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ORIGINAL ARTICLE

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THE INVENTION OF CHEMICAL COMPOUNDS OF HERBAL MEDICINE CONTAINING PIRIDINE FOR CORONA VIRUS (COVID – 19. MERS). HIV/AIDS. AND HEPATITIS

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ABSTRACT

Drugs that many currently developed progressing well from natural materials and structures, quite a long period of 25 years, especially drugs for the inhibition of virus Corona, HIV / AIDS, a retrovirus (ARV) drugs such as Lamivudine and Generative her yet retrovirus capable of completely killing, is still limited to inhibiting (inhibition) for this paper to compare the strength of inhibition between drugs derived from chemical structures and Herbs.

Research in the Tobelo year period 2014-2019 in STIKMAH Tobelo involving several laboratories such as the Laboratory of DKI, LIPI Laboratory, Laboratory of IPB Bogor and Others.

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Provide a reference for researchers, especially in the field of Pharmaceutical Chemistry, Nanomedicine and foremost also for WHO that supplements should not be underestimated and there is no benefit. Derived supplement China today is recognized as the world a malaria drug.

Results found among other things that the power of the drugs inhibit retrovirus Lamivudine reached 46% while Golobe (Zingiberaceae) 43% and leaves Pangi reached 94.80%. This needs to be the seriousness of the world because there does not already over 45 million HIV / AIDS patients awaiting life-style drugs to raise expectations, as well as comparisons between Golobe and Lamivudine 46.75% inhibition and as anti-toxins, which also has the benefit of preventing golobe poison. Inhibition of RNA viruses, Corona Handling Family (COVID-19 mers) HIV / AIDS and Hepatitis. Compounds - compounds in Golobe 2,3-Dihydro-3,5-Dihydro-6-methyl (5:31%), 2-formyl-5-isopropyl-8-Methylspiro (2.22%), 2,6-Diethylpyridine (5.88%), Cholest-5-en-3-one, 4,4-dimethyl (6.08%), hexadecanoic acid, ethyl ester (43%). The compound contained in the leaves of Pangi 3R-acetamido-IC, 6C-bis (acetoxo) 5T-dimethyl-Cyclohexene lamino (1.03%), (+) - 2-endo, 3-endo-dimethylbornane (1.24%), 3, 5-dimethyl-1-dimethyl dodecyl silyl oxy benzene (1.62%), 2- (1-methyl-1,5,6,7-tetrahydro benzo pyrazole-3-yl) -6- (2-methyl-4,5,6, 7- tetrahydro benzo pyrazole-3-yl) pyridine (2.59%), Phytol (10.33%), Squalene Dimethylamino (21.22%) (94.80%), red sea star-containing compound Butanoic acid, 3-methyl (13.64%), 2-piperidone (27.24%), 2-hydroxy-3,5,5-trimethyl-cyclohex-2-Enone 28 682 (6.79%), 3 - ISOBUTHYLHEXAHDROPYPROLO [1,2-a] pyrazine (1.87%), hexadecanoic acid (8.51%), 9.17-Octadecanienal, (Z) - (16.47%), Octadecanoic Acid (6.23%), 9,12-Octadecadicnoic acid (z, z) - (5.73%), (6Z, 9z) -6.9-Pentadecadien-1-OL (1.95%), 6-Octadecenoic acid. (4, 85%).

A comparison between herbal ingredients more strongly inhibits the virus such as Corona Virus (COVID-19). Pangi leaves of chemical drug Lamivudine, while golobe has the same strength as well as inhibits virus lamivudine COVID-19 mers, HIV and Hepatitis.

INTRODUCTION

Nanomedicine and Nanotechnology today has made a major contribution to the breakthrough in the field of medicine pharmaceuticals including the

development of the herbs that have a compound content in inhibiting viruses such as Golobe (Zingiberaceae), Pangi, Stars the Red Sea, these compounds containing derivatives Dipiridin which has been used for the treatment of RNA viruses, such Retroviral HIV, AIDS, Hepatitis from Corona family (COVID-19 Mers CoV, SARS CoV) ^{1,2}

The development of herbal Medicine with a collaboration system among various laboratories and competencies provides good results in the *In Vitro* laboratory test as well as some cases of HIV AIDS patients give good results seen aspects of clinics ad laboratories. As the weight of 37 kg to 59 kg while the other patient had a CD4 of 300 to 500. These figures give the impression that the herbs which have piridine compounds can be used as a health supplement in reducing the power not to be a severe infection. Golobe with antioxidants tested with DPPH has 6.5 ug/mg (ppm), would give new hope to maintain the quality of healthcare, and assists in the inhibition of viral RNA both to HIV / AIDS and Family Corona and hepatitis. As well as hepatitis.

Red Sea Star is still in wait Kultur Inhibition Test Retrovirus, in the Laboratory of IPB Bogor. It's very important that the discovery supplement Health to inhibit viral RNA As Corona is expected, therefore STIKMAH Tobelo Wish Tests *In Vitro* soon may be increased to a clinical trial, given the current pandemic COVID-19 experienced 186 countries in World. The absence of bidders for treating Corona Virus - 19, then STIKMAH Tobelo currently developing health supplements Corona Virus Inhibition of the first in the world. As Golarend (Zingiberaceae). Pangi and star of the Red Sea, and the Red Pinahong A new hope to suppress and reduce lethal infection ^{2,3,4,5,6,7}

METHODS

Using some sophisticated tools, such as the Trans Former Infrared (FTIR) spectrometer MB 3000, USA, where it can see the character of this kind of Herbal medicine Golobe and Pangi. Where to see the Institute of Chemistry also viewed damping and vibration. Chemistry with a physical process, including test Nanomedicine.

Extract Golobe and Pangi is also done using the Virus Inhibition Test Laboratory Primate IPB. Bogor, West Java Province. Indonesia Since 2017 ago. This laboratory test compared with Lamivudine by looking at inhibition Virus, follow photocells. On day 1 through day 7. These results illustrate that new hope as a health

supplement that can contribute to tackling cases of the virus was present and future as the current pandemic

facing COVID - 19 SARS - Cov 2. Nor cases Virus infections such as HIV / AIDS and Hepatitis^{3,4,5,6,7}

Table 1. Inhibition Test Results.

Table caption:

1. Compounds in the Pangi act as a retroviral inhibitor with a total of 38.03%. A strong Inhibitor reaches 94.80% Pytol and Squalene has an important role in inhibiting the transkriptase of the HIV Virus enzyme. Pyridine and dimethyl have the role of Virus inhibition.

NO	NAMA BAHAN	AKTIFITAS	PERSENTASE	GAMBAR	RUMUS	INHIBISI
1	PANGI					
	1. Dimethyl → Virus	Virus	1,03			94,80 %
	2. Hidroxyanthylborane → Virus	Virus	1,24			
	3. Phytol → Virus	Virus	10,33			
	4. Pyridine → Virus	Virus	2,59			
	5. Squalen	Virus	21,22			
	6. Dimethyl dodeciloxy	Virus	1,62			
			38,03 %			
2	GOLOBE					
	1. Dehydroxy - 6 - methyl	Virus	5,31			43 %
	2. Methyl Spiro	Virus	2,22			
	3. Dietilpyridine	Virus	5,58			
	4. Dimetyl	Virus	6,08			
	5. Ethyl ester	Virus	1,22			
	6. Asam Amino					
			20,49 %			
3	LAMIVUDIN					
	-1-(2r, 5) - 2 - (Hydroxymethyl)					46 %
	-1,3 - (oxatiolen - 5 - yl) - 1,2 - dihydro (Pyrimidine)					

RESULTS AND DISCUSSION

Based on the findings above using the GCMS, FTIR, Lab IPB Bogor, it can provide an overview and new hope in the future. There are chemical bonds of Herbal Medicine is located at 614 cm⁻¹, 1652 cm⁻¹ (NA Bending), and 3457 cm⁻¹ (OH), in testing with FTIR for Golobe. There is NH (Bonding) in 1562 cm⁻¹ C≡C in 2070 and CH at 3013 cm⁻¹, where NH (Bonding) has

energy activities associated with wet, protective immunity or immunity in improving the human body.

For testing GCMS on herbal ingredients that have a compound piperidinone namely, Golobe, Pangiar, and the Star of the Red Sea, piperidinone is derivate that was used in the case of Middle East respiratory syndrome coronavirus and SARS Cov for the piperidone contained in the three compounds from herbal ingredients is able to inhibit the activity of Virus RNA including COVID - 19.^{3,4,5,6,7,8,9}

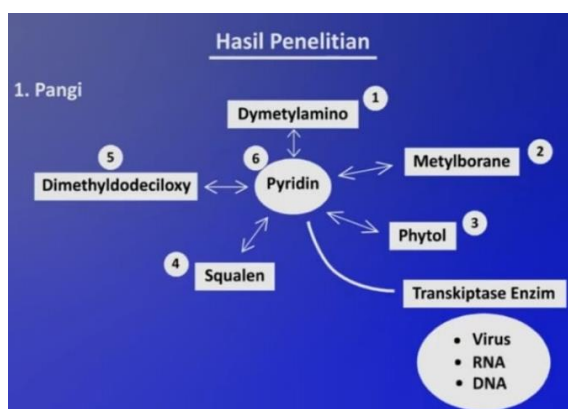


Figure 1. Results Pangi

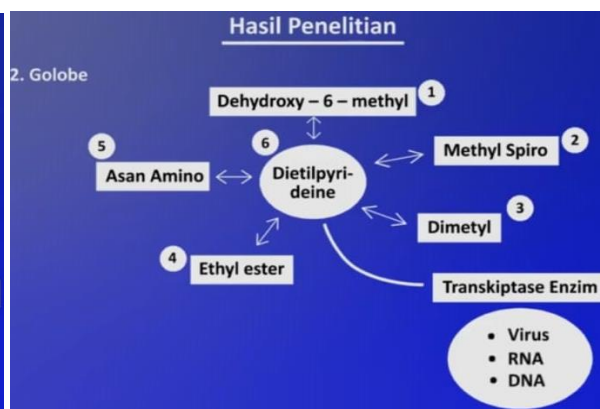


Figure 2. Results Golobe

Results GCMS piperidone at 2.6 Diethylpyridine Golobe ie 5.88%, ie Pangiar hydrobenzopyrozal Tetra-3-yl) - pyridine 2.59% From Red Sea Star has a content of

2 - piperidinone 27.20%. In the literature that piperidone has merit as antiviral RNA, Anti-Mers, Anti Fungus Anti-cancer, Anti-seizure, anti-microbial.

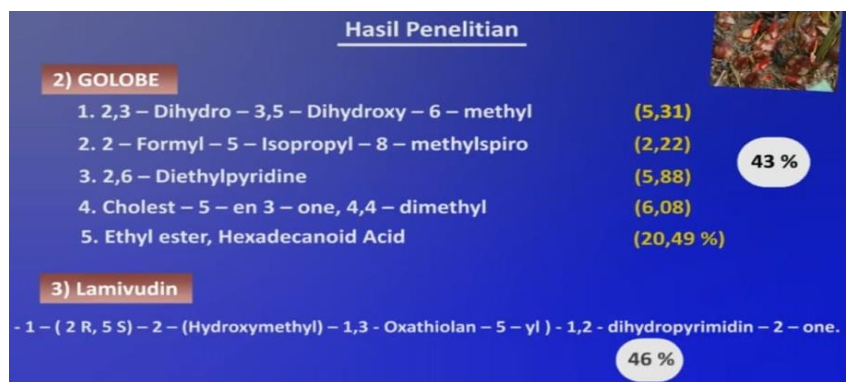


Figure 3. Results The content GCMS compound Golobe

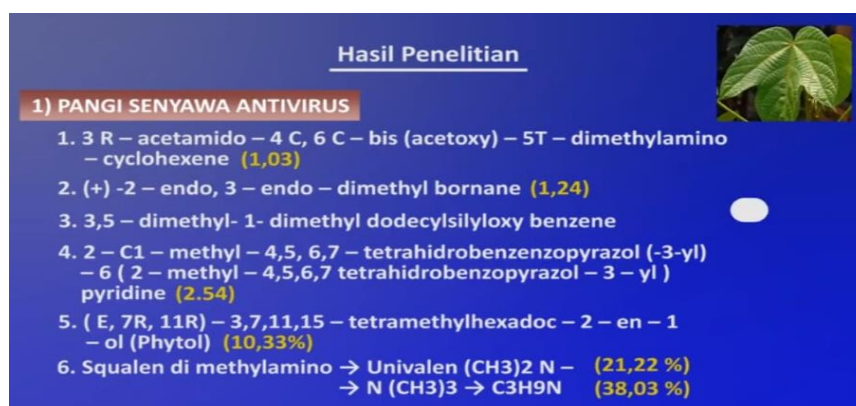


Figure 4. Results The content GCMS compound Pangli

Table 2. Results The content GCMS Compound Red Sea Star (Source: Laboratory of DKI Jakarta)⁷

Compound	Contents
Butanoic Acid, 3-methyl-	(13.64%)
2-piperidone	(27.24%)
2-Hydroxy-3,5,5-trimethyl-cyclohex-2-Enone 28682	(6.79%)
3-ISOBUTHYLHEXAHDROPYPROLO [1,2-a]pyrazine	(1.87%)
hexadecanoic Acid	(8.51%)
9.17-Octadecanienal, (Z) -	(16.47%)
Octadecanoic Acid	(6.23%)
9,12-Octadecadicnoic acid (z, z) -	(5.73%)
(6Z, 9z) -6.9-Pentadecadien-1-OL	(1.95%)
6-Octadecenoic acid	(4.85%).
Hexadecanoic acid, 3-Hydroxy-, methyl ester	(1.06%)
Methyl 3-Hydroxyhexadecanoate	(1.03%)
Cholest -7-EN-3-OL	(3.22%)

In laboratory testing in IPB Bogor by comparing the inhibition of retroviral RNA in the culture medium, the results from the first day up to 7, with a photocell in a comparison between Pangiar, Golobe and Lamivudine prove significant results, which Pangiar have inhibitory at 800 ppm at 94, 80%. While Golobe at 800 ppm,

43.35%, Lamivudine at 100 ppm at 46, 37%. Red Sea Star is still awaiting test results Lab In Vitro (Table 1).

In this study illustrate that Piperidines have good activity within inhibit RNA viruses, such as HIV / AIDS, inhibits the enzyme Transkriptase stage (Figure 5)^{3,4,6,8}

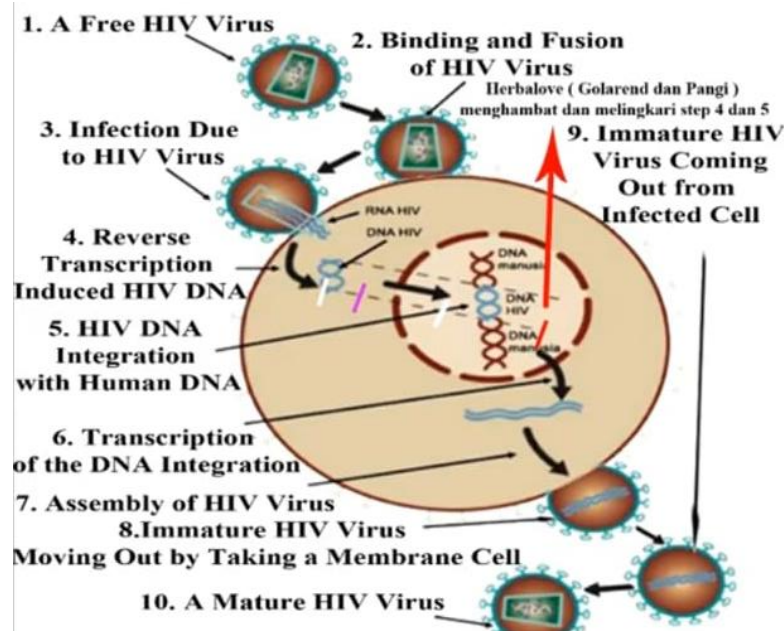


Figure 5. Compounds That Inhibit HIV / AIDS

Piperidine ring for the peptidyl component will result in a new structure capable peptidomimetil orient recognition elements R_3 and R_4 in the correct vector relationships for optimal interaction with inhibitors of dipeptidyl Sate₃ and sate₄ equivalent to tetrapeptidyl inhibitors with potential pK The Reduced (Figure 7).

The chemical formula piperidine has the ability in the case of Mers Corona Virus, SARS and COVID - 19. Need do advanced research-based benefits piperidine Herbs for handling cases of RNA viruses, retroviruses, HIV / AIDS^{2,3,8,9,10}

Hipotesis :

- (1) Cincin piperidin untuk komponen peptidil akan menghasilkan peptidomimetic struktural baru mampu mengorientasikan elemen pengenalan R_3 dan R_4 dalam hubungan vektor yang benar untuk interaksi optimal dengan site S_3 dan S_4 .
- (2) inhibitor dipeptidyl setara dengan inhibitor tetrapeptidyl dengan potensi PK yang berkurang.
- (3) memberikan cara yang fleksibel untuk optimasi paralel yang dipandu struktur ADMET / PK dan sifat fisikokimia menggunakan situs keanekaragaman R_3 dan R_4 dalam inhibitor.

Evolusi desain dan struktur umum inhibitor. Nilai EC_{50} inhibitor GC376 dan GC813 ditentukan terhadap MERS-CoV dalam kultur sel.

Figure 6. Inhibitor Tetrapeptidyl

(Source: Anushka C. Galasiti Kaukanamalage of all, 2018)

Fenetil side chain m-Cl clearly indicated for placing S₄ hydrophobic site. In addition to a bond arrangement - H with Gln 192, Glu 169 and Gln 167 and inhibitors, which serves to meposisi inhibitor properly in the active site, inhibitors interact with the site S₁, S₂ and S₄ but not with S₃.

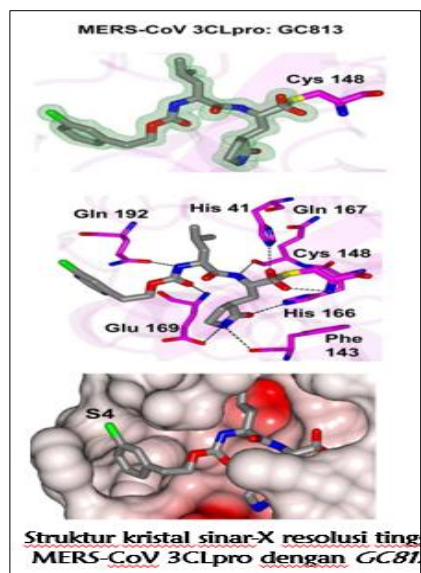
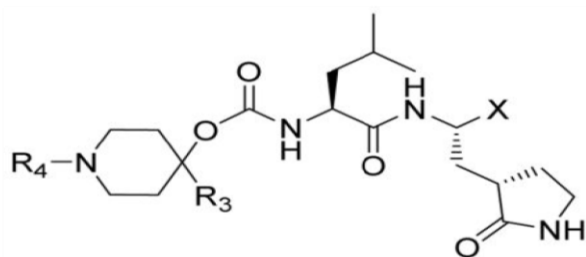


Figure 7. X-ray crystal structure of high-resolution Mers-CoV 3CLpro with GC813
(Source: Anushka C. Galasiti Kaukanamalage of all, 2018)

Anti-coronavirus activity of compounds **9a–f** and **10a–f** in the FRET enzyme assay.



Compound	R ₃	R ₄	X	IC ₅₀ (μM)		
				MERS-CoV	SARS-CoV	FIPV
9a	H	Boc	CHO	0.6	2.1	0.8
10a			CH(OH)SO ₃ Na	0.4	5.1	2.4
9b	H	CH ₃ SO ₂	CHO	0.7	28.8	3.5
10b			CH(OH)SO ₃ Na	0.6	42.1	2.3
9c	(C ₆ H ₅)CH ₂	Boc	CHO	0.8	5.2	1.6
10c			CH(OH)SO ₃ Na	0.7	6.3	2.1
9d	H	CH ₃ SO ₂	CHO	0.7	3.9	0.8
10d			CH(OH)SO ₃ Na	0.9	4.3	1.1
9e	CH ₃ CH ₂	Boc	CHO	6.1	5.5	5.5
10e			CH(OH)SO ₃ Na	7.5	4.1	6.7
9f	H	CH ₃ CH ₂ O(CO)	CHO	0.6	3.2	1.3
10f			CH(OH)SO ₃ Na	0.5	8.8	1.1

Table 3. The inhibitory activity of compounds synthesized against 3CLpro Middle East respiratory syndrome coronavirus, SARS-CoV and anti-viral activity of two representative compounds (compounds 10a and 10c)
(Source: Anushka C. Galasiti Kaukanamalage of all, 2018)

CONCLUSION

The research looked natural herbal ingredients such Halmahera Golobe (Zingiberaceae), Pangi

(Pangiar), star of the Red Sea, which has a compound piperidinone which has been used as an antidote to the virus RNA, Retrovirus RNA, retroviruses like HIV / AIDS, hepatitis, Middle East respiratory syndrome

coronavirus, SARS Cov and Sars Cov - 2 (COVID - 19). Further research is needed on clinical Trials (In-vitro) in patients with pandemic COVID - 19.

Commitment

Many thanks to the laboratory IPB, LIPI Chemistry, Laboratory of Jakarta, Yayasan Medika Mandiri Halmahera, Department of Pharmacy College of Health Sciences Makariwo Halmahera (STIKMAH) Tobelo. Until recently, did not have problems with anyone.

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