparasitics). We will focus on both, health care associated infections (HaI) as Staphylococcus aureus methicillin-resistant (MRSA) and vancomycin-resistant (VRSA), Enterococcus faecium, vancomycin-resistant or Clostridium difficile infections (CDI) as well as on the most serious infection diseases caused by pathogens spread in the community (tuberculosis caused by MDR Mycobacterium tuberculosis or resistant forms of malaria). For this purpose, we will exploit natural sources of bioactive metabolites from diverse sources: European and Asian habitats, soil and marine biotopes, plant and bacteria species. The project will consist of two objectives. Objective 1: Hunt for novel bioactive metabolites derived from plant and microorganism; Objective 2: Development of promising nature derived compounds into drugs. Within Objective 1 we will aim to discover new compounds from SEA habitats by employing innovative targeted metabolomic approach GNPS molecular networking“. New targets for rediscovered compounds will be searched and the compounds of interest will be characterized for their potency to become pharmaceuticals applicable in clinical practice (bioactivity, toxicity, stability). Regarding the commercial potential, the most promising compounds to be tested in the project are hybrid lincosamide compounds, derivatives of CELIN (Objective 2). These advanced molecules were developed by the CZ team using knowledge-based rational design approaches described in Objective 1. Specifically these molecules are based on the combination of two existing lincosamide natural products, lincomycin and celesticetin. Our CELIN derivatives exhibit not only higher efficiency, but also mitigated risk of CDI which otherwise limits wider use of clindamycin. Our ambition is thus to replace on the market both currently produced lincosamide antibiotics, lincomycin and even one of the world leading antibiotics, clindamycin. The added value of this international (Czech-Thai-Indonesian) project lies in the involvement of mutually complementary teams: The CZ team having 1) set of compounds ready for proof of concept testing on malarial targets (available from Thai team) and 2) know-how for knowledge based and technologically innovative high throughput search for new compounds, which will be shared with both SEA teams. The SEA teams on the other hand have the access to huge yet unexplored source of compounds (plant/marine/mangrove microbial samples) and knowhow regarding sampling and strain isolation. This mutually beneficial interconnection of teams is a guaranteeof long-term cooperation.

Kata kunci maksimal 5 kata

Antimicrobial, natural product, metabolomics, antibiotics.

Latar belakang penelitian tidak lebih dari 500 kata yang berisi latar belakang dan permasalahan yang akan diteliti, tujuan khusus, dan urgensi penelitian. Pada bagian ini perlu dijelaskan uraian tentang spesifikasi khusus terkait dengan skema.

LATAR BELAKANG

Resistance to an antimicrobial had become a major public health problem in worldwide, because it has a significant negative impact on the outcome of therapy, and increase the risk of cross-infection in hospitals. Many of the bacterial associated with epidemics of human disease have evolved into multi-drugs resistant forms subsequent to antibiotic use including *Pseudomonas aeruginosa*. *P. aeruginosa* is opportunistic Gram-negative bacterium which common cause nosocomial infections. It is difficult to control due to presence of outer membrane cell which act as a permeability barrier, as well as by the expression of efflux pump which is out the accumulation of antibiotic inside the cells (1). Currently, the most prevalence resistant, particularly in hospital is methicillin-resistant *S. aureus* (MRSA). The acquisitions of the *mecA* gene and over expression of efflux pumps as well as β-lactamase hydrolysis enzyme are such causes that underline resistant of MRSA toward many antibiotics, especially β-lactam antibiotics (2). Few new antibiotics have been used for the treatment of infections caused by Gram-positive bacteria. In contrast, infections caused by Gram-negative bacteria were harder to treat.

The development of new antibiotics with new target and mode of action is urgently needed. However, there is some challenging to find out the new antibiotics, for instance time and cost consuming to get the new antibiotics and may lead the new resistant when it is frequently used in clinical. The use of combination conventional antibiotics and some agents in order to enhance the activity of antibiotic has been an alternative strategy to overcome resistant problem. A use of drug in combination may increase their biological activities due to the interaction of each compound. Different compounds may have different target sites and influence each site to achieve the same response that lead to enhanced biological activities in the cells. On the other hand, the different compounds might affect the same target site, and that could result in an agonistic activity (3).

Natural products are a major source of chemical diversity and have provided important therapeutic agents for many bacterial diseases. In continuation of our studies (4-10) for novel bioactive metabolites derived from plant, we have strategy to combat the antibiotic (antibacterial and anti parasitic) crisis exploits natural products that proved to be a superior source of drug-able compounds. We will use modern biology and chemistry methodology for this purpose – genome mining, mass spectrometry-based metabolomics and we will focus on testing multiple targets, i.e. multiple pathogens including those clinically most important and threatening.

Natural products are considered superior to synthetic compounds for the development of pharmaceuticals (while 0.001% of total number of synthetic compounds have become drugs, this number for microbial metabolites is 0.2-0.3%, i.e., higher by at least two order of magnitudes). Microbial metabolites are particularly remarkable in the case of antibiotics–most of current antibiotics are derived from Actinobacteria specialized metabolites. Furthermore, metabolites of Actinobacteria are often highly versatile, they have been developed and applied as antitumor (eg. doxorubicin), antiparasitic (eg. ivermectin), immunosuppressant (eg. rapamycin), etc., drugs. A particularly promising yet to a large extent unexplored source of bioactive metabolites are marine Actinobacteria. Perhaps the most advanced marine-derived bacterial metabolite in terms of drug development is salinosporamide A discovered in 2003. The compound is produced by Actinobacteria *Salinispora tropica* isolated from a sediment collected in Chub Cay, Bahamas (11). Salinosporamide A is currently under development by Nereus Pharmaceuticals, Inc. undergoing Phase I clinical trials as an anticancer agent for patients with solid tumor malignancies. It is likely that natural products represent privileged structures for drug discovery because their ability to bind a target (enzymes, receptors, DNA, etc.), i.e., to have a biological

function, is the reason why they evolved and why their energetically demanding biosynthesis by the producing organism was retained. The fact that the number of protein folds, DNA motifs, etc. is limited and that many building blocks of humans, animals, plants, microbes are (partly) common explains why a great deal of microbial and plant metabolites have been turned into drugs applicable in human and veterinary medicine.

Tinjauan pustaka tidak lebih dari 1000 kata dengan mengemukakan *state of the art dan* peta jalan (*road map*) dalam bidang yang diteliti. Bagan dan *road map* dibuat dalam bentuk JPG/PNG yang kemudian disisipkan dalam isian ini. Sumber pustaka/referensi primer yang relevan dan dengan mengutamakan hasil penelitian pada jurnal ilmiah dan/atau paten yang terkini. Disarankan penggunaan sumber pustaka 10 tahun terakhir.

TINJAUAN PUSTAKA

Project motivation and current state of knowledge

The current antibiotic crisis represents a global problem of fundamental importance, comparable with other global challenges as e.g. climate change or sustainable energetics, but far less discussed in the society. Without active approach right now the, the infectious diseases will soon become the most frequent cause of death worldwide.

Antimicrobial resistance

Antimicrobial resistance is a serious threat to global public health. The occurrence of multi-drug resistant (MDR) bacteria limits the available treatment alternatives for the infections. Bacterial pathogens that are most commonly associated with antibiotic resistance include *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterococcus faecium* (12). WHO has recently extended the ESKAPE list to 12 bacteria against which new antibiotics are urgently needed (13). In some cases, ESKAPE bacteria are resistant even to so-called ´last-resort´ antibiotics, which represent the ultimate available choice of drugs with no alternative in the case of their failure. What is more, due to improving economic situation, antibiotic usage rises in the low- and middle- income countries (14), however, often with lack of appropriate mechanisms of its control (15-16). This is associated with the emergence and expansion of MDR pathogens in both humans and livestock (17). In addition to this, traveling and global trade contribute to the spreading of the pathogens around the world.

Antibiotic-associated colitis

Another red flag of current antibiotic crisis is *Clostridium difficile* infection (CDI) causing pseudomembranous colitis. CDI occurs globally with clearly increasing trend for both community-associated and even more remarkably healthcare-associated infections (18-19). CDI has become the most common health care associated infection in USA with 453 000 cases in 2011, resulting in 29.000 deaths and exceeding thus even methicillin-resistant *Staphylococcus aureus* (MRSA) (18). Typically, the onset of CDI is associated with antibiotic treatment and has been described after the use of almost all antibiotics except for vancomycin. However, the most commonly implicated drugs have been fluoroquinolones, clindamycin, penicillins and cephalosporins. Proper antibiotic prescribing is thus the most efficient method for preventing CDI. After the CDI outbreak, vancomycin (with significant side effects) or less efficient metronidazole are the only available drugs. Therefore, we urgently need new antibiotics.

Tuberculosis

Tuberculosis is one of the top 10 causes of death worldwide. About a quarter of theb world's population is infected by *Mycobacterium tuberculosis*; i.e., at the risk of developing tuberculosis.

Current treatment regimens for tuberculosis require combinations of multiple drugs, ranging from a duration of 6 months for drug susceptible tuberculosis to 9-20 months for rifampicin-resistant or MDR tuberculosis. Duration and complexity of the treatment are associated with toxic side effects. For these reasons, the world public would highly appreciate novel drugs for the treatment of tuberculosis (20).

Malaria

Malaria remains a major global health problem, affecting a large population of the world. According to WHO there were an estimated 219 million cases and 435 000 death-related cases in 2017 (21). With continuing global threat of malaria, there is an urgent need to search not only for new drugs, but also for effective drug combinations (22). A major obstacle to this goal is the reliance on anti malarial chemotherapy to control the parasite because vector control and vaccination strategies are inadequate. New drugs with novel modes of action are required to overcome parasite resistance to existing drugs, and to eliminate parasites at different stages of their life cycle (23).

Mass spectrometry-based metabolomics

Metabolomics represents a challenge due to the remarkably high chemical diversity of the studied molecules compared to other OMICs such as genomics or proteomics. Despite enormous instrumental development in the field of mass spectrometry (MS), the difficulties in data processing persist – it is far from a routine. The reason lies behind large amount of data and their complex structure that consists of not straight forward-to-interpret MS and fragmentation MS/MS spectra. A unique platform that enables advanced data processing for MS-based metabolomics is the global natural product social (GNPS) molecular networking developed by P. Dorrestein group from University of California San Diego (UCSD), USA. This is the first platform that relies on an innovative algorithm that compares MS/MS spectra within a dataset and results in molecular networks, in which related compounds are clustered together and can be visualized with metadata (e.g. different species, wild type vs. mutant strain, different treatments, nutrition, culture media composition, taxonomy, time-course experiments, etc.). Metadata give the important context to the MS & MS/MS data, facilitating data mining. Importantly, the workflow also includes the in silico and statistical tools and it enables compound annotation using community-based and third party-derived GNPS spectral libraries with more than 200 000 MS/MS spectra. Specifically, GNPS facilitates compound annotation and dereplication and it 5 automatically identifies metabolites of interest and importance in terms of the metadata (e.g. unique compounds across the data set, discrimination of compounds present in extracts with no bioactivity etc).

Genome mining and metabolites with 4-alkyl-L-prolines

Genomic DNA of typical microbial producers of specialized metabolites contains tens of gene clusters encoding biosynthesis of these compounds. Many of the clusters are silent, i.e., they are not expressed under laboratory conditions. However, biosynthetic gene sequences in combination with the available knowledge of biosynthetic pathways of specific metabolites can be used to identify gene clusters encoding biosynthesis of specific metabolites of interest, which can be expressed using traditional or advanced methods of genetic engineering. Among other groups of natural products, we will focus on compounds with a motif of 4-alkyl-L-proline (APD) derivatives, which are rare when compared to L-proline containing specialized metabolites (24). Yet, metabolites that incorporate 4-alkyl-L-proline are significantly more effective than their counterparts that incorporate L-proline; this was documented for two groups of metabolites with different mode of action: antimicrobial lincosamides (targeting bacterial ribosome or apicoplast

of Plasmodia) and antitumor pyrrolobenzodiazepines. We assume that this applies analogously to all metabolites with 4-alkyl-L-proline moieties; otherwise there would be no selective pressure during the evolution to replace canonical L-proline for biosynthetically complex 4-alkyl-Lproline that are derived from L-tyrosine (25). Biosynthetically but also functionally remarkable metabolite with an unusual 4-alkyl-L-proline moiety is lincomycin belonging to lincosamide antibiotics, which represent a flagship of the part of this project that aims to achieve TRL3-4.

Metode atau cara untuk mencapai tujuan yang telah ditetapkan ditulis tidak melebihi 600 kata. Bagian ini dilengkapi dengan diagram alir penelitian yang menggambarkan apa yang sudah dilaksanakan dan yang akan dikerjakan selama waktu yang diusulkan. Format diagram alir dapat berupa file JPG/PNG. Bagan penelitian harus dibuat secara utuh dengan penahapan yang jelas, mulai dari awal bagaimana proses dan luarannya, dan indikator capaian yang ditargetkan. Di bagian ini harus juga mengisi tugas masing-masing anggota pengusul sesuai tahapan penelitian yang diusulkan.

METODE

1. **Collection of metabolite sources (activity 1-1)**

Metabolites will be purified from plant material or from cultures of Actinobacteria isolates. ***CZ team***: 800+ Actinobacteria isolated from six different locations in EU countries; performed pre-experiments: 16S RNA sequencing, HPLC-DAD analysis, bioassays of crude extracts (35% extracts were active). ***TH team****:* 1000+ compounds, 400+ Actinobacteria isolated from deep sea (10+ isolates), Mangrove sediments (150+), cave and limestone area (200+); limited data of bioactivity. ***All teams:*** collection of plant, sponge material and Actinobacteria based on geological, seasonal, climate, and biodiversity criteria; focus on mangrove and marine Actinobacteria (eg. Nakhon si thammarat, Trang provinces, Thailand).

2. **Taxonomical characterization (activity 1-2)**

Taxonomical characterization of Actinobacteria (16S RNA sequencing) to remove duplicates and to identify rare Actinobacteria and genera known for rich specialized metabolism). Whole genome sequencing will be performed for rare (*eg.* non-Streptomyces) Actinobacteria; the data will be used for genome mining.

3. **Bioassays of extracts and fractions (activity 1-3)**

Crude extracts (1000+) and/or HPLC fractions (5000+) will be tested for biological activities that cover a number of different targets to increase the rate of positive hits; the activities are specified in 2.4.1.

4. **Untargeted mass spectrometry-based metabolomics (activity 1-4)**

Crude extracts and HPLC fractions will be analyzed by state-of-the-art LC-MS/MS and processed with advanced MS data processing platforms: GNPS molecular networking, MS2LDA unsupervised substructure discovery, and others including the recent Agilent metabolomics workflow (Mass Profiler Pro 15, Profinder 10, etc.). These approaches will facilitate to dereplicate already known compounds, reveal unique compounds within the data set, i.e., compounds with low frequency of occurrence that we should prioritize. Further, GNPS and other commercial spectral MS/MS libraries including in silico tools will be used to annotate a significant portion of the detected metabolites. (LC-MS/MS – ***CZ and INDO teams + TH team visitors***; data processing training – ***CZ team***; data processing – ***all teams*** after the training).

5. **Genome mining (activity 1-5)**

Sequenced bacterial genomes will be searched for specific biosynthetic genes that encode proteins involved in the biosynthesis of structural motifs of interest. Specifically, we will search

for novel lincosamide antibiotics (using the sequence of *lmbD* as a probe) and metabolites with a 4-alkyl-proline moiety (using the sequence of *apd1*, *apd2* and/or *apd6* as probes) – ***CZ team***. Identified biosynthetic gene clusters of interest will be expressed (OSMAC, heterologous expression, repressor gene inactivation, targeted induction) – ***CZ and TH teams***.

6. Metabolite identification (activity 1-6)

Metabolites with remarkable biological activities and those resulting from genome mining targeted search will be purified from the culture broth in mgs amounts (***all teams***) for subsequent biological assays and structural characterization (IR, NMR, crystallization) (***CZ and INDO teams***).

7. **Library creation from promising drug candidates (activity 1-7)**

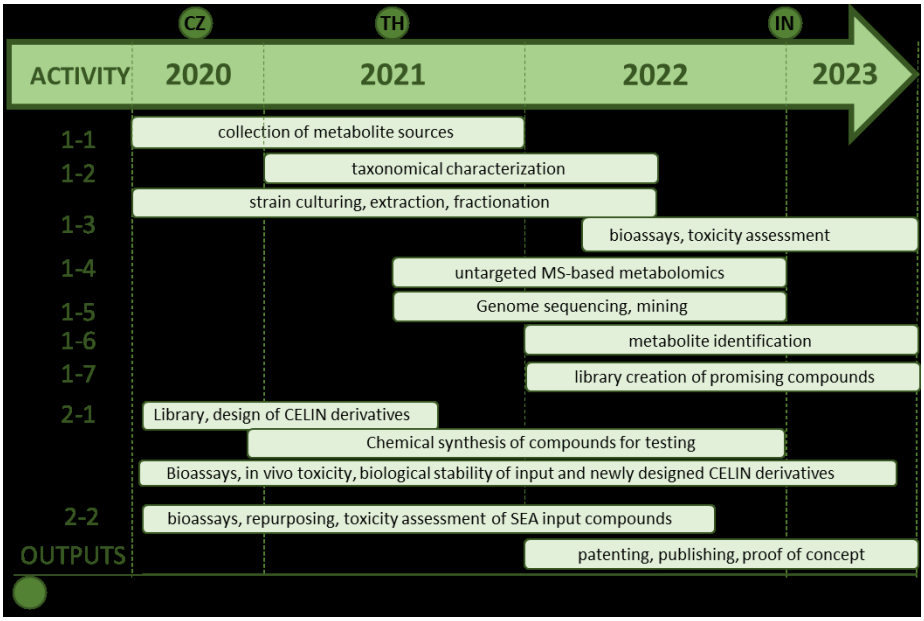
A library of derivatives will be created from identified metabolites of remarkable bioactivities in to obtain a suitable drug candidate in terms of activity, stability, and toxicity. Further, metabolites active against G+ strains only will be developed in antibiotics targeting also G- pathogens (in silico predictions from compound planarity and flexibility) – ***CZ team***.

8. Development of CELIN derivatives into drugs (activity 2-1)

Process proof of concept will be performed for two compounds *od*CELIN and *cli*CELIN implemented in the project as the intellectual property of CZ partner institution. Additionally, we will involve 1-3 CELIN derivative compounds designed exclusively by ***CZ team***. ***CZ*** and ***TH team*** will cooperate in testing these compounds for antimalarial and antibacterial activities. All other parts of proof of concept process will be done within project exclusively by ***CZ team*** (chemical synthesis, evaluation of toxicity and biological stability in vivo, etc.). In parallel, but not included in the project, the ***CZ team*** will perform in silico simulation to design optimal CELIN derivatives.

9. Development of promising compounds of SEA teams into drugs (activity 2-2)

Already available promising compounds will be considered for further development into drugs: plumbagin, elliptinone, droserone, rhinacanthin C, α- and γ-mangostin, chamuangone, phenylbutanoids (***TH team***), artocarpin, dihydromorin, norartocarpetin, artocarpanone, cyanomaclurin (***INDO team***). We will explore the spectrum of bioactivities in more detail including the ability to inhibit MDR species.



Jadwalpenelitiandisusundengan mengisi langsung tabel berikut dengan memperbolehkan penambahan baris sesuai banyaknya kegiatan.

JADWAL

Tahun ke-1

No	Nama Kegiatan	Bulan											
		1	2	3	4	5	6	7	8	9	10	11	12
1	Collection of metabolite sources	x	x	x	x	x	x	x	x	x	x	x	x
2	Strain culturing, extraction, fractionation	x	x	x	x	x	x	x	x	x	x	x	x
3	Library, design of CELIN derivatives	x	x	x	x	x	x	x	x	x	x	x	x
4	Bioassays, in vivo toxicity, biological stability of input and newly designed CELIN derivatives	x	x	x	x	x	x	x	x	x	x	x	x
5	Bioassays, repurposing, toxicity assessment of SEA input compounds	x	x	x	x	x	x	x	x	x	x	x	x

Tahun ke-2

No	Nama Kegiatan	Bulan											
		1	2	3	4	5	6	7	8	9	10	11	12
1	Collection of metabolite sources	x	x	x	x	x	x	x	x	x	x	x	x
2	Taxonomical characterization	x	x	x	x	x	x	x	x	x	x	x	x
3	Strain culturing, extraction, fractionation	x	x	x	x	x	x	x	x	x	x	x	x
4	Untargeted MS-based metabolomics							x	x	x	x	x	x
5	Genome sequencing, mining							x	x	x	x	x	x
6	Library, design of CELIN derivatives	x	x	x	x	x	x	x	x				
7	Chemical synthesis of compounds for testing	x	x	x	x	x	x	x	x	x	x	x	x
8	Bioassays, in vivo toxicity, biological stability of input and newly designed CELIN derivatives	x	x	x	x	x	x	x	x	x	x	x	x
9	Bioassays, repurposing, toxicity assessment of SEA input compounds	x	x	x	x	x	x	x	x	x	x	x	x

Tahun ke-3

No	Nama Kegiatan	Bulan											
		1	2	3	4	5	6	7	8	9	10	11	12
1	Taxonomical characterization	x	x	x	x	x	x						
2	Strain culturing, extraction, fractionation	x	x	x	x	x	x	x	x	x	x	x	x
3	Bioassays, toxicity assessment				x	x	x	x	x	x	x	x	x

No	Nama Kegiatan	Bulan											
		1	2	3	4	5	6	7	8	9	10	11	12
4	Untargeted MS-based metabolomics	x	x	x	x	x	x	x	x	x	x	x	x
5	Genome sequencing, mining	x	x	x	x	x	x	x	x	x	x	x	x
6	Metabolite identification	x	x	x	x	x	x	x	x	x	x	x	x
7	Library creation of promising compounds	x	x	x	x	x	x	x	x	x	x	x	x
8	Chemical synthesis of compounds for testing	x	x	x	x	x	x	x	x	x	x	x	x
9	Bioassays, in vivo toxicity, biological stability of input and newly designed CELIN derivatives	x	x	x	x	x	x	x	x	x	x	x	x
10	Bioassays, repurposing, toxicity assessment of SEA input compounds	x	x	x	x	x	x	x	x	x			
11	Patenting, publishing, proof of concept	x	x	x	x	x	x	x	x	x	x	x	x

Daftar pustaka disusun dan ditulis berdasarkan sistem nomor sesuai dengan urutan pengutipan. Hanya pustaka yang disitasi pada usulan penelitian yang dicantumkan dalam Daftar Pustaka.

DAFTAR PUSTAKA

1. Venter, H., Mowla, R., Ohene-Agyei, T., and Ma, S. (2015). RND-type drug efflux pumps from Gram-negative bacteria: moleculer mechanism and inhibition. *Fron. Microbiol*., 6, 377.
2. Qin, R., Xiao, K., Li, B., Jiang, W. (2013). "The combination of catechin and epicatechin gallate from fructus *Crataegi potentiates* β-lactam antibiotics against methicillin-resistant *Staphylococcus aureus* (MRSA) i*n vitro* and *in vivo*". *Int. J. Mol. Sci.*, 14, 1802-1821.
3. Yang Y, Zhang Z, Li S, et al. (2014). Synergy effects of herb extracts: Pharmacokinetics and pharmacodynamics basis. *Fitoterapia*, 92, 133-147.
4. Dachriyanus, Sargent MV., Skelton B.W., Soediro I., Sutisna M., White A. H. Yulinah E. (2002) Rhodomyrtone, an antibotic from Rhodomyrtus tomentosa. *Australian Journal of Chemistry* 55: 229-232.
5. Suryati S., Nurdin H, Dachriyanus D & Hj Lajis M. (2011). Structure elucidation of antibacterial compound from *Ficus deltoidea* Jack leaves. *Indonesian Journal of Chemistry, 11*(1), 67-70. /*doi:http://dx.doi.org/10.22146/ijc.21422*/
6. M Taufik Ekaprasada, Hazli Nurdin, Sanusi Ibrahim, Dachriyanus. (2015). Antibacterial Activity of methyl gallate isolated from the leaves of *Toona sureni*. *International Journal on Advanced Science, Engineering and Information Technology* 5(4): 280-282
7. M Taufik Ekaprasada, Hazli Nurdin, Sanusi Ibrahim, Dachriyanus. (2009). Chemical Composition and Antibacterial Activity of the Essential Oil of the Toona sureni (Blume) Merr. *Jurnal Riset Kimia* 3(1): 90-95
8. Hazli Nurdin Suryati, Md Nordin Hj Lajis Dachriyanus. (2010). Characterization antibacterial constituent from *Ficus deltoideus* Jack leaves. *Majalah Farmasi Indonesia* 21(2): 134-138.
9. Krisyanella, Meri Ardianti, Dachriyanus. (2016). Uji Aktivitas Antimikroba Ekstrak Metanol Daun Tabat Barito (*Ficus deltoidea* Jack). *Jurnal Farmasi Higea* 1(1) : 29-35.

10. Elfita, Supriyatna, Husein H Bahti, Dachriyanus. (2007). Komponen Utama Fraksi Aktif Antibakteri dari Kulit Batang Kandis Gajah (*Garcinia griffithii* T. Aners) Terhadap Bakteri Uji Penyebab Diare Escherichia coli dan Shigella dysentriae. *Jurnal Farmasi Indonesia (Pharmaceutical Journal of Indonesia)* 5(2): 106-112
11. Feling R.H., Buchanan G.O., Mincer T.J., Kauffman C.A., Jensen P.R., Fenical W. Salinosporamide A: A highly cytotoxic proteasome inhibitor from a novel microbial source, a marine bacterium of the new genus Salinospora. Angew. Chem. Int. Ed., 2003, 42, 355-357.
12. Rice LB. (2008). Federal Funding for the Study of Antimicrobial Resistance in Nosocomial Pathogens: No ESKAPE. J Infect Dis 197:1079–1081. doi:10.1086/533452
13. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, Pulcini C, Kahlmeter G, Kluytmans J, Carmeli Y, Ouellette M, Outterson K, Patel J, Cavaleri M, Cox EM, Houchens CR, Grayson ML, Hansen P, Singh N, Theuretzbacher U, Magrini N, Aboderin AO, Al-Abri SS, Awang Jalil N, Benzonana N, Bhattacharya S, Brink AJ, Burkert FR, Cars O, Cornaglia G, Dyar OJ, Friedrich AW, Gales AC, Gandra S, Giske CG, Goff DA, Goossens H, Gottlieb T, Guzman Blanco M, Hryniewicz W, Kattula D, Jinks T, Kanj SS, Kerr L, Kieny MP, Kim YS, Kozlov RS, Labarca J, Laxminarayan R, Leder K, Leibovici L, Levy-Hara G, Littman J, Malhotra-Kumar S, Manchanda V, Moja L, Ndoye B, Pan A, Paterson DL, Paul M, Qiu H, Ramon-Pardo P, Rodríguez- Baño J, Sanguinetti M, Sengupta S, Sharland M, Si-Mehand M, Silver LL, Song W, Steinbakk M, Thomsen J, Thwaites GE, van der Meer JW, Van Kinh N, Vega S, Villegas MV, Wechsler-Fördös A, Wertheim HFL, Wesangula E, Woodford N, Yilmaz FO, Zorzet A. (2018). Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 18:318–327. doi:10.1016/S1473-3099(17)30753- 3
14. Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, Teillant A, Laxminarayan R. (2015). Global trends in antimicrobial use in food animals. Proc Natl Acad Sci 112:5649–5654. doi:10.1073/pnas.1503141112
15. Nadimpalli M, Delarocque-Astagneau E, Love DC, Price LB, Huynh BT, Collard JM, Lay KS, Borand L, Ndir A, Walsh TR, Guillemot D, De Lauzanne A, Kerleguer A, Tarantola A, Piola P, Chon T, Lach S, Ngo V, Touch S, Andrianirina ZZ, Vray M, Richard V, Seck A, Bercion R, Sow AG, Diouf JB, Dieye PS, Sy B, Ndao B, Seguy M, Watier L, Abdou AY. (2018). Combating Global Antibiotic Resistance: Emerging One Health Concerns in Lower-and Middle-Income Countries. Clin Infect Dis 66:963–969. doi:10.1093/cid/cix879
16. WHO. (2017). Global Antimicrobial Resistance Surveillance System (GLASS) Report Early implementation 2016-17. Geneva: World Health Organization. doi:10.1016/S1473-3099(18)30060-4
17. Garce D. (2015). Review of evidence on antimicrobial resistance and animal agriculture in developing countries. doi:10.12774/eod_cr.june2015.graced
18. Kadlcik, S., Kamenik, Vasek, D., Nedved, M., Janata, J. (2017): Elucidation of salicylate attachment in celesticetin biosynthesis opens the door to create a library of more efficient hybrid lincosamide antibiotics. *Chemical Science*, 8(5), 3349-3355.
19. Kamenik, Z., Kadlcik, S., Gazak, R., Vobruba, S., Palanova, L., Kuzma, M., Janata, J. (2017): Diversity of alkylproline moieties in pyrrolobenzodiazepines arises from

postcondensation modifications of a unified building block. *ACS chemical biology*, 12(8), 1993-1998.
20. Kornsakulkarn, Jittra, Chawanee Thongpanchang, Rittikorn Chainoy, Wilunda Choowong, Sutichai Nithithanasilp, and Tienthong Thongpanchang. (2010). "Bioactive Metabolites from Cultures of Basidiomycete Favolaschia Tonkinensis." Journal of Natural Products 73 (4): 759–62.
21. Ghebreyesus, T.A. and Admasu, K. (2018). Countries must steer new response to turn the malaria tide. Lancet (London, England), 392(10161), pp.2246-2247.
22. Talawanicha, Y., Kamchonwongpaisana, S., Sirawarapornb, W. and Yuthavong, Y. (2015). Use of bacterial surrogates as a tool to explore antimalarial drug interaction: synergism between inhibitors of malarial dihydrofolate reductase and dihydropteroate synthase. Acta Tropica, 149, 64–69
23. Aroonsri A, Akinola O, Posayapisit N, Songsungthong W, Uthaipibull C, Kamchonwongpaisan S, Gbotosho GO, Yuthavong Y, Shaw PJ. (2016) Identifying antimalarial compounds targeting dihydrofolate reductasethymidylate synthase (DHFR-TS) by chemogenomic profiling. Int J Parasitol., 46(8):527-535.
24. Janata, J., Kamenik, Z., Gazak, R., Kadlcik, S., Najmanova, L. (2018): Biosynthesis and incorporation of an alkylproline-derivative (APD) precursor into complex natural products. *Natural product reports*. 35(3): 257-289.
25. Jiraskova, P; Gažák, R; Kameník, Z; Steiningerová, L; Najmanová, L; Kadlčík, S; Novotná, J; Kuzma, M; Janata, J (2016): New Concept of the Biosynthesis of 4- Alkyl-L-Proline Precursors of Lincomycin, Hormaomycin, and Pyrrolobenzodiazepines: Could a gamma-Glutamyltransferase Cleave the C-C Bond? *Frontiers in Microbiology*, 7:276..

LAMPIRAN 1. BIODATA PENGUSUL

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Publikasi di Jurnal Internasional terindeks

No	Judul Artikel	Peran (First author, Corresponding author, atau co-author)	Nama Jurnal, Tahun terbit, Volume, Nomor, P-ISSN/E-ISSN	URL artikel (jika ada)
1	Comparison between High Performance Thin Layer Chromatography and High Performance Liquid Chromatography methods for determination of rubraxanthone in the stem bark extract of …		Pharmacognosy Journal, 2018, 10, 6, -	https://www.phcogj.c
2	Anti-inflammatory Activity of Isolated Compounds from the Stem Bark of Garcinia cowa Roxb		Pharmacognosy Journal, 2017, 9, 1, 0975-3575	http://www.phcogj.co
3	Determination of Rubraxanthone in the Latex of Asam Kandis (Garcinia cowa Roxb) by Reverse Phase High Performance Liquid Chromatography.		Pharmacognosy Journal, 2017, 9, 2, 0975-3575	http://www.phcogj.co
4	Effect of Arginine on IL-6, IL-17 and TGF-β levels in high-fat Diet-Induced Hypercholesterolemia Rat		Journal of Young Pharmacists, 2017, 9, 1, 0975-1505	https://www.jyoungph
5	High performance thin layer chromatography: Densitometry method for determination of rubraxanthone in the stem bark extract of Garcinia cowa Roxb	first author	Pharmacognosy research, 2017, 9, -, -	https://www.ncbi.nlm
6	In vivo Study of Tetraprenyltoluquinone, An Anticancer Compounds from Garcinia cowa Roxb		J Young Pharm, 2017, 9, 2, 0975-1483	https://www.research
7	Cytotoxic properties and complete nuclear magnetic resonance assignment of isolated xanthones from the root of Garcinia cowa Roxb.	corresponding author	Pharmacognosy magazine, 2016, 12, -, -	https://www.ncbi.nlm
8	Antibacterial Activity of Methyl Gallate Isolated from the Leaves		advanced science engineering information	http://insightsociet

	of Toona sureni		tecnology, 2015, 5, 4, 2088-5334	
9	Cytotoxic compounds from the leaves of Garcinia cowa Roxb.	corresponding author	Journal of Applied Pharmaceutical Science, 2015, 5, 2, -	https://scholar.goog
10	CYTOTOXICITY STUDIES OF TETRAPRELYLTOLUQUINONE, A PRENILATED HYDROQUINONE FROM GARCINA COWA ROXB ON H-460, MCF-7 AND DU-145		International Journal of Pharmacy and Pharmaceutical Sciences , 2015, 7, 3, 0975-1491	https://www.research
11	Cytotoxicity study of ethanol extract of the stem bark of asam kandis (Garcinia Cowa Roxb) on T47D breast cancer cell line		Asian Pacific Journal of Tropical Biomedicine, 2015, 5, 3, 2221-1691	http://www.sciencedi
12	Cytotoxic xanthones from the stem bark of Garcinia cowa Roxb	corresponding author	Journal of Chemical and Pharmaceutical Research, 2015, 7, 1, 0975-7384	https://www.research
13	DEVELOPMENT AND VALIDATION OF RP-HPLC METHOD FOR QUANTITATIVE ESTIMATION OF α-MANGOSTIN IN THE RIND EXTRACT AND FRACTIONS OF GARCINIAMANGOSTANA L. AND THEIR CYTOTOXIC ACTIVITY ON T47D BREAST CANCER CELL LINE		International Journal of Pharmacy and Pharmaceutical Sciences, 2015, 7, 2, 0975-1491	http://www.academia.
14	Formulation of Sunscreen Cream of Germanicol cinnamate from the Leaves of Tabat barito (Ficus deltoides Jack) and an Assay of its' Sun Protection Factor		Int. J. Pharm. Sci. Rev. Res., 2015, 32, 1, 0976 – 044X	https://www.research
15	Tetraprenyltoluquinone, an Anticancer Compound from Garcinia cowa Roxb Induce Cell Cycle Arrest on H460 Non Small Lung Cancer Cell Line		Int. J. Pharm. Sci. Rev. Res, 2015, 32, 2, 0976 – 044X	https://www.research
16	Tetraprenyltoluquinone, an Anticancer Compound from Garcinia cowa Roxb Induce Cell Cycle Arrest on H460 Non Small Lung Cancer Cell Line	co-author	Int J Pharm Sci Rev Res, 2015, 27, -, -	https://www.research
17	Cytotoxicity study of ethanol extract of the stem bark of asam kandis (Garcinia cowa Roxb.) on T47D breast cancer cell line		Asian Pacific Journal of Tropical Biomedicine, 2014, 5, 3, 2221-1691	http://www.sciencedi
18	Development and Validation of a HPLC Method for Determination and Quantification of a-mangostin in Bark Extract of Garcinia cowa Roxb		Int. J. Res. Pharm.Sci, 2014, 5, 4, 0975-7538	https://www.research
19	Development and validation of Thin-Layer Chromatographic		International Journal of Research in Pharmaceutical	https://www.research

	method for determination of α-mangostin in young pericarp, ripe pericarp and bark extract of Garcinia mangostana L. Using TLC-Densitometry		Sciences , 2014, 5, 4, 0975-7538	
20	Phenolic contents, antioxidant and cytotoxic activities of Elaeocarpus floribundus Blume		Pak J Pharm Sci. , 2013, 26, 2, 23455191	http://www.ncbi.nlm.
21	Structure elucidation of antibacterial compound from Ficus deltoidea Jack leaves	co-author	Indonesian Journal of Chemistry, 2011, 11, 1, 1411-9420	https://journal.ugm.
22	Antioxidant activity of methyl gallate isolated from the leaves of Toona sureni	co-author	Indonesian Journal of Chemistry, 2009, 9, 3, 1411-9420	https://journal.ugm.
23	Antiplasmodial and other constituents from four Indonesian Garcinia spp.	co-author	Phytochemistry, 2009, 70, 7, -	https://www.sciencedirect
24	Chemical Composition and Antibacterial Activity of the Essential Oil of the Toona sureni (Blume) Merr	co-author	J. Ris. Kim., 2009, 3, 1, 1978-628X	http://jrk.fmipa.una
25	Diprenylated Xanthone From The Stem Bark of Kandis Gajah (Garcinia griffithii)	co-author	Indonesian Journal of Chemistry, 2008, 8, 1, -	https://journal.ugm.
26	5-Hydroxy-3, 3′, 4′, 5′, 7-pentamethoxyflavone (combretol)	first author	Acta Crystallographica Section E: Structure Reports Online, 2004, E60, -, 1600-5368	https://scripts.iucr
27	A new ring-reduced tetraprenyltoluquinone and a prenylated xanthone from Garcinia cowa	co-author	Australian journal of chemistry, 2004, 57, 3, -	https://www.publish.
28	rac-Eudesm-7 (11)-en-4-ol	first author	Acta Crystallographica Section C: Crystal Structure Communications, 2004, 60, 7, 0108-2701	https://scripts.iucr
29	Rhodomyrtone, an antibiotic from Rhodomyrtus tomentosa	first author	Australian Journal of Chemistry, 2002, 55, 3, -	https://www.publish.
30	Indole alkaloids from two species of Ophiorrhiza	first author	Australian Journal of Chemistry, 2000, 53, 3, -	https://www.publish.
31	(+)-Isochimonanthine, a pyrrolidinoindole alkaloid from Argostemma yappii King	first author	Australian Journal of Chemistry, 2000, 53, 2, -	https://www.publish.
32	Unusual indole alkaloids from Ophiorrhiza blumeana Korth	co-author	Journal of the Chemical Society, Perkin Transactions 1, 1998, 16, -, -	https://pubs.rsc.org
33	Bracteatine, a quaternary glucoalkaloid from Ophiorrhiza bracteata	co-author	Australian journal of chemistry, 1997, 50, 11, -	https://www.publish.
34	Isomalindine-16-carboxylate, a zwitterionic alkaloid from Ophiorrhiza cf. communis	co-author	Australian Journal of Chemistry, 1997, 50, 11, -	https://www.publish.

Publikasi di Jurnal Nasional Terakreditasi Peringkat 1 dan 2

No	Judul Artikel	Peran (First author, Corresponding author, atau co-author)	Nama Jurnal, Tahun terbit, Volume, Nomor, P-ISSN/E-ISSN	URL artikel (jika ada)
1	Induksi ketahanan tanaman jahe terhadap penyakit layu Ralstonia solanacearum ras 4 menggunakan fungi mikoriza arbuskula (FMA) indigenus		JHPT Tropika, 2011, 11, 1, 1411-7525	-
2	Inokulasi Fungi Mikoriza Arbuskula (FMA) Indigenus pada Bibit Jahe untuk Pengendalian Penyakit Layu Ralstonia solanacearum Ras 4		Jurnal Natur Indonesia, 2011, 14, 1, 1410-9379	http://ejournal.unri
3	Uji aktivitas Sitotoksik senyawa dari kulit batang kandis terhadap sel kanker kolon hct-116		Buletin The Indonesian Society Natural Products Chemistry, 2011, 11, 22, 1411-9269	-
4	Formulation of An Anti-Plaque Toothpaste of Standardized Gambir Extract and It's Antimicrobial Assay Against Streptococcus mutans		Jurnal Farmasi Indonesia, 2010, 5, 2, 1412-1107	www.jfi.iregwaw.com

Prosiding seminar/konverensi internasional terindeks

No	Judul Artikel	Peran (First author, Corresponding author, atau co-author)	Nama Jurnal, Tahun terbit, Volume, Nomor, P-ISSN/E-ISSN	URL artikel (jika ada)
1	Pengaruh Fraksi Air Ekstrak Etanol Daun Salam (Syzygium polyanthum Wight.) Terhadap Kadar Asam Urat Darah Pada Tikus Putih Jantan Hiperurisemia–Diabetes	co-author	Prosiding Seminar Nasional dan Workshop “Perkembangan Terkini Sains Farmasi dan Klinik IV” tahun 2014, 2014, -, -, -	https://www.research

Buku

No	Judul Buku	Tahun Penerbitan	ISBN	Penerbit	URL (jika ada)
1	Apoteker Cilik Pintar Dengan Obat	2019	9786026953629	Andalas University Press, Padang	-
2	Orang Tua Pintar Dengan Obat	2019	9786026953636	Andalas University Press Padang	-
3	Pintar Dengan Obat: Cerdas Penggunaannya, Cegah Penyalahgunaannya	2018	9786026953605	Andalas University Press	-

4	Analisis Struktur Senyawa Organik Secara Spektroskopi	2017	978-602-60613-5-5	Lembaga Pengembangan Teknologi Informasi dan Komunikasi (LPTIK) Universitas Andalas	-
5	Kromatografi Cair Kinerja Tinggi	2014	9786028821667	Andalas University Press	http://carano.pustak

Perolehan KI

No	Judul KI	Tahun Perolehan	Jenis KI	Nomor	Status KI (terdaftar/granted)	URL (jika ada)
1	PROSES PEMBUATAN EKSTRAK RIMPANG JAHE SEBAGAI PENGHAMBAT SEL KANKER PAYUDARA T47D.	2015	Paten	IDP000046855	Granted	https://pdki-indones
2	PEMBUATAN METILGALAT DARI DAUN SURIAN DENGAN FRAKSINASI POLAR	2013	Paten	IDP000053551	Granted	https://pdki-indones

Riwayat penelitian didanai Kemenristekdikti

No	Judul	Tahun	Dana Disetujui
1	PENGUJIAN MEKANISME AKTIVITAS ANTIKANKER SENYAWA TETRAPRENILTOLOQUINON DARI KULIT BATANG ASAM KANDIS (Garcinia cowa. Roxb) DAN PENGEMBANGAN POTENSINYA SEBAGAI KANDIDAT FITOFARMAKA	2021-2022	193,050,000
2	PENGUJIAN MEKANISME AKTIVITAS ANTIKANKER SENYAWA TETRAPRENILTOLOQUINON DARI KULIT BATANG ASAM KANDIS (Garcinia cowa. Roxb) DAN PENGEMBANGAN POTENSINYA SEBAGAI KANDIDAT FITOFARMAKA	2020-2021	213,112,000
3	PENGUJIAN MEKANISME AKTIVITAS ANTIKANKER SENYAWA TETRAPRENILTOLOQUINON DARI KULIT BATANG ASAM KANDIS (Garcinia cowa. Roxb) DAN PENGEMBANGAN POTENSINYA SEBAGAI KANDIDAT FITOFARMAKA	2019-2020	241,000,000
4	Uji Preklinis dan Klinis Sediaan Topikal Rhodomyrtone, Senyawa Antibakteri Hasil Isolasi dari Tumbuhan Rhodomyrtus tomentosa (Ait)Hassk) Untuk Pengobatan Infeksi Kulit	2013-2014	47,500,000
5	Uji Preklinis dan Klinis Sediaan Topikal Rhodomyrtone, Senyawa Antibakteri Hasil Isolasi dari Tumbuhan Rhodomyrtus tomentosa (Ait)Hassk) Untuk Pengobatan Infeksi Kulit	2013-2013	45,500,000

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Publikasi di Jurnal Internasional terindeks

No	Judul Artikel	Peran (First author, Corresponding author, atau co-author)	Nama Jurnal, Tahun terbit, Volume, Nomor, P-ISSN/E-ISSN	URL artikel (jika ada)
1	Chemical characterization and anti-inflammatory activity of Piladang Leaf (Coleus Atropurpureus) Extract		Journal of Chemical and Pharmaceutical Sciences, 2016, 9, 4, 0974-2115	http://jchps.com/iss

Publikasi di Jurnal Nasional Terakreditasi Peringkat 1 dan 2

No	Judul Artikel	Peran (First author, Corresponding author, atau co-author)	Nama Jurnal, Tahun terbit, Volume, Nomor, P-ISSN/E-ISSN	URL artikel (jika ada)

Prosiding seminar/konverensi internasional terindeks

No	Judul Artikel	Peran (First author, Corresponding author, atau co-author)	Nama Jurnal, Tahun terbit, Volume, Nomor, P-ISSN/E-ISSN	URL artikel (jika ada)

Buku

No	Judul Buku	Tahun Penerbitan	ISBN	Penerbit	URL (jika ada)

Perolehan KI

No	Judul KI	Tahun Perolehan	Jenis KI	Nomor	Status KI (terdaftar/granted)	URL (jika ada)
1	Formulasi Ekstrak Tanaman Obat Tradisional Sebagai Antigout	2016	Paten		Terdaftar	-

NOTA KESEPAHAMAN

ANTARA
PT KIMIA FARMA (PERSERO) TBK
DENGAN
UNIVERSITAS ANDALAS

TENTANG

KERJASAMA DI BIDANG PENDIDIKAN, PENELITIAN DAN PENGABDIAN MASYARAKAT

Nomor : 01/KF/MOU/I/2018

Pada hari ini, Rabu tanggal Sepuluh bulan Januari tahun Dua ribu delapan belas.(10-01-2018), kami yang bertanda tangan di bawah ini:

I. **PT KIMIA FARMA (PERSERO) TBK** adalah Badan Usaha Milik Negara (BUMN) Farmasi yang bergerak dibidang layanan kesehatan, yang berkedudukan di di Jalan Veteran No. 9, Jakarta Pusat 10110, dalam hal ini diwakili oleh **Honesti Basyir** dalam kedudukannya sebagai **Direktur Utama** sesuai Anggaran Dasarnya terakhir dimuat dalam Akta Nomor: 49 Tanggal 20 April 2017 yang sudah mendapat pengesahan dari Menteri Hukum dan Hak Asasi Manusia Republik Indonesia sesuai Surat Keputusan Nomor: AHU-0053827.AH.01.11 Tahun 2017 Tanggal 17 Mei 2017 dan susunan pengurus yang tercantum dalam Akta Nomor: 48 Tanggal 20 April 2017, yang dibuat dihadapan Mochamad Nova Faisal, Notaris di Jakarta Selatan, yang telah mendapat persetujuan dari Menteri Hukum dan Hak Asasi Manusia Republik Indonesia Nomor AHU-0053827.AH.01.11 Tahun 2017 Tanggal 26 April 2017 dan sah bertindak untuk dan atas nama PT Kimia Farma (Persero Tbk) dan selanjutnya dalam Kontrak ini disebut sebagai **PIHAK PERTAMA**

II. **Universitas Andalas** adalah Perguruan Tinggi Negeri yang dengan ini diwakili oleh Tafdil Husni selaku Rektor, sesuai dengan ketentuan Anggaran Dasar beserta perubahannya, terakhir dimuat dalam PP nomor 24 tahun 1956 dan telah diumumkan dalam Lembaran Negara RI nomor 40 tahun 1956 tanggal 8 September 1956 dan selanjutnya dalam Perjanjian ini disebut **PIHAK KEDUA**

PIHAK PERTAMA dan PIHAK KEDUA selanjutnya secara bersama-sama disebut **PARA PIHAK**, dan masing-masing disebut **PIHAK**, **PARA PIHAK** dengan ini terlebih dahulu menerangkan hal-hal sebagai berikut :

a. Bahwa **PIHAK PERTAMA** adalah Badan Usaha Milik Negara yang bergerak dalam bidang industri farmasi, *healthcare* yang meliputi poduksi, distribusi, pemasaran, retail, serta *research and development*;

b. Bahwa **PIHAK KEDUA** adalah suatu Perguruan Tinggi Negeri di Sumatera Barat, dalam mewujudkan tri darma perguruan tinggi (pendidikan, penelitian dan pengabdian kepada masyarakat) dan hilirisasi hasil penelitian, bermaksud melakukan kerjasama yang saling menguntungkan dengan PIHAK PERTAMA;

Berdasarkan hal tersebut di atas, **PARA PIHAK** sepakat untuk menuangkan pokok-pokok kesepakatan dalam Nota kesepahaman tentang Pendidikan, Penelitian dan Pengabdian kepada Masyarakat), dengan ketentuan sebagai berikut:

PASAL 1
TUJUAN

Tujuan Nota Kesepahaman ini adalah dalam rangka mewujudkan rencana pelaksanaan kerjasama tri darma perguruan tinggi (pendidikan, penelitian dan pengabdian kepada masyarakat) dan hilirisasi hasil penelitian yang akan dilakukan oleh PARA PIHAK.

PASAL 2
LINGKUP KEGIATAN

Lingkup kegiatan Nota Kesepahaman ini meliputi seluruh kegiatan yang berhubungan pelaksanaan kerjasama tri darma perguruan tinggi (pendidikan, penelitian dan pengabdian kepada masyarakat) dan hilirisasi hasil penelitian yang akan dilakukan oleh PARA PIHAK

PASAL 3
PELAKSANAAN

(1) Pelaksanaan kegiatan dimaksud Pasal 2 di atas yang bersifat teknis, akan diatur lebih lanjut oleh PARA PIHAK dalam perjanjian kerjasama tersendiri yang mengatur rincian pekerjaan, pelaksanaan pekerjaan, hak dan kewajiban PARA PIHAK, serta hal-hal lain yang dipandang perlu.

(2) Sejak berlakunya Nota Kesepahaman ini, PARA PIHAK segera menindaklanjuti kegiatan yang telah tertuang dalam Nota Kesepahaman ini.

PASAL 4
JANGKA WAKTU

Nota Kesepahaman ini berlaku untuk jangka waktu 5 (lima) tahun, terhitung sejak ditandatangani oleh PARA PIHAK dan dapat diperpanjang atas kesepakatan PARA PIHAK.

PASAL 5
ADDENDUM

Hal-hal yang belum diatur dalam Nota Kesepahaman ini, akan diatur lebih lanjut berdasarkan kesepakatan PARA PIHAK dalam bentuk addendum dan merupakan satu kesatuan yang tidak terpisahkan dari Nota Kesepahaman ini.

PASAL 6
PENYELESAIAN PERSELISIHAN

Setiap perselisihan yang timbul sebagai akibat dari pelaksanaan dan/atau penafsiran Nota Kesepahaman, PARA PIHAK ini akan menyelesaikannya secara musyawarah untuk mufakat.

Nota Kesepahaman ini dibuat dalam rangkap 2 (dua) asli, bermeterai cukup dan ditandatangani oleh PARA PIHAK, serta mempunyai kekuatan hukum yang sama untuk masing-masing PIHAK.

PIHAK PERTAMA	PIHAK KEDUA
PT Kimia Farma (Persero) Tbk	Universitas Andalas
METERAI TEMPEL 6000 ENAM RIBU RUPIAH	KEMENTERIAN RISET, TEKNOLOGI DAN PENDIDIKAN TINGGI UNIVERSITAS ANDALAS REKTOR
HONESTI BASYIR	**TAFDIL HUSNI**
Direktur Utama	Rektor

LAMPIRAN 3. BUKTI PEROLEHAN KI

REPUBLIK INDONESIA
KEMENTERIAN HUKUM DAN HAK ASASI MANUSIA

SERTIFIKAT PATEN

Menteri Hukum dan Hak Asasi Manusia atas nama Negara Republik Indonesia berdasarkan Undang-Undang Nomor 13 Tahun 2016 tentang Paten, memberikan Paten kepada:

Nama dan Alamat Pemegang Paten	:	UNIVERSITAS ANDALAS Gd Rektorat Lt. 2, Kampus Unand Limau Manis Padang 25163 INDONESIA
Untuk Invensi dengan Judul	:	PROSES PEMBUATAN EKSTRAK RIMPANG JAHE SEBAGAI PENGHAMBAT SEL KANKER PAYUDARA T47D.
Inventor	:	Dr. Netty Suharti, MS Prof. Dr. Dachriyanus Dr. Fatma Sri Wahyuni
Tanggal Penerimaan	:	01 Desember 2015
Nomor Paten	:	IDP000046855
Tanggal Pemberian	:	17 Juli 2017

Perlindungan Paten untuk invensi tersebut diberikan untuk selama 20 tahun terhitung sejak Tanggal Penerimaan (Pasal 22 Undang-Undang Nomor 13 Tahun 2016 tentang Paten).

Sertifikat Paten ini dilampiri dengan deskripsi, klaim, abstrak dan gambar (jika ada) dari invensi yang tidak terpisahkan dari sertifikat ini.

a.n. MENTERI HUKUM DAN HAK ASASI MANUSIA
REPUBLIK INDONESIA
DIREKTUR JENDERAL KEKAYAAN INTELEKTUAL
u.b.
Direktur Paten, Desain Tata Letak
Sirkuit Terpadu dan Rahasia Dagang,

00-2017-203984

(20) RI Permohonan Paten

(19) ID **(11) IDP000053551** **(13) A**

(51) IPC : A61K 31/00, A61P 3/06

(21) No. Permohonan Paten : P00201304715

(22) Tanggal Penerimaan Permohonan Paten :
29 Nov 2013

(30) Data Prioritas :
(31) Nomor (32) Tanggal (33) Negara

(43) Tanggal Pengumuman Paten :
28 Aug 2014

(71) Nama dan Alamat yang Mengajukan Permohonan Paten :
LPPM UNIVERSITAS ANDALAS , Kampus Unand Limau Manis Padang (u.p. Prof. Dr. Herwandi, M.Hum), ID

(72) Nama Inventor :
Dr. Suhatri, MS, Apt., ID
Prof. Dr. Dachriyanus, Apt., ID
Prof. Dr. dr. Ellyza Nasrul Sp PK (K), PA, ID
Prof. Dr. dr. Yanwirasti, PA., ID

(74) Nama dan Alamat Konsultan Paten :
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-
-

(54) Judul Invensi : PEMBUATAN METILGALAT DARI DAUN SURIAN DENGAN FRAKSINASI POLAR

(57) Abstrak :

Invensi ini berhubungan dengan metil galat yang di isolasi dari daun surian (Toona Sureni Bl Merr) untuk pencegah penyakit aterosklerosis. Dari 3,6 kg daun surian Toona sureni kering fraksi etil asetat sebanyak 351 gram (37,34%). Dari 351 gram fraksi etil asetat yang didapat hanya 160 gram. Setelah dikromatografi kolom diperoleh metil galat sebanyak 9,74 gram (6,088%). Metilgalat yang diperoleh berbentuk kristal berwarna putih dengan jarak titik leleh 181 -184°C. Pada pola noda pada plat KLT memberikan Rf 0,44 yang diamati pada plat KLT silika gel PF 254 dengan eluen Etil asetat : N-hexan : Metanol (5:4,5:0,5). Metilgalat yang diisolasi dari daun surian memberikan reaksi positif dengan FeCl3 dan memiliki panjang gelombang maksimal pada λ 271 nm dengan absorban 0,44. Metilgalat dosis 5 mg/kg BB dapat digunakan mencegah terjadinya disfungsi sel endotel ditandai dengan dapat mempertahan kadar NO/ EDRF tetap normal. Metil galat dosis 5 mg/kg BB dan 10 mg/kg BB mencegah terbentukanya atheroma/plag yang ditandai dengan tidak terjadi proliferasi sel otot polosan tidak terjadi penebalan pembuluh darah dan tidak terjadi kerusakan lapisan endotel dan sub endotel pembuluh aorta tikus hiperkolesterol.

PERSETUJUAN USULAN

Tanggal Pengiriman	Tanggal Persetujuan	Nama Pimpinan Pemberi Persetujuan	Sebutan Jabatan Unit	Nama Unit Lembaga Pengusul
-	-	-	-	-