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OPTIMIZATION OF SOURSOP LEAVES EXTRACT APPLICATION (*ANNONA MURICATA L.*) USING ENCAPCULATION WITH POWDERED MILK AS A HEALTH SUPPLEMENTS

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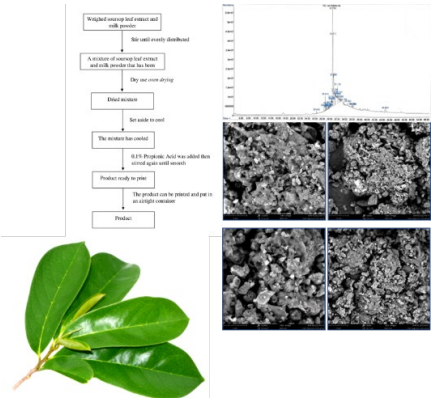
Graphical abstract



Abstract

Soursop leaves have untapped potential and are often considered waste. They contain beneficial compounds such as flavonoids, acetogenins, and polyphenols, which known to have an antioxidant and anti-cancer effects. However, these compounds are prone to degradation. In that case this study is aimed to optimize the encapsulation process of soursop leaf extract using variety of material formulations, temperatures, and drying time. The best condition was obtained with a ratio of 1:1.2 and a drying time of 120 minutes at a temperature of 55°C. Encapsulation enhances the stability of the extract, making it suitable for use as a health supplement. The encapsulation results were also analyzed using SEM-EDX to observe the structure of the encapsulated material and GC-MS to determine the composition of the extract. The major component detected in the extract was ketorolac, which accounted for 73.64% and 2.74% of the composition.

Keywords: soursop leaves, encapsulation, milk powder, ketolorac, health supplements.,

1.0 INTRODUCTION

Health become one of major compartment of life itself. Free radicals could become the source of a disease., These free radicals could be spread via smoke such as cigarette and vehicle emission which inhaled continuously and accompanied by unhealthy lifestyles. Many health problems can be caused by these free radicals, such as diabetes mellitus, neurodegenerative diseases, cardiovascular disease, and even cancer [1]. An abnormal level of free radical can initiate tissue damaged and strike vulnerable compound such as lipids and protein[2]. Antioxidants play a vital role to counter free radicals which are able to be obtained from compound that contains flavonoids, phenolics, alkaloids, saponins, steroids, and triterpenoids [3]. Human body produced antioxidant naturally but could not fully protect human body from oxidative stress [2]. Therefore, additional antioxidants have a very significant role to prevent the terrible effect of free radicals.

Plants have medicinal properties and has been used in Indonesia as an effort to overcome health problems. Knowledge about herbal medicine has become a habit in Indonesia which is obtained from experience and skills passed down from generation to generation [3]. This traditional knowledge is a valuable resource for promoting natural remedies.

However, soursop leaves (*Annona muricata L.*) have not been widely utilized and are still considered waste. This research aims to increase the additional use by utilizing this existing natural resource [4]. Soursop plant (*Annona muricata L.*) originated from Karibia, South America. In the 19th century, it spread over Asia and cultivated mainly in Thailand, Malaysia, and Indonesia[5]. Soursop plant has many active ingredients, such as anti-cancer, anti-convulsion, anti-parasite, and anti-diabetic[6]

The active substances in soursop leaves that can be used for anti-cancer are annonaceous acetogenins which are strong inhibitors of complex I mitochondria or NADH dehydrogenase. This substance will result in a decrease in ATP production which will cause cancer cell death, then trigger the activation of the

apoptotic pathway , followed by the activation of p53 which can stop the cell cycle to prevent uncontrolled proliferation [7].

Today's modern society expects a product that has functional components in terms of nutrition, practical use and longevity. One method that can be done is to use the encapsulation method on soursop leaf extract [8].

Extraction of soursop leaves (*Annona muricata L.*) is usually done by the maceration method using ethanol or n-hexane as a fractionation solvent. This process can be done on soursop leaves which still have moisture content or which have been dried and macerated for 1-2 days, and are then tested using a standard solution to determine the phenol content or by spectrophotometric test [9].

Encapsulation is an efficient way to increase the selling value of soursop leaf extract so that it has a longer shelf life without reducing the quality of the ingredients [10].

Soursop leaf processing into soursop leaf extract powder can be done by encapsulation. Encapsulation requires the addition of encapsulants, such as a mixture of dextrin and casein. However, the amount of addition to the dextrin and casein mixture needs to be limited, excessive amount of these compound will produce a product with low levels of anti-oxidants. Meanwhile, if the amount is not enough, the drying process will be difficult [11].

The method used in this research is to mix soursop leaf extract with a mixture of milk powder which is then dried to produce products that can be consumed. Addition of propionic acid to the product aims to prevent microbial growth in the active substance, thereby prolonging the shelf life of the product.

Based on several previous researches, we know that milk flour contain protein that could increase fenol and flavonoid [12]. Encapsulation using protein also help with the longetivity of the product which is better than polysaccharide[13].

Propionic acid also help with the matter of longetivity. This statement are already proved by a a previous research which was done by adding propionic acid to wheat bread. The addition of propionic acid to wheat bread could delayed wheat bread expiration until 13 month[14]. The allowed dosage of use for the propionic acid are only 0,2% of the total product mass[15].

2.0 METHODOLOGY

Materials used in this study were sour soup leaf extract, milk powder, distilled water and propionic acid.

The method that has been carried out in this study consisted four steps (Figure 1). Firstly, sour soup leaf extract was prepared and mixed with solution consisted of milk powder and distilled water. After the mixture were well dispersed, the mixture was then dried using oven at various temperatures and times. After the drying process was done, 0.1% wt. propionic acid was added to the dried mixture. Analysis and characterization were done to study the obtained product. In this study, the properties of the encapsulated extract were measured and characterized using friability test, dissolution test, hardness test, Scanning Electron Microscope (SEM), and Gass Chromatography Mass Spectrometry (GC-MS).

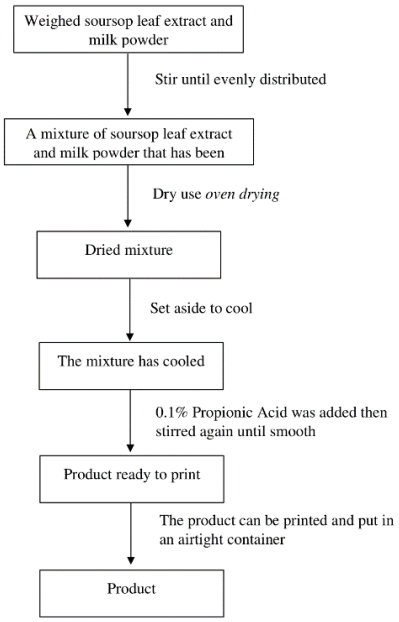


Figure 1 Research Flowchart

In addition, separate test to determine which temperature and drying time are the best and most suitable for this process were also conducted. It was done by analysing evaporation profile of the various sample by using equation (1)

$$\%Yield = \frac{Weight\ of\ extract\ (final)}{Weight\ of\ simplicia\ (initial)} x\ 100\% \quad \text{.....(1)}$$

As for the friability test, equation (2) is used.

$$(F) = \frac{A-B}{A}\ X\ 100\% \quad \text{.....(2)}$$

with A is the initial weight and B is the final weight.

3.0 RESULT AND DISCUSSION

In this study, the mass of soursop leaf extract was used as a fixed variable. While the independent variables used variations in time (60, 90, 120 minutes), variations in drying temperature in the oven (40, 45, 50, 55°C), and comparisons of soursop leaf extract with milk powder (1:1; 1:1,2; 1:1,4; 1:1,6).

3.1 Drying Test Results

Optimization of drying process for soursop leaf extract and flour were carried out by using some variables, including variations in time (60, 90, 120 minutes), variations in drying temperature in the oven (40,45,50,55 °C), and comparisons of soursop leaf extract with milk powder (1:1; 1:1, 2; 1:1,4; 1:1,6).

The data will be explained in terms of product weight from time to time in grams and will also display the percent yield of the product obtained from the formula. Product Yield Percentage Formula:

Researchers will look for products that have the smallest yield value. This proves that the evaporation of water in these

variables takes place more optimally which causes the resulting product to be lower in humidity and drier. Another factor observed is in terms of physical appearance which will be categorized into 3 categories, namely: D = Dry; FD = Fairly Dry; S = Soft.

Based on these 3 factors, the following data is obtained:

1) Temperature 40°C

Table 1 Table Shows Weight in Grams

Weight Comparison	Time (minute)			
	0	60	90	120
1:1	30.00 g	29.34 g	29.13 g	28.84 g
1:1.2	30.00 g	28.86 g	28.60 g	28.13 g
1:1.4	30.00 g	29.44 g	28.50 g	28.12 g
1:1.6	30.00 g	29.00 g	29.00 g	29.00 g

Table 2 Table Shows Percent Yield

Weight Comparison	Time (minute)			
	0	60	90	120
1:1	100.00%	97.80%	97.10%	96.13%
1:1.2	100.00%	96.20%	95.33%	93.77%
1:1.4	100.00%	98.13%	95.00%	93.73%
1:1.6	100.00%	96.67%	96.67%	96.67%

Table 3 The Table Shows the Physical Appearance of the Product

Weight Comparison	Time (minute)			
	0	60	90	120
1:1	S	S	FD	FD
1:1.2	S	S	FD	D
1:1.4	S	S	D	D
1:1.6	S	S	S	S

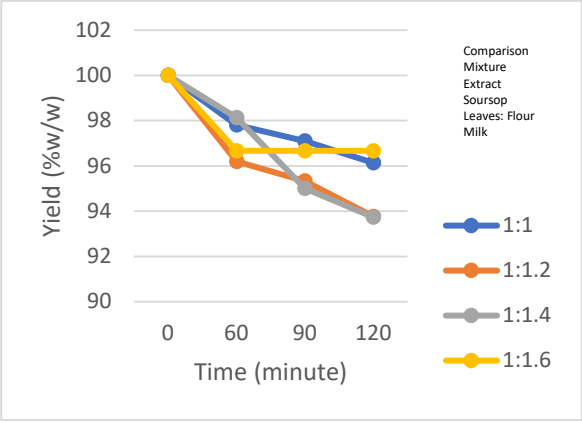


Figure 2 Graph of % Yield of Soursop Leaf Extract with Milk Flour at 40°C

Based on Figure 2, Table 1, and Table 2 and Table 3 we can conclude that weight comparison of 1:1,4 has better drying than other composition at 40°C.

2) at Temperature 45°C

Table 4 Table Shows Weight in Grams

Weight Comparison	Time (minute)			
	0	60	90	120
1:1	30.00 g	28.37 g	27.52 g	26.67 g
1:1.2	30.00 g	28.69 g	27.88 g	27.04 g
1:1.4	30.00 g	29.35 g	28.76 g	28.05 g
1:1.6	30.00 g	27.50 g	26.25 g	25.40 g

Table 5 Table Shows Percent Yield

Weight Comparison	Time (minute)			
	0	60	90	120
1:1	100.00%	94.57%	91.73%	88.90%
1:1.2	100.00%	95.63%	92.93%	90.13%
1:1.4	100.00%	97.83%	95.87%	93.50%
1:1.6	100.00%	91.67%	87.50%	84.67%

Table 6 The Table Shows the Physical Appearance of the Product

Weight Comparison	Time (minute)			
	0	60	90	120
1:1	S	S	FD	FD
1:1.2	S	S	FD	D
1:1.4	S	S	FD	FD
1:1.6	S	S	S	S

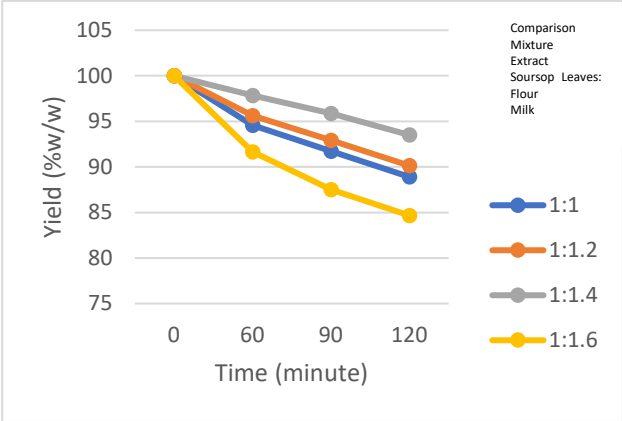


Figure 3 Graph of % Yield of Soursop Leaf Extract with Milk Flour at 45°C

Based on Figure 3, Table 4, Table 5 and Table 6 we can conclude that weight comparison of 1:1,6 has better drying than other composition at 45°C.

3) at Temperature 50°C

Table 7 Table Shows Weight in Grams

Weight Comparison	Time (minute)			
	0	60	90	120
1:1	30.00 g	27.96 g	27.53 g	27.00 g
1:1.2	30.00 g	27.26 g	27.17 g	25.62 g
1:1.4	30.00 g	28.72 g	28.42 g	27.32 g
1:1.6	30.00 g	28.22 g	28.19 g	27.12 g

Table 8 Table Shows Percent Yield

Weight Comparison	Time (minute)			
	0	60	90	120
1:1	100.00%	93.20%	91.77%	90.00%
1:1.2	100.00%	90.87%	90.57%	85.40%
1:1.4	100.00%	95.73%	94.73%	91.07%
1:1.6	100.00%	94.07%	93.97%	90.40%

Table 9 The Table Shows the Physical Appearance of the Product

Weight Comparison	Time (minute)			
	0	60	90	120
1:1	S	FD	S	D
1:1.2	S	FD	S	D
1:1.4	S	S	FD	D
1:1.6	S	S	FD	D

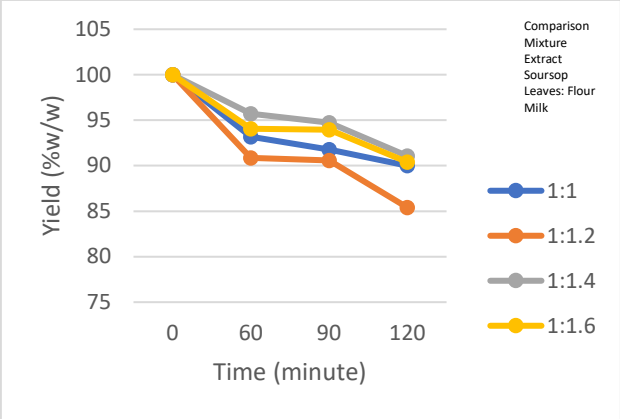


Figure 4 Graph of % Yield of Soursop Leaf Extract with Milk Flour at 50°C

Based on Figure 4, Table 7, Table 8 and Table 9 we can conclude that weight comparison of 1:1,2 has better drying than other composition at 50°C.

4) at Temperature 55°C

Table 10 Table Shows Weight in Grams

Weight Comparison	Time (minute)			
	0	60	90	120
1:1	30.00 g	28.38 g	26.90 g	25.46 g
1:1.2	30.00 g	27.66 g	26.09 g	24.68 g
1:1.4	30.00 g	28.85 g	27.55 g	26.28 g
1:1.6	30.00 g	27.77 g	26.22 g	25.00 g

Table 11 Table Shows Percent Yield

Weight Comparison	Time (minute)			
	0	60	90	120
1:1	100.00%	94.60%	89.67%	84.87%
1:1.2	100.00%	92.20%	86.97%	82.27%
1:1.4	100.00%	96.17%	91.83%	87.60%
1:1.6	100.00%	92.57%	87.40%	83.33%

Table 12 The Table Shows the Physical Appearance of the Product

Weight Comparison	Time (minute)			
	0	60	90	120
1:1	S	FD	D	D
1:1.2	S	FD	D	D
1:1.4	S	FD	D	D
1:1.6	S	FD	D	D

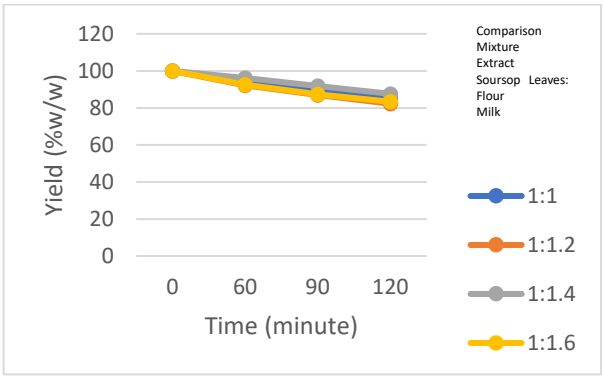


Figure 5 Graph of % Yield of Soursop Leaf Extract with Milk Flour at 55°C

Based on Figure 5, Table 10, Table 11 and Table 12 we can conclude that weight comparison of 1:1,2 has better drying than other composition at 55°C.

Based on the tests conducted, it can be concluded that the best mixture was obtained from a ratio of 1:1.2 and a temperature of 55°C for 120 minutes. The higher the temperature, the better the drying process, this is due to the greater difference in vapor and air pressure so that the water on the surface of the material evaporates more quickly [16]. Temperature of 55°C is the most optimal temperature in this study because it has a difference with the temperature of the furthest material. The longer the drying time will also increase the drying rate because the longer the drying time will increase the contact time of the material with heat so that the contact with heat is greater [17].

3.2 Weight Uniformity Test Results

The weight uniformity test on the product results in a ratio of 1:1.2 with a temperature of 55°C for 120 minutes was carried out to find out whether the resulting tablets have the same weight and dimensions between one another. The following test results are presented in Table 13.

From the powder formula which are made into tablet, and then measuring the thickness and diameter of the tablets using a measuring device. According to the *Indonesian Pharmacopoeia 4*, the requirement for size uniformity is that the diameter of the tablet does not deviate and is not more than 3 times the thickness of the tablet [19]. For weight deviations that can be tolerated according to the Indonesian Pharmacopoeia 4 for weights above 300 mg is 5-10% [20].

Table 13 Table Weight Uniformity Test Results

Code	Weight (mg)	Diameter (mm)	Thickness (mm)
1	680	10	7.9
2	700	10	8.5
3	680	10	8.2
4	670	10	8.5
5	670	10	8,5
6	680	10	8.1
7	700	10	8.4
8	700	10	8.2
9	670	9.9	7.5
10	700	10	8.5
11	660	9.9	7.9
12	700	9.9	7.9
13	670	10	8.5
14	670	10	8.4
15	690	10	8.3
16	690	9.9	8.1
17	690	10	8.5
18	700	9.9	7.9
19	680	9.9	7.8
20	670	10	7.8
Average	683.5	9.97	8.17

In accordance with the quotation above, the resulting tablets have fulfilled the requirements given by the Indonesian Pharmacopoeia 4 where the tablet diameter is not more than 3 times the thickness and is still within the tolerance limit for weight uniformity where the greatest distance of weight deviation is 6%.

3.3 Dissolution Test Results

Based on the analysis of the disintegration time test, the product yields a ratio of 1:1.2 with a temperature of 55°C for 120 minutes using a dissolution tester and 800 ml of distilled water and a temperature of 37°C with stirring at 100rpm disintegrates in 11 minutes [21]. The rules of the Indonesian Pharmacopoeia state that if the solubility is above 70% in 30 minutes, it will pass the dissolution test [22]. This can meet the requirements set by the UNNES Pharmaceutical Laboratory, which is destroyed in less than 15 minutes.

3.4 Friability Test Results.

For the friability test at a ratio of 1:1.2 with a temperature of 55°C for 120 minutes, 10 tablets were used with two replications using a friability tester that moved 100 turns in 4 minutes, which was then weighed again according to the (2) formula [18]. According to [18], if the reduction in weight that occurs below 5% then the tablet is included in the good category. Which show by the test result on Table 14 that all the final weight has less than 5% reduction.

Table 14 Table Friability Test Results

Replication/ Variable	Initial Weight (g)	Final Weight (g)	Percentage (%)
1	6.82	6.76	99.12
2	6.71	6.64	98.96

3.5 Hardness Test Results

The hardness test on the product yields a ratio of 1:1.2 with a temperature of 55°C for 120 minutes using a hardness tester using 20 samples with crushing requirements on a scale in testing between 4-8 kg [18]. Based on this it is known that the majority of samples passed the hardness test with results of 4-8.4 with a note that if the scale is above 8 then it is classified as a slow-release drug or slow to disintegrate. The Tablet Hardness, test result, are shown in Table 15.

Table 15 Table Hardness Test Results

Code	Weight (mg)	Diameter (mm)	Thickness (mm)
1	680	10	7.9
2	700	10	8.5
3	680	10	8.2
4	670	10	8.5
5	670	10	8,5
6	680	10	8.1
7	700	10	8.4
8	700	10	8.2
9	670	9.9	7.5
10	700	10	8.5
11	660	9.9	7.9
12	700	9.9	7.9
13	670	10	8.5
14	670	10	8.4
15	690	10	8.3
16	690	9.9	8.1
17	690	10	8.5
18	700	9.9	7.9
19	680	9.9	7.8
20	670	10	7.8

3.6 Scanning Electrone Microscope (SEM) Test Results

The SEM test at a ratio of 1:1.2 with a temperature of 55°C for 120 minutes was carried out at two points (spots) and used two scales at each point, namely magnifications of 5000X and 12000X on soursop leaf extract powder plus milk powder and propionic acid. Based on Figure 1a and 1b at the first point and 2a and 2b at the second point.

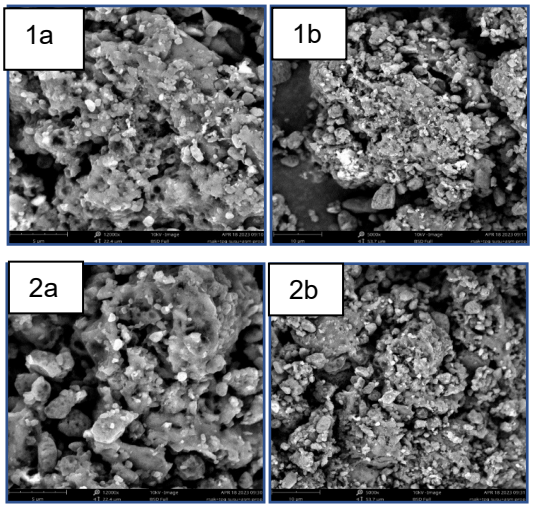


Figure 6 Scanning Electrone Microscope (SEM) Test Results

Figure 6 show Images of the product with a magnification of 12000X use a scale of 5µm while at a magnification of 5000X use a scale of 10µm. In the SEM test results it is known that the product has hollow columns with column spacing between 1-3µm. Meanwhile, the particle morphology of soursop leaf extract powder added with milk powder and propionic acid itself has an irregular and non-uniform shape.

For the EDX test conducted at 1 point which aims to determine the elemental content in the product mixture, the soursop leaf extract powder product plus milk powder and propionic acid has the following contents:

Table 16 Table Hardness Test Results

Element Symbol	Atomic Conc.	Weight Conc.	Oxide Symbol	Stoich Tw Conc.
C	64.35	56.47	-	-
O	27.47	32.11	-	-
Ca	6.28	6.42	-	-
N	0.62	1.81	-	-
K	0.64	1.44	-	-
P	0.36	1.03	-	-
Mg	0.26	0.67	-	-
Cl	0.03	0.06	-	-

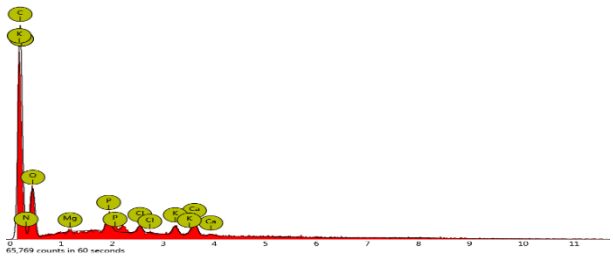


Figure 7 Scanning Electrone Microscope (SEM) Test Results

Based on Table 16 and Figure 7, at the third point it is known that the element carbon contains 60.15%. While other elements such as O = 29.83% atoms, Ca = 0.28% atoms, N = 8.7% atoms, K = 0.4% atoms, P = 0.37% atoms, Mg = 0.12% atoms, and the element Cl = 0.15% atoms.

Carbon is the highest element, this can be understood because one of the main components of the mixture is soursop leaves, where 45-50% of the plant's dry matter is composed of carbon[22]. The presence of calcium content is influenced by the presence of a mixture of milk flour which is one of the product mixtures.

3.7 Gas Chromatography and Mass Spectrometry (GC-MS) Test Results

Based on the GC-MS test on product results with a ratio of 1:1.2 at 55°C for 120 minutes, it is known that soursop leaf extract has the following contents and percentages:

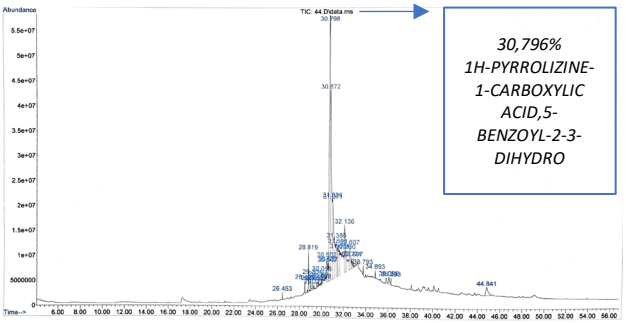


Figure 8 Percentage of Soursop Leaf Extract Content from GC-MS.

Table 17 Table Percentage of Soursop Leaf Extract Content from GC-MS

Retention Time	Name	Area (%)
28.817	*Neophytadiene*	1.5
30.5	*1H-Pyrrolizine-1-Carboxylic Acid,5-Benzoyl-2-3-Dihydro*	2.74
30.796	*1H-Pyrrolizine-1- Carboxylic Acid,5-Benzoyl-2-3-Dihydro*	73.64
31.5	*14-Beta-H-Pregna*	3.72
32.134	*12-Methyl-7-(2-methylpropyl)benz[a] anthracene*	4.2
32.231	*Triacontyl acetate*	2.04
32.61	*5H-Dibenzo[c,g] carbazole,6,7-dihydro*	2.81
44.842	*Cholest-5-En-3Ol-23 Ethyl-(3 Beta,23S)*	2.14

Based on Figure 8, Table 17 that soursop leaf extract consists of 7 constituent components including Neophytadiene, 1h-Pyrrolizine-1-Carboxylic Acid, 5-Benzoyl-2-3-Dihydro, 14-Beta-H-Pregna, 12- Methyl-7-(2-Methylpropyl)Benz[A] Anthracene, Triacontyl Acetate, 5H-Dibenzo[C,G] Carbazole,6,7-Dihydro, Cholest-5-En-3Ol-23 Ethyl-(3 BETA,23S). 1h-Pyrrolizine-1-Carboxylic Acid,5-Benzoyl-2-3-Dihydro was detected 2 times with different percentages, namely 73.64% and 2.74%.

Neophytadiene was detected at 1.5% and is an alkene hydrocarbon compound with the formula C_20 H_38. Neophytadiene belongs to the sesquiterpenoid group which has the potential to be a safe pesticide for humans. Neophytadiene has anti-inflammatory and anti-bacterial properties [23].

1h-Pyrrolizine-1-Carboxylic Acid,5-Benzoyl-2-3-Dihydro or can be called ketolorac was detected 2 times, namely 73.64% and 2.74%. Ketolorac is a basic ingredient of anti-inflammatory drugs which are commonly used in pain relievers, fever reducers and anti-inflammatories [24].

14-Beta-H-Pregna was detected as much as 3.72% and includes a hydrocarbon compound with the formula C_21 H_36 which has anti-diabetic properties [25].

Triacontyl acetate was detected at 2.04% and belongs to the fatty alcohol group [18]. Fatty alcohol has uses as a raw material for cosmetics and detergents such as soap, shampoo and laundry detergent. Fatty acids are also used in the textile and agricultural industries [26].

Ketolorac which is the main compound of soursop leaf extract is a compound that has been recognized by the Food and Drug Administration (FDA) since 1989 as a pain reliever drug as well as a drug that can reduce cancer risk. Based on research conducted in 2010 consuming ketorolac can reduce the risk of breast cancer by up to 55%. Ketorolac also functions for the treatment of postoperative cancer which can increase postoperative recovery by up to 57% at 60 months postoperatively [27].

4.0 CONCLUSION

It is known that the best mixture is obtained from a mixture ratio of 1: 1.2 and a temperature of 55°C and a drying time of 120 minutes. In this experiment the researchers found that the higher the temperature the better the drying process and it was known from testing that 55°C was the most optimal temperature, the longer the drying process the better the product produced and it was known from testing that 120 minutes was the most optimal time. optimally, a mixture ratio of 1:1.2 is the most optimal mixture ratio because it has the most stable drying rate and the highest water evaporation rate at 50 and 55°C. From the research, the product is considered to have passed all given pharmaceutical tests such as friability test, hardness test, and dissolution test. Based on the SEM/EDX test it was known that the product had an irregular and non-uniform shape and was dominated by carbon elements and based on the GC-MS test it was known that the main component of soursop leaf extract was ketorolac which was detected as much as 73.64% and 2.74% which had a lot of functions include as an anti-cancer agent, anti-inflammation, pain reliever, and fever reducer.

Acknowledgement

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