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Formulation of Nutraceutical Dosage Form Cempedak Leaves (*Artocarpus integer* (Thunb.) Merr) Cereal as Immunity Booster for Children

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ABSTRACT

Cempedak (*Artacorpus integer* (Thunb.) Merr) is a plant whose fruit is commonly consumed by the public. However, the leaves are still not widely used and have been reported to have various benefits as efficacious herbal medicines. This is due to its phenolic compounds which play a role in counteracting free radicals and indirectly positively impact the body's immunity. This study aims to formulate cempedak leaf cereal as a new nutraceutical for children. The stages carried out include making extracts, cereal formulations, and evaluating the characteristics of cempedak leaves cereal including organoleptic, specific gravity, compressibility index, flow rate, granule repose angle, moisture content, reconstitution time, organoleptic and pH tests after reconstitution, sedimentation volume, and physical stability test. The formulations were three variations, namely F1 (containing 1% extract), F2 (containing 3% extract), and F3 (containing 5% extract) in the form of granules using wet granulation methods. The formulation and evaluation results of the three formulations are not much different from one another. However, based on the results of the compressibility index, F2 met the good standard criteria, namely 9.23%. The aroma and taste of the formulation are the same as commercial cereals, so we are sure that children will like them. In addition, the results of phytochemical tests also showed that the secondary metabolites contained in cempedak leaf extract could act as immune boosters. The three formulations also showed good stability for 30 days. Based on the results, our formulation met the criteria as nutraceuticals.

Keywords: Nutraceutical; Cereal; Cempedak leaves extract; Immune booster

INTRODUCTION

Immunity is the ability of an organism to fight infection with pathogens or defend itself against foreign chemicals or organisms (antigens). After the pandemic, when schools reopened offline, parents were concerned and aware of their children's health. The main line of defense against infectious diseases is strengthening a child's immune system. Immunity protects life by leveraging cellular responses and the immune system. The body promotes systematic immune processes by regulating the formation of T lymphocytes, antibodies, and cytokines.[1] Preventing and treating disease and promoting health through a nutrient-rich diet play an important role in disease prevention and disease resistance in children.

Eating habits and lifestyle have changed a lot from the past, which not only contributes to the emergence of physical health problems in children but also reduces their ability to fight disease. It is important to raise awareness among

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mothers and caregivers about the importance of boosting children's immunity through diet. Parents and other adults who are responsible for their children must be informed about the factors that affect immunity and strategies for boosting it.[2] Body immunity is affected by a person's overall nutritional status, nutritional state, and food intake patterns (consisting of food, nutrients, and non-nutritional bioactive compounds), and this impact can be felt at the level of physical barriers (such as the skin and intestinal mucous membranes), microbiome, innate immune system (such as macrophage function and polarization), and adaptive immune system (such as T- and B-cell function).[3] The aim of providing healthy and nutritious food is one of the recommended efforts to increase immunity at an early age, as an effort to ensure that children's bodies are healthy and develop optimally and normally.[4]

Overcoming this problem, it is necessary to increase immunity for children with nutraceuticals which are currently being developed and are in great demand because of the delicious taste, namely cereal, while this cereal is also made from natural ingredients, namely cempedak leaves. Cempedak leaves are one of the ingredients that are widely available in Indonesia. The ethanol extract of cempedak leaves has antioxidant activity which is included in the active category with an IC_{50} value of 52.7705 ppm (10). + 0.415% w/w).[5]

Compounds contained in cempedak leaves are flavonoids, phenols, and heteroflavones C which are phenolic compounds.[6] Phenolics have strong antioxidant abilities and can act as neutralizers for free radicals that cause damage to cells in the body.[7] Oxidative stress is caused by the generation of abundant reactive oxygen species, linked to the reduced capacity of endogenous systems of organisms to counteract them. Activation of pro-oxidative pathways and increased inflammatory cytokines are invariably encountered in viral infections. Antioxidants prevent oxidative processes, by inhibiting the formation of harmful radical species[8] and protecting cells and tissues from oxidative damage and dysfunction.[9] Thus, antioxidants can also boost the immune system[10] in children.

Until now there has been no research on nutraceuticals of cempedak leaves cereal as a child's immunity enhancer. Several other studies have been carried out related to natural ingredients from cempedak leaves, namely research on the formulation and evaluation of spray gel preparations for sunscreen ethyl acetate fraction of cempedak leaves with the results of SPF values from highest to lowest respectively, namely formula I (2.186); formula II (2.141) and formula III (1.870), this research was motivated by cempedak leaves having antioxidant activity and containing secondary metabolites in the form of flavonoid compounds which are known to have potential as sunscreens due to the presence of chromophore groups (conjugated single double bonds) which can absorb sunlight UV.[11] Then another study, namely the physical stability test of serum anti-aging ethyl acetate extract of cempedak leaves which contains antioxidants.[12] So from these studies that cempedak leaves have just been made in the form of spray gel and anti-aging serum preparations, research on the nutraceuticals of cempedak leaves cereal is a novelty in this study.

METHODS

There are two stages of this research, including preparation and verification of raw materials, and formulation of cempedak leaves cereal.

Equipment and materials

The equipment used includes a rotary evaporator (Buchi), oven (Memert), sifter mesh no. 10; 16; and 40 (Lionstar), macerator (Harapan Jaya), mixer (Han River), glass type (Pyrex), stopwatch, test tube (Iwaki), moisture balance (Sartorius), flow tester granul (DMS), tap density (Biobase) pH meter (Morinome EZ-9908), mortar and stamper.

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The materials used includes cempedak leaves (Kebun Mini Herbal-PT. Palapa Muda Perkasa), garut flour (Lingkar Organik), sucrose (Refined Crystal Sugar), stevia (Royal Stevia), coconut milk powder (Sasa), non-dairy creamer (Ellenka), xanthan gum (Fufeng), sodium benzoate (Purox), eggs, powdered soy milk (Unisoy), vanilla essence (Koe poe-koe poe), aquades, and 96% ethanol.

Procedures

1. Cempedak leaves simplicial production

Cempedak leaves are sorted to separate from leaves with unfavorable conditions, then cleaned with running water, and dried in an oven at 40°C for 2 x 24 hours.

2. Cempedak leaves extract production

Simplicia of cempedak leaves as much as 1000 g was extracted by maceration in 5 L 96% ethanol, for 3 x 24 hours at room temperature with several times of shaking to optimize the extraction process. Every 1x24 hours the solvent is replaced. The resulting liquid extract was then filtered using filter paper and the filtrate obtained was concentrated with a rotary evaporator to obtain a thick extract. Then a physical evaluation of the extract was carried out including examining the color, smell, and taste of the extract.

3. Phytochemical test of cempedak leaves extract

Phytochemical tests of cempedak leaves extract included tests for saponins, alkaloids, flavonoids, steroids/ triterpenoids, and tannins. The test methods are saponin test using foam test, alkaloid test using Mayer's reagent, flavonoid test using magnesium powder, steroid/triterpenoid test using Liebermann-Burchard reagent, and tannin test using $FeCl_3$.

4. Ethanol content test of cempedak leaves extract

An ethanol content test was carried out to ensure whether there was any ethanol content in the extract. Cempedak leaves extract was tested using the ethanol esterification test, by adding extract samples with concentrated sulfuric acid and acetic acid which were then heated. A negative reaction is indicated by the absence of a distinctive ethyl acetate odor.

5. Formulation of cempedak leaves cereal

In this research, cempedak leaf cereal will be made in the form of granules with 3 different formulas as described in Table 1. Cempedak leaves cereal granule formulation was made by weighing cempedak leaves extract and then sifting the ingredients of arrowroot flour, sucrose, stevia, coconut milk powder, vegetable creamer, xanthan gum, sodium benzoate, and soy milk using mesh no. 40. All of these ingredients were then weighed and mixed until homogeneous using a mixer for 10 minutes. The eggs are added little by little until a granular mass is formed, and then the essence is added. The granule mass obtained was sifted with mesh no. 10, then dried using an oven at 50 oC for 3 hours to obtain granules with a moisture content of 2 – 4%. The dried granules were then sieved using mesh sieve no. 16 and continued with the evaluation of granule characteristics.

Table 1 Formulation of cempedak leaves cereal

Materials	Formula (% w/w)		
	F1	F2	F3
Cempedak leaves extract	1	3	5
Garut flour	20	20	20
Sucrose	20	20	20
Stevia	3	3	3
Coconut milk powder	20	20	20
Non-dairy creamer	5	5	5
Xanthan gum	1	1	1
Sodium benzoate	0,1	0,1	0,1
Eggs	3,5	3,5	3,5
Essence	7	7	7
Powdered soy milk	19,4	17,4	15,4

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6. Evaluation of characteristic cempedak leaves cereal

The resulting cempedak leaves cereal granules were then evaluated which included organoleptic tests, specific gravity, compressibility index, flow rate, granule repose angle, moisture content, reconstitution time, organoleptic tests after reconstitution, pH tests after reconstitution, sedimentation volume evaluation, and physical stability test.

a. Organoleptic test

Organoptical evaluation was carried out by visual observation of gummy candies preparations which were obtained through shape, color, taste, and smell.[13]

b. Compressibility index and Hausner ratio

A total of 25 grams (M) of cempedak leaves cereal granules was put into a 100 ml measuring cup which was tilted at an angle of 45^{o} quickly, then the measuring cup was straightened and shaken quickly to level the surface, and then the volume (V_{bulk}) was measured to obtained apparent density = (M/V_{bulk}) g/mL. The measuring cup containing the granules is then tapped 300 times and the compressed volume will be obtained and the compressed specific gravity is calculated using the formula: tapped density (ρ_{tapped}) = (M/V_{tapped}) g/mL. The compressibility index value is calculated according pharmacopeia using the equation:[14]

$$\%\ compressibility\ index = \frac{\rho tapped - \rho bulk}{\rho tapped}\ x\ 100\%$$

Hausner ratio also calculated using the equation:

$$Hausner\ ratio = \frac{Apparent\ volume\ (Vo)}{Final\ tapped\ volume\ (Vf)}$$

c. Flow rate

A total of 100 grams of cempedak leaves cereal granules were weighed and flow time tested. The flow rate of the granules is expressed in units of grams/second and the granules flow no more than 10 seconds.[14]

d. Angle of repose

Cempedak leaves cereal granules as much as 100 g is poured into the funnel with the bottom of the funnel hole closed. After that, the bottom of the funnel was opened and the time it took for all the granules to flow to the flat surface was recorded. The measurement of the angle of repose is stated to be between 25-40°C. The angle of repose is determined by equation:[14]

$$Tan\ \alpha = \frac{h}{r}$$

e. Moisture content

Testing the moisture content by using a moisture balance. Granules as much as 5 grams are measured for their moisture content with a tool. Good moisture content is 1-5%.[15]

f. Reconstitution time

Cempedak leaves cereal granules from each formula were reconstituted as much as 30 grams (1 sachet) in 150 mL of pure water, then stirred. The time required for the granules to be completely dispersed was calculated using a stopwatch. Terms of good granules can dissolve in less than 5 minutes.[15]

g. Organoleptic test after reconstitution

Organoleptic evaluation of cempedak leaves cereal was carried out on the parameters of color, taste, smell, and consistency.[16]

h. pH test

pH evaluation was carried out on reconstituted cempedak leaves cereal using a pH meter instrument (Morinome EZ-9908).

i. Sedimentation volume evaluation

The reconstituted cereal was put into a 100 mL measuring cup and stored at room temperature, then observed every 15 minutes until the 60th minute. The volume of cempedak leaves cereal that was filled at the beginning was the initial volume (Vo) and the volume at 60 minutes was recorded as the final volume (Vu). Sedimentation volume is determined using the equation F=Vu/Vo.[17]

j. Physical stability test

The physical stability test of cereals was carried out for 30 days of observation at room temperature storage of 30±2°C. Observations were made every 7 days, with observation parameters including color, smell, and taste.[17]

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RESULTS AND DISCUSSION

Cempedak leaf extract was obtained by maceration method using 96% ethanol. The yield of the concentrated cempedak leaves extract obtained was 40.04%. Furthermore, phytochemical tests were carried out on cempedak leaf extract including tests for saponins, alkaloids, flavonoids, steroids/triterpenoids, and tannins which are presented in Table 2.

The results of the phytochemical test that we carried out were slightly different from the results of the previous test conducted, namely that the saponin test results were negative, while our results were positive.[6] So, based on the results of our phytochemical tests, cempedak leaf extract contains secondary metabolites including saponins, flavonoids, and tannins.

Table 2 Phytochemical test of cempedak leaves extract

Secondary Metabolites	Results
Saponin	Positive
Alkaloid	Negative
Flavonoid	Positive
Steroid/ Triterpenoid	Negative
Tannin	Positive

The content of these secondary metabolites plays a role in the pharmacological activity of cempedak leaf extract. In terms of its role in enhancing immunity, the antioxidant activity of cempedak leaf extract which has previously been reported can contribute as an immune booster.[18] The pharmacological activity was reported due to the role of the phenolic compounds contained in the cempedak leaf extract. Phenolic group compounds are able to deactivate free radicals which will have an impact on increasing the immune system.[19] Not only phenolics, flavonoids and tannins also play a positive role in enhancing the immune system through the elimination of free radicals.[20,21]

The results of the ethanol content test of cempedak leaf extract showed a negative result, which means it is safe for further use as a nutraceutical formulation.[22]

Cempedak leaves extract was then formulated with 3 different formulation designs marked with F1 (formulation 1), F2 (formulation 2), and F3 (formulation 3) which have been described in Table 1. The results of the formulation were then sieved and then in the oven for 2 hours and the results sifted back. The result is in the form of granules as shown in Figure 1.

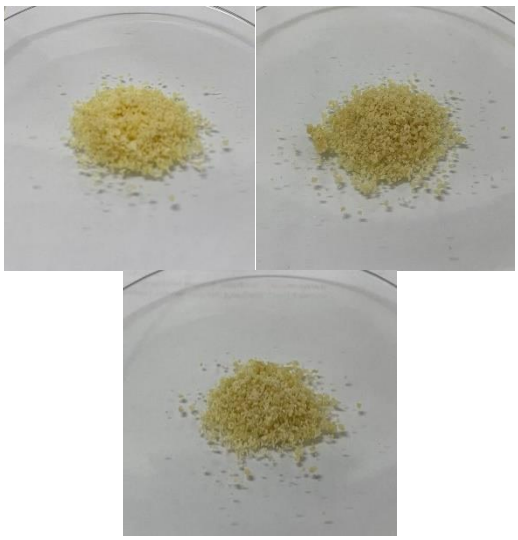

Figure 1 Formulation results of cempedak leaves cereal (a) F1, (b) F2, and (c) F3

Organoleptic tests of cereal granules are presented in Table 3 where there are differences in color between F1, F2, and F3. Together with other evaluation tests, it includes compressed density and calculating compressibility index values. Evaluation of granule density is carried out to predict the ability of granules to flow and fill the volume of space. Particles with high density can generally flow freely.[23] The measurement of density carried out is a measurement of incompressible index related to the calculation of the Hausner

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ratio.[24] Formula F2 had Hausner ratio with value 1.09 that indicate granules had excellent flow character. Meanwhile formula F1 and F2 had Hausner ratio 1.24 and 1.28 repectively that indicate granules had fair flow character. The Hausner ratio is the fiber density (porosity) expressed in percent, namely the ratio between volume and total volume of a granule. The smaller the Hausner ratio, the better, because the resulting granules are more compact due to smaller pores.[25]

The results of calculating the compressibility index of cempedak leaves cereal granules were F1 19.23%, F2 8.33%, and F3 18.60% respectively. The good compressibility index is <10%[26], whereas of the three granule formulations we used, only F2 has a good compressibility index. Granule size that is still not uniform can be the cause of the poor compressibility index results.

The flow rates of the three formulations of cempedak leaves cereal granules were <10 grams/second, this indicated that all three of them flow easily.[27] Good flow characteristics are defined as the ability of particles not to consolidate and to flow independently under the influence of gravity. The mechanism for increasing the flowability of granules is caused by several factors, namely particle size, particle shape, particle surface morphology, and changes in surface force.[28]

Good flow properties are defined as the ability of the particles not to consolidate or collect and to flow assisted by the force of gravity. The increase in the flow properties of granules is determined by many factors such as particle size, particle shape, particle surface morphology, and changing forces on the surface.[29] The categories of flow properties and attachment to the angle of repose are very good (<25°), good (25-30°), adequate (30-40°), and very poor (>40°).[30] The results of the evaluation of the angle of repose of the three successive granule formulas were 32.38 (F1); 26.33 (F2); and 28.97 (F3) meet the good criteria.

Granule moisture measurement aims to determine the moisture content of the granules that have been made after drying. Drying aims to control so that the granule mass is not easy for fungi and microbes to grow.[31] In addition, the high moisture content also causes the granules to stick to the container. Granular products with herbal ingredients must have a moisture content below 4%.[32] Moisture content is needed to form bonds between particles so that one particle with another particle merges into one to form a more compact and spherical mass.[33] On the other hand, a moisture content that is too high can cause aggregation and agglomeration of small particles, making it more difficult for the particles to flow.[34] The moisture content of the three granule formulations complies with the requirements, namely F1 3.44%, F2 3.65% and F3 2.96%.

The resulting cempedak leaves cereal granules were then continued to evaluate the physical and chemical characteristics after reconstituting. Cempedak leaves cereal granules as much as 30 grams (1 sachet) in 150 mL of distilled water. The reconstitution results showed that cempedak leaves cereal was dispersed in suspension, yellow in color, smelled of vanilla, and had a sweet taste. The results of reconstitution can be seen in Figure 2.

Cempedak leaves cereal which had been reconstituted after being organoleptically observed was then subjected to sedimentation tests and pH measurements. The results of the sedimentation measurements were carried out with a time of 0, 30, and 60 minutes, and the three formulas did not show

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sedimentation. This can be caused by the use of suspending agents such as xanthan gum so that the resulting suspension characteristics are good and homogeneous. Xanthan gum has the characteristics of being able to produce high viscosity at low concentrations and has good dispersion power. This can increase the physical stability of the preparation before consumption.[35]

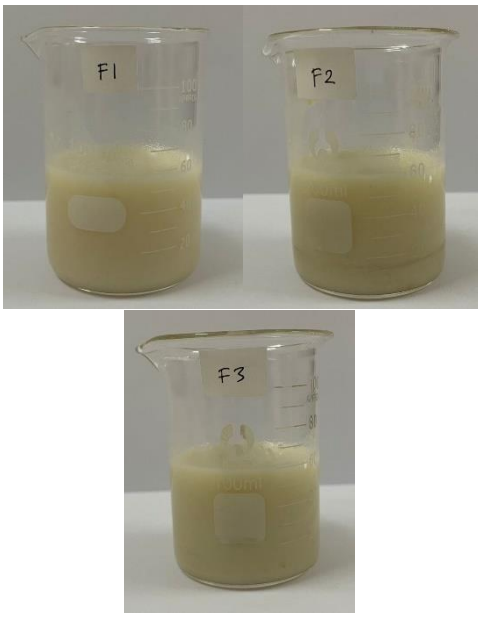

Figure 2 Reconstitutions result of cempedak leaves cereal (a) F1, (b) F2, and (c) F3

The next evaluation is measuring the pH of cempedak leaves after reconstituting. This pH measurement was carried out to determine the level of acidity of cereals because it can affect the stability of chemical compounds contained in cempedak leaves and the acceptability of cereals. According to the reference article, acceptable cereal pH is in the range of 5.5-7.8.[36] The evaluation results of the three formulations were 7.07 (F1); 6.90 (F2); and 6.04 (F3). These results indicate that the three formulations of cempedak leaf cereal meet the pH standard of cereals.

The results of the stability test we carried out on the Cempedak leaf cereal formulation for 30 days with physical observations every 1 week. Physical observations that we do include color, smell, and taste. The results of physical observations for 30 days of the three formulations showed good results marked by no change in color, smell, and taste. This shows that the formulation of cempedak leaf cereal is ideal and can be produced for commercial needs.

Table 3 The results of characteristic evaluation of cempedak leaves cereal

Parameters	F1	F2	F3
Organoleptic	pale yellow, granule form, vanilla scent, sweet flavour	yellow, granule form, vanilla scent, sweet flavour	deep yellow, granule form, vanilla scent, sweet flavour
Compressibility index	23.96%	9.23%	23.10%
Flow rate	9.92 g/s	6.61 g/s	5.64 g/s
Granule angle of repose	32.38˚	26.33˚	28.97˚
Moisture content	3.44%	3.65%	2.96%
Reconstitution time	1.18 minutes	1.17 minutes	1.32 minutes
Organoleptic (post-reconstitution)	pale yellow suspension, vanilla scent, sweet flavour	yellow suspension, vanilla scent, sweet flavour	deep yellow suspension, vanilla scent, sweet flavour
pH	7.07	6.90	6.04
Sedimentation volume (F)	1.00	1.00	1.00

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CONCLUSION

Cempedak leaves extract can be made into cereal nutraceuticals and the results of phytochemical tests also show that the secondary metabolites contained in cempedak leaf extract can act as an immune enhancer. Three formulations of cempedak leaves cereal have met good criteria as nutraceuticals from the results of the preparation evaluation. Based on the compressibility index value, the best formulation is F2 with 8.33%.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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