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The Formation and Characterization of Multicomponent Crystal Caffeic Acid-Tromethamine Using the Solvent Drop Grinding Technique

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ABSTRACT
Caffeic acid is a polyphenol compound with low solubility in water. This study aims to prepare and characterize multi-component crystals of caffeic acid, using tromethamine as a coformer, to enhance the dissolution rate without lessening its antioxidant effect. Multi-component crystals were prepared by the solvent-drop grinding method. The mole ratio of caffeic acid to tromethamine was 4:6 based on the results of a binary phase diagram showing that it had a eutectic point after which multi-component crystals were formed. Powder X-Ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), FTIR spectroscopy, Scanning Electron Microscopy (SEM), and dissolution tests were used to characterize the multi-component crystals. The antioxidant effect was evaluated by the DPPH test. The characterization results revealed a decrease in intensity and new X-ray diffraction patterns, a lower melting point on the DSC thermogram, a non-significant wavenumber shift on the FTIR analysis, and a new crystal habit of multi-component crystals from the SEM. The dissolution rate of caffeic acid increased 1.23 times ($p<0.05$). The antioxidant test yielded 11.32 g/mL, 33.11 g/mL, and 28.35 g/mL compared with the IC50 values of gallic acid, caffeic acid, and multi-component crystals. There was an increase in the antioxidant activity of caffeic acid in the form of multi-component crystals, but not significantly different from the IC50 of pure caffeic acid. Our findings show that after forming multi-component crystals, the dissolution rate of caffeic acid increased without reducing antioxidant activity.

Keywords: *caffeic acid, tromethamine, multi-component crystal, solvent drop grinding, antioxidant, dissolution rate.*

1. INTRODUCTION

Caffeic acid (3,4-hydroxycinnamic acid) is a polyphenol compound and a phenylpropanoid metabolite found in *Polygonum aviculare*, mint, *Eucommia*, blueberries, coffee beans, apples, and other plants [1–3]. Caffeic acid also has many pharmacological effects, including antimutagenic, anticancer, antibacterial, immunomodulatory, and antioxidant [4–7]. As an antioxidant, caffeic acid works by inhibiting and reducing free radicals and oxidizing compounds [8]. Caffeic acid has poor solubility in water (less than 1 mg/mL), with a melting point of 225 ˚C and a pKa of 4.62 [9]. Drugs with low water solubility are not generally freely available. Sometimes, dissolution is the rate-limiting step in drug absorption [10]. Several studies have reported that caffeic acid solubility can be improved by using solid lipid nanoparticles [11], inclusion complexes [12], nanoparticulate gels [13], the ethosomal system [14], and phytophospholipid complexes [15].

Multi-component crystals can increase drug dissolution rate via crystal engineering techniques [16]. Multi-component crystals are composed of two or more molecules combined into a single crystalline phase [17] and can become cocrystals, salts, or solvates [17–19]. Research on the preparation of multi-component piperine and curcumin crystals from natural materials was shown to increase the dissolution rate. Researchers are therefore interested in increasing the solubility of caffeic acid by forming it into multi-component crystals.

In this study, we formed multi-component caffeic acid crystals using tromethamine, which is a weakly basic amine compound, easily soluble in water [20], with a pKa of 8.07 [21]. Tromethamine has been shown to increase the dissolution rate of the active substance in several methods, including the formation of a binary system with sulfamethoxazole [22] and the formation of multi-component crystals with gliclazide [23], mefenamic acid [21], and glibenclamide [24]. The manufacture of caffeic acid-tromethamine multi-component crystals should increase the dissolution rate of caffeic acid so that it is absorbed more quickly and achieves the desired therapeutic effect.

Tromethamine can be used to increase the dissolution rate of caffeic acid as a coformer to form multi-component crystals. Since caffeic acid has a carboxylic group and tromethamine has an amine group, hydrogen bonds should be formed between the substances. The method used to achieve this effect is the solvent-drop grinding method, which is a modification of the neat grinding method that adds a small amount of solvent during the grinding process [25]. The solvent in this method acted as a catalyst to accelerate the crystallization rate [26, 27].

X-ray diffraction, differential scanning calorimetry (DSC), FTIR spectroscopy, scanning electron microscope analysis, dissolution testing, and antioxidant testing were all used to characterize the multi-component crystals. Our study hypothesized that the dissolution rate would be increased without lowering the antioxidant effect, allowing the full potential of caffeic acid as an active drug to be achieved.

2. METHODS

2.1. Materials

The materials used in this study were caffeic acid (TCI, Japan), tromethamine (Merck, Germany), ethanol pro analysis (Merck, Germany), HCl 12 N (Bratachem, Indonesia), distilled water, Whatman filter paper (size 0.45 µm), a desiccator, and aluminum foil.

2.2. Preparation of multi-component crystal

Caffeic acid and tromethamine were mixed at a mole ratio of 4:6. Then the mixture was ground continuously for 10 minutes while 91 µL of ethanol was added. The multi-component crystals that were formed were stored in a desiccator.

2.3. Preparation of the physical mixture

A physical mixture of caffeic acid and tromethamine was prepared at a mole ration of 4:6. The mixture was mixed homogenously, stored in a sealed container, and kept in a desiccator.

2.4. DSC analysis

The thermodynamic properties of caffeic acid, tromethamine, a physical mixture of caffeic acid-tromethamine, and the multi-component crystals of caffeic acid-tromethamine were measured using a DSC apparatus (Shimadzu DSC-60 Plus, Japan). A small amount of sample (4 mg) was placed in a sealed aluminum pan. The instrument temperature was increased from 30 ˚C to 250 ˚C at a rate of 10 ˚C per min.

2.5. Powder X-ray diffraction analysis

The measurements were conducted using X-ray diffractometer (XPERT PRO PAN analytical, The Netherlands) for caffeic acid, tromethamine, a physical mixture of caffeic acid and tromethamine, and the multi-component crystals of caffeic acid-tromethamine Samples were placed on the sample holder and leveled. Measurements were performed from 50 to 500 on the 2θ scale in a range. The measurements used Cu as the target metal, a Kα filter, a voltage of 45 kV, and a current of 40 mA.

2.6. Infrared spectroscopy analysis

The analysis was performed using a FTIR spectrophotometer (Thermo Scientific, USA) for caffeic acid, tromethamine, a physical mixture of caffeic acid and tromethamine, and the multi-component crystals of caffeic acid-tromethamine, at a wavenumber of 4000–400 cm^{-1}. The sample was placed on the ATR crystal so that it covered all the crystal surfaces.

2.7. SEM analysis

The samples were then observed under an SEM (Hitachi S-3400N, Japan) at various magnifications. The powder samples were placed in an aluminum sample holder and coated with palladium to a thickness of 10 mm. The instrument was set with a 20 kV voltage and a 12 mA current.

2.8. Dissolution test

The dissolution profiles of caffeic acid and the caffeic acid-tromethamine multi-component crystals were determined using a type 2 dissolution apparatus (SR8 Plus Dissolution Test Station Hanson Virtual Instrument, USA). The dissolution profile was determined in 900 mL of 0.1 N HCl medium at a speed of 50 rpm at 37 ±0.5 ˚C. The powder was then put into the medium, and 5 mL of dissolution solution was pipetted after 5, 10, 15, 30, 45, and 60 minutes. The medium that was taken was replaced with a dissolution medium (same volume and temperature when pipetting). Each pipetted solution was put into a volumetric flask and tested using a UV-Visible spectrophotometer at a predetermined max wavelength in 0.1 N HCl so that the absorbance value could be obtained and the dissolution profile of both the caffeic acid and the multi-component caffeic acid crystals-tromethamine could be calculated.

2.9. Antioxidant test

The antioxidant test used gallic acid as a comparison compound since it has potent radical scavenging potential and is similar to caffeic acid in that they both have phenolic and carboxylic groups [27]. We used the DPPH (1,1 diphenyl-2-picrylhydrazyl) method for the

antioxidant testing. Based on this method, the antioxidant ability of a compound is expressed by the IC50 value. The DPPH method provides information on the reactivity of the tested compound with a stable radical. DPPH gives strong absorption at a wavelength of 516 nm, producing a dark violet color. Free radical scavengers cause electrons to become unpaired, which causes a loss of color proportional to the number of electrons taken.

The sample was produced in series of concentrations whose absorbances were measured at a wavelength of 516 nm. The concentration series were selected based on the percent inhibition of the sample, which was around 50%.

3. RESULTS AND DISCUSSION

The ratio of caffeic acid to tromethamine when preparing the multi-component crystals was determined based on melting point and fusion energy. A lower melting point and fusion energy indicate that the mixture's lattice energy has decreased, so it is predicted to provide a better solubility than mixtures with different molar ratios or pure compounds [28]. A binary phase diagram was used to calculate the ratio of caffeic acid to tromethamine that offers the lowest melting point with a single endothermic peak (Figure 1). The single endothermic peak in the caffeic acid-tromethamine binary mixture reveals the binary's eutectic temperature. At ratios of 2:8, 3:7, 4:6, and 9:1, the caffeic acid-tromethamine binary mixture showed one endothermic peak, indicating the eutectic temperature of the binary mixture (Figure 2). The eutectic point is the temperature at which a mixture of compounds fuses simultaneously [29]. The ratios of 2:8, 3:7, and 4:6 showed a single endothermic peak at 121.71 ˚C, 122.09 ˚C, and 122.96 ˚C, respectively, with fusion energies of 81.86 J/g, 57.18 J/g, and 50.84 J/g (Table 1). According to our data, the eutectic point of multi-component caffeic acid-tromethamine crystals is at a ratio of 4:6, as this ratio generates a slender and smooth endothermic peak at the lowest temperature.

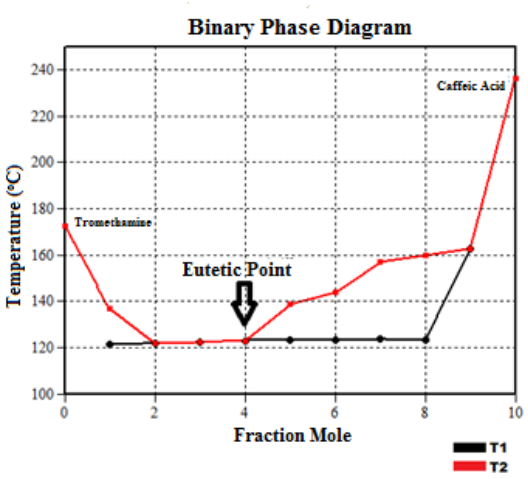

Figure 1. Eutectic point of caffeic acid-tromethamine mixture

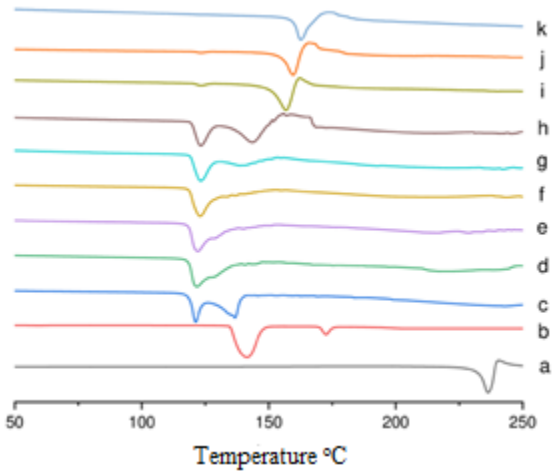

Figure 2. Thermogram binary phase diagram of caffeic acid (a), tromethamine (b), caffeine-tromethamine multi-component crystals 1:9 (c), 2:8 (d), 3:7 (e), 4:6 (f), 5:5 (g), 6:4 (h), 7:3 (i), 8:2 (j), 9:1 (k).

Table 1. Thermogram data of caffeic acid-tromethamine multi-component crystals

Caffeic acid : Tromethamine	T_1 (ºC)	T_2 (ºC)
Tromethamine	141.45	172.36
1:9	121.20	136.69
2:8	121.71	
3:7	122.09	
4:6	122.96	
5:5	123.23	138.53
6:5	123.27	143.61
7:3	123.45	156.81
8:2	123.35	159.61
9:1	162.59	
Caffeic acid	236.34	

X-ray diffraction is a characterization method for observing the light refraction pattern of material composed of atoms in its crystal lattice [30]. The specificity of the diffraction pattern becomes qualitative analysis to distinguish pure compounds from multi-component crystal compounds [31]. A new crystalline phase is formed when the multi-component crystal diffractogram pattern is different from the active substance and coformers. Significant changes will be seen in the diffraction pattern of components with distinct peaks [32]. The pattern and intensity of the specific X-ray diffraction peaks of caffeic acid, tromethamine, physical mixtures, and multi-component crystals are shown in Figure 3.

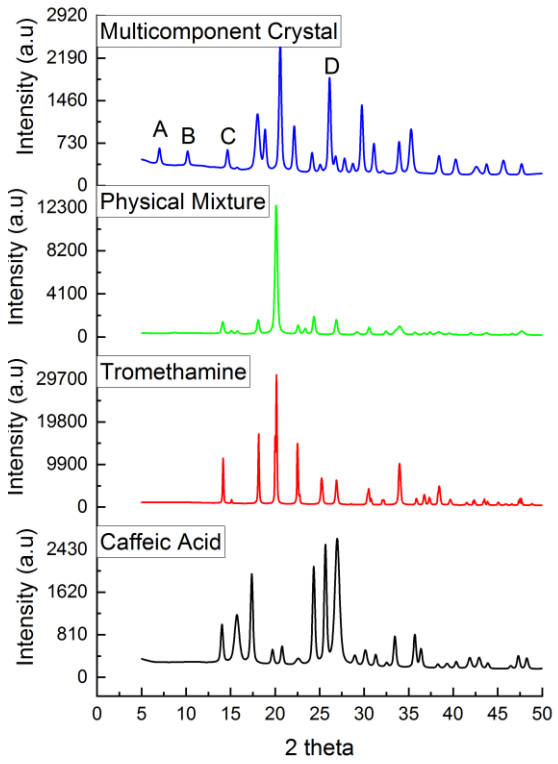

Figure 3. Diffractogram of caffeic acid, tromethamine, physical mixture, and multicomponent crystal

The X-ray diffractogram shows that caffeic acid has a typical diffraction pattern at 2θ = 14.02, 15.70, 17.36, 24.32, 25.66, and 26.97. Tromethamine has a high degree of crystallinity with a typical diffraction peak at 2θ = 14.11, 18.09, 20.13, and 22.49. The physical mixture of caffeic acid-tromethamine has a superimposition diffractogram of interference peaks and decreased intensity at 2θ = 14.11, 18.09, 20.13, 24.32, and 26.97. Furthermore, the diffractogram of multi-component crystals showed a decrease intensity of crystallinity and a different pattern with the appearance of a new peak at 2θ = 7.06, 10.19, 14.83, and 26.14. These results indicate the formation of a new multi-component crystal phase in an equimolar ratio of 4:6. The pKa value can predict whether the interaction of the two solid phases (active substance and coformer) forms cocrystals or salt. Cocrystals will be formed if the value of pKa < 2, and salt will be formed if pKa > 3 [25]. Caffeic acid and tromethamine have pKa values of 4.62 and 8.07, respectively. In this study, the difference in pKa between these two solid phases was 3.45 (> 3). Based on the pKa rule, we can assume that the interaction between caffeic acid and tromethamine will form a salt-like multi-component crystal.

DSC evaluates the changes in thermodynamic properties when applying heat energy [31]. New crystal formation can be determined by the presence of an exothermic or endothermic peak on the DSC thermogram [31]. Based on the observation of thermal analysis, there is a decrease in the melting points of both the multi-component crystal (122.96 ˚C) and caffeic acid (236.34 ˚C) (Figure 4). A lower melting point indicates that the lattice energy has become weaker, thus allowing an increase in the dissolution rate of caffeic acid.

In addition, the multicomponent caffeic acid-tromethamine crystal decreases the heat of fusion enthalpy, which also lowers the melting point (Table 2). The enthalpy of fusion of caffeic acid is 162.83 J/g, while the enthalpy of fusion of multi-component crystals is 52.72 J/g. The decrease in enthalpy indicates that the energy required for melting is lower, meaning that the proportion of multi-component crystal is less than that of its constituent components.

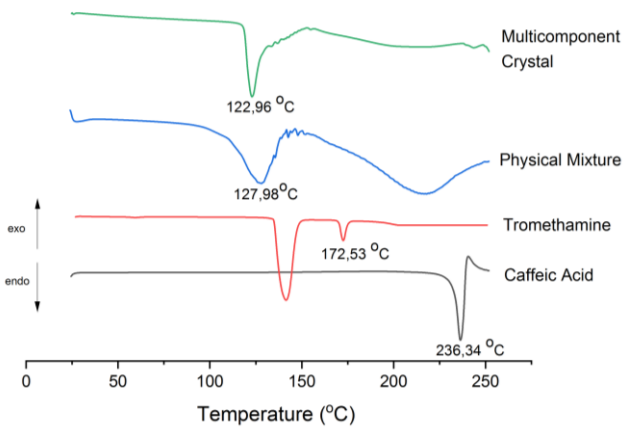

Figure 4. Thermogram of caffeic acid, tromethamine, physical mixture, and multi-component crystals

Table 2. Thermal analysis data of caffeic acid, tromethamine, physical mixture, and multi-component crystals

Sample	Melting point (°C)	ΔH Fusion(J/g)
Caffeic acid	236.34	161.74
Tromethamine	172.53	37.53
Physical mixture	127.98	118.20
Multi-component crystal	122.96	50.84

In a crystalline multi-component system, FTIR analysis determines the presence of interactions [21]. The formation of additional peaks or changing peaks in a multi-component crystal system indicates interaction between components [33]. A shift in wavenumber confirms the presence of hydrogen bonds created between the two substances [16]. Figure 5 shows the spectrum and FTIR data for caffeic acid, tromethamine, physical mixtures, and multi-component crystals.

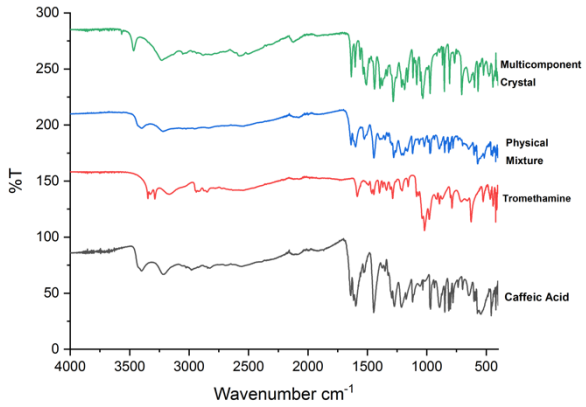

Figure 5. Figure 5. Figure 5. Fourier transform infrared spectrum of caffeic acid, tromethamine, physical mixture, and multi-component crystals

Figure 5 also reveals numerous absorption peaks at the wavenumbers for caffeic acid and tromethamine. The wavenumber of the physical combination does not change significantly. However, the multi-component crystal does reveal the absorbance band of the NH stretching band at a wavenumber of 1509.32 cm^{-1}. We can assume that the shift in wavenumber in the spectrum of the multi-component crystals is caused by interactions involving proton transfer. The wavenumber shift in the multi-component crystal spectrum may be due to proton transfer between two interacting species [21]. Proton transfer may occur because of the significant differences in pKa value (>3) between caffeic acid and tromethamine. This result is in line with the results of the DSC analysis, which showed a decrease in the melting point, and the results of the XRD analysis, which revealed a new diffraction pattern in the multi-component crystal system.

SEM analysis was used to characterize the crystal morphology. The process of forming multi-component crystals can produce different crystal habits of the active substance and coformers. Crystal habit affects flowability, compressibility, dissolution rate, and bulk particle density [34]. The results of the SEM analysis of the caffeic acid compound at 1000x magnification, tromethamine at 400x magnification, physical mixture at 1000x magnification, and multi-component crystals at 500x magnification can be seen in Figure 6.

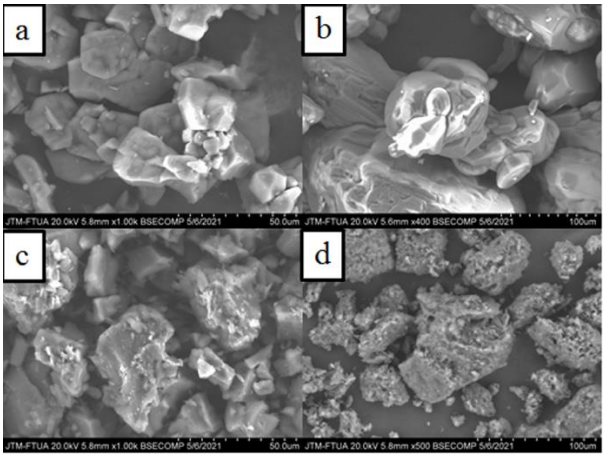

Figure 6. Scanning electron microscopy of caffeic acid at mafnification x1000 (a), tromethamine at mafnification x400 (b) , physical mixture at mafnification x1000 (c), and multi-component crystals at mafnification x500 (d)

Figure 7 shows the results of the dissolution rate test. The percentage of caffeic acid, physical mixture, and multi-component crystals that dissolved after 60 minutes were 80.741%, 84.541%, and 99.362%, respectively. There were significant differences in the dissolution rates of caffeic acid, physical mixes, and multi-component crystals ($p<0.05$) and indicated that the dissolution rate of caffeic acid had increased.

The dissolution rate of the multi-component crystals increased 1.23 times and 1.17 times, respectively, compared with the caffeic acid and the physical mixes. Data such as decreased melting point and decreasing peak intensity confirmed the rise in dissolution percentage. Caffeic acid is a weak acidic molecule that

dissolves slowly in acid due to its nonionic origin. The multi-component crystal quickly ionizes in acid because of more basic tromethamine content, resulting in more solubility.

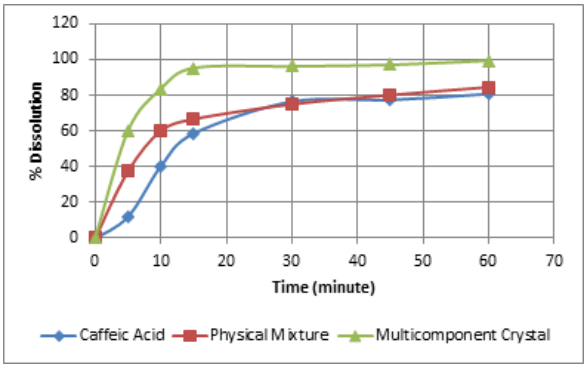

Figure 7. Dissolution profile in 0.1 N HCl medium

An antioxidant test was carried out using the DPPH radical scavenging method. Unpaired electrons in the DPPH structure bind to a compound that can donate electrons, resulting in a decrease in the color intensity or absorbance of the DPPH solution [35]. The antioxidant activity of the test compound was expressed by the IC50 value, which is obtained from the linear regression equation that states the relationship between the concentration of the test compound and the percentage of radical scavenging it possesses. The smaller the IC50 value, the more active a compound is as an antioxidant. This study used gallic acid as a comparison compound as it is known to have potent radical scavenging potential [27]. The antioxidant test was conducted to examine whether multi-component crystal formation influenced caffeic acid's antioxidant activity as measured by the IC50 value. The antioxidant test results for the caffeic acid, multi-component crystal, and gallic acid are shown in Table 3. The IC50 values of caffeic acid, multi-component crystalline, and gallic acid were 33.10 g/mL, 28.35 g/mL, and 11.32 g/mL, respectively. Based on these values, we can observe an increase in the antioxidant activity of caffeic acid in the form of multi-component crystals, but not significantly different from the IC50 of pure caffeic acid. Therefore, we can conclude that the antioxidant activity of caffeic acid is not affected when it takes the form of multi-component caffeic acid-tromethamine crystal

4. CONCLUSION

Multi-component crystals of caffeic acid-tromethamine were formed at a ratio of 4:6 based on the results of X-ray diffraction analysis, thermal analysis, FTIR analysis, and SEM. Forming caffeic acid-tromethamine multi-component crystals increased the dissolution percent of caffeic acid in 0.1 N HCl medium by 1.23 times but did not affect the antioxidant activity.

Table 3. antioxidant test results using the DPPH method

Sample	Concentration (µg/mL)	Inhibition percentage (%)	Used inhibition percentage (%)	Regression equation	IC 50 (µg/mL)
Caffeic acid	1	-0.321		y = 1.53x – 0.6403	33.10 ± 0.485
	5	6.358			
	10	14.644	14.644		
	25	37.636	37.636		
	50	75.851	75.851		
	100	94.990			
Caffeic acid-tromethamine	2	1.927		y = 0.7307x – 1.7983	28.35 ± 0.513
	4	5.523			
	10	16.506	16.506		
	20	34.682	34.682		
	40	71.291	71.291		
	80	93.770			
Gallic acid	1	3.147		y = 4.1297x + 3.2541	11.32 ± 0.293
	5	23.443	23.443		
	10	45.472	45.472		
	15	64.740	64.740		
	20	81.824			
	25	92.614			

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