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Antifungal Potential of Nanosimplicia Gummy Candy Formulated from Pineapple Stem (*Ananas comosus*) and Melon Seeds (*Cucumis melo* L.) Against *Candida albicans*–Induced Oral Ulcers

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Abstract: Oral candidiasis is an infection caused by the fungus *Candida albicans*. Antifungal agents commonly used in the community are mostly synthetic chemicals. Long-term use of synthetic chemicals often causes negative effects such as fungal resistance and other systemic side effects. Metabolites found in pineapple stems act as antifungal agents, namely saponins, flavonoids, tannins, alkaloids, phenolics, and bromelain enzymes. Bromelain is a mixture of proteolytic enzymes first discovered in pineapple stems. Melon seeds contain tannin, flavonoid, and saponin metabolites, alkaloids, terpenoids, proteins, and carbohydrates. The metabolite compounds found in both natural waste materials are classified as BSC-2 (low solubility and unstable bioavailability) in the biopharmaceutical classification. This means that the active substances are difficult to dissolve in physiological fluids. To overcome this problem, an innovative nanosimplisia technology was developed in the form of gummy candy. This study began with the formulation of nanosimplisia from pineapple stems and melon seeds with varying sonication times, which were then formulated into gummy candy preparations (0:0.5; 0.5:1; 1:1.5). Antifungal activity tests were then conducted on Candida albicans fungi. The results obtained showed that the best formulation obtained from the combination of both nanosimplisia at a ratio of 1:1.5 showed an inhibition zone of 30.23 ± 0.06 mm at a concentration of 750 ppm.

1 INTRODUCTION

Oral candidiasis is an infection caused by the fungus *Candida albicans*, which is part of the normal flora in the mouth. The onset of this fungus is often caused by long-term use of antibiotics, use of corticosteroids, age factors such as elderly people, diabetes mellitus, poor oral hygiene, chronic irritation of the oral mucosa, and prostheses (Glick et al, 2021).

The use of antifungal agents in the community predominantly involves synthetic chemical compounds. Long-term use of synthetic antifungal agents often leads to negative effects, such as the development of fungal resistance and other systemic adverse effects (Chaurasi, 2025).

To minimize the negative effects associated with the use of synthetic chemical agents, natural materials derived from pineapple fruit stem waste and melon seeds were utilized.

Pineapple (*Ananas comosus*) is a fruit with numerous health benefits and contains water, minerals, organic acids, sugars, proteins, nitrogen, bromelain, and various vitamins, particularly vitamin D. The utilization of pineapple is mostly focused on the fruit itself, whereas other parts of the pineapple, such as the fruit stem, also possess health benefits.

The pineapple stem contains various metabolites with antifungal activity, including saponins, flavonoids, tannins, alkaloids, phenolic compounds, and the enzyme bromelain. Bromelain is a mixture of proteolytic enzymes that was first identified in the pineapple fruit stem (Tampubolon, 2023).

Putri et al. (2018) stated that the pineapple stem contains flavonoid and phenolic metabolites, vitamin C, and carotenoids, which act as natural antioxidants, with an IC_{50} value of 46.49 µg/mL. Meanwhile, Nadia et al. (2023) reported that the pineapple peel juice extract contains flavonoids, carotene, and vitamin C, with an IC_{50} value of 93.58 µg/mL.

Melon fruit (*Cucumis melo* L.) is one of the fruits with high consumption potential due to the pleasant taste of its flesh. Another part of the fruit is the seed; however, melon seeds are rarely utilized because they are often considered waste. Melon seeds contain metabolites such as tannins, flavonoids, saponins, alkaloids, terpenoids, as well as proteins and carbohydrates. The flavonoids present in melon are part of phenolic compounds that exhibit strong antioxidant properties (Kurniawati, 2015). Sitinjak (2019) reported that the vitamin C content of melon (*Cucumis melo* L.), determined using UV spectrophotometric analysis, showed an average concentration of 1.6118 mg/100 g and demonstrated strong antioxidant activity. Furthermore, Biswas et al. (2025) revealed that melon seeds exhibited significantly stronger antioxidant activity than the fruit flesh, as indicated by an IC_{50} value of 11.13 µg/mL, whereas the melon flesh showed a considerably higher IC_{50} value of 522.39 µg/mL, reflecting lower antioxidant potency. The metabolite compounds present in both natural waste materials, based on biopharmaceutic classification, are categorized as BCS Class II (*low solubility and variable bioavailability*). Consequently, the active compounds are poorly soluble in physiological fluids (Panwar et al., 2021).

To overcome problems in biopharmaceuticals, innovative nanosimplisia technology has been developed in the form of gummy candy preparations. Nanosimplisia preparations in the field of pharmacy have advantages such as smaller particle size (nanometers), high bioavailability, better treatment effectiveness due to specific targeting, minimal side effects, higher stability, and controlled release (Ghosh et al, 2025).

Gummy Candy is a type of nutraceutical preparation that has a soft, jelly-like texture and is made from a mixture of cooked sugar and the necessary solid ingredients. Gummy candy preparations have pleasant colors, flavors, shapes, and textures that are easy to chew, making them more appealing (Chandra et al, 2025).

The objective of this study is to develop innovative technology by utilizing natural waste materials from pineapple stems and melon seeds in the form of nanosimplisia gummy candy preparations that are effective as antifungal agents against Candida albicans fungi.

2 RESEARCH METHODS

This study was conducted experimentally using a post-test only design, in which observations were carried out after the treatment was administered.

2.1 Tools and Materials

2.1.1 Research Tools

The tools used in this study were 40 and 60 mesh sieves, ultrasonication, a particle size analyzer, a climatic chamber, wire mesh, a Bunsen burner, molds, glassware, and flannel cloth.

2.1.2 Research Materials

The materials used in this study were pineapple stems, melon seeds, mannitol, sucrose, gelatin, corn oil, essence, citric acid, distilled water, food coloring, and *Candida albicans* fungus.

2.2 Procedure for Making Nanosimplisia

Pineapple stems and melon seeds are separated from impurities, washed thoroughly, and drained. They are then dried for 3-5 days by airing or placing them in a drying cabinet. The dried pineapple and melon stems and seeds are then ground and sifted using 40 and 60 mesh sieves. After that, ultrasonication is carried out with variations in sonication time of 10 minutes, 20 minutes, and 30 minutes, resulting in pineapple stem and melon seed nanosimplisia. After that, particle size testing is carried out. After particle measurements are obtained based on variations in time and smallest size, the nanosimplisia from pineapple stems and melon seeds are formulated into gummy candy preparations.

2.3 Gummy Candy Formulation

Basic Formula

R/ Sucrose 1
Mannitol 10
Corn oil 2
Essence 8
Coloring 1

Gelatin 15
Citric acid 0,5
Distilled water ad 100 (Agustina et al, 2023)

Modification of Gummy Candy Formula

Ingredients (b/b)	F0	F1	F2	F3
Nanosimplisia pineapple stems	-	-	0.5	1
Nanosimplisia melon seeds	-	0.5	1	1.5
Sucrose	1	1	1	1
Mannitol	10	10	10	10
Corn oil	2	2	2	2
Essence	8	8	8	8
Coloring	1	1	1	1
Gelatin	15	15	15	15
Citric acid	0.5	0.5	0.5	0.5
Distilled water	Ad 100	Ad 100	Ad 100	Ad 100

2.4 Procedure for Making Gummy Candy

Heat the mannitol base and add corn oil at a temperature of around 80℃ (solution A). Dissolve sucrose, citric acid, and sodium benzoate in distilled water (solution B). Solutions A and B are then mixed and stirred until homogeneous (solution C). Next, pineapple stem and melon seed nanosimplisia are added and stirred until evenly distributed. Solution C is then placed in an evaporating dish, followed by the addition of pineapple essence and coloring while continuing to stir until homogeneous. This formula is heated using a water bath and poured into gummy candy molds with a size of about 3 grams per gummy. Next, the formula is left for two 24-hour periods at room temperature (15-30°C) to allow the formula to harden and be removed from the mold (Egita et al, 2021).

2.5 Preparation Evaluation

The evaluation conducted on the gummy candy nanosmplisia pineapple sticks and melon seeds included organoleptic properties (color, smell, aroma, shape, and texture), pH, moisture content, and elasticity.

2.6 Antifungal Testing Using the Disc Diffusion Method

Antifungal activity testing was conducted using the disc diffusion method with a disc diameter of 6 mm. First, liquid agar medium was poured into sterilized Petri dishes and left to solidify at room temperature. After solidification, the prepared suspension was spread evenly on the surface of the agar medium using an L-shaped rod. Sterile disc paper was immersed in all solutions used, namely the gummy candy test solution. After that, the disc paper was left for a while to absorb the test solution, then placed on the agar surface using sterile tweezers. After that, the clear zone was observed and measured using a caliper (Simaremare et al, 2020).

2.7 Data Analysis

Data analysis in this study used the one-way analysis of variance (ANOVA) method, where normality and homogeneity tests were conducted first.

3 RESULTS AND DISCUSSION

The study began with the processing of pineapple stems and melon seeds sourced from Siak Regency, Riau Province. Five kilograms of stems and seeds were collected from each source and then ground into dried simplisia, yielding 511.4 g and 502.3 g of simplisia powder from each material, respectively.

3.1 Results of The Evaluation of Prticle Size of Pineapple Stem and Melon Seed Nanosimplisia

The evaluation of nanosimplisia from pineapple stems and melon seeds was observed based on the results of particle size reduction using an ultrasonicator with variations in time of 10 minutes, 20 minutes, and 30 minutes. The results of the nanosimplisia evaluation can be seen in **Table 1** below.

Table 1 Results of Evaluation of Particle Size of Pineapple Stem and Melon Seed Nanosimplisia

Ingredients	Time Variations (minutes)		
	10 minutes	20 minutes	30 minutes
	Particle Size ± SD	Particle Size ± SD	Particle Size ± SD
Nanosimplisia pineapple stems	130.53 ± 0.66	110.6 ± 0.46	102.27 ± 0.05
Nanosimplisia melon seeds	250.57 ± 0.38	220.13 ± 0.21	205.3 ± 0.1

The particle size evaluation results obtained for pineapple stem nanosimplisia with a sonication time of 30 minutes had the smallest particle size of 102.27±0.05 nm; the particle size evaluation results for melon seeds with a sonication time of 30 minutes had a particle size of 205.3±0.1 nm.
The particle size of seed nanosimplisia tends to be larger than stem nanosimplisia due to differences in anatomical structure and chemical composition of the initial material. Seed tissue structure is denser and harder, making it more resistant to size reduction during ultrasonication, resulting in seed particles being difficult to fragment into smaller sizes. The high lignin content in seeds makes the seed material more complex and elastic, so that the crushing process produces particles that are relatively larger than those from stems. Stem tissue is composed of xylem and phloem with larger intercellular spaces, making it easier to disrupt mechanically and produce finer particles during the nanosizing process. Different responses to mechanical energy During ultrasonication, stems tend to undergo more efficient fragmentation, while seeds undergo more deformation without breaking completely (Govindon et al, 2022).

3.2 Organoleptic Evaluation Results of Gummy Candy

The organoleptic evaluation was conducted on color, smell, aroma, taste, and texture. The results of the organoleptic evaluation of the gummy candy can be seen in **Table 2.**

Table 2 Organoleptic Evaluation Results for Gummy Candy

Formula	Color	Taste	Smell	Texture
F0	Pale yellow	Sweet-slightly sour	Dintinctive gummy candy smell	Chewy
F1	Brownish yellow	Sweet-slightly sour	Pineapple smell	Chewy
F2	Brownish yellow	Sweet-slightly sour	Pineapple smell	Chewy
F3	Brownish yellow	Sweet-slightly sour	Pineapple smell	Chewy

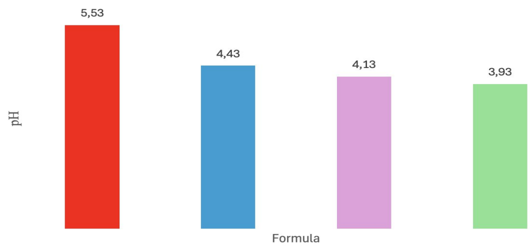
Description:
F0: gummy candy without nanosimplisia
F1: gummy candy (0:0.5)
F2: gummy candy (0.5:1)
F3: gummy candy (1:1.5)

The organoleptic test results show that F0 has a slightly different color from F1, F2, and F3. This is because F0 does not contain pineapple stem nanosimplisia and melon seeds. In terms of taste, aroma, and texture, all four formulas have the distinctive characteristics of pineapple aroma and chewiness.

3.3 pH Evaluation Results

The pH evaluation results were conducted to determine the acidity level of gummy candy. The evaluation results can be seen in **Figure 1** below.

Figure 1 pH Gummy Candy Pineapple Stem Nanosimplisia and Melon Seed Nanosimplisia



The pH test results for the gummy candy preparation were in the range of pH 3.0-4.5. F0 had a pH of 5.53. This indicates that F0 did not contain pineapple stem and melon seed nanosimplisia. The normality test results show that the significance value is $p>0.05$ (1.000). This indicates that the pH results are normally distributed. The follow-up test results are in the form of a one-way ANOVA test with a significance value of $p<0.05$ (0.000). This indicates that there are significant differences between each preparation based on the pH produced.
The pH of gummy candy preparations should be acidic because pectin-based gummies are most stable at a pH of 3.0-3.8 and help in the formation of a chewy gel that is not easily mushy and does not synergetize. An acidic pH (<4.5) inhibits the growth of bacteria and fungi, thereby extending shelf life without excessive preservatives. This pH provides a fresh, sour taste, but if it is too acidic, it can cause irritation or discomfort (Ginting et al, 2023).

3.4 Moisture Content Test Results

Moisture content testing is conducted to determine the physical stability of preparations and assess product quality and consistency. Moisture content test results are shown in **Table 3** below.

Table 3 Gummy Candy Moisture Content Test Results

Formula	Moisture Content (%)±SD
F0	12.17±0.06
F1	14.33±0.06
F2	13.43±0.06
F3	14.37±0.06
F4	13.57±0.38

Description:
F0: gummy candy without nanosimplisia
F1: gummy candy (0:0.5)
F2: gummy candy (0.5:1)
F3: gummy candy (1:1.5)

The moisture content test results of the four preparations ranged from 12-14.5%. The lowest moisture content test result was found in F0 (12.17%±0.06) and the highest in F3 (14.37%±0.06). The normality test results showed a significance value of $p<0.05$ (0.018). This indicates that the data generated is not normally distributed. A follow-up Kruskal-Wallis test was conducted with a significance value of $p<0.05$ (0.000). This can be interpreted as meaning that there are significant differences between each formula based on the differences in the concentration of nanosimplisia between pineapple stems and melon seeds. The high moisture content was caused by the combination of high concentrations of pineapple stem and melon seed nanosimplisia, which required more water.

Testing the moisture content of gummy candy preparations is related to storage and the resulting texture. High moisture content will cause gummy candy to have a soft texture and lead to mold and bacterial growth, while low moisture content will cause gummy candy to be hard and lose its plasticity (elasticity), which affects the texture of gummy candy (Indonesian National Standards Agency, 2008).

Water is an important component in food ingredients because it can affect the appearance, texture, palatability, flavor, and shelf life of food. All four formulas meet the requirements of the Indonesian National Standard (SNI) for soft confectionery, which stipulates that the maximum water content must not exceed 20% (Rowe et al, 2009).

3.5 Elasticity Test Results

Elasticity tests were conducted on the gummy candy preparations to compare their elasticity with that of products currently on the market. The results of these elasticity tests are shown in **Table 4** below.

Table 4 Gummy Candy Elasticity Test Results

Formula	Before withdrawal	After withdrawal
F0	2.31±0.01	2.53±0.06
F1	2.32±0.00	2.61±0.00
F2	2.20±0.01	2.66±0.00
F3	2.33±0.01	2.73±0.01
F4	3.13±0.06	2.74±0.00

Description:
F0: gummy candy without nanosimplisia
F1: gummy candy (0:0.5)
F2: gummy candy (0.5:1)
F3: gummy candy (1:1.5)

The elasticity test results are one of the parameters that determine whether gummy candy will be accepted by consumers or not. Gummy candy with good elasticity will be appreciated by consumers who consume it. The longest elasticity test result after pulling was found in F3 (2.73 cm±0.01). This is because F3 has the highest concentration of pineapple stem and melon seed nanosimplisia, giving it an elasticity value close to that of gummy candy preparations on the market.

The higher the concentration of nanosimplisia gummy candy, the higher its elasticity. Another contributing factor is the pectin content. In order for pectin to function properly and have good elasticity, the addition of acidic ingredients is also necessary. The acid produced does not only come from citric acid, but also from nanosimplisia melon seeds, which are high in vitamin C. Variations in concentration ratios affect the chewiness of gummy candy (Huda et al., 2015).

3.6 Results of Antifungal Activity Tests on *Candida albicans*

Antifungal activity testing is a method used to determine whether a substance can inhibit the growth of fungi/mold. The test was conducted using the Kirby Bauer (disc diffusion) method on Candida albicans fungus at concentrations of 750 ppm, 500 ppm, 250 ppm, and 100 ppm. The results of the antifungal activity test can be seen in **Table 5** below.

Table 5 Measurement Results of Average Diameter of Pineapple Stem Nanosimplisia and Melon Seed Nanosimplisia (mm±SD)

Concentration (ppm)	F0	F1	F2	F3	F4
100	0	12.27 ± 0.06	22.73 ± 0.06	25.23 ± 0.06	22.63 ± 0.06
250	7.37 ± 0.15	15.27 ± 0.06	23.47 ± 0.06	28.23 ± 0.06	24.23 ± 0.06
500	8.33	16.23	25.43	29.47	26.23

	± 0.06	± 0.06	± 0.06	± 0.06	± 0.06
750	6.23 ± 0.06	17.27 ± 0.06	27.23 ± 0.06	30.23 ± 0.06	27.07 ± 0.06

Description:
F0: gummy candy without nanosimplisia
F1: gummy candy (0:0.5)
F2: gummy candy (0.5:1)
F3: gummy candy (1:1.5)

The antifungal inhibition criteria are very strong if the inhibition diameter is > 20 mm (Al Fakih et al, 2022). F2, F3, and F4 fall into the very strong inhibition zone criteria. F3 had the highest inhibition diameter (30.23 mm±0.06) at a concentration of 750 ppm. F1 falls under the criteria for a strong inhibition zone (11-20 mm), while F0 falls under the criteria for a weak inhibition zone (<5 mm). The normality analysis yielded a significance value of $p>0.05$ (0.234). This indicates that the average inhibition diameter measurement results of pineapple stem nanosimplisia combined with melon seeds are normally distributed. The follow-up test results in the form of a one-way ANOVA test showed a significance value of $p<0.05$ (0.000). This indicates that there are significant differences between each preparation based on the inhibition zone diameter against Candida albicans fungus.

The ability of an antimicrobial to inhibit microorganisms depends on the concentration of the antimicrobial agent produced. The higher the concentration of an antimicrobial, the more active substances it contains, thereby increasing its effectiveness in inhibiting bacteria and producing a wider clear zone.

Another factor that causes differences in the diameter of the inhibition zone of gummy candy preparations is the difference in the concentration of active compounds. The size of the inhibition zone is influenced by several factors, such as the sensitivity level of the test organism (Jawetz et al, 1996).

Bromelain is a proteolytic enzyme obtained from pineapple stems and fruit and is known to have antifungal activity. The main mechanism of bromelain in inhibiting the growth of Candida albicans is related to its ability to degrade the structural proteins that make up the cell wall and membrane of fungi. Damage to these structures causes an increase in cell membrane permeability, resulting in the leakage of intracellular components that are essential for the survival of fungi and ultimately leading to cell dysfunction.

In addition to damaging cell structure, bromelain also plays a role in inhibiting the formation of Candida albicans biofilm. Biofilm is one of the main virulence factors that increases the fungus's resistance to the environment and antifungal agents. Bromelain's proteolytic activity can degrade adhesin proteins that play a role in the attachment process and biofilm matrix formation, thereby reducing the fungus's ability to attach, colonize, and grow optimally. Furthermore, bromelain has been reported to interfere with the morphological transition of Candida albicans from yeast to hyphae, which is an important stage in the process of tissue invasion and increased virulence. Disruption of hyphae formation reduces the invasive ability of fungi and inhibits their growth and spread. The combination of cell damage, biofilm inhibition, and morphological disruption makes bromelain a potential natural antifungal agent against Candida albicans (Medawati et al, 2023).

Vitamin C, which is abundant in melon seeds, has antifungal activity through its ability to create an environment that is unfavorable for the growth of Candida albicans. As an acidic compound, vitamin C lowers the pH of the environment surrounding fungal cells. A more acidic pH can disrupt the ion balance and intracellular enzyme activity of C. albicans, thereby inhibiting the metabolism and growth of the fungus. In addition to its acidifying effect, vitamin C also plays a role in increasing oxidative stress in fungal cells. At certain concentrations, vitamin C can act as a pro-oxidant by increasing the formation of reactive oxygen species (ROS). The accumulation of ROS causes damage to the cell membrane, proteins, and genetic material of the fungus, thereby disrupting the structural integrity and function of Candida albicans cells. Furthermore, vitamin C has been reported to inhibit the formation of Candida albicans biofilms, which are an important factor in fungal virulence and resistance. Vitamin C can reduce the ability of fungal cells to adhere to surfaces and inhibit the morphological transition from yeast to hyphae. The combination of environmental acidification, increased oxidative stress, and biofilm inhibition makes vitamin C a potential antifungal agent in inhibiting the growth of Candida albicans (Chen et al., 2024).

Nanosimplisia preparations in the form of gummy candy on pineapple stems and melon seed nanosimplisia also contain flavonoid compounds. Flavonoids are natural polyphenolic compounds that have antifungal activity, and their effectiveness can be enhanced through nanoformulation. Reducing particle size to the nano scale increases the surface area, solubility, and penetration ability of flavonoids into the walls and membranes of Candida albicans cells. Nano-flavonoids interact more easily with the lipid and protein components of fungal cell membranes, causing increased membrane permeability and leakage of cell contents, which ultimately leads to cellular dysfunction.

In addition to damaging membranes, nano-flavonoids also play a role in inhibiting the enzymatic system and metabolism of fungal cells. Flavonoids can bind to important proteins and enzymes involved in cell respiration and cell wall synthesis in Candida albicans. In nano form, these compounds are more stable and more effective at producing oxidative stress through increased production of reactive oxygen species (ROS), which causes damage to fungal proteins, lipids, and genetic material. Furthermore, nano-flavonoids have been reported to inhibit biofilm formation and the morphological transition of Candida albicans from yeast to hyphae, which is a major factor in fungal virulence. Biofilm inhibition occurs due to disruption of the fungal cell adhesion process to surfaces and damage to the biofilm extracellular matrix. Thus, the combination of increased cell penetration, membrane damage, metabolic disruption, and biofilm inhibition makes flavonoids in nanoformulations more effective in inhibiting the growth of Candida albicans than flavonoids in conventional forms.

4 CONCLUSIONS

Gummy candy preparations made from nanosimplisia of pineapple stem and melon seeds contain active compounds such as flavonoids, phenolics, and vitamin C, which contribute to the inhibition of *Candida albicans*. The best formulation obtained from the combination of both nanosimplisia at a ratio of 1:1.5 showed an inhibition zone of 30.23 ± 0.06 mm at a concentration of 750 ppm.

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