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Original Article

Antigout Activity of Terap (*Artocarpus odoratissimus* Blanco) Leaves Extract: Leaves Characteristic and *In Vitro* Studies

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ABSTRACT

Terap leaves (*Artocarpus odoratissimus* Blanco) contain various chemical constituents, making it a herbal medicine prospective source, particularly as an antigout. This research aim to determinate characteristics of terap leaves and in vitro antigout activity of terap leaves ethanolic extract. The determination leaves characteristics included macroscopic and microscopic analysis, water and ethanol soluble extract content, and drying shrinkage. The extract antigout activity was determinated through inhibition of xanthine oxidase enzyme in vitro. Leaves characteristics analysis revealed that mature leaves are approximately 31.5 cm long and 18 cm wide. Terap leaves are single leaves, elliptical, blunt leaf tips, rounded bases, rough surfaces, undulating edges, pinnate veins, and yellow veins. Microscopic analysis reveals the presence of anomocytic-type stomata, trichomes, glandular hairs, resin ducts, and trachea. Terap leaves have a water-soluble extract content of 8.72%, ethanol-soluble extract content of 4.29%, and drying shrinkage of 11.38%. The antigout activity tests results indicates that ethanol extract inhibits xanthine oxidase enzyme with an IC_{50} of 89.63 µg/mL. Terap leaves have antigout properties, so they have the potential to be developed into a quality antigout herbal medicine.

Keywords: Artocarpus odoratissimus, Antigout Activity, Xanthine Oxidase Enzyme, Macroscopic and Microscopic Analysis.

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INTRODUCTION

Gout is the disease as results from the buildup of monosodium urate crystals in the body tissues, leading to an inflammatory response that causes pain, swelling, and redness in the joints. These symptoms are most pronounced when experiencing advanced hyperuricemia, which is characterized by elevated levels of uric acid in the blood exceeding 7 mg/dL in men and 5.7 mg/dL in women [1,2]. The formation of uric acid commences with purines converting into hypoxanthine and xanthine, which then convert into uric acid. Xanthine oxidase is an enzyme that assists in these changes [3,4].

Synthetic compounds, such as allopurinol, can inhibit the action of the xanthine oxidase enzyme. These drugs competitively inhibit the xanthine oxidase enzyme, thereby limiting uric acid production. It forms metabolites that are more water-soluble than uric acid and xanthine, simplifying their excretion from the body [5]. The administration of allopurinol as an antigout medication results in various side effects, including sickness, retching, erythema, renal dysfunction and alopecia. Some of these adverse effects render the use of allopurinol unpleasant for extended periods by gout patients. This leads some patients with gout to lean towards the application of herbal medicines to alleviate their ailment.

Some chemical compounds present in medicinal plants used as anti-gout agents are flavonoids, alkaloids, and steroids. These compounds exhibit antigout activity by inhibiting the xanthine oxidase enzyme. This group of secondary metabolites has demonstrated its antigout effectiveness through the inhibition of xanthine oxidase enzyme [6-9].

One of the plants in Indonesia that has the potential to be developed into herbal medicine to treat gout is terap (*Artocarpus odoratissimus*). This plant belongs to the Moraceae family [10]. Terap has a kinship with cempedak, jackfruit and breadfruit, and can be found in Borneo (Kalimantan, Sabah, Sarawak, Brunei). Based on research from Naspiah, et.al., 2021 and Yen, et.al, 2017, it is known that Terap Leaves (*A. odoratissimus*) contains chemical compounds in the form of stigmasterol, β-sitosterol, alkaloids, flavonoids, phenolics, and steroids/ triterpenoids [11,12]. These chemical compounds make terap leaves have various pharmacological activities, such as antioxidant, antigout, antidiabetic, antibacterial, and anticancer [13,14]. Empirical data from the local people of North Kalimantan stating that terap leaves can be used to treat gout conditions, scientifically proven through research by Naspiah, et.al., in 2021 which states that the content of secondary metabolites in terap leaves, namely flavan-3-ol has activity as an antigout through its interaction with the xanthine oxidase enzyme in silico [11].

The chemotaxonomic approach also suggests that terap plants have antigout activity. This is because terap belongs to the Artocarpus genus, where other plants from the Artocarpus genus, such as Artocarpus communis and Artocarpus elasticus are known to contain flavonoid compounds (cyclogeracommunin and artonol A) which have the ability to inhibit the action of xanthine oxidase enzyme. This causes these two plants to be used as an antigout [15]. Based on this, terap are also thought to have potential as an antigout.

Based on empirical and scientific evidence, as well as the chemotaxonomic approach, terap leaves (*A. odoratissimus*) are believed to have significant

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potential for development of high-quality herbal medicines for gout treatment. As a result, it is essential to investigate the antigout activity of terap leaves extracts by evaluating their inhibition of xanthine oxidase enzyme in vitro. In addition, objective scientific data is required to establish the characteristics of dry terap leaves, which will serve as the foundation for developing high-quality herbal medicines. This information encompasses organoleptic test, macroscopic and microscopic tests, phytochemical screening, water and ethanol soluble extracts, and drying shrinkage. This study aimed to assess dried leaves characteristics and investigate in vitro antigout activity of extract.

MATERIALS AND METHODS

Instruments and Materials

The equipment used in this study included heating furnaces, micro pipettes, rotary evaporators, microscopes, microplate readers, 96-well plates, cutting tools (scissors and cutters), and glassware (beaker glass, measuring glass, test tubes, Erlenmeyer flasks with lids, glass funnels, pipettes, vials, etc.).

The material studied was terap leaves (*A. odoratissimus*) in dry form taken from North Kalimantan. In addition, the materials used in this study were distilled water, aluminum foil, chloroform, H_2SO_4, filter paper, NaOH, xanthine substrate, xanthine oxidase enzyme, and phosphate buffer.

METHODS

Sample Preparation

Terap leaves were taken from Tanjung Selor City, North Kalimantan. Sample preparation was carried out by cleaning all parts of leaves by washing them with clean water, then drying them indirectly from sunlight. Furthermore, the dried leaves were cut into small pieces.

Characteristics of Terap Leaves

1) Organoleptic Test

The organoleptic test of dried leaves powder includes color, taste, smell, and form.

2) Macroscopic and Microscopic Analysis

The macroscopic analysis was carried out by visually observing the morphology of fresh leaves and measuring the length and width of leaves in general. In addition, color and parts of leaves were also observed, including shape, type of leaf vein, edge, tip, base, type, and surface of the leaves.

The microscopic analysis were carried out by observing cross-sections and longitudinal sections of dried terap leaves under a microscope. Cross-sections of terap leaves are made by making thin cross-sections on leaves with a cutter. Then the slices were placed on the object glass, then added a few drops of water and covered with a cover glass. Next, the preparations were observed under a microscope with a strong magnification of 400x. Cross-sections were made by making cross-sections through the midrib of leaves and longitudinal sections were made by making longitudinal slices in the upper and lower epidermis.

3) Water Soluble Extract Content

Determination of water-soluble extract content was carried out by macerating 5 g of dried leaves for 24 hours with 100 mL of water-chloroform LP using a closed flask while shaking repeatedly for the first 6 hours, then allowed to stand for 18 hours, and filtered. Evaporated 8 mL of filtrate to dryness in an evaporating cup. The residue was heated at 105°C to constant weight. The tested samples were made with 3 replicates. The concentration of the compound dissolved in water was calculated by the initial weight of the dried leaves.

$$\text{Water Soluble Extract} = \frac{(\text{weight before drying} - \text{weight after drying}) \times 5}{\text{dried sample weight}} \times 100\ \%$$

4) Ethanol Soluble Extract Content

Determination of ethanol-soluble extract content was carried out by macerating 5 g of dried leaves for 24 hours with 100 mL of ethanol 96 % using a closed flask while shaking repeatedly for the first 6 hours, then allowed to stand for 18 hours, and filtered. Evaporated 8 mL of the filtrate to dryness in an evaporating cup. The residue was heated at 105°C to constant weight. The tested samples were made with 3 replicates. The concentration of the compound dissolved in ethanol was calculated by the initial weight of the dried leaves.

$$\text{Ethanol Soluble Extract} = \frac{(\text{weight before drying} - \text{weight after drying}) \times 5}{\text{dried sample weight}} \times 100\ \%$$

5) Drying Shrinkage

Determination of drying shrinkage is carried out by placing 1 g of dried leaves in a cup whose weight is known. Heat the cup in a heating furnace at 110°C until the weight remains constant. Before each drying, the dishes are allowed to cool in a desiccator. The tested samples were made with 3 replicates. Determine the final weight of the dried leaves and calculate the drying shrinkage.

$$\text{Drying Shrinkage} = \frac{(\text{weight before drying} - \text{weight after drying}) \times 5}{\text{weight before drying}} \times 100\ \%$$

Extraction

Extraction was carried out by maceration method using 70 % ethanol for 3 x 24 hours. Each extract was concentrated using a rotary evaporator to obtain a thick extract, which was then subjected to phytochemical screening.

Antigout Activity Test through Xanthine Oxidase Enzyme Inhibition

The method of testing antigout activity through inhibition of xanthine oxidase enzyme was carried out based on the method of Quy and Xuan in 2019, with minor modifications. The assay was performed by mixing 50 µL of extract, 30 µL of 70 mM phosphate buffer solution pH 7.5, and 30 µL of 0.2U/mL xanthine oxidase enzyme solution into a 96-well plate.

Furthermore, pre-incubation was carried out at 25°C for 15 minutes. Then 60 µL of 0.15 mM xanthine substrate solution was added to the previously mixed solution. The solution mixture was incubated at 25°C for 30 minutes, then 25 µL 1 N HCl was added to the solution mixture that had been incubated to stop the enzymatic reaction. The absorbance of the solution was measured using a microplate reader at a wavelength of 290 nm (result of wavelength optimization[16]. Absorbance measurements were also carried out on the allopurinol test solution as a positive control. The percent inhibition calculation of xanthine oxidase enzyme is carried out using the following formula.

$$\%\ Inhibition = \frac{(A - B) - (C - D)}{A - B} x\ 100\ \%$$

Where A = Absorbance of the unsampled solution; B = Absorbance of the solution without sample and enzymes; C = Absorbance of the solution with the sample; D = Absorbance of the solution with sample and without enzyme.

Data on the inhibition percentage of xanthine oxidase enzyme activity at each solution concentration were processed using linear regression analysis to determine the IC_{50} value (50 % Inhibition Concentration).

RESULTS

Artocarpus odoratissimus, commonly known as Terap by the people of North Kalimantan. Terap is typically found in Borneo (Kalimantan, Sabah, Sarawak, Brunei). Terap belongs to the moraceae family [10].

Terap leaves utilised in this analysis were obtained from Tanjung Selor City, North Kalimantan. The leaves collected were relatively old and had a dark green in colour, as depicted in Figure 1. Furthermore, the leaves are converted into a dried form to extend their shelf life. Additionally, the process of verifying the dried terap leaves was conducted to ascertain their identity. The identity of terap leaves is a crucial factor for the future development and quality utilization of herbal medicinal products. To obtain the identity of plant, determinations were made. The determination process was carried out in the Mulawarman Herbarium section, at the Ecology and Conservation Laboratory of Tropical Forest Biodiversity, Faculty of Forestry, Mulawarman University, Samarinda City, East Kalimantan, Indonesia. The plant parts used for determination process are leaves, young fruits, petioles, and stems.

After the determination process, it is known that terap have the Latin name *Artocarpus odoratissimus* Blanco, which is locally known in Indonesia as terap or tarap. Its synonym is *Artocarpus mutabilis* Becc. The dried terap leaves are ground into a powder. Moreover, organoleptic assessments were conducted on the powdered terap leaves to evaluate their shape, colour, taste, and aroma. This was done to determine the organoleptic characteristics of dried terap leaves. The results of organoleptic are coarse powder form, dark green colour, tasteless, and typical leaf aroma. Furthermore, both macroscopic and microscopic analysis were conducted on terap leaves. The results of the macroscopic analysis are presented in Table 1.

Figure 1. Leaves of Terap.

Table 1. The Results of Macroscopic Analysis.

No	Description	Results	Picture
1	Size	− Lenght : ± 31,5 cm − Width : ± 18 cm	
2	Colour	− Above : Dark green − Under : Light green	
3	Leaves Character − Type − Form − Edge − Base − Surface − Side − Bones − Bone colour	 − Single − Elliptic − Blunt − Rounded − Rough − Undulate − Pinnate − Yellow	

Table 2. Characteristics of Terap Leaves.

No	Parameters	Results (%) (± SD)
1	Water soluble extract content	8.72 (± 0.7)
2	Ethanol soluble extract content	4.29 (± 0.1)
3	Drying shrinkage	11.38 (± 0.35)

Microscopic analysis was conducted to identify the characteristics of terap leaves through their anatomical structure. Figure 2 and Figure 3 presents the results of the microscopic analysis. The microscopic analysis results for cross-sections of terap leaves indicate the presence of epidermis, anomocytic stomata, trichomes, nuclei, glandular hairs, resin ducts, parenchyma, xylem, phloem, and secretory glands. Similarly, the longitudinal section of terap leaves showed epidermis, anomocytic stomata, nuclei, parenchyma, and trachea.

Drying shrinkage testing seeks to establish the number of compounds that are lost due to the drying process, including water and volatile compounds from leaves. Table 2 presents the findings of the drying shrinkage test, suggesting that the compounds lost in drying are not excessive. In parallel, testing the content of water-soluble and ethanol-soluble extracts aims to determine the quantity of these compounds dissolved in water and ethanol solvents, respectively.

The results of the activity test on terap leaves ethanol extract, as reflected in Table 3, demonstrate its potency in inhibiting xanthine oxidase enzyme, with an IC_{50} of 89.63 µg/mL. Notably, the positive control in this experiment, allopurinol, exhibits very high activity against xanthine oxidase, with an IC_{50} of 1.6 µg/mL.

DISCUSSION

Plant characterization involves a series of procedures and parameters that inform the extract's character and pharmaceutical quality, ensuring stability as a pharmaceutical product. This study aimed to characterize terap leaves in both their fresh and dried forms, determining their unique characteristics and identity. The identification involved several standard parameters, including organoleptic evaluations, macroscopic and microscopic analysis, water-soluble and ethanol-soluble extracts, and drying shrinkage.

Fresh leaves were observed visually for their morphology during the macroscopic analysis. In contrast, dried terap leaves were utilized for the microscopic analysis where cross-sections and longitudinal sections were observed. Microscopic analysis was conducted to identify the characteristics of terap leaves through their anatomical structure. The test involved observations of cross-sectional and longitudinal sections of terap leaves under a microscope. Sections through the midrib of the leaf were used for cross-sections, while longitudinal slices of the upper and lower epidermis were made for longitudinal sections. The microscopic analysis results for cross-sections of terap leaves indicate the presence of epidermis, anomocytic stomata, trichomes, nuclei, glandular hairs, resin ducts, parenchyma, xylem, phloem, and secretory glands. Similarly, the longitudinal section of terap leaves showed epidermis, anomocytic stomata, nuclei, parenchyma, and trachea.

Please note, epidermal tissue is the tissue located on the outer surface of plant organs. Its function is to shield the internal parts of plant organs from external conditions, including water loss due to evaporation, mechanical harm, temperature changes, and loss of food substances. Parenchymal tissue, on the other hand, is known as basic tissue. It acts as a site for the production and storage of food [17]. The nucleus, the largest organelle in the cell, is centrally located and has a round or oval shape. It consists of the nuclear membrane, nucleolus, nucleoplasm, and chromosomes or chromatin. Stomata in the epidermal tissue arise as gaps bordered by two specialized epidermal cells called guard cells. There are different types of stomata, such as the anomocytic type found

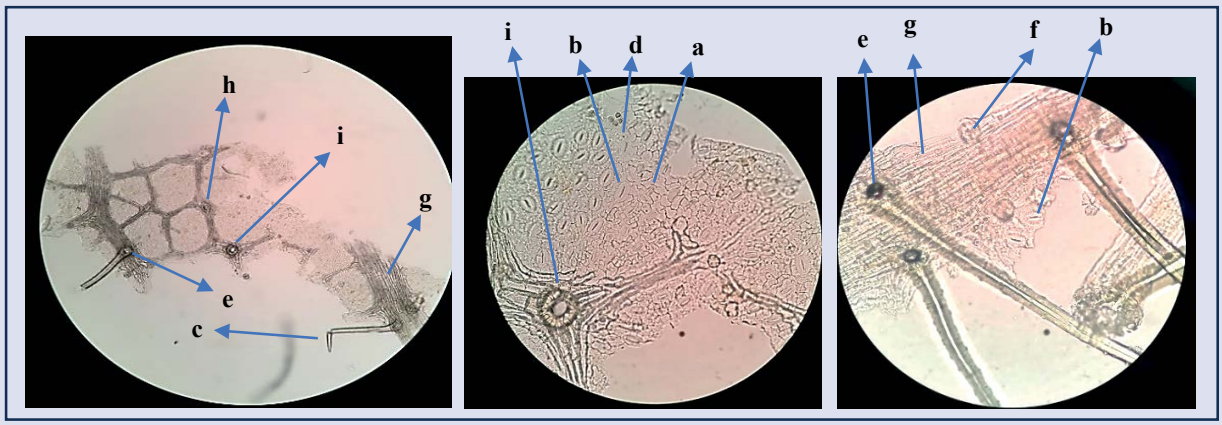

Figure 2. The Results of Microscopic Analysis (Cross section through the midrib of leaf). a : Epidermis; b : Anomocytic type stomata; c : Trichome; d : Nucleus; e : Glandular hair; f : Resin channel; g : Parenchima; h : Xylem and Phloem; i : Secretory glands.

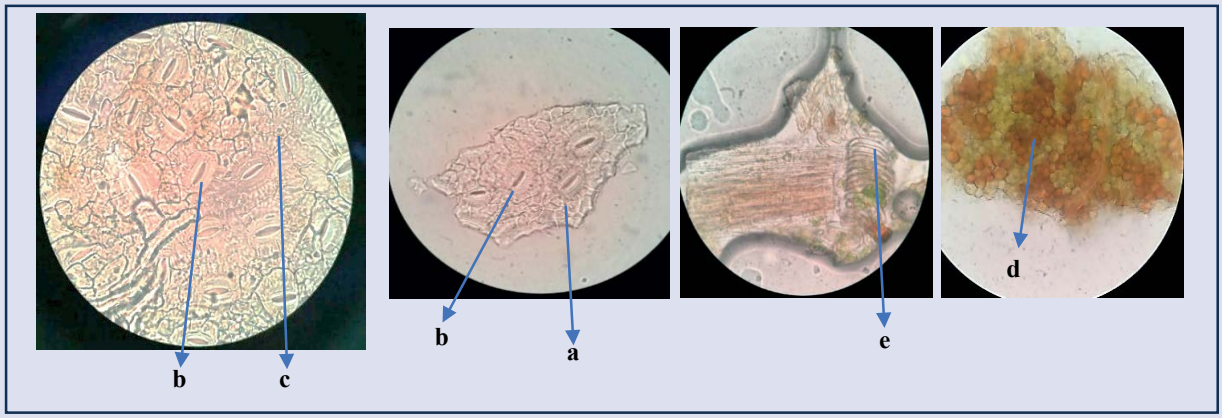

Figure 3. The Results of Microscopic Analysis (Longitudinal sections on the upper and lower epidermis of leaf). a : Epidermis; b : Anomocytic type stomata; c : Nucleus; d : Parenchima; e : Trachea

Table 3. The Results of Antigout Activity Test from Terap Leaves 70 % Ethanol Extract and Allopurinol.

No	Sample	Concentration (µg/mL)	% Inhibition (± SD)	IC_{50} (µg/mL)	Sample	Concentration (µg/mL)	% Inhibition (± SD)	IC_{50} (µg/mL)
70 % Ethanol Extract					Allopurinol			
1	Et1	10	26,04 (± 1,73)		Allo1	5	56,65 (± 0,9)	
2	Et2	50	31,2 (± 2,04)		Allo2	10	65,66 (± 0,25)	
3	Et3	100	51,6 (± 2,71)	**89,63**	Allo3	15	72,54 (± 0,57)	**1,6**
4	Et4	150	70,8 (± 2,14)		Allo4	20	86,88 (± 0,17)	
5	Et5	200	92,8 (± 0,18)		Allo5	25	92,26 (± 0,37)	

in terap leaves. Anomocytic stomata are defined by the presence of covering cells encircled by several cells with the same shape and size as the adjacent epidermal cells [18].

Xylem, the tissue responsible for transporting water and nutrients from a plant's roots to its leaves, consists of wood vessels. The phloem complements this by consisting of sieve tubes, which distribute photosynthesized food substances from the leaves throughout the entire plant. Additionally, leaves also have tracheids, which are cylindrical cells that form water transport tubes through fusion of their ends. Trichomes consist of glandular or secretory hairs, as well as non-glandular hairs, scales, papillae, and root hairs for absorption [17]. Glandular trichomes and secretory glands constitute secretory tissue, a type of plant tissue comprising cells that release various compounds (secretions) from within the plant, including water, minerals, mucus, oil sap, and fat [19]. Additionally, resin ducts are observable on terap leaves. These ducts contribute to the secretory tissue. They consist of a channel that is bordered by finger parenchyma cells or epithelial cells.

According to the test results presented in Table 2, it can be observed that the extract or compounds derived from terap leaves exhibit greater attraction or dissolution in water solvents. Therefore, it is inferred that the efficacy of terap leaves as a medicinal agent is more pronounced when employed with water solvents as compared to ethanol solvents.

The results of activity test on terap leaves ethanol extract, as reflected in Table 3, demonstrate its potency in inhibiting xanthine oxidase enzyme, with an IC_{50} of 89.63 µg/mL. Notably, the positive control in this experiment, allopurinol, exhibits very high activity against xanthine oxidase, with an IC_{50} of 1.6 µg/mL. It is worth mentioning that allopurinol is a synthetic compound frequently prescribed for

gout treatment. Allopurinol is a single compound that has activity in inhibiting xanthine oxidase enzyme, while 70% ethanol extract of terap leaves is a plant consisting of many compounds that have diverse activities against xanthine oxidase enzyme. This causes the activity of allopurinol and extracts cannot be compared.

Based on the results, it is known that the higher concentration of the extract, the higher percentage of enzyme inhibition, indicating that the enzyme inhibitory activity depends on the dose of terap leaves. In addition, from the IC_{50} value of the extract and allopurinol, it is known that 70% ethanol extract of terap leaves has an activity in inhibiting xanthine oxidase enzyme.

Although this is not comparable to the IC_{50} of allopurinol as a positive control, but when compared with the IC_{50} of other plants that also have inhibitory activity of xanthine oxidase enzyme, it can be said that 70% ethanol extract of terap leaves has good activity in inhibiting xanthine oxidase enzyme. Please note, other medicinal plants that also have inhibitory activity against xanthine oxidase enzymes are *Orthosiphon aristatus* herbs (IC_{50} : 84.78 µg/mL) [20]. In addition, the water extract of this plant is proven to significantly reduce uric acid levels in human blood [21]. Based on this, it can be seen that with an IC_{50} of 84.78 µg/mL against xanthine oxidase enzyme, it is proven to have quite good antigout activity if tested in humans. This is most likely also the case with 70% ethanol extract of terap leaves with an IC_{50} that is not much different from *Orthosiphon aristatus* herbs extract. Further research in humans needs to be done to confirm the antigout activity of terap leaves extract. The results of activity test on terap leaves 70 % ethanol extract suggest that they have great potential as a source for antigout herbal remedies, due to their ability to inhibit the function of xanthine oxidase enzyme.

Meanwhile, the ethanol extract of terap leaves comprises several secondary metabolites that cooperatively inhibit xanthine oxidase enzyme activity. The compounds comprise alkaloid, flavonoid, and steroid/triterpenoid compounds. These are a class of compounds that possess inhibitory activity against the xanthine oxidase enzyme, which may be utilized for treating gout [6-9, 11, 22]. In addition, the compounds found in terap leaves possess a range of pharmacological activities, including antioxidant, antigout, antidiabetic, antibacterial and anticancer properties [13,14]. Given the variety of secondary metabolites which possess medicinal properties, in particular as an antigout herbal medicine, terap leaves appear to have potential as a herbal medicine.

CONCLUSION

Based on the results, it is known that terap leaves have a good character and match with requirements of the other artocarpus genus. In addition, terap leaves have antigout properties, so they have the potential to be developed into a quality antigout herbal medicine.

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