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Original Article

EFFECT OF VANILLIN QUALITY ON THE SYNTHESIS AND SOLID DISPERSION SYSTEMS ON PGV-0 ANTIOXIDANT CAPACITY

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ABSTRACT

Objective: Pentagamavunon-0 (PGV-0) was a curcumin analog with antioxidant properties and has been synthesizing with improvement techniques using vanillins with different qualities. PGV-0 has a low bioavailability but could be increased solubility by making a solid dispersion system. This study aimed to determine the antioxidant properties of PGV-0 that were synthesized with different quality starting materials of vanillin and also to obtain the effect of PEG 6000 and maltodextrin solid dispersion systems.

Methods: PGV-0 was synthesizing by mixing cyclopentanone into two different groups of vanillins (vanillin pro analysis and vanillin "Kapal Layar") using an HCl catalyst. The purity of products was identified with TLC (Thin Layer Chromatography) and spectrophotometrically compared with PGV-0 standard. Solid dispersion system consisting of two treatment groups: PEG 6000 and maltodextrin groups. The measurement of antioxidant properties was examined by Cupric Ion Reducing Antioxidant Capacity (CUPRAC).

Results: PGV-0 of vanillin pro analysis group (EC_{50}= 13.62 ppm) was found higher antioxidant capacity as compared to the vanillin "Kapal Layar" group (EC_{50}= 15.35 ppm). The solid dispersion system of PGV-0-PEG 6000 at ratio 1:10 has shown powerful antioxidant capacity (EC_{50}= 9.00 ppm) than the PGV-0-PEG 6000 at ratio 1:5 group (EC_{50}= 10.65 ppm). PGV-0-maltodextrin at ratio 1:10 (EC_{50}= 11.96 ppm) also has powerful antioxidant activity when compared with PGV-0-maltodextrin at ratio 1:5 (EC_{50}= 13.63 ppm).

Conclusion: The results of the study showed that the use of vanillin with different qualities in PGV-0 synthesis and also solid dispersion systems can affect the antioxidant activity of PGV-0.

Keywords: PGV-0, Vanillin, Solid dispersion system, PEG 6000, Maltodextrin, Antioxidant

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INTRODUCTION

Curcumin compounds can be found in many types of Curcuma species and are the main pigment in turmeric (*Curcuma longa*). The broad range of biological and pharmacological activities of curcumin and its derivatives have been widely explored and reported include antimetastatic, antibacterial, anticancer, antitumor, antimalarial, and antioxidant activities [1]. Curcumin has a prominent chemical structure containing two ferulic acid residues connected by a methylene bridge. It has two hydrophobic phenyl domains connected by flexible linkers (seven carbons). Although curcumin has unique structural features, it lacks stability and bioavailability features [2].

Pentagamavunon-0 (PGV-0) is an approach that has been taken to overcome the curcumin stability problem. PGV-0 is a curcumin analog with many potential activities, especially antioxidant properties. PGV-0 is one of cyclopentanone derivatives with identical symmetrical aromatic rings of curcumin that has been synthesizing with improvement techniques using a different quality source of vanillin [3]. The main problem in PGV-0 development was the same as curcumin with poor water solubility and low bioavailability because of their two hydrophobic phenyl domains. This problem could be dissolved with increased solubility by making a solid dispersion system as has been applied to curcumin [4, 5].

A solid dispersion system can increase solubility by increasing the area of contact of the active substance with the solvent with the aid of dispersing agents [6]. In this research, maltodextrin and polyethylene glycol 6000 (PEG 6000) were used as dispersing agents to increase solubility. Maltodextrin and PEG were some of the excipients that were often used as carriers to increase the dissolution rate in the form of solid dispersions [7]. Maltodextrin had high water solubility and could give a solubilizing effect on drugs [8]. Meanwhile, PEG polymers are often used due to their hydrophilicity, low toxicity, low melting point, chemical compatibility, and has a fast solidification level or compaction rate [7, 9].

The DPPH (2,2-diphenyl-1-picrylhydrazyl) scavenging activity of PGV-0 has been proven including a very strong antioxidant category but the ability to reduce or chelating metal was never reported [10]. Several studies reported solid dispersion system can increase the activity of some antioxidant compounds because of their solubility was increase [11-13]. This study aimed to determine the antioxidant properties of PGV-0 that were synthesized with different quality starting materials of vanillin and also to obtain the effect of PEG 6000 and maltodextrin solid dispersion systems towards Cupric Ion Reducing Antioxidant Capacity (CUPRAC).

MATERIALS AND METHODS

Chemicals and instruments

All chemicals, solvents, and reagents used in the experiments were purchased from Merck KGaA were of analytical grade, except one of vanillin material from the market that have been used for food with the brand name "Kapal Layar" and standard PGV-0 from Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia. All spectrophotometric measurements were made with a pair of matched quartz cuvettes using a PG Instruments-T60 UV-Vis spectrophotometer.

PGV-0 synthesis

PGV-0 was synthesizing according to Ritmaleni's (2016) research by mixing cyclopentanone into two different groups of vanillins (vanillin pro analysis [VPA] and vanillin "Kapal Layar" [VKL]) using an HCl catalyst without solvent, stirred with a magnetic stirrer and a new improvement technique of maceration was applied [3].

Identification of product purity

The purity of PGV-0 was determined by a TLC (Thin Layer Chromatography). PGV-0 product, PGV-0 standard, and vanillins were running on TLC plate then eluted with a mobile phase of n-hexane: ethyl acetate (2:1). The plate was then dried, the propagation length of

the compounds was observed under UV lamps of 254 nm and 366 nm and the Retention factor (Rf) value of each spot was measured. PGV-0 product also analysis spectrophotometrically compared with vanillins and PGV-0 standard [14].

Solid dispersion system (SDs)

Solid dispersion system consisting of two treatment groups: PEG 6000 and maltodextrin groups. In this work, the SDs of PGV-0 were obtained using three different technologies, including solvent evaporation and melting-dissolution techniques. The preparation of drug-carrier dispersions was easy and convenient in terms of mass ratio and molar ratio. Therefore, these mass ratios were prepared in this study. The making of solid dispersion PGV-0 was done by a solvent evaporation method using maltodextrin and melting-dissolution method using PEG 6000 and each system mixed in a ratio 1: 5 and 1: 10.

a) Solvent evaporation (SE)

The SD of PGV-0 was prepared by the SE method in different ratios of PGV-0 to Maltodextrin, which was coded as PGV-0-MD with two different mass ratios (1:5, and 1:10). PGV-0 and maltodextrin were dispensed into a beaker in which the required amount of ethanol was added for the dissolution of PGV-0 and maltodextrin. In the preparation of SDs of drugs, organic solvents were evaporated completely with a rapid evaporation rate, which cannot be achieved using a rotary evaporator. The preparation was cooled in ice and solidified for 12 h, and the obtained mass was stored and then pulverized using a pestle and mortar. The obtained mass was sieved using sieve no. 60 in order to obtain the particles of uniform size [11].

b) Melting-dissolution

PGV-0-PEG 6000 SDs were prepared by the melting-dissolution method using the different ratios of PGV-0 to PEG 6000, which was mass ratios 1:5, and 1:10. Each SD was heated to a molten state at 60 °C, and the calculated amount of PGV-0 was included. The molten mass was continuously stirred with a glass rod till the complete dissolution of PGV-0. The obtained dispersion was solidified at ambient temperature. The dispersion was transferred in a desiccator for 24 h and then pulverized using a porcelain mortar and pestle. The obtained mass was sieved again using sieve no. 60 to obtain the particles of uniform size [11]

Quantitative antioxidant capacity with CUPRAC assay

The CUPRAC method based on Ramadhan *et al.* (2020) is comprised of mixing the antioxidant solution (1 ml of each serial concentration of two PGV-0 groups and their solid dispersions) with a copper (II) chloride solution 0.01 M (1 ml), an ethanolic neocuproine 0.0075 M (1 ml), an ammonium acetate aqueous buffer 1 M at pH 7 (1 ml), an aquadest of 0.1 ml, and subsequently measuring the developed absorbance at 450 nm after 30 min. The antioxidant activity against the CUPRAC reagent was expressed as a percent capacity of each dilution that was calculated as follows:

$$\text{Ts} = -\text{Log Abs. Sample}$$

$$\%\ \text{capacity} = (1 - \text{Ts}) \text{x}\ 100\%$$

Ts was the negative log value of the sample absorbance and Abs. Sample was the absorbance of each concentration of the test solutions that have been reacted with CUPRAC reagent. The results were expressed as EC_{50} value (EC_{50} was the effective concentration at which 50% of its maximal effect is observed) and were obtained by interpolation of the equation y = a+bx that was determined through linear regression, where x was the concentration (ppm) of the substance measured and y was the percentage of capacity (%). The EC_{50} value was obtained as the x value using y = 50 [15-17].

Statistical analyses

All tests were carried out independently in triplicate. Data are expressed as mean±standard deviation. One-way analysis of variance (ANOVA) was used to determine significant differences between groups were considered significant at $p<0.05$.

RESULTS AND DISCUSSION

PGV-0 synthesis

Pentagamavunon-0 (PGV-0), known by the chemical name 2,5-bis (4-hydroxy-3-methoxybenzilidine) cyclopentanone, is an α,β unsaturated compound. Pentagamavunon-0 (PGV-0) was one of the modified curcumin compounds. The aim of modification of curcumin is to increase the stability of curcumin which was very easily influenced by environmental pH and light, and in an aqueous environment with alkaline conditions, curcumin is easily hydrolyzed and degraded. To increase the stability of curcumin, It can be overcome by modifying curcumin through synthesis to form curcumin analogs. Curcumin analog was a modification of curcumin with 3 pharmacophore groups similar to curcumin with the parent compound [18]. PGV-0 was a curcumin analog that has been widely studied for its biological activity, especially the DPPH radical scavenging activity [10]. Previous research stated that PGV-0 has a stronger antioxidant and anti-inflammatory potential than other curcumin analog compounds but they have low solubility in water [19]. The main problem faced in the development of PGV-0 is its poor solubility in water and low bioavailability, thus affecting the resulting activity for disease therapy [6]. Poor solubility leads to a low dissolution rate which results in scarce absorption systemically, which leads to poor performance PGV-0 in terms of bioavailability and high inter-subject variation [20]. To solve this problem, an increase in solubility was carried out using the solid dispersion method, so it is hoped that the increased solubility of PGV-0 can affect the antioxidant activity of PGV-0. In addition, this study also aims to determine the effect of the quality of the vanillin used on the antioxidant activity of PGV-0.

The study began with the synthesis of PGV-0 using two types of vanillin with different qualities, each mixed with cyclopentanone. PGV-0 from vanillin pro analysis (VPA) gives 31.175% randemen of the product; meanwhile, vanillin "Kapal Layar" also has a similar % of randemen which is 31.997%. The results still not good enough for the value of randemen because after the maceration treatment of synthesis product just left for two hours, different with Ritmaleni (2016) left the product for 14 d that why resulting maximum randemen [3]. Organoleptic identification based on fig. 1 and table 1 showed a little different color of the product if compared with standard, but % recovery of the product showed maximum values which is PGV-0 of VPA has a higher value of % recovery (90.186%) than PGV-0 of VKL (86.769%). Based on the results, the quality of the starting material could be affecting the purity of the synthesis product.

Fig. 1: PGV-0 product of (A) VKL, (B) VPA, and (C) standard

Table 1: Organoleptic identification of products

Organoleptic identification	PGV-0		
	VKL	VPA	Standard
Color	Yellow	Pale orange	Orange
Smell	Odourless	Odourless	Odourless
Shape	Crystal	Crystal	Crystal

Identification of product purity

The purity of the synthesis product was proven by TLC using the mobile phase n-hexane: ethyl acetate (2:1), which showed a single spot on each product and was parallel to standard PGV-0 with Rf = 0.22 (fig. 2). The spots of product and standard on each plate showed a significant difference with vanillin (Rf = 0.59), so it can be said that the resulting product has high purity [21]. These results were supported by UV-Vis spectrophotometric analysis as shown in fig. 3. The UV-Vis spectrum shows the similarity of the curve and wavelength of the PGV-0 product derived from VPA with standard PGV-0, which is 408 nm. PGV-0 derived from VKL shows a difference in wavelength which is 410 nm, but this difference could still be tolerated if the difference was less than or equal to 2 nm.

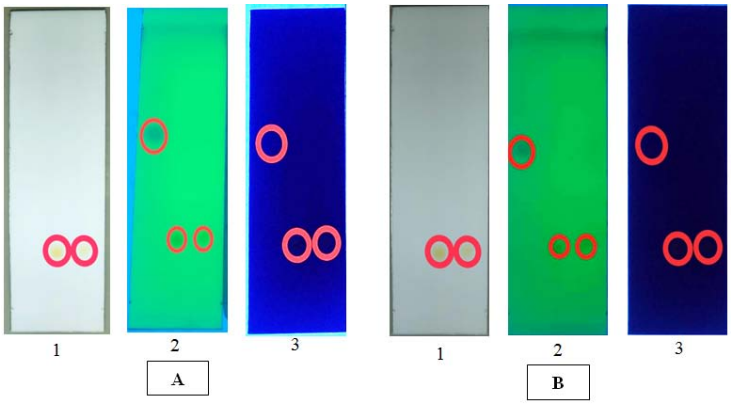

Fig. 2: Purity identification of (A) PGV-0 (VPA) and (B) PGV-0 (VKL) with TLC in the mobile phase of (2:1) n-hexane: ethyl acetate; (1) visually, (2) under UV 254 nm, and (3) under UV 366 nm

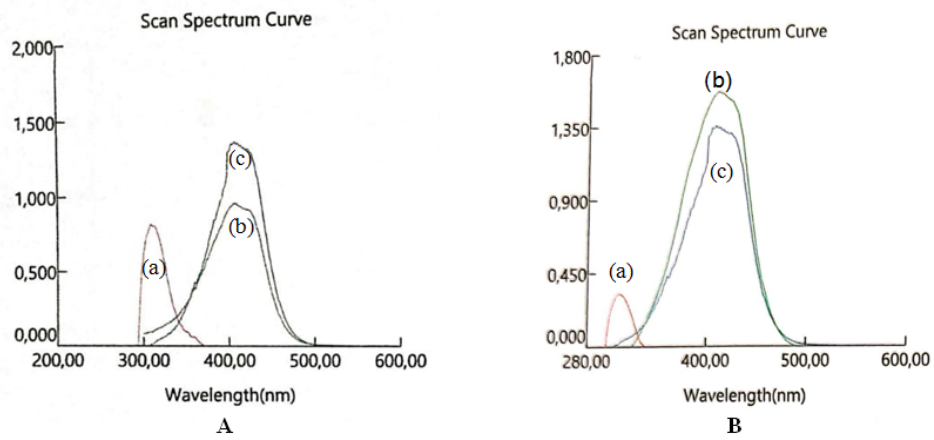

Fig. 3: Comparison UV-Vis spectrum of (a) vanillin, (b) PGV-0 standard, and synthesis product of (A) PGV-0 from VKL and (B) PGV-0 from VPA

Solid dispersion system (SDs)

The formation of solid dispersions can help increase solubility and dissolution rates of drugs that are difficult to dissolve in water. A solid dispersion system is a dispersion system of one or more substances active in an inert carrier or water-soluble matrix in its solid form prepared by the methods of smelting, dissolving, as well as a combination of smelting and dissolving. The choice of the carrier also influences the dissolution rate of the dispersed drug. The water-soluble carriers will accelerate the release of the drug from the matrix, while the carriers which are difficult to dissolve water will slow the release from the matrix [22]. The product of each PGV-0 was prepared for the manufacture of different solid dispersion (SD) systems using two different methods. The solvent evaporation method involves the solubility/miscibility of PGV-0 and maltodextrin as a carrier in absolute ethanol, and then the organic solvent was evaporated in a water bath. The key point of this method was to ensure complete solubility/miscibility of PGV-0 in the carrier and disperse uniformly.

The formulation PGV-0-SD was obtained with the carrier maltodextrin and PEG 6000 at the different mass ratios of 1:5, and 1:10 using different techniques. The mass ratios of 1:5 and 1:10 were selected randomly as there was no issue of miscibility/solubility of the carrier with most of the organic solvents used in the preparation of SD. In the preparation of solid dispersions

using solvent evaporation, the drugs and polymers are separately dissolved in organic solvents. Then, the drug solutions and polymer solutions were mixed together, and organic solvents were evaporated in order to obtain SD (fig. 4) [11]. Maltodextrin was used because of a hydrophilic polymer with high solubility in water and porous structure. Its circular structure creates a greater surface area resulting in more efficient rehydration; thus a mixture of maltodextrin with other compounds can increase solubility. PEG was very effective in an aqueous environment and forms two different phases of polymer systems. When PEG is attached to another polymer molecule, it can affect the chemical properties and solubility of the drug molecule so that it can dissolve easily in bodily fluids [23].

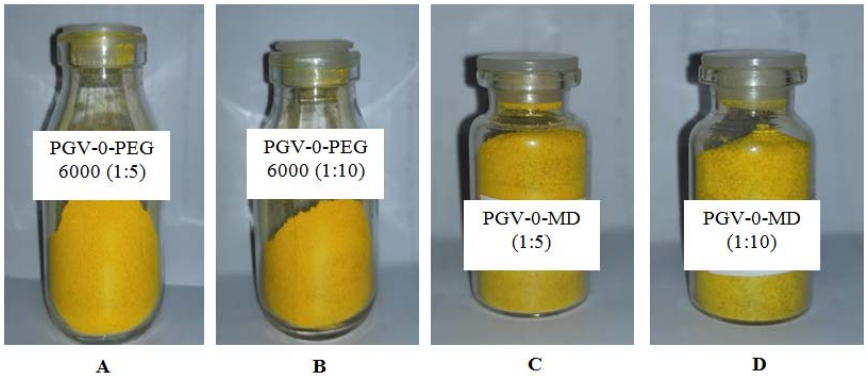

Fig. 4: Solid dispersion products of (A) PGV-0-PEG 6000 (1:5), (B) PGV-0-PEG 6000 (1:10), (C) PGV-0-maltodextrin (1:5), and (D) PGV-0-maltodextrin (1:10)

Quantitative antioxidant capacity with CUPRAC assay

The CUPRAC assay measured the ability of PGV-0 and its SD as antioxidants to reduce Cu(II)-Nc cation to an orange-yellow colored Cu(I)-Nc cation at pH 7, and the absorbance of the Cu(I) chelate formed as a result of the redox reaction with reducing polyphenols was measured at 450 nm [24]. The results of the CUPRAC assay were presented as EC_{50} (effective concentration at which 50% of its maximal effect is observed). The EC_{50} values of samples were obtained based on the calculation results of the linear regression equation in fig. 5. PGV-0 of the VPA group (EC_{50}= 13.62 ppm) was found higher antioxidant capacity as compared to the VKL group (EC_{50}= 15.35 ppm). The solid dispersion system of PGV-0-PEG 6000 at ratio 1:10 has shown powerful antioxidant capacity (EC_{50}= 9.00 ppm) than the PGV-0-PEG 6000 at ratio 1:5 group (EC_{50}= 10.65 ppm). The same thing happened to PGV-0-MD at ratio 1:10 (EC_{50}= 11.96 ppm) also has powerful antioxidant activity when compared with PGV-0-MD 1:10 (EC_{50}= 13.63 ppm) (table 2).

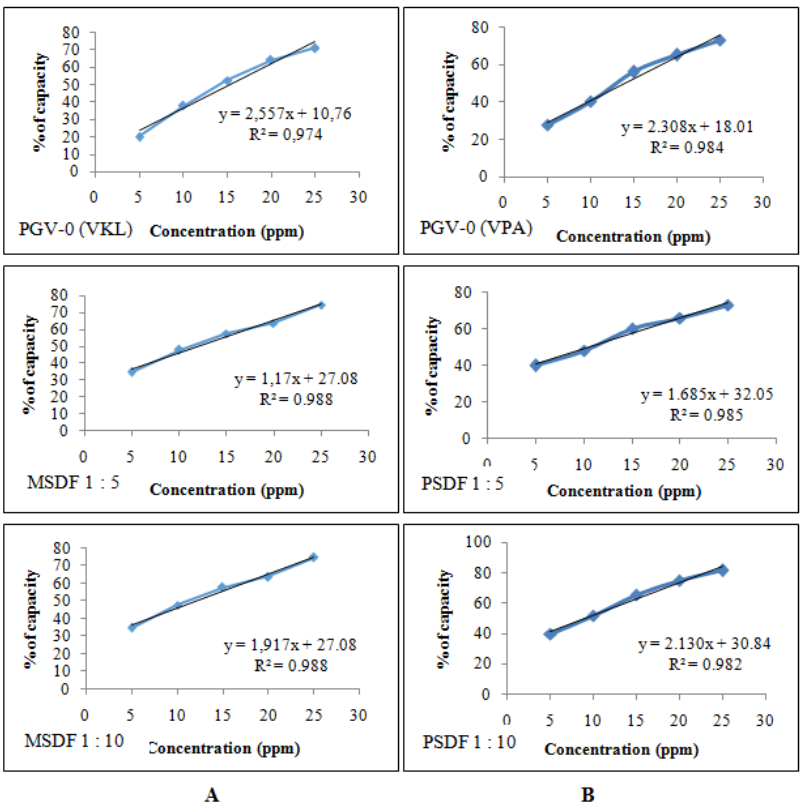

Fig. 5: Linear regression equation curve of concentration vs % capacity of (A) PGV-0 (VKL) with maltodextrin solid dispersion formula (MSDF) and (B) PGV-0 (VPA) with PEG 6000 solid dispersion formula (PSDF)

Table 2: Comparison of antioxidant capacities result using CUPRAC assay

Sampel	EC_{50} (ppm)
PGV-0 (VPA)	13.62
PGV-0 (VKL)	15.34
PGV-0-Maltodextrin (1:5)	13.63
PGV-0-Maltodextrin (1:10)	11.95
PGV-0-PEG 6000 (1:5)	10.65
PGV-0-PEG 6000 (1:10)	9.00

The result of the study showed a significant increase ($p<0.05$) of CUPRAC capacity for PGV-0-SDs) than pure PGV-0. Among the two prepared SD, the highest CUPRAC capacity showed by PGV-0-PEG 6000 (1:10) followed by PGV-0-PEG 6000 (1:5). CUPRAC capacity of PGV-0-PEG 6000 was found significantly higher than that of PGV-0-maltodextrin and pure PGV-0 ($p<0.05$). The significantly higher antioxidant activity result was achieved due to the higher solubility of PGV-0 in the used carrier PEG 6000. The results of the study revealed that the formation of PGV-0-SD showed good antioxidant activities. PGV-0-SD showed the ability in exhibiting the most active cupric ion reducing capacity as compared to pure PGV-0. Although previous research reported DPPH radical scavenging activity of PGV-0, which is IC_{50} = 11. 627 ppm more powerful than cupric ion reducing capacity [25], but a solid dispersions system could increase the capacity. These results indicate that the selection of the CUPRAC method was more suitable for determining the antioxidant activity of solid dispersion because it can be applied to overcome various sample matrices. This method was quite appropriate for determining the power of the phenolic group compared to the DPPH method because it can be applied to compounds that are hydrophilic or lipophilic [24].

Based on the results of the antioxidant activity test can be seen the formation of solid dispersion affects the antioxidant activity. The higher the value solubility, the better of antioxidant value which has reported with the formation of phenolic compounds [26]. Several studies reported that powders of natural products produced with maltodextrin showed higher antioxidant capacity due to its high soluble nature, which supports the results of this study [27]. Furthermore, maltodextrin as a drying agent significantly increased the antioxidant activity of spray-dried amla juice powder [28]. However, due to the use of vanillin quality in the synthesis process, it appears to affect antioxidant activity. The PGV-0 used in the PGV-0-maltodextrin solid dispersion uses vanillin sold in the market for food additives while the PGV-0-PEG 6000 solid dispersion uses vanillin pro analysis. This turned out to affect the antioxidant activity of each PGV-0 solid dispersion. So that the PGV-0-PEG 6000 solid dispersion has a greater antioxidant activity compared to the PGV-0-maltodextrin solid dispersion.

CONCLUSION

The results of the study show that the use of vanillin with different quality in PGV-0 synthesize and also solid dispersion systems can affecting the antioxidant activity of PGV-0. PGV-0 from vanillin for synthesis resulted in powerful antioxidant activity compared with PGV-0 of vanillin food grade. The greater the ratio of PGV-0 to the dispersing agent, the higher the PGV-0 antioxidant capacity in reducing cupric ion.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Authors declare no conflict of interest.

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