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## **The Effectiveness of Extract Snack Head Fish and Virgin Coconut Oil (VCO) on Sputum Conversion and Levels of Interferon- $\gamma$ in Patients with Pulmonary TB Multi Drug Resistant (MDR) in Labuang Baji Hospital Makassar**

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### **Abstract**

Treatment of pulmonary MDR TB disease is relatively very expensive and takes a long time to heal, This study aims to determine the effect of treatment DOTS-Plus capsules supplemented catfish albumin protein coupled VCO can affect the conversion of sputum smear and levels of interferon- $\gamma$  in pulmonary MDR TB patients who received treatment DOTS-Plus in Labuang Baji Hospital, Makassar. This study is a quantitative study with randomized controlled quasi-experimental approach with a sample size of 30 people (15 experimental, 15 control). Data analysis was done using the Independent Sample T Test with a confidence level of 95%. All the data were Analyzed by SPSS software, version 21.0 (SPSS, Inc., Chicago, IL).

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All the groups in which I no conversion. The intervention began in the second conversion of 80% and all had more conversions in III. Control in II started there is a conversion of 53.3% and until VI there are still 3.3% which is not convertible. The average levels of interferon gamma first month (intervention:  $153.26 \pm 27.19$ ; control  $150.60 \pm 29.55$ ), three month (intervention:  $179.00 \pm 48.89$ ; control:  $140.46 \pm 20, 03$ ) . Sixth months (intervention:  $152.00 \pm 70.74$ ; Controls:  $150.93 \pm 18.65$ ). The results showed pulmonary MDR TB patients receive treatment DOTS Plus capsules albumin supplemented catfish coupled VCO accelerate the conversion of sputum ( $p = 0.038$ ) and improve the levels of interferon- $\gamma$  ( $p = 0.011$ ). In conclusion, MDR pulmonary tuberculosis patients received treatment DOTS Plus capsules albumin supplemented catfish plus VCO will accelerate the conversion of sputum, improve levels of interferon- $\gamma$ . By him that, to be considered for albumin supplementation capsules catfish coupled VCO in the treatment of pulmonary tuberculosis.

**Keywords:** MDR Pulmonary TB; VCO; cork fish albumin capsule; albumin; interferon gamma.

## **1. Introduction**

In 2013, the World Health Organization (WHO), reported that pulmonary TB disease remains a global health problem. Globally averaged around 9.0% of patients with pulmonary MDR TB. Advances in the detection of pulmonary TB that is resistant to OAT has been facilitated by the use of new rapid diagnostics, gene-X pert it is estimated that 300,000 cases of pulmonary MDR TB to be detected [1]. In Indonesia, there are 97,000 new cases of pulmonary TB patients were receiving anti-TB in 2013 with a treatment success rate of 48% [2]. According to WHO, the cost of the treatment per patient for pulmonary MDR TB in low-income countries on average US \$ 9,235 and US \$ 48,553 in the middle-income countries to above (WHO, 2014). The goal of treatment of pulmonary MDR TB is to cure, maintaining quality of life, prevent death, prevent recurrence, prevent transmission, and prevent the occurrence of XDR-TB [3,4].

WHO recommends treatment for the duration of the intensive phase of 7 to 8.5 months from a total of 20 months of treatment. To determine the response to treatment is required as culture and sensitivity test every 2 months of treatment and sputum examination is conducted every month during the intensive. In the continuation phase, sputum smear examination performed every two months. Free time to sputum smear conversion in pulmonary MDR TB patients are affected by age, gender, treatment compliance, nutritional status, nutrition balanced, their co-morbidities, smoking habits, sleep habits, and knowledge about the disease tuberculosis [5]. A study also reported THAT elderly poor nutrition lead to T-cell function is not optimal and it affects the severity of TB disease [6].

Prasad and his colleagues (2012) reported treatment with DOTS-PLUS strategy for the treatment of pulmonary MDR TB. The result shows the cure rates (cure rate) of 92.5%, with sputum smear conversion time ( $3.4 \pm 2.1$  months) for pulmonary TB and MDR cure rate of 87.7%, with sputum smear conversion time of  $4.6 \pm 2, 5$  months for pulmonary tuberculosis XDR. While on a study conducted in Hong Kong, which uses a combination of four or more OAT (second-line drugs), reported that the success rate of treatment, 69.3% (187 patients) with an average time of conversion  $\pm 3$  months. [7]. The nutritional status of patients with pulmonary tuberculosis TB is one of the major risk factors sputum smear conversion failed on treatment with a less risky strategy

Nutritional DOTS. Status conversion failure 8.9 times greater than the normal nutritional status and poor nutritional status at risk of conversion failure 30.9 times greater than the normal nutritional status [7].

A person's nutritional status, influence susceptibility to infectious disease including pulmonary tuberculosis [8]. IFN- $\gamma$  levels in the blood serum of patients with pulmonary tuberculosis decreased statistically significantly, one of the causes of malnutrition [9]. One factor in the inability to produce innate immunity (innate immunity) and acquired immunity (acquired immunity) in patients with pulmonary TB as substances of macro and micronutrients are lacking. Supplementation substances macro and micronutrients such as albumin catfish (Common Snake Head Fish Extract) rich in protein albumin, acid-essential amino acids, vitamins and minerals or Virgin Coconut Oil (VCO) is classified as medium chain fatty acids (MCFA) containing ingredients Glycerol monolaurate (GML) can improve the efficacy of treatment of TB patients [10,11].

Albumin and VCO reported to have antimicrobial effects strong, according to [12], is antinoceptive, and anti-inflammatory [13] and can improve appetite and weight gain pulmonary TB patients with cachexia [14]. A study in patients with pulmonary TB-DOTS treatment MDT albumin supplemented catfish and virgin coconut oil (VCO) reported an average time of 2.5 weeks BTA sputum conversion [15].

## **2. Materials and Methods**

### **2.1. Design**

Quantitative research with quasy experimental randomized control approach. The intervention group received 500mg albumin catfish, 3 x 2 capsules per day for 2 months with VCO 10 mg capsules, 3x2 capsules per day for two months. The control group was given a capsule with a shape similar to the capsule albumin and VCO and contains sugar.

### **2.2. Sampling**

The research subjects who meet the inclusion and exclusion criteria. Subjects were divided into two groups: one that received the supplement (cases) and group 2 who received placebo (control). The sample selection based on day of the visit when recruited. Patients were recruited on Monday, Wednesday, Friday included in the case group and on Tuesday, Thursday, included in the control group.

The Inclusion criteria limits for Patients diagnosed with pulmonary TB MDR <1 month, Based in the city of Makassar, Age of TB patients 18-50 years old and Signed consent to participate in research. Whereas the exclusion criteria Average disease: Pleural effusion, COPD, severe pneumonia, chronic asthma, Broncho pneumoni weight, diabetes and HIV-AIDS. In addition, research instrument such as a). Levels of serum IFN- $\gamma$  TB patients examined with the analytical techniques Enzyme Linked Immuno sorbent Assay (ELISA) Kit in the research laboratories of the medical Hospital Faculty of Medicine, Hasanuddin University. Examination carried out on all research subjects for 3 times (at the beginning, in the third and sixth month of the study). b). BTA sputum conversion time is the time required for a change of sputum smear positive to smear negative sputum. Smear positive, if at least two of three specimens of sputum smear positive result SPS or 1 sputum specimen

SPS smear positive result and chest X-ray shows a picture of tuberculosis or one specimen SPS results are smear positive and culture-positive TB germs. BTA negative, if the SPS 3 sputum specimens negative smear result. c.) Examination of sputum smear sample using Ziehl Neelsen method, which is conducted each month for 6 months in the laboratory Labuang Baji hospital, Makassar. How the study was done.

### ***2.3 Research Ethics***

Permit implementation of the study was obtained from the Ethics Committee FK UH Makassar. After that, the researcher explained to the respondent about the objectives, the benefits of research and data collection procedures. Researcher asked respondents signed informed consent as an endorsement willing to become respondents.

### ***2.4 Data Analysis***

The statistical test used is Independent Sample T Test with a confidence level of 95% and the value of  $\alpha \leq 0:05$ . All data were analyzed using SPSS version 21.0 (SPSS, Inc., Chicago, IL).

## **3. Results**

In this study, potential respondents prior examination of Gen-X Pert to determine pulmonary TB is resistant to treatment or not. Furthermore, patients who agreed to sign an agreement respondent. Then the respondents were divided into two groups: the intervention group and the control group. Furthermore, given appropriate intervention group and was observed up to 6 months.

In the study period, there were some respondents who drop out as many as 67 people due to: drug withdrawal Please make more information why people withdrawal from the study (34), move the domicile (28), and died (5), so that the remaining 30 respondents who completed until the sixth month study period.

### ***3.1 Demographic characteristics***

Of the 30 samples of this study indicate that there are no differences between the intervention group and control group according to age ( $p = 0.505$ ), gender ( $p = 0.501$ ), and employment ( $p = 0.705$ ) (Table 1).

### ***3.2 OAT resistant type of intervention and control groups***

### ***3.3 Sputum smear conversion***

All groups in there that I have not conversed treated. The group of intervention DOTS Plus albumin supplemented catfish coupled VCO, began the conversion in the second by 80% and all had more conversions in III.

Different results of the control group were treated with DOTS Plus supplemented placebo, in II started there were only 53.3% conversion and until VI there are still 3.3% which is not convertible (Table 3).

**Table 1:** Respondent Characteristics

Characteristics	Group						p*
	Intervention		control		Total		
	n (15)	%	n (15)	%	n (30)	%	
Age							
18-45 year	9	60,0	6	40,0	15	50,0	0,505
46- 65 year	6	40,0	9	60,0	15	50,0	
Sex							
Male	7	46,7	10	66,7	17	56,7	0,501
Female	8	53,3	5	33,3	13	43,3	
Occupation							
Civil servant	5	33,3	6	40,0	11	36,7	0,705
Non Civil servant	10	66,7	9	60,0	19	63,3	

\* Chi square Test

**Table 2:** OAT resistant type of intervention and control groups

No	OAT group	Cases number	
		Intervention group	Control group
1	Isoniazid (H) +	12 Cases	13 Cases
	Rifampisin (R)		
2	Isoniazid (H)+	1 Cases	1 Cases
	Etambutol (E)		
3	Isoniazid (H) +Rifampisin (R)+	2 Cases	1 Cases
	Etambutol (E)		

**Table 3:** Sputum BTA Conversion

Sputum	Group					
	Intervention		control		Total	
	n (15)	%	n (15)	%	n (30)	%
<b>Pre Test</b>						
Positive	15	100,0	15	100,0	30	100,0
Negative	0	0,0	0	0,0	0	0,0
<b>Month I</b>						
Positive	15	100,0	15	100,0	30	100,0
Negative	0	0,0	0	0,0	0	0,0
<b>Month II</b>						
Positive	3	20,0	7	46,7	10	33,3
Negative	12	80,0	8	53,3	20	66,7
<b>Month III</b>						
Positive	0	0,0	5	33,3	5	16,7
Negative	15	100,0	10	66,7	25	83,3
<b>Month IV</b>						
Positive	0	0,0	3	20,0	3	10,0
Negative	15	100,	12	80,0	27	90,0
<b>Month V</b>						
Positive	0	0,0	2	13,3	2	6,7
Negative	15	100,	13	86,7	28	93,3
<b>Month VI</b>						
Positive	0	0,0	1	6,7	1	3,3
Negative	15	100,	14	93,3	29	96,7

The average month sputum conversion BTA intervention group (mean 2.20 with SD 0.414), while the control group (mean 3.20 with SD 1.656). Rata The average difference between the intervention group with the control (Mean - 1,000 with SE 0.441). from the statistical result the average difference in sputum smear conversion between the intervention group and control group  $p = 0.038$  ( $p < 0.5$ ), meaning that patients with pulmonary MDR TB DOTS plus treatment supplemented with albumin catfish plus VCO can accelerate time to sputum conversion BTA patients (Table 4).

**Table 4:** The time average of BTA sputum conversion

Group	n	Sputum conversion (month )		Different		p*
		Mean	SD	Mean	SE	
Control Intervention	15	2,20	0,414	-1,000	0,441	<b>0,038</b>
	15	3,20	1,656			

\* T Test Independent Sample

### 3.4. Levels of interferon- $\gamma$

Average levels of interferon gamma differences between the intervention group than the control group almost the same (Mean SE 3.20 to 10.37), the results of the statistical test obtained by value  $p = 0.760$  ( $p > 0.5$ ) is not meaningful showed no difference significant levels of interferon gamma in the intervention group compared to the control group average. The different changes in levels of interferon gamma test results in the third month of the intervention group than the control group (mean SE 38.53 to 13.64), the statistical test obtained by value  $p = 0,011$  ( $p < 0.5$ ), meaning that patients with pulmonary MDR TB DOTS plus treatment supplemented with albumin catfish coupled VCO increases levels of interferon the gamma after albumin supplementation catfish coupled VCO at patients. However, difference in mean change between the levels of interferon gamma intervention sixth month compared to the control group (mean SE 1.06 to 18.88), the statistical test obtained by value  $p = 0.955$  ( $p > 0.5$ ), meaning that there is no significant difference in mean change levels of interferon gamma in the intervention group decreased compared to the control group increased (Table 5) (Figure 3).

## 4. Discussion

Results of statistical test indicated the average difference in sputum smear conversion between the intervention group and control group  $p = 0.038$  ( $p < 0.5$ ), meaning that patients with pulmonary MDR TB DOTS Plus treatment supplemented with albumin catfish plus VCO can accelerate time to sputum conversion the patient with BTA. Treatment with DOTS-PLUS strategy for the treatment of pulmonary MDR TB, the results obtained cure rates (cure rate) of 92.5%, with sputum smear conversion time ( $3.4 \pm 2.1$  months ). While the results of studies conducted in Hong Kong, which uses a combination of four or more OAT (second-line drugs), reported that the success rate of treatment, 69, 3% (in 187 patients) with an average time of conversion  $\pm 3$  months [7].

**Table 5:** Average different of gamma interferon between intervention and control groups

Time	Interferon Gamma		different		p*
	Mean	SD	Mean	SE	
Pre Test					
Intervention	153,26	27,19	3,20	10,37	0,760
Control	150,06	29,55			
Month III					
Intervention	179,00	48,89	38,53	13,64	<b>0,011</b>
Control	140,46	20,03			
Month VI					
Intervention	152,00	70,74	1,06	18,88	0,955
Control	150,93	18,65			

\* T Test Independent Sample

Supplementation albumin catfish accelerate the conversion of sputum smear in patients with pulmonary tuberculosis MDR treatment DOTS Plus, because albumin catfish contains amino acids essential such as: acid aspartate, acid glutamate, serine, glycine, histidine, arginine, threonine, alanine, proline, tyrosine, valine, methionine, systin, isoleucine, leucine, alanine and lysin. Selain phenil it also contains the minerals calcium, magnesium, iron, copper, zinc, manganese, Nikkel, cobalt, selenium, phosphorus and vitamins A, C, D, E and B complex, especially vitamin B12 [11]. The content of amino acid lysine, arginine and glutamate acid albumin catfish increase cytokine levels to stimulate CD4 + Th1 lymphocytes produce IFN- $\gamma$  to activate macrophages [16,17]. Refer to the research Green and his colleagues (2000) that the cytokine CD4 + cells are essential to stimulate helper 1 (Th1) produce IFN- $\gamma$  by activating the macrophages alveolar. Study supported by results [17], that the alveolar macrophages can stimulate CD4 + T lymphocytes active pulmonary tuberculosis patients to stimulate Th1 produce IFN- $\gamma$ . similar study from Hanekom and Hussey show, that the content of macro nutrients such as protein albumin and amino acids and micronutrients such as vitamin A and zinc albumin catfish stimulate Th1 lymphocytes produce IFN- $\gamma$  on lung. Research of TB mentioned above are supported by the results of research McMurray [18], that vitamin A, zinc and vitamin D enhances the effect of anti-tuberculosis drugs (OAT) after 2 months of treatment and accelerate the conversion of sputum BTA. Giving of vitamin A, B complex, C, E and selenium dose of 6-10 tablets per day for 1 month increases cytokine CD4 +, and reduce the risk of extra-pulmonary TB [19].

Supplementation of VCO accelerates the conversion of sputum smear in patients with pulmonary tuberculosis



MDR treatment DOTS Plus, because the VCO contain a proportion of saturated fatty acid chain is in the form of Glycerol monolaurate or "monolaurin", which has the effect of chemical and biological anti-microbial strong kill germs pulmonary tuberculosis by penetrating the membranes and synthesis and inhibit reproduction and replication TB germs [20]. Rotor [12] conducted in vitro on pulmonary TB germs by Glycerol monolaurate will change so that no cleavage morphology sel. Supplement of VCO is proven to help increase the killing power Mycobacterium TB Dalmacion, [21] the results of the study Endaryanto and his colleagues (1996) that the VCO improve the activity of hormone receptors and increases the sensitivity of actively encouraging response to the balance of Th1 to Th2 producing IFN- $\gamma$ . Giving of VCO in mice reported to increase the percentage of lymphocytes result leukocyte differentiation which normalizes the levels of basophils and neutrophils [22]. VCO administration improve oral lesions in HIV-AIDS because it stimulates the formation of The 1 cells to boost the immune system [23].

Patients with pulmonary MDR TB DOTS Plus treatment supplemented with albumin catfish plus VCO can accelerate time to sputum smear conversion patients, compared to only DOTS Plus treatment supplemented placebo. Study experiment Malle [24] in Makassar BBPKM that gave the capsule albumin (protein catfish) for 60 days in patients with pulmonary TB can accelerate the conversion of sputum smear. Research by Arifin, M in Makassar BBKPM that gave capsules of fish cork coupled VCO albumin in patients with pulmonary TB-DOTS received MDT treatment can accelerate the conversion of sputum smear his.

#### **The levels of interferon gamma (IFN- $\gamma$ )**

According to Pottumarthy and Bellete [25] showed the sensitivity of IFN- $\gamma$  examination for the diagnosis of TB by 58-79%. Changes in levels of interferon gamma pulmonary MDR TB patients receive treatment DOTS Plus albumin supplemented catfish coupled VCO, were compared with DOTS Plus treatment plus placebo was evaluated three times, namely; The first month (baseline), the third and in the sixth month (end of study).

There is no difference in the levels of interferon gamma value in the first month (baseline), between the intervention group than the control group (Mean SE 3.20 to 10.37), the results of the statistical test obtained by value  $p = 0.760$  ( $p > 0.5$ ) is not meaning that showed no significant difference between the levels of interferon gamma intervention group than in the comparison control group. In the third month intervention group than the control group (Mean SE 38.53 to 13.64), the statistical test obtained by value  $p = 0.011$  ( $p < 0.05$ ), meaning that patients with pulmonary MDR TB DOTS plus treatment supplemented with albumin catfish coupled VCO increases levels of interferon the gamma after albumin supplementation catfish coupled VCO at the patient. However, differences in average levels of interferon gamma in the intervention group than the control group yesterday sixth (mean SE 1.06 to 18.88), the statistical test obtained by value  $p = 0.955$  ( $p > 0.5$ ), meaning that there was no significant difference in the average decreasing levels of interferon gamma in the intervention group than the control group at the end research (the sixth month).

The results of this study, the third month of pulmonary MDR TB patient who was treated with DOTS Plus albumin supplemented catfish coupled VCO increases levels of interferon the gamma, after albumin supplementation catfish plus VCO for 2 months. However, sixth month either the intervention group or the

control group fell levels of interferon Gamma (IFN- $\gamma$ ) in blood serum. This is due to the body is not producing cytokines IFN- $\gamma$  against pulmonary TB germs in the body of the patient (after being treated for 6 months) because the patient had the same cured. Results of research Wen-Lin S and Wann -Cheng [26] and Su [27] levels of IFN- $\gamma$  blood serum of pulmonary tuberculosis patients before and after receiving treatment OAT (program DOTS) for 6 months significantly the value obtained significantly decreased levels of IFN- $\gamma$  end treatment. Study by Widjaja [28] found levels of IFN- $\gamma$  blood serum of healthy people (not suffering from pulmonary TB) is lower than the levels of IFN-TB patient's blood serum  $\gamma$  lung. It can also decreased levels of interferon gamma, particularly in the intervention group due to the suppression of the cellular immune system patients with pulmonary TB infection characterized by decreasing levels of interferon gamma (IFN- $\gamma$ ) in the blood serum [29].

## **5. Conclusion**

Pulmonary tuberculosis patients received treatment DOTS Plus supplemented capsule albumin catfish coupled VCO, can have speed healing time and shorten the treatment period, evidenced from the results of this study, namely: accelerating the conversion of sputum smear and increases levels of interferon gamma (IFN- $\gamma$ ) on the third month after the administration of albumin capsules 2 months with catfish coupled VCO.

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