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RESEARCH ARTICLE

FORMULATION OF COMBINATION OF WULUH STARFRUIT GEL EXTRACT (*AVERRHOA BILIMBI.L*) AND PAPAYA LEAF EXTRACT (*CARICA PAPAYA*) AS ANTIBACTERIACAUSES OF ACNE

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ABSTRACT

Acne sufferers sometimes hate themselves, away from interpersonal relationships. This disease is triggered by the bacteria Propionilbacterium acne, and Staphylococcus aureus. Various acne treatments are offered in the community, but not all acne drug products are guaranteed safe. The purpose of this study was to obtain an acne gel preparation, a combination of extracts of star fruit and papaya leaves which have antibacterial activity against Streptococcus aureus and Propionibacterium acnes To determine the compounds that have antibacterial activity, bioautography using GCMS analysis was carried out. The preparation was made by mixing carbophol 940, triethanolamine, methyl paraben, propylene glycol, sodium metabisulfite. The results of the evaluation of the preparation at room temperature storage did not experience significant changes and were relatively stable, while at hot and cold temperatures there was a slight change in pH, dispersion, viscosity and flow properties. Peaks include 1,3-Diacetoxy-butane, 1-Pentanamine, Pentadecanoic acid, 9-Octadecenoic acid, and 1,2-Benzenedicarboxylic acid.Formula 3 has almost the same stability as formula 1 and formula 2. Formula 3 has room temperature storage for 3 months, including: organoleptic preparations dark brown in color, slightly entangled homogeneous, pH 5.11 preparations, spreadability of preparations 2628.01 mm² viscosity of preparations 79666, 67-258333,33 cPs flow properties 184466,33- 286282,17 cPs, the results of the antibacterial activity showed the Inhibitory Diameter (RD) on P acnes 14,56±0,1131 mm and S aureus 15,18±0, 0424mm . The formula was non-irritating to test animals.

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INTRODUCTION

Healthy facial skin is synonymous with smooth facial skin free from skin problems such as acne.[1] Acne is a disease that occurs due to blockage in pilosebaceous which is characterized by the presence of blackheads, papules, pastels and scars on the face, neck, upper arms, chest and back. The disease is triggered by the bacteria *Propionibacterium acnes* and *Staphylococcus aureus*. These Gram-positive bacteria live in fatty acid areas in the sebaceous gland pockets, in the oil glands (sebum) hidden in the pores of the skin, those bacteria produce propionic acid which cause inflammation in acne.[2] When the skin pores are closed, these anaerobic bacteria grow rapidly and release a lot of chemicals that can damage the tissue in the skin pores which later form acne lesions. *Propionibacterium acnes* and *Staphylococcus aureus* release a type of irritant that will irritate the skin, which later cause the skin to redden and swell. Moreover, it also causes pus under the skin's surface, all of these effects are a form of resistance by the body's immune system to neutralize irritants produced by bacteria and repair irritated skin tissue.[3-4]Although acne is not a fatal disease, mild acne is often considered a physiological disease, and may botheringbecause it can reduce appearance and self-confidence. A study shows that acne can have a very negative impact on social interactions for sufferers. Acne sufferers sometimes hate themselves, withdrawn, and distant from interpersonal relationships. [5] Various types of acne treatment in the community, with various advantages of each. However, not all acne drug products offered are guaranteed safety. Several cosmetic products, including quite well-known ones, were withdrawn from circulation by the POM. An action that is full of caution against the presence of these compounds in cosmetics which are feared can cause health risks to consumers. Hazardous compounds found in cosmetics include retinoic acid and other synthetic materials. Retinoic acid can cause dry skin, burning sensation, teratogenic (defects in the fetus). The use of various chemicals contained in acne medications can actually make acne worse or cause unwanted scars, such as severe scarring.[5]

The concept of back to nature or back to nature is a form of treatment using natural ingredients that we hear more and more often in recent years. The use of natural ingredients is preferred because it is believed to have fewer side effects than treatment using synthetic materials.[5]Many plants that have anti-acne properties include papaya (Carica papaya L.) and starfruit (Averrhoa bilimbi L.). These two types of plants are plants that are easily available and known in Indonesia. Papaya leaves contain papain enzyme compounds, karpain alkaloids, karikasantin, violaksantin, flavonoids. The antioxidant content of papaya leaves, namely secondary metabolites such as alkaloids or saponins which are dominantly giving a bitter taste to papaya leaves which act as antioxidants, antibacterial, anticancer, and anti-inflammatory.[6] Papain has an exfoliating ability that works on the sebaceous glands (where sebum is produced), which removes dead skin cells and helps the growth of new skin cells, so that facial skin will be cleaner, whiter and glowing. and pectin. Flavonoid compounds are suspected as active anti-bacterial compounds contained in star fruit wuluh. 7 Starfruit extract combined with papaya leaf extract was used as an active substance in this study with the aim of getting a synergistic work as an anti-acne-causing bacteria. However, the synergistic action of this combination of extracts has not been studied. The gel form was chosen because this preparation is suitable for topical use, besides that the clear and elegant gel preparation is made as an anti-acne preparation. easy to use, absorbent and easy to clean with water. In addition, the ability to spread well, gives a cooling effect (slow evaporation from the skin). The gel was chosen because it does not contain oil so it will not aggravate acne, is clear, easily dries to form a film that is easy to wash, also the gel dosage form is suitable for topical therapy on acne, especially patients with oily skin types.. [8]This study aims to utilize wuluh starfruit (Averrhoa bilimbi L.) and papaya leaves (Carica papaya L.) into gel preparations as an antibacterial that causes acne.8

MATERIALS AND METHODS

Wuluh starfruit (Averrhoa bilimbi L.), papaya leaf (Cacarica papaya L), Carbophol 940 (Brataco), Triaethanolamine (Brataco), Propylene glycol (Brataco), Methyl paraben (Brataco), Sodium metabisulfite (Brataco), Aquadest, Reagent – reagents for phytochemical screening The test bacteria used in this study were Propionibacterium acnes and Staphylococcus aureus cultures from the Microbiology Laboratory, Faculty of Medicine, University of Indonesia.

Methods

Identification of Wuluh Starfruit and Papaya Leaf Plants and Fruits: Plant determination was carried out at the Herbarium Bogoriense, LIPI Biology Research Center, Bogor, West Java. The simplicia of star fruit wuluh as much as 2 kg and 1 kg of papaya leaf simplesia, the thick extract obtained was weighed and compared with the weight of the initial sample. The ratio in percent represents the yield value of the extract. The size of the yield value shows the effectiveness of the extraction process. The extraction of star fruit and papaya leaves was made by maceration with 96% ethanol as solvent. Then it is rotated at 40°C

Extract Characteristics and Quality Check: Examination of the characteristics and quality of the extract included: organoleptic examination, pH examination, identification of flavonoids, tannins, saponins, alkaloids, phenols, essential oils and antibacterial activity tests.

Antibacterial Test: In this study, Nutrient Agar media was used to show optimal results on bacteria, so it was easy to observe because NA media was a general medium and was not selective.[9] The agar diffusion test method was used to determine the anti-bacterial activity that causes acne. The test microbes were mixed with 15–20 ml of Nutrient agar media and poured into a Petri dish and 100 ul of each bacterium was added to form an agar plate. In the agar plate, holes are drilled to form a well area. Each well was inputted with an extract concentration of 20 ul. After the incubation process, the diameter of the inhibition was measured in the form of a clear zone around the well area which indicated the inhibition of microbial growth. According to Wibowo, the method of measuring the inhibition zone is done by measuring in a straight line the center of the inhibition zone or measured from the right edge to the left edge of the inhibition zone formed.According to Davis and Stout in a study conducted by Mercy Ngajow et al, it was stated that the antibacterial power was categorized based on the classification.

Bioautography Test Combination of Wuluh Starfruit Extract and Papaya Leaf Extract: Bioautography test is a detection method to find an antimicrobial compound that has not been identified by localizing the antimicrobial activity on a chromatogram. This method utilizes the Thin Layer Chromatography (TLC) method. First, determine the appropriate eluent so that the spot results from the elution on the Thin Layer Chromatography (TLC) silica plate are separated according to their polarity. This bioautography test was carried out with a 20µl of 20µl silica gel TLC plate with a capillary tube at the center of the lower boundary line of the TLC plate, which was placed in a saturated vessel. Various preliminary eluent comparison tests were carried out, and it was found that (ethyl acetate) 2: 8 (Toluene) is the best eluent because it can separate compounds, so the eluent is used for bioautography tests. Observations in appendix 37 for the presence of spots using the appearance of spots on UV light 254 nm and 366 nm mark the spots that appear Rf 2.5/6 and Rf 4/6. The TLC plate measuring 3 x 8 cm with visible spots was planted on nutrient agar which had solidified in a petri dish that had been planted with bacteria. The TLC plate was attached for 30 minutes by marking the position of the spot on the bottom of the petri. Lift and remove the TLC plate from the surface of the agar inocula (Incubate the petri dish from the plate that has been removed for 24 hours at a temperature of 35-37 0C). The presence of a clear zone on the petri dish marked the spot area on the TLC plate showing Rf 4/6. The spots at Rf 4/6 contain compounds that act as antimicrobials. The silica gel on the TLC plate at Rf 4/6 was scraped off and extracted with ethyl acetate, then analyzed by GCMS.

RESULTS

Characteristic examination of the thick extract of star fruit and papaya leaf extract: The organoleptic test in this study aims to observe any important changes in the application of the quality of pharmaceutical preparations. The results of the organoleptic test can be seen in Table 1. The results of the physical characteristics test for star fruit extract and papaya leaf extract both have almost the same extract, namely blackish brown.

Both extracts mix well when dissolved in propylene glycol. The specific gravity of the extracts was close to the specific gravity of water, namely .0.983 and 0.967, close to 1.00 this indicates that the two extracts have a fairly good concentration, the pH of the two extracts tends to be acidic, especially starfruit because of the high content of acidic compounds. The results of the two extracts in the examination of water content tend to be higher, namely 35.25% and 31.31%. This result is not in accordance with the requirement that the water content of the extract is not more than 10%.[10]It can be possible when simplicia drying is less than optimal. It is very possible in this study that the wrong drying method can result in "Face hardening", ie the outside of the material is dry while the inside is still wet. This can be caused by a slice of simplicia material that is too thick, the drying temperature is too high, or by some other condition that causes evaporation of surface water of the material much faster than the diffusion of water from the inside to the surface, so that the surface of the material becomes hard and inhibits further drying. , so that high water content can be a good medium for fungal growth and trigger enzymatic reactions in the extract which can cause the chemical content in the extract to be degraded.[9], This shows that the simplicia used in the manufacture of extracts after the drying process has poor quality, because the enzymatic reactions that occur in the simplicia can cause the simplicia to be damaged. Damage to the extract can be prevented in storage at low temperatures in the refrigerator, with low temperatures inhibiting microbial activity and the extract remains in good condition.

The ash content showed that the metal ions in the simplicia were 2.34% and 8.05%. The determination of the ash content was also intended to control the amount of pollutant organic matter such as soil, sand which is often included in the preparation. Ash content is insoluble in star fruit extract. wuluh ie 0.23% and papaya leaf extract 0.31%, indicating that the ash content of the wuluh star fruit is not acid soluble in accordance with the requirements of the herbal pharmacofee, which is not more than 0.3%. While the papaya leaf extract slightly exceeds that required by the herbal pharmaco. These two extracts signify the quality and purity of herbal medicine.[10] The water soluble extract content and the alcohol soluble extract content showed that the extract contained polar organic compounds (soluble in water and ethanol). The content of organic matter from secondary metabolites contained in plants is a chemical identity and specific characteristics of plants related to the pharmacological effects that are caused, because the secondary metabolites produced by plants have characteristics for each genus, species and certain varieties. The data obtained in the table shows that the extract contains flavanoid compounds, tannins, saphonins, alkaloids and phenols.

Anti-Bacterial Activity Test on Publimum Fruit Extracts and Papaya Leaf Extract Against *Propionibacterium acnes*and *Staphylococcus aureus:* In this study, Nutrient Agar media was used to show optimal results on bacteria, so it was easy to observe because NA media was a general medium and was not selective. [11]The agar diffusion test method was used to determine the anti-bacterial activity that causes acne. The test microbes were mixed with 15-20 ml of Nutrient agar medium, poured into a Petri dish and 100 ul of each bacteria were added to form an agar plate. In the agar plate, holes are drilled to form a well area. Each well was inputted with an extract concentration of 20 ul. After the incubation process, the diameter of the inhibition was measured in the form of a clear zone around the well area which indicated the inhibition of microbial growth. Menurut Wibowo[12]how to measure the inhibition zone is done by measuring a straight line in the middle of the inhibition zone or measured from the right edge to the left edge of the inhibition zone formed.According to Davis and Stout in research conducted by Mercy Ngajow dkk[13]mentions that the antibacterial power is categorized based on the classification. From the test of the diameter of the inhibition zone with the well method, the results are shown in table 2. In papaya leaf extract with a concentration of 50 mg in 5 mL (100%) with dilutions as extract concentrations of 25%, 50%, and 100%, obtained with a concentration of 25% extract of papaya leaf extract against Propionibacterium cnes bacteria has an inhibition zone of weak category that is equal to 3.30±0.14. Strong categories for concentrations of 50% and 100%. Likewise, the RD test as seen in the table, both tests on P acne and S aureus with papaya leaf extract concentrations gave almost the same inhibitory power from each concentration. The blank does not show a clear zone, so the clear zone formed is the influence of papaya leaf extract. This result is supported by the statement of Prawata and Dewi [14]that the effectiveness of an antibacterial substance is influenced by the concentration of the substance. The increase in the concentration of substances causes an increase in the content of active compounds that function as antibacterials, so that their ability to kill bacteria is also greater.

Based on research conducted by Reny Siti Syarifah et al[15]Testing the antibacterial activity of papaya leaf extract against Propionibacterium acnes was carried out by agar diffusion method with a concentration of 7% resulting in an inhibitory diameter of 14 mm. This is different in this study at a concentration of 25% in 50 mg/5ml resulting in an average inhibitory diameter of the two bacteria of 3.30±0.14 mm. The papaya extract in this study had a small diameter of inhibition and was categorized as weak, in this study it was probably due to several factors in the papaya extract containing a fairly high water content. A large amount of water content in the extract can be overgrown with microorganisms and reduce the quality of the extract [16] .

HASIL BIOAUTOGRAFI KOMBINASI EKSTRAK UNTUK MENENTUKAN KOMPONEN YANG AKTIF SEBAGAI ANTI BAKTERI DENGAN ANALISA GCMS

In Table 6. This study showed that the active fraction of star fruit extract (Averrhoa bilimbi L) and papaya leaf extract (Carica papaya) was the fraction with ethyl acetate solvent with Rf values of 0.42 and 0.67. The component of the active compound as an antibacterial is Rf with a value of 0.67. The results of the observations in appendix 39 using GCMS analysis based on the initial threshold 23 obtained 5 peaks. In the GCMS analysis test, the combination of star fruit extract and papaya leaf extract, the compounds contained in the initial threshold 23 are mostly organic acids which have active components as antibacterials including Pentadecanoic acid, 9-Octadecenoic acid, 1,2-Benzenedicarboxylic acid, which functions as Preservatives are also known as antimicrobials. Based on the results of phytochemical tests that have been carried out previously, it is possible that the compounds contained in the sample are flavonoid compounds, phenols, and tannins. However, from the five compounds above, there was no compound from this group, this is presumably because the presence of these compounds in the sample has a small concentration. The bioautography of this extract combination is in accordance with research conducted by Kusmiyati and Ni

Table 1. Characteristic of the thick extract of star fruit and papaya leaf extract

No	Evaluation	Extract Wuluh Starfruit	Extract Papaya leaf	Extract Requirement Wuluh starfruit[9]	Extract Requirement Daun Pepaya [9]
1	Organoleptic				
	Form	Viscous liquid	Viscous liuid	Thick	Thick
	Odor	Typical aromatic	Typical Aromatic	Typical Aromatic	Typical Aromatic
	Color	Dark Chocolate	Black	Dark chocolate	Black
2	Specific Gravity	0,983	0,967	-	-
3	pH	0,95	5,33	-	-
4	Water Content	35,26%	31,31%	≤ 10 %	≤ 10 %
5	Ash Content	2,34%	8,05%	≤ 6,51%	
6	Acid insoluble ash content	0,23%	0,31%	≤ 0,30%	≤ 0,30%
7	Acid insoluble ash content	63,03%	68,04%	-	-
8	Juice content in alcohol	62,05%	38,61%	-	-
9	Identification of Safonins	+	+	-	-
10	Identification of Tannin	-	+	-	-
11	Identification of Flavonoids	+	+	-	-
12	Identification of Phenol	+	+	-	-
13	Identification of Alkaloids	+	+	-	-

Table 2. Test results of bacterial growth activity in star fruit extractwuluh against Propionibacterium acnes and Staphylococcus bacteria aureus

Bacteria	Repetition	Resistance Diameter (RD) Concentration (%) (Wuluh Starfruit) 50mg in 5 ml (100 %)							
		KP	KN	5	10	15	20	40	80
P. acne	I	21,40	0	0	0	0	9,20	13,40	18,20
	II	21,20	0	0	0	0	9,30	13,60	17,60
	Average	21,30	0	0	0	0	9,25	13,50	17,90
	Standard Deviation	0,14	0	0	0	0	0,07	0,14	0,42
S. aureus	I	22,25	0	0	0	0	11,50	14,50	18,75
	II	22,35	0	0	0	0	11,40	14,70	18,55
	Average	22.30	0	0	0	0	11,45	14,60	18,65
	Standard Deviation	0,07	0	0	0	0	0.07	0,14	0,14

KN = Negative control KP = Positive control

Table 3. Test results of bacterial growth activity on papaya leaf extractagainst Propionibacteriumacne and Staphylococcus aureus

Bacteria	Repetition	Resistance Diameter (RD) Concentration (%) (Wuluh Starfruit) 50mg in 5 ml (100 %)							
		KP	KN	10	15	20	25	50	100
P. acne	I	20,2	0	0	0	0	3,40	10,65	14,90
	II	21,3	0	0	0	0	3,20	11,25	15,15
	Average	20,75	0	0	0	0	3,30	10,95	15,25
	Standard Deviation	0,14	0	0	0	0	0,14	0,42	0,18
S. Aureus	I	21,3	0	0	0	0	3,25	12.15	15,75
	II	21,2	0	0	0	0	3,55	11,75	16,05
	Average	21,25	0	0	0	0	3,40	11,95	15,90
	Standard Deviation	0,78	0	0	0	0	0,21	0,28	0,21

Table 4. The results of the RD test for the combination of star fruit extract and leavespapaya against P. acnes bacteria

Bacteria	Repetition	Resistance Diameter (RD)				
		KP	KN	I	II	III
P. acne	I	20,75	0	2,2	9.80	13,85
	II	20,45	0	2,1	10,1	14,15
	Average	20,6	0	2,15	9,95	14
	Standard Deviation	0,21	0	0,07	0,21	0,21

KN = Negative Control
KP = Positive Control
I = B wuluh starfruit 20 % : 25% Papain leaf in 50mg/5ml (100 %)
II = B wuluh starfruit 40 % : 25% Papain leaf in 50mg/5ml (100 %)
III = B wuluh starfruit 80 % : 25% Papain leaf in50mg/5ml (100 %)

Table 5. The results of the RD test for the combination of wuluh starfruit extract and papaya leaves against S aureus

Bacteria	Repetition	Resistance Diameter (RD)				
		KP	KN	I	KP	III
S aureus	I	20.45	0	2,25	10,7	14,75
	II	20,15	0	2,55	10,6	15,05
	Average	20,3	0	2,4	10,65	14,9
	Standard Deviation	0,21	0	0,21	0,07	0,21

KN = Negative Control
KP = Positive Control
I = B wuluh starfruit 20 % : 25% Papain leaf in 50mg/5ml (100 %)
II = B wuluh starfruit 40 % : 25% Papain leaf in 50mg/5ml (100 %)
III = B wuluh starfruit 80 % : 25% Papain leaf in 50mg/5ml (100 %)

Table 6. The results of the bioautography of the combination of star fruit extractwuluh and papaya leaves

PEAK	RT	AREA (%)	Posibble compound	QUAL
1	2.360	20.51	1,3-Diacetoxy-butane	59
2	2.781	10.89	1-Pentanamine	50
3	8.143	13,16	Pentadecanoic acid	97
4	9.279	10.23	9-Octadecenoic acid	99
5	11.866	45.21	1,2-Benzenedicarboxylic acid	90

Wayan Sri Agustini.[17]in the identification results with Gas Chromatography Mass Spectrometry (KGSM) obtained 9-Octadecenoic acid compound has antibacterial activity. Likewise with the research conducted by Bustanussalam[18]et al.Bioautography using GCMS analysis found that 1,2-Benzenedicarboxylic acid has antibacterial activity.

DISCUSSION

Based on research conducted by Juliantina [19]that the karpain alkaloid compounds in papaya leaf extract have antibacterial activity by inhibiting the formation of peptidoglycan in bacterial cells so that the cell wall layer is not formed completely resulting in cell death in bacteria. According to Fitrianti Dwi AR dkk[20]It is suspected that the compounds that have antibacterial activity are polyphenol compounds. The mechanism of action of polyphenols is to interfere with the function of enzymes and their substrates. In Anaisa B .'s research [21]It was mentioned that flavonoid compounds and tannins are compounds that can kill bacteria with the mechanism of action of flavonoids damaging cell membranes and followed by the release of intracellular compounds. The mechanism of action of tannins inhibits the enzyme reverse transcriptase and DNA topoimerase so that bacterial cells are not formed. In this study also performed Bioautography with GCMS analysis. Based on this method, the results can be seen in Table V.13. The results of the analysis obtained the 5 largest compounds from the GC-MS program Library data, the possibility of other compounds contained as antibacterial according to previous studies were also present in the GCMS analysis, but very little concentration levels. The combination of extracts listed in Table V. 13 The results of the bioautgraphy of the combination of extracts.

From the diameter test of the inhibition zone of the combination of star fruit extract and papaya leaf extract, the results are shown in Table V.11. and Table.V.12. The concentration of the extract combination was made in 3 combinations by comparison. Combination 1 with 20% (belimbing wuluh): 25% (papaya), combination 2 with 40% (belimbing wuluh) : 25% (Papaya), and combination 3 with 80% (belimbing wuluh) : 25% (papaya). From the results of the RD test, the results are shown in table V.12. Against P acnes bacteria, the results of combination 1 were 2.1 5 ± 0.07 mm, combination 2 was 9.95 ± 0.21 mm, and combination 3 was 14.00 ± 0.21 mm, the combination positive control against bacteria P. acnes by 20.60±0.21. From the results of the RD test, the results are shown in Table V.12. Against S aureus bacteria, the results of combination 1 of 2.40 ± 0.21 mm, combination 2 of 10.65 ± 0.07 mm, and combination 3 of 14.90 ± 0.21 mm, positive control from the combination of extracts obtained were 20.30±0.21 The concentration of the combination of star fruit extract and papaya leaf extract used in the formulation of the gel preparation, was 50 mg in 5 mL of distilled water for each concentration of extract, papaya leaf concentration of 25% as "Y" and 20% for wuluh star fruit as“X” The concentration of star fruit extract and papaya leaf extract were used in the gel formulation, for formula 1 was X:Y, formula 2 was 2X:Y, and formula 3 was 3X:Y. The concentration of starfruit used is greater, this is in the manufacture of the formula does not require expensive costs, because the selling price of star fruit in the market is low and not many people consume it. Wuluh star fruit is often left to rot on the tree or allowed to fall to the ground. From the results of the RD test on the combined extract, there was a decrease in the activity of the extract against bacterial growth inhibition. This could be due to the lack of papaya leaf extract giving the effect of anti-bacterial activity compared to star fruit extract. In this study, a preliminary test has been carried out with cross and parallel combination tests. The resulting diameter of inhibition decreased in parallel combinations, as well as in cross-combination of extracts with a ratio of the quantity of papaya leaf extract greater than that of star fruit extract, a decrease in the diameter of the inhibitory power. In the cross-combination test with the quantity of star fruit extract greater than papaya leaf extract, the diameter of the inhibitory power was obtained, but it did not produce the same or more than the single extract test, so the combined inhibitory diameter test in this study did not have synergistic antibacterial activity. The difference in mechanism between papaya leaf extract and wuluh starfruit extract causes an antagonistic effect after the combination, because compounds that are bactericidal when combined with bacteriostatic compounds, the bacteriostatic effect will stop the growth of bacterial cells, so that the bactericidal compounds become inactive against bacteria. because the bactericidal compound in its mechanism of action requires the growth of microorganisms[22]. Menurut Adwan dan Mhanna[23]the combination is better done on extracts that have been diffracted or pure compounds than using crude extracts. This is because in the crude extract there are still many compounds that are possible to react with one another so that it can affect its activity. In addition, the effect of decreasing activity can also be influenced by the chemical and physical stability of the extract when combined.

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