World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

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Juju Jam: Natural anti-cancer food from Bidara fruit for cancer risk patients

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World Journal of Advanced Research and Reviews, 2023, 17(03), 800–808

Publication history: Received on 16 February 2023; revised on 22 March 2023; accepted on 24 March 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.17.3.0490

Abstract

Cancer is the second leading cause of mortality worldwide, responsible for one in six deaths. Conventional treatments have been advancing and becoming more effective, but scientists continue to seek alternative and complementary treatments. Nature is the main source of alternative medicine for various diseases, including cancer. For example, mineral-rich plants are widely available in Indonesia and have been used traditionally to treat illnesses. One of them is the bidara fruit (*Ziziphus mauritiana*), which has medicinal compounds such as flavonoid, phenolic and tannin. The 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) antioxidant assay test shows an IC50 234,2139 ppm and classifies bidara fruit extract as a medium antioxidant. Meanwhile, the Brine Shrimp Lethality Test (BSLT) test shows an LC50 4,5449 and classifies bidara fruit extract as having high toxicity.

Keywords: Bidara Fruit; Antioxidant; Antibacterial; Anti-Cancer; Flavonoid; Extract

1. Introduction

Cancer is one of the deadliest diseases worldwide, caused by cells mutating and developing the ability to proliferate uncontrollably, invade locally, and perform distant metastasis. In the view of modern cellular biology, the basic mechanisms of cancer are abnormal growth and migration of cells with uncontrolled cell cycles, continuous self-renewal and reproduction of cancer stem cells [8, 12, 25, 34].

Globally, cancer is the second leading cause of mortality (after cardiovascular disease), being responsible for one in six deaths. The prevalence of cancer worldwide has increased from 17.5 million cancer cases and 8.7 million deaths in 2015 to 19.3 million new cases and about 10.0 million deaths in 2020 [5, 7, 11, 21]. The most prevalent cases are lung, breast, prostate, and colorectal cancers, whereas the deadliest are lung, colorectal, stomach, and liver cancers [34].

The current treatments for cancer include surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy [3, 10, 13, 30]. However, these treatments can cause an extensive list of side effects, such as nausea, pain, fatigue, and diarrhoea [34]. Chemotherapy alone has been shown to cause severe side effects such as vomiting ~12 times per day [Schirrmacher]. Other treatments, such as surgery and radiation, may lead to urinary symptoms and sexual dysfunction [20]. These side effects may affect a patient's quality of life (QoL) and may become life-threatening when severe neutropenic infections are detected [34]. The search for new treatment options is necessary. Therefore, research on complementary or alternative therapies from natural compounds has been conducted to provide better treatments and outcomes with fewer side effects [3, 6].

Indonesia has wide plant biodiversity, including medicinal plants. People have used various herbal medicine to cure diseases from generation to generation. Medicinal plants are widely available in all regions, providing rich mineral

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resources for natural medicine. One of the popular medicinal plants is bidara (Ziziphus mauritiana), more commonly known as jujube.

Studies have shown that the bidara fruit has anti-cancer properties and is rich in antioxidant compounds, such as flavonoid, phenolic, and tannin [23, 24, 27, 31, 33]. Flavonoid is considered a potential natural antioxidant due to its ability to eliminate and inhibit the formation of free radicals. Research has shown that flavonoid content is highly correlated with antioxidant activity and that it has an anti-cancer biological effect. Another notable characteristic is the chelation of metal ions to inhibit lipid peroxidation. As such, flavonoids can treat pathophysiological conditions caused by free radicals [1, 4, 15, 18].

In this research, the bidara fruit was extracted using ethanol solvent. Then, the extract was tested using phytochemical screening to determine the power of antioxidant-based IC50 value. The anti-cancer property was examined in preliminary testing using BSLT. The finding of this research can be considered as an alternative herbal medicine for degenerative diseases such as cancer. It will then be formed into a jam and will be tested for acceptability in the public.

2. Material and methods

2.1. Extraction of *Bidara* Fruit

Two-hundred grams of fresh *bidara* fruit were cleaned and cut into slices. The sliced fruit was then macerated using 2 litres of 96% ethanol and left for three days (3 x 24 hours). Next, the extract was filtered using a paper filter and incorporated into the rotary evaporators to obtain the viscous extract.

2.2. Phytochemical Testing

After the ethanol extract of *bidara* fruit was obtained, the sample was screened phytochemically to discover the secondary metabolite contents: alkaloid, flavonoid, phenolic, and tannin. Alkaloid was identified using the *Mayer* and *Wagner* reactors. The *Mayer* reactor test was conducted by adding two drops of *Mayer* reactor to 1 ml of the *bidara* fruit extract. The reaction was considered positive if a lump of white or yellow precipitate was formed. Likewise, the *Wagner* reactor test was conducted by adding a few drops of the *Wagner* reactor to 1 ml of the *bidara* fruit extract. The reaction was considered positive if a brown precipitate was formed and negative if the colour did not change. Meanwhile, the flavonoid was identified using the *Bate Smite-Metcalfe* reactor and NaOH 10% reactor. The *Bate Smite-Metcalfe* reactor test was conducted by adding a few drops of concentrated HCl to 1 ml of the *bidara* fruit extract, followed by heating. The reaction was considered positive if the colour turned red. The NaOH 10% test was conducted by adding a few drops of NaOH 10% to 1 ml extract. The reaction was considered positive if there the colour turned orange. Next, the phenolic was identified using 1% of $FeCl_3$ added to the *bidara* fruit extract until the colour changed. The reaction was considered positive if the colour became darker than the pure extract. The degrees were adjusted with the change of colour that occurred. Finally, tannin was identified using NaCl 10% + Gelatin 1%. The test was run by adding a small amount of gelatine solution and 5 ml of 10% NaCl to 1 ml of the *bidara* fruit extract. The reaction was considered positive if a yellow precipitate was formed [14].

2.3. Antioxidant Test Using DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate)

Ten mg of *bidara* extract was dissolved in methanol as a solution, which was then split into various concentrations. Each concentration was put in a test tube and added 1.0 ml DPPH and 2,0 ml methanol. The tubes were then incubated at a temperature of 37°C for 30 minutes. Next, the absorption was measured at wavelengths 497 nm, 517 nm and 537 nm. Quercetin was used as a standard for comparison.

2.4. BSLT (*Brine Shrimp Lethality Test*)

The extract and isolated compound were evaluated in a test for lethality to brine shrimp (Meyer et al., 1982) with minor modifications. Toxicities of samples were tested at 62.5, 125, 250, 500, and 1000 ppm in 10 mL sea-water solution with 1% DMSO (v/v). Fifteen one-day nauplii were used in each test and survivors were counted after 24 h. Three replications were used for each concentration. Using probit analysis, the lethality concentration (LC50) was assessed at a 95% confidence interval. LC50 of less than 100 ppm was considered potent (active), less than 1000 µg/mL was toxic while LC50 value greater than 1000 µg/mL was non-toxic.

2.5. Antibacterial Test

The antibacterial test used in this study was a modified version of the antibacterial test done by Simanjunak Helen Anjelilina (2020). Preparation of the antibacterial test began with sterilizing the tools and materials to be used, followed by rejuvenation of bacteria and the creation of media, bacterial suspense, *bidara* fruit extract test solutions, and comparative standard solutions. The determination of the antibacterial activity was carried out with sterilized NA media inserted into 20 mL sterile Petri dishes, which were then allowed to condense at room temperature. The media were added with 0.1 mL of bacterial suspension test and flattened using an L bar until smooth and dry. A sterile disk paper with a diameter of 6 mm was added with 10 µL of 96% *bidara* fruit ethanol extract in different concentrations: 12.5%, 25%, 50%, 75%, and 100%. These were subsequently placed on the media that had been dripped with a bacterial suspension test. Ten per cent of DMSO was the negative control, and chloramphenicol was the positive control. These were incubated at 37^{o}C for 24 hours. After that, the clear zone was measured using callipers. The test was replicated three times.

2.6. The Production of Juju Jam

Thirty grams of *bidara* fruits were blended with 150 grams of sukkari dates. Water was added until they turned into a smooth jam. The jam was then taken out of the blender and heated on a pan for around five minutes or until the jam showed the right viscousness. One tbsp of cinnamon was added. After the jam was cooked, it was put into the packaging and ready to be consumed.

2.7. Organoleptic test

The organoleptic test was done to know whether the product was acceptable. The organoleptic test was done with 33 panellists who rated the Juju Jam based on these criteria: taste, aroma, texture, appearance, and packaging. The panellists would then be asked 'Would you buy it?' The data were used to determine the acceptability of the product.

3. Results and discussion

The *bidara* fruit extract was obtained by maceration technique. The solvent used in this research was 96% ethanol. From 200 grams of fresh *bidara* fruit, we obtained 13 grams of concentrated extract (thick extract), as shown in Fig 1.

Figure 1 Concentrated extract of the bidara fruit

The phytochemical test was carried out to determine the secondary metabolisms contained in the *bidara* fruit ethanolic extract. The results are shown in Table 1.

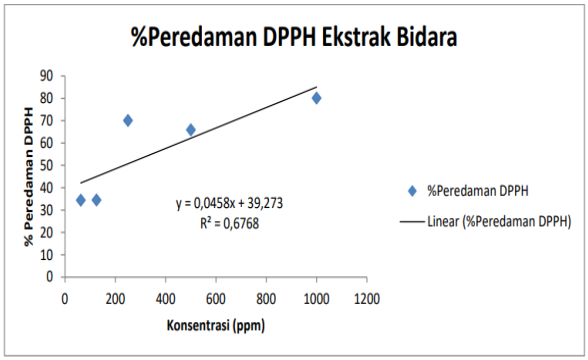
Table 1 shows that the extract of the *bidara* fruit contains flavonoid, phenolic, and tannin compounds as secondary metabolites. This result is in line with the research of Yahya Y. The most important active ingredient in the list of secondary metabolites compounds is flavonoid, potential natural antioxidant due to its ability to eliminate and inhibit the formation of free radicals [17]. Eliminating free radicals is important for anti-cancer activity because an increase in free radicals causes oxidative damage in cells, which is likely to be one of the key mechanisms involved in cancer and some of the other symptoms documented in the scientific literature [12].

Table 1 The Results of the Phytochemical Test

Phytochemical Test	Reagents	Results	Conclusion (+)
Alkaloid	Mayer	Yellow precipitation	+
	Wagner	Brown precipitation	
Flavonoid	Bate Smite-Metcalfe	Red Colour	+++
	+ NaOH 10%	Orange Colour	+++
Phenolic	FeCl3 1%	Darker colour	+++
Tannin	NaCl 10% + Gelatin 1%	Yellow Precipitation	+++

Table 2 Results of Antioxidant Test using DPPH

Sample Concentration (ppm)	Absorbance (A) in λ			%DPPH Inhibition
	497 nm	517 nm	537 nm	
1000	0.0829	0.0698	0.0627	80.11988012
500	0.1047	0.106	0.0977	65.86746587
250	0.0981	0.0952	0.0875	70.06327006
125	0.1657	0.1901	0.1787	34.53213453
62.5	0.1667	0.1903	0.1799	34.43223443
DPPH	0.2391	02836	0.2725	



IC_{50} = 234,2139 ppm

Figure 2 Graph of the DPPH Test Results

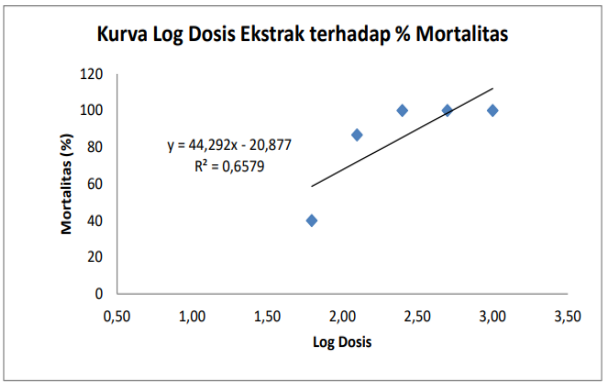
Based on the data, the value of IC_{50} is 234,2139 ppm, which is classified as a strong antioxidant compound.

The data show that the value of LC50 is 4,5449 ppm, which is classified as very toxic. The BSLT method was applied in this study because the BSLT method has a positive correlation with the cytotoxic test using cancer cell culture. Therefore, the BSLT method was commonly used as a screening for anti-cancer compounds [27].

The organoleptic test was carried out with 33 panellists to determine whether the product was acceptable. The test was done by giving some samples to the panellists and having them rate from a scale of one to five on the basis of taste, aroma, texture, appearance, and packaging. We then asked them whether they would buy the product they rated.

Table 3 The Results of BSLT

Sample Concentration (ppm)	Log Dosage	Early Life	Death	Alive	Mortality (%)
1000	3.00	15	15	0	100
500	2.70	15	15	0	100
250	2.4	15	15	0	100
125	2.10	15	13	2	86.67
62.5	1.80	15	6	9	40
Blanko (DMSO 1%)		15	0	15	



LC50 = 4,5449 ppm

Figure 3 Graph of BSLT Results

Table 4 The Results of the Antibacterial Test

Using Disc Diffusion Method				
Concentration (%)	Repetition			
	R1 (mm)	R2 (mm)	R3 (mm)	Mean (mm)
100	22.4	20.3	20.8	21.1
75	21.4	17.1	18.4	18.9
50	16.3	15.6	18.4	16.7
25	15.3	15.6	18.4	15.3
12.5	12.8	12.2	13.4	12.8
Eryhomycin	7.7	7.1	7.7	7.5
Ethanol	7.6	7.8	7.2	7.3

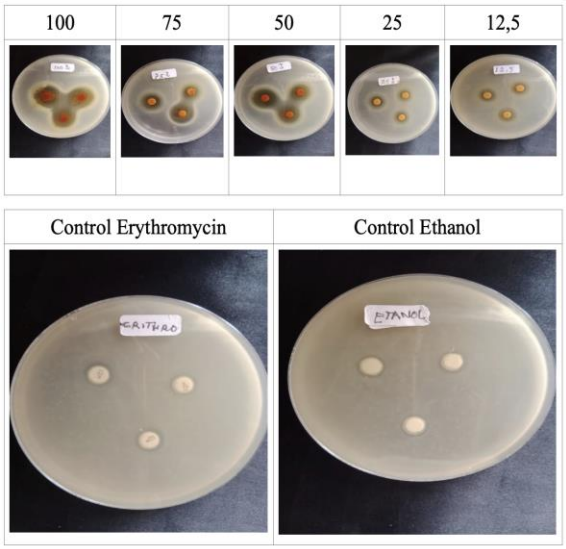


Figure 4 Results of the Antibacterial Test

Based on the data above, the *bidara* fruit ethanolic extract is shown to have antibacterial capabilities against *Salmonella typhi* bacteria in a range from 12.8-21.1 mm. Compared to previous research done by Nurrahma (2022), in a concentration of 12.8%, the *bidara* leaf extract showed an inhibition power of 12.58 mm. This indicates that the *bidara* fruit has similar inhibition power against *Salmonella typhi* to the *bidara* leaf.

The antibacterial activity was divided into four levels, namely weak, moderate, strong, and very strong. Bacterial activity is considered weak if the diameter of the inhibition zone is <5 mm, moderate if the diameter is between 5-10 mm, strong if it is between 10-20 mm, and very strong if >20 mm. It could be concluded that the inhibition power of the *bidara* fruit, which ranged from 12.8-21.1 mm, is strong in a concentration of 12.5 %-75 % and very strong in a concentration of 100% [17].

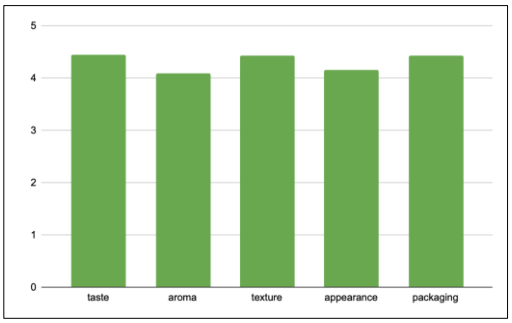


Figure 5 Graph Results of Organoleptic Test

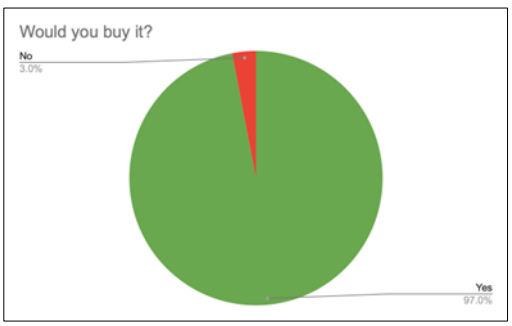


Figure 6 Graph of Organoleptic Test Results (Would you buy it?)

Based on the result of the organoleptic test, the Juju Jam could be accepted well by 33 panellists.

4. Conclusion

The extract of jujube fruits mostly contains flavonoid, phenolic, and tannin compounds as secondary metabolites. Based on the results of the antioxidant activity testing on bidara fruit ethanol extract using DPPH the IC50 of the extract was 234,2139 ppm and was considered to be a strong antioxidant. Based on the results of BSLT testing, the LC50 of the extract was 4,5449 ppm, which classifies the extract as having high toxicity. The antibacterial test shows that the bidara fruit had strong or very strong antibacterial activity against Salmonella Typhi depending on the concentration. From the information above, the bidara fruit extract could be used as an anti-cancer agent and with strong or very strong antibacterial activities. The results also show that Juju Jam can be accepted well.

Compliance with ethical standards

Acknowledgments

We want to acknowledge the contribution of the Chemistry Department of Hang Tuah University and Biology departement of Airlangga University who help in carrying out the experiments.

Disclosure of conflict of interest

Authors have no conflict of interest.

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