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Original Article

FORMULATION AND DETERMINATION OF QUALITY PARAMETERS OF PROPOLIS EXTRACT MICROCAPSULE TABLETS FROM *TETRAGONULA SAPIENS*

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ABSTRACT

Objective: The study aimed to develop the dry powder of propolis microcapsules into tablet preparations.

Methods: The tablet preparation was developed by direct compression method using Avicel PH 102 (filler-binder-disintegrant) with variations in Avicel PH 102 concentration of 50%, 75%, and 100%, respectively. Each of the tablets from these formulations was determined by the quality parameters of the preparation.

Results: The results showed that the dry powder microcapsules had a yellow-brown powder physical form, flow time of 0.413g/second, compressibility of 18.56%, and fine powder was 80.04%. Out of the three formulae produced, formula III was the best with a tablet diameter of 11.11±0.01 mm, the thickness of 5.26±0.03 mm, disintegration time of 9.40±0.14 min, hardness of 15.46±0.84 kg/cm^2, weight uniformity of 506.74±2.86 mg, friability of 0.28±0.03%. Meanwhile, Pb and Cd metal contamination were not detected, microbial contamination with Total Plate Number gave (ALT) 4.20 x 10^2 colonies/g, Yeast Mold Number 1.18 x 10^2 colonies/g, and the water content of the tablet was 5.75%. The evaluation results also showed that formula III with a 100% Avicel PH 102 concentration had a relatively better disintegration time than others.

Conclusion: Propolis extract microcapsule tablet has been success developed. The best formula was used 100% Avicel PH 102 concentration.

Keywords: Microcapsules, Propolis, Formulation, Tablet, Direct compress, Avicel pH 102, Quality parameters

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INTRODUCTION

Propolis is used as an anti-inflammatory, antioxidant, immunomodulator, and has potential as an antiviral drug [1–6]. Therefore, a previous study has shown that propolis is an active compound produced by bees, which is widely used in the health sector [3]. It is a dark sticky material that consists of bee saliva and resin (sap) of living plants and is collected by bees [7]. Furthermore, propolis contained some compounds such as phenolic and caffeic acids, phenethyl ester (CAPE), flavonoids, terpenoids, fatty acids, steroids, aromatic aldehydes, and alcohol [8]. Propolis extract also has an immunomodulatory and anti-inflammatory effect by inhibiting pro-inflammatory cytokines [4]. Moreover, propolis is produced from several types of stingless bees, such as *Tetragonula sapiens*, which is among the most propolis honey-producing bees [9]. Due to the benefits of propolis, several opportunities have been created for its development as a dose form of traditional medicine.

However, its low water solubility characteristics, sticky physical appearance, and bitter taste hinder the application of propolis in pharmaceutical drugs. This led to the microencapsulation of the propolis extract into a dry powder using maltodextrin and gum arabic through spray drying as an alternative to reduce this problem. According to Pratami, D. K., *et al.*, microencapsulation using spray drying improved physical appearance, solubility index, protection, and increased propolis bioactive compounds [10]. Previous studies have shown that its physical appearance and solubility index can be improved by microencapsulation using the spray drying method [7].

This study aimed to formulate the dry powder of propolis microcapsules in tablet preparations with the addition of auxiliary ingredients by direct compression method using Avicel PH 102, lactose DC, aerosil, and magnesium stearate. The tablets were made of 3 formulae with different concentrations of Avicel PH 102 of 50%, 75%, and 100%. Meanwhile, Avicel PH 102 was used as a filler-binder and a tablet crusher due to its good compressibility properties to produce hard tablets. Lactose DC was also used as a filler to show good flow properties, which makes it suitable for tablet formulations using the direct impression method, while Aerosil was used as a glidant and magnesium stearate as a lubricant [12]. With pharmaceutical technology, propolis microcapsules powder can be developed into a tablet form that meets the safety and quality requirements of traditional medicine according to the Regulation of the Food and Drug Supervisory Agency Republic of Indonesia, Number 32, 2019.

MATERIALS AND METHODS

Sample of propolis

Tetragonula beehives were taken from Masamba, North of Luwu district, South Sulawesi Province of Indonesia. The propolis was extracted by RIN Biotek Co. (Tangerang Selatan, Banten, Indonesia) by using ethanol 70% [3]. Then, the ethanolic extract was microencapsulated into propolis microcapsule powder using maltodextrin and gom arab using spray drying at Phytochemindo Reksa Co. (Bogor, West Java, Indonesia) [11].

Materials

Avicel PH 102, magnesium stearate, aerosil, DC lactose, methanol, Karl Fischer reagent, ethanol, sulfuric acid P, 10% nitric acid, aquadest, phosphate buffer (pH 7.2), Nutrient Agar and Potato Dextrose Agar.

Instruments

Analytical balance (AND type HR-120), caliper (Tricle brand), stopwatch, tablet printing machine (Erweka), particle size distribution tester (Sieve shaker machine), flow property tester (Granule Flow Tester), compressibility test equipment (Bulk Density Tester), tablet hardness tester (Tablet hardness tester YD-3), tablet crispness tester (Friabilator), disintegration tester (Disintegration Tester BJ-2), filter paper, kiln (Thermolyne Furnace 48000), mortar pestle, desiccator, Vortex mixer (H-VM-300), Autoclave, hotplate, Laminar Air Flow (LAF), Atomic Absorption Spectrophotometer (Shimadzu AA-7000), and Karl-Fischer (870 KF TITRINO Plus Methorm).

Evaluation of propolis microcapsule powder

The evaluation included organoleptic, flow properties (flow rate and angle of repose), compressibility, and particle size distribution.

Formulation of propolis microcapsule tablets

The formula for propolis microcapsules tablet was shown in table 1.

Determination of quality parameters

The parameters measured included the determination of water content metal and microbial contamination tests. This was based on the requirements stated in the Regulation of the Food and Drug Supervisory Agency Number 32, 2019 concerning the Safety and Quality Requirements of Traditional Medicines, while water content was determined using the Karl Fischer method.

Table 1: Propolis microcapsule tablet formula

Formula material	Weight (% b/b)		
	Formula I	Formula II	Formula III
Propolis microcapsule powder	200 mg	200 mg	200 mg
Magnesium Stearate	2	2	2
Aerosil	1	1	1
Filler (Avicel PH102: Lactose DC)	50:50	75:25	100:0

Heavy metal contamination test

The content of heavy metals in tablet preparations was analyzed using Atomic Absorption Spectrophotometer (Shimadzu AA-7000) and the levels of lead and cadmium were determined.

Microbial contamination test

The microbial contamination in tablet preparations was analyzed to determine the Total Plate Number (ALT) in the 1.0 g of powder added with phosphate buffer (pH 7.2) to 10 ml. A further dilution was made up to 10^{-6}, where 1 ml of each dilution was pipetted into a sterile petri dish and made in triplicate. Subsequently, 15-20 ml of Nutrient Agar (45±1 °C) media was poured into a petri dish, shaken, rotated until the suspension was evenly distributed, and blanks were made in 1 petri dish filled with 1 ml of diluent and agar medium. ALT was expressed based on the number of colonies that grew on petri dish incubation at a temperature of 35-37 °C for 24 h in an inverted position. The Yeast Mold Numbers (AKK) were determined in the same procedure with the plate method using Potato Dextrose Agar (PDA) seed media.

Data analysis

The data on the response to the tablet preparation test were analyzed using one-way statistical analysis of variance (ANOVA) to determine the effect of Avicel PH 102 concentration on the response tested in the form of disintegration time, tablet hardness, and tablet friability.

RESULTS AND DISCUSSION

Powder evaluation results

The organoleptic evaluation is presented in table 2; the propolis powder is shown in fig. 1, while the printed mass powder for formulae I, II, and III are shown in fig. 2. The evaluation of the propolis microcapsules powder organoleptic showed that the fine powder was yellow-brown with a characteristic aromatic odor and a bitter taste, which was due to a fairly high alkaloid content in the propolis extract [13]. The results showed that the three formulae are identical, which in powder form, are pale yellow, characteristically aromatic smelling, and have a bitter taste.

Fig. 1: Propolis microcapsules

Table 2: Evaluation results of powder organoleptic

No.	Organoleptic	Propolis microcapsule powder	Formula I	Formula II	Formula III
1.	Form	Fine powder	Powder	Powder	Powder
2.	Color	Brownish-yellow	Pale yellow	Pale yellow	Pale yellow
3.	Flavor	Bitter	Bitter	Bitter	Bitter
4.	Smell	Aromatic	Aromatic	Aromatic	Aromatic

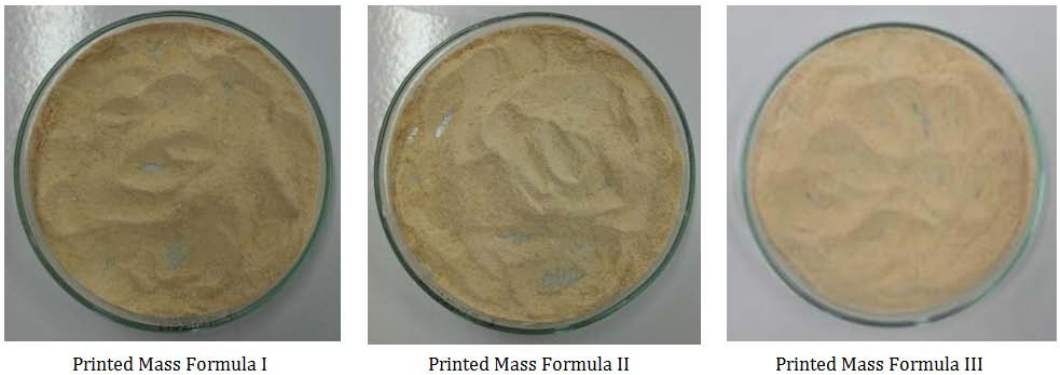

Fig. 2: Printed mass of propolis tablets of formula I, II, and III

Flow properties

The results of the evaluation of the angle of repose are shown in table 3. The evaluation of powder flow properties included flow velocity and angle of repose [14]. The requirement for a good angle of repose is 30° [15]; meanwhile, in this study, the evaluation of the propolis microcapsules powder angle of repose gave a value of 32.828°, which was due to the smaller particle size of the spray drying powder [16]. Generally, the size of the powder usually affects the angle of repose, where at a larger size, there is an attractive force between small particles and the frictional force between large powders for easy flow [17]. Meanwhile, evaluation of the angle of repose of the three formulae obtained very good results, which were 24.5334°, 24.3358°, and 24.1910°, respectively, and is closely related to the cohesive properties of the powders. This showed that the flatter the powder pile, the smaller the slope, which makes the powder flow at a constant rate and amount [18].

Table 1: Evaluation results of angle of repose

Formula	α average (°)	Conclusion
Propolis microcapsule powder	32.8280±2.0880	Fairly good
I	24.5334±1.1019	Very good
II	24.3358±0.5279	Very good
III	24.1910±0.9773	Very good

Flow rate

The results of the flow velocity evaluation are shown in table 4. A good flow rate requirement is 4-10 g/sec [19]; meanwhile, the result of the flow rate was 0.413g/sec, which indicated that the powder can not flow freely. Based on the evaluation of the flow rates of the three formulae, formulae II and III met the requirements with 4.2762g/sec and 4.8961g/sec; therefore, the powder can flow freely. However, the formula I was 3.751g/sec, which showed that the powder can not flow freely. A higher value of the Avicel PH 102 concentration also enhances a better flow property as shown by the increasing flow velocity between formulae [20]. Since powders with good flowability cause the filling into the compression chamber to be constant, the weight and content of the active substance of the tablet become uniform. Free-alcohols propolis powders produced by Irigoiti *et al.* (2021) with low propolis contents had good flowability; however, the increase of propolis extract affected the flow properties of the powders [21]. The good physicochemical properties of propolis powders would be an advantage during the processing and storage of the final products such as tablet, caplet, and capsule.

Table 2: Evaluation results of flow rate

Formula	Average flow rate (g/sec)	Conclusion
Propolis microcapsule powder	0.413±0.0242	Very hard to flow
I	3.751±0.0755	Difficult to flow
II	4.2762±0.1317	Easy to flow
III	4.8961±0.2766	Easy to flow

Compressibility

The results of the compressibility evaluation are shown in table 5. Propolis microcapsule powder showed fairly good compressibility of 18.56%; meanwhile, the good compressibility requirement is 12-16% [21]. Since it is compressed more in form of powder, it does not have high compactibility. Meanwhile, the results of the compressibility of formulae I, II, and III are 21.01%, 16.8%, and 15.50%, respectively. This showed that formula I had good compressibility, while formulae II and III had fairly good compressibility. Meanwhile, the poor compressibility of propolis microcapsule powder can be improved by adding Avicel PH 102 because at higher concentration, the better the compressibility [20]. This is indicated by the decreasing compressibility value between formulas. However, lower compressibility of the powder leads to higher density after compression, which makes the mass to be more compact. A good compressibility value indicated that the printed mass has good compatibility; therefore, the tablet to be printed will have less brittleness.

Table 3: Evaluation results of compressibility

Compress	Compressibility (%)			
	Propolis microcapsule powder	Formula I	Formula II	Formula III
10	15.98	10.08	12.8	12.40
50	16.49	20.17	13.6	13.18
100	17.53	21.01	16.8	14.73
500	18.56	21.01	16.8	15.50
Conclusion	Fairly good	Fairly good	Good	Good

Particle size distribution

The results for the three formulae did not meet the particle size distribution requirements because they did not follow the normal distribution curve and the amount of fine powder from the three formulae was 81.28%, 77.93%, and 75.2%. These showed that the particle size is not evenly distributed, meanwhile, the results are shown in table 6.

Table 4: Evaluation results of particle size distribution

No. Mesh	Average diameter (μm)	% Weight			
		Propolis microcapsule powder	Formula I	Formula II	Formula III
20	>850	1.58	1.79	1.93	1.09
20/40	637.5	5.84	3.21	2.47	2.43
40/60	337.5	4.26	2.18	2.14	1.82
60/80	215	3.54	5.04	6.53	7.52
80/100	165	4.73	6.50	9.00	11.95
100/120	137.5	5.29	0.90	1.05	1.52
120	<125	74.75	80.38	76.88	73.68
Amount of fine powder		80.04	81.28	77.93	75.2

The requirement for the particle size distribution test is a bell-shaped distribution curve with the number of fines>10%. Based on the evaluation, the propolis microcapsule powder did not meet the particle size distribution requirements. This is because the particle size distribution curve did not follow the normal distribution curve and the amount of fine powder obtained was 80.04%. Spray-drying of propolis was a viable option to increase its use in food, traditional medicine, and pharmaceutical applications [22].

The organoleptic tablet evaluation results

The results of the organoleptic evaluation are shown in table 7 and fig. 3. The organoleptic evaluation of the tablets of the three formulae showed the same results, which were pale yellow, had a characteristic aromatic odor, and bitter taste. Meanwhile, variations in the concentration of Avicel PH 102 did not affect the three formulae.

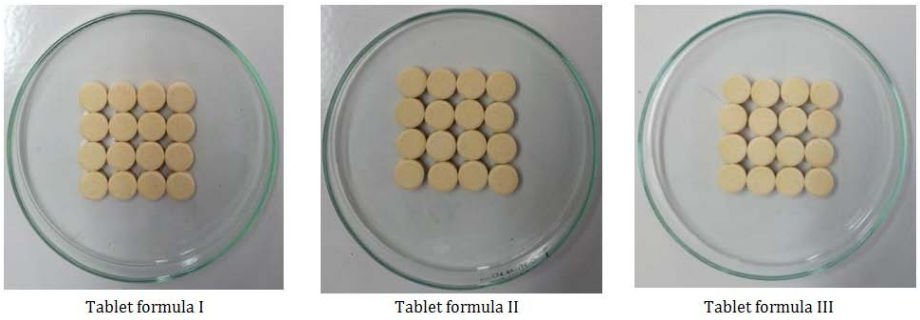

Fig. 3: Propolis tablets formula I, II, and III

Table 5: Evaluation results of organoleptic tablets

No.	Organoleptic	Formula I	Formula II	Formula III
1.	Color	Pale yellow	Pale yellow	Pale yellow
2.	Taste	Bitter	Bitter	Bitter
3.	Smell	Aromatic	Aromatic	Aromatic

The Indonesian propolis tablet containing 200 mg spray dry propolis extract, It can be used as medicine. The propolis tablet supplementation (containing 300 mg Iranian green propolis extract) on clinical symptoms in patients with coronavirus (COVID-19) has been used for three times a day for a period of 2 w at Al-Zahra hospital in Isfahan city, Isfahan, Iran [24].

Size uniformity

The results of the size uniformity evaluation are shown in table 8. According to the Indonesian Pharmacopoeia IV edition, a tablet meets the requirements for size uniformity when the diameter is not more than three times the thickness and not less than 4/3 the thickness [25]. Based on the results, it showed that the uniformity of tablet size of the three formulae meets the requirements. The uniformity of tablet size affects the appearance or aesthetic value of the tablet preparation, therefore, the more uniform the tablet size, the better the appearance. Furthermore, the variation of Avicel PH 102 concentration did not affect the three formulas.

Table 6: Evaluation results of size uniformity

Formula	Average	
	Diameter (cm)	Thickness (cm)
I	1.1116±0.0019	0.5354±0.0017
II	1.1113±0.0017	0.5346±0.0017
III	1.111±0.0015	0.5263±0.0025

Disintegration time

The results of the evaluation of the disintegration time are shown in table 9. A good disintegration time requirement for tablets is to abrade slowly in 15 min or less [26]. In this study, the disintegration time of the tablets for formulae II and III met the requirements, with values 14.3283 and 9.3983 min, while formula III was 37.675 min and did not meet the requirements. This showed that the higher the concentration of Avicel PH 102, the faster the tablet disintegration time. Similarly, tablets that can be properly destroyed and quickly have a quick effect on the body. Statistical test using Kruskal-Wallis showed p-value<0.05 (0.001<0.05), which indicated that there is a significant difference in tablet disintegration time between each formula. The Mann-Whitney test also showed that the disintegration time of the tablet formulae I, II, and III were significantly different. This showed that an increase in the concentration of Avicel PH 102 significantly affected the speed of tablet disintegration.

Table 7: Evaluation results of disintegration time

Formula	Disintegration time (min)
I	37.675±5.3510
II	14.3283±0.1170
III	9.3983±0.1372

Hardness

The results of the hardness evaluation are shown in table 10. The requirements for tablet hardness are 4-8 kg/cm^2; meanwhile, the results of the three formulae in this study did not meet the requirements, where the average value was more than 8 kg/cm^2. This is due to the presence of Avicel PH 102, which functions as a filler-binder with a sufficiently high concentration. Therefore, the greater the concentration of Avicel PH 102 used, the stronger the bond between the particles, leading to a harder tablet. Statistical test using one-way ANOVA showed a p-value<0.05 (0.000<0.05) which indicated that there is a significant difference in tablet hardness between each formula. The results of the Tukey test also showed that there is a significant difference between the hardness of the tablet formulae I, II, and III. This showed that an increase in the concentration of Avicel PH 102 significantly affected the tablet hardness [20].

Table 8: Evaluation results of tablet hardness

Formula	Hardness (kg/cm^2)
I	9.5205±0.9598
II	13.226±0.8836
III	15.463±0.8389

Weight uniformity

The results of the evaluation of the uniformity of weights showed in table 11. The evaluation of the uniformity of tablet weights for formulae II and III met the requirements, where none of the

formulae deviated more than 5% and 10% from the average weight. Meanwhile, the formula I did not meet the requirements, due to the presence of 3 tablets that deviated more than 5% of the average weight. This is because the mass flow properties of the formula I print are not good and contain excess fine powder with a small particle size, which inhibited the free flow during the filling process in the compression chamber. The uniformity of weights that meet the requirements indicated that the tablet has a uniform dose of the active substance [26].

Table 9: Evaluation results of weight uniformity

Formula	Weight (mg)	% Weight deviation (%)
I	505.185±14.7249	1.97±2.0945
II	505.56±7.8475	1.29±0.8176
III	506.74±2.8614	0.47±0.2935

Friability

The results of the evaluation of the uniformity of weights are shown in table 12. The friability results of tablets that meet the requirements are<1%; therefore, formulae I, II, and III with friability of 0.34%, 0.31%, and 0.28%, met the requirements. Friability is also influenced by the hardness of tablets because the higher the hardness, the lower the friability results [27]. This occurred because the amount of Avicel PH 102 used in each formula is significantly large, which provides sufficient tablet resistance. The evaluation showed that the high concentration of Avicel PH 102 allows the formation of stronger bonds between particles. Therefore, the tablet has good resistance to shock as well as friction, and it is expected to be durable during the printing process until distribution to consumers. The statistical test using one-way ANOVA showed a p-value>0.05 (0.289>0.05), which indicated that there is no significant difference in tablet friability between each formula. This showed that an increase in the concentration of Avicel PH 102 did not significantly affect the friability of tablets.

Table 10: Evaluation results of friability

Formula	Friability (%)
I	0.34±0.0404
II	0.31±0.0436
III	0.28±0.0252

Water content

The results of the evaluation of the uniformity of weights are shown in table 13. The results of the examination of the moisture content in the propolis microcapsule tablet formulations of formula I, II, and III were 6.75, 5.93, and 5.75%, respectively. The examination was determined using the Karl-Fischer apparatus and the results meet the requirements by BPOM for tablet preparations, which is 10% [26]. The water content was determined to stabilize the tablet preparations for long-term use. Therefore, the less water contained, the less possibility of tablet preparations being contaminated by microorganisms because water is a medium for microbial growth.

Table 11: Water content test results

No.	Formula	Water content (%)	Requirement (%)
1.	I	6.75	≤10%
2.	II	5.93	
3.	III	5.75	

Amount of metal contaminants

The results of the evaluation of the uniformity of weights are shown in table 14. Pb and Cd are heavy metals that need to have limited amounts in preparation because they interfere with health and are toxic when consumed for a long time. In this study, the levels of Pb in the tablet formulations of formulae I, II, and III were-0.3051,-1.1247,-1.5920 mg/kg, respectively, while the Cd was-0.2901,-0.3834,-0.4086 mg/kg. This showed that the metal content of Pb and Cd is not detected and meets the requirements allowed by the BPOM, where Pb (≤ 10 mg/kg) and Cd (≤ 0.30 mg/kg) [26].

Table 12: Metal contamination test results

No.	Metal	Formula	Determination results (mg/kg)	Requirement (mg/kg)
1.	Pb	I	-0.3051	≤ 10
		II	-1.1247	
		III	-1.5920	
2.	Cd	I	-0.2901	≤ 0.3
		II	-0.3834	
		II	-0.4086	

Amount of microbial contamination

The results of the evaluation of the uniformity of weights are shown in table 15. In the determination of microbial contamination, the ALT results in the tablet preparations of formulae I, II, and III were 2.93 x 10^2, 4.03 x 10^2, and 4.20 x 10^2 colonies/g, respectively, while the AKK in the tablet formulations were 1.86 x 10^2, 0.93 x 10^2, and 1.18 x 10^2 colonies/g. These results meet the requirements allowed by BPOM for tablet preparations, where ALT≤ 10^5 colonies/g and AKK ≤ 10^3 colonies/g [26].

Table 13: Microbial contamination test results

No.	Types of contamination	Formula	Determination results colony/g)	Requirement (colony/g)
1.	Total plate number	I	2.93 x 10^2	≤ 10^5
		II	4.03 x 10^2	
		III	4.20 x 10^2	
2.	Yeast mold number	I	1.86 x 10^2	≤ 10^3
		II	0.93 x 10^2	
		III	1.18 x 10^2	

CONCLUSION

The results of tablet evaluation showed that formula III was the best with a diameter of 11.11±0.01 mm, the thickness of 5.26±0.03 mm, disintegration time of 9.40±0.14 min, tablet hardness of 15.46±0.84 kg/cm^2, weight uniformity of 506.74±2.86 mg, and tablet friability of 0.28±0.03%. Pb and Cd metal contamination was not detected, microbial contamination with Total Plate Number (ALT) 4.20 x 10^2 colonies/g, Yeast Mold Number 1.18 x 10^2 colonies/g, and tablet moisture content of 5.75%. Furthermore, one-way ANOVA statistical

analysis showed a p-value<0.05, which indicated that variations in the concentration of Avicel PH 10^2 gave significant differences in the hardness and disintegration time of tablet preparations.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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