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Prita Anggraini Kartika Sari:

We have reached a decision regarding your submission
of Consumption of Vegetables and Fruit on T-glutathione

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Effect of Consumption of Vegetables and Fruit on T-glutathione Levels in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Glutathione is an antioxidant that plays a role in preventing free radicals and reducing oxidative stress, including in patients with type 2 diabetes mellitus (DMT2). One of the factors that affect glutathione status is the individual's ability to produce glutathione and in diabetic patients, T-glutathione levels have decreased. This study aims to determine the effect of fruit and vegetable consumption habits on plasma levels of T-Glutathione. This research method is analytic observational with cross sectional findings, the sample used is 85 subjects in the form of archives of biological materials. Data on habits of consuming vegetables and fruits were collected through interviews, plasma T-GSH levels were determined biochemically using the Elabscience GSH Assay Kit and then analyzed using the Mann Whitney test. The results showed that the average plasma T-GSH levels in patients with the habit of consuming vegetables and fruit and those who did not, were 13.54 ± 3.34 mol/L and 12.73 ± 1.44 mol/L, respectively, but not found a significant difference relationship (p = 0.222). This study provides information that the habit of consuming vegetables and fruit does not provide a significant difference to plasma T-GSH levels in T2DM patients. But these habits still need to be done for health maintenance. Further research is needed that is more specific to the amount and type of certain vegetables and fruits consumed and how to cook them.

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Keywords: Diabetic, Fruit, Habit, T2DM, T-Glutathione, Vegetables

Commented [L1]: Hubungan sebab akibat apakah dalam waktu yang bresamaan ..

Dengan komsumsi ….. apakah glutation .. dapat meningkat …

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INTRODUCTION

Diabetes is one of the top ten diseases in the world that causes death with a significant percentage increase of 70% since 2000 (Kochanek et al., 2019). Globally, the estimated prevalence of diabetes in the US for 2018 is 34.2 million people of all ages or 10.5% of the US population has diabetes (CDC, 2020). Indonesia is ranked 7th among the 10 countries with the highest number of people with diabetes (Kemenkes RI, 2020). Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both (Kharroubi, 2015). According to the American Diabetes Association (ADA), the classification of diabetes is divided into type 1 diabetes, type 2, other types, and gestational diabetes mellitus (Kharroubi, 2015) and type 2 Diabetes Mellitus (T2DM) is one of the most common metabolic disorders worldwide(Galicia-Garcia et al., 2020).

Glutathione is a tripeptide (cysteine, glycine, and glutamic acid) which is found in relatively high concentrations in body tissues. Glutathione plays an important role in reducing oxidative stress, maintaining redox balance, increasing metabolic detoxification, and regulating the immune system (Minich & Brown, 2019). Studies have reported that l-cystiene (LC) supplementation decreased markers of oxidative stress in type-2 diabetic patients as well as normal subjects (Jain et al., 2016). In addition, the provision of antioxidants as a therapeutic strategy is also recommended to prevent diabetes complications and restore insulin sensitivity (Rajendiran et al., 2018). Epidemiological studies reveal a strong association between dietary antioxidant intake and protection against diabetes (Rajendiran et al., 2018)

Glutathione status is influenced by the degree of variability in an individual's ability to produce glutathione, primarily due to genetic variability in the enzymes involved in its production and/or regeneration. Some of these enzymes require nutritional cofactors. The need for glutathone may be greater in the presence of oxidative stress, malnutrition or increased toxic load due to exposure to environmental contaminants (Minich & Brown, 2019) as well as because circulating and tissue levels of glutathione (GSH) decline with age and diabetes (Jain et al., 2016)

Diabetes is associated with lower glutathione levels as evidenced by the study of Kalkan et al (2013) with the results obtained that the average GSH concentration value is 3.9 ± 1.1 µM in subjects with DM and 8.37 ± 1.04 µM in normal subjects. The mean levels of GSH in subjects with DM were significantly reduced compared normal subjects (Kalkan & Suher, 2013). Therefore, it is important to know how to maintain or increase GSH levels in the body, one of which is by consuming vegetables or fruits that contain glutathione and this study aims to determine the effect of differences in vegetable and fruit consumption habits on GSH levels.

Commented [L3]: Yang ini mohon lebih di ringkas,, kemudian di tambahakan bawah salah satu upaya untuk meningkatkan glutathion dengan mengkonsumsi ….

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Commented [L5]: mengetahuai hubungan antara konsumsi ….. dengan kadar GSH

MATERIALS AND METHOD

Materials

The equipment used in this study included a 3ml syringe, 3ml Ethylene diamine tetraacetic acid (EDTA) vaculab blood tube, test tube, centrifuge, vortex, micropipette, micro-plate reader (550 nm), 37oC water bath, micro-plate reader. (405 nm). The materials used in this study included NO Assay Kit E-BC-K036 and Total Glutathione/Oxidized E-BC-K097.

Methods

This research is analytic observational with a cross sectional research design. 85 samples were used in the form of blood plasma of DMT2 patients at the Jetis 1 Health Center, Bantul, Yogyakarta which was obtained in the study of Akrom et al., (2018). Furthermore, measurements of T-GSH levels in the blood plasma of the DMT2 patient were carried out

The population in this study were all patients diagnosed with T2DM by a doctor with or without comorbidities. The inclusion criteria were male and female patients aged 18 years and over (who had signed and filled out the informed consent) who were diagnosed or had a history of T2DM, had uncontrolled and controlled blood glucose levels, had an HbA1C value above normal (4%) -

5.7%), had a moderate to high level of compliance as assessed by the Medication Adherence Report Scale (MARS) compliance questionnaire, had regular treatment at the Jetis 1 Public Health Center during the study period, willing to participate in research. Exclusion criteria were patients with mental disorders, pregnant and resigned as respondents during the study.

Patients are said to consume vegetables/fruits if they consume vegetables and fruit once a day. This data was obtained through the interview process….

Commented [L6]: Ini kepatuhan dalam konsumsi vegetable ya?

Di bagian intisari kok belum disampaikan

Commented [L7]: Selama berapa tahun pasien atau responden mengkonsumsi sayuran ?

Measurement of T-GSH plasma levels

T-GSH levels in plasma samples were measured by colorimetric technique using a micro-plate reader (λ: 405 nm), expressed in mol/L. Measurements were carried out by a trained operator according to the manual instructions Total Glutathione/Oxidized Glutathione Assay Kit E-BC-K097 (appendix 5).

Samples (plasma) of 100 L were added with 400 L of reagent 4 working solution and mixed using a vortex for 30 seconds, then allowed to stand for 5 minutes at 4°C. Then the sample was centrifuged at a speed of 3500 rpm for 10 minutes. The supernatant obtained was used for measurement and could be stored at 4°C or -20°C for 1 night.

Commented [L8]: Ini maksudnya satu malam ,, aau menggunakan jam saja ya …

To each sample and standard solution (50 mol/L standard GSH) was added 100 L of reagent 1 and 10 L of reagent 2. Furthermore, the working solution of reagent 3 was added and the absorbance was recorded at the same time, at the 30th (A1) and 630th (A2) seconds.

Data Analysis

The data obtained were analyzed using the Statistical Package for the Social Sciences (SPPS). Demographic data (age and sex) and consumption habits of vegetables and fruit in T2DM patients were analyzed using a descriptive test presented in the form of frequency. Then the homogeneity and normality tests were carried out using the explore of descriptive tests and the Kolmogorov-Smirnov Test to determine the type of further analysis.

The test results showed that the data obtained were homogeneous ($p > 0.05$) but not normally distributed ($p < 0.05$) so the further test was to determine the relationship between the differences between the independent variables (age, gender and consumption of vegetables and fruit) and the dependent variable. (T-GSH levels in blood plasma of DMT2 patients) using a nonparametric test, namely the Mann Whitney Test. Results were considered to be statistically significant at $P < 0.05$.

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RESULT AND DISCUSSION

Demographic Profile and Lifestyle of T2DM Patients

Table 1 Demographic Profile and Lifestyle of T2DM Patients at Jetis 1 Public Health Center, Bantul, Yogyakarta (statistical test: frequency distribution)

Variable				∑ (n=85)	Percentage (%)
Demographics	1.	Age	< 55	32	37,6
			≥ 55	53	62,4
			Mean ± SD	57,6 ± 9,1	
	2.	Sex	Male	33	38,8
			Female	52	61,2
Lifestyle	3	Consumption habits of vegetables and fruit	Yes	70	82,4
			No	15	17,6

This study involved 85 patients with the average age of the patients was 57.6 ± 9.1 years. The proportion of female 61.2% and male 38.8% and there were 82.4% of patients who had habit of consuming vegetables and fruit.

Table 2 The relationship between differences in characteristics and lifestyle of patients with T-GSH levels in blood plasma of DMT2 patients at Jetis 1 Health Center Bantul Yogyakarta (Statistical test: Mann Whitney Test, significant (p<0.05))

	Variabel		N	T-GSH (µmol/L)		
				Mean ± SD	(min-max)	*p*
Demographics	Age	<55	32	13,28 ± 3,47	(6,82-22,73)	0,884
		>=55	53	13,46 ± 2,88	(6,82-20,45)	
	Sex	Male	33	13,84 ± 3,08	(6,82-20,45)	0,153
		Female	52	13,11 ±3,10	(6,82-22,73)	
Lifestyle	Consumption habits of vegetables and fruit	Yes	70	13,54 ± 3,34	(6,82-22,73)	0,222
		No	15	12,73 ± 1,44	(9,09-13,64)	
Kadar T-GSH				13,39 ± 3,10	(6,82-22,73)	

Association of age with plasma T-GSH levels in diabetes patients

The mean plasma T-GSH level in T2DM patients with age less than 55 years (13.28 ± 3.47 µmol/L) was slightly lower than plasma T-GSH levels in T2DM patients aged more than or equal to 55 years (13.46 ± 2.88 µmol/L). There was no significant relationship between age difference in T2DM patients and plasma T-GSH levels (p > 0.05).

Association of plasma T-GSH levels with gender in diabetes patients

The mean plasma GSH levels in male patients were (13.84 ± 3.08 µmol/L) higher than female (13.11 ± 3.10 µmol/L). There was no significant relationship between gender differences and plasma T-GSH levels (p > 0.05) (table IV).

Association between consumption habits of vegetables and fruit ~~plasma T-GSH levels~~ with plasma T-GSH levels ~~consumption habits of vegetables and fruit and non~~ in diabetes patients

The mean T-GSH levels in patients who consumed vegetables and fruit (13.54 ± 3.34 µmol/L) were lower than those who did not consume vegetables and fruit (12.73 ± 1.44 µmol/L). No significant relationship was found between differences in vegetable and fruit consumption habits and T-GSH levels (p > 0.05). The results obtained are contrary to the hypothesis of this study. However, a similar pattern was found in the study of Rohim et al, who did not find a significant difference in cholesterol levels after consuming foods rich in glutathione (Rohim Tualeka' et al., n.d.).

Many factors can affect the level of GSH consumed, including how to cook it. Peeling and chopping vegetables before cooking can remove the epidermis and have a protective effect when cooked. Cooking duration, especially the baking and frying method, can significantly affect GSH levels. In addition, although not significant, cooking at high temperatures (baking, frying, and grilling) can reduce GSH levels by as much as 40% (Drinkwater et al., 2015). Any form of food processing will reduce the content of phytochemicals, including CItrus plants (Zou et al., 2016).

Another influencing factor is the characteristics of the vegetables and fruits themselves in terms of their phytonutrient content. In line with this, Zou et al's research stated that citrus plants contain very diverse and varied phytochemicals that can affect antioxidant capacity (Zou et al., 2016). Other supporting research shows that Se supplementation significantly increases blood glutathione

Commented [L10]: Korelasi usia dengan plasma T GSH

Sesuai dengan judul tabel

Commented [L11]: Yang ini kolesterol ya ,,, .. kata rich ,,

Commented [L12]: Yang ini sebaiknya di awali dengan ,, hasil penlitian tidak ada korelasi antara kebiasan konsumsi sayuran dan buah dengan level glutatian pada sampel darah responden ,, ,, hal ini kemungkin disebabkan oleh ,, bagaiman cara mengkonsumsi …

Atau faktor misalnya jensi atau jumlah jumlah sayuran …

(Sedighi et al., 2014), the selection of vegetables and fruits consumed with greater Se content will also have a greater chance of increasing glutathione levels. The amount of vegetables and fruit consumed also affects the increase in glutathione peroxidase activity (Hermsdorff et al., 2012). However, it is recommended that a variety of vegetables be consumed daily to obtain health benefits, including reducing the risk of diabetes (Dias, 2012).

It is known that type 2 diabetic patients have lower plasma glutathione concentrations than non-diabetic controls. This is probably due to reduced synthesis and increased irreversible utilization by non-glycemic mechanisms (Lutchmansingh et al., 2018). The habit of consuming vegetables and fruit regularly can improve antioxidant status. Research shows that consuming one serving of broccoli has significantly increased GST activity in plasma (Bahadoran et al., 2011) (Riso et al., 2014). The same thing was seen in type 2 diabetes patients who did a low-calorie diet of 2 pieces per day, the results obtained were significantly increased glutathione reduction (Hegde et al., 2013).

Our study has several limitations. First, we did not compare plasma glutathione concentrations in the group of patients with T2DM with that of a healthy control group. Second, the number of samples used was not so large and many confounding factors were not excluded in this study, including the method of preparation and cooking. However, despite the aforementioned challenges it is apparent that optimizing dietary intake of glutathione precursors, co-factors, and whole foods that have been shown to enhance glutathione status or are a source of glutathione would be a relatively simple, low cost, and safe approach that could improve health by optimizing glutathione status in an individual (Minich & Brown, 2019).

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Sehingga pengambilan sampel daahnya ,, mungkin jadi tidak seragam waktu konsumsinya ..

Kemungkinan juga ,, perbandingan antara yang tidak konsumsi dan yang konsusmsi ,, beda jauh ya ,, 70 dan 15 ya

CONCLUSION

The relationship between lifestyle and degenerative diseases has been widely recognized. In this study, differences in lifestyle associations in the form of habits of consuming vegetables and fruit on T-GSH levels were assessed, because they will provide an overview of the influence of nutrition on disease development. In conclusion, this study did not show that lifestyle habits in consuming vegetables and fruit did not significantly affect plasma T-GSH levels. However, consuming vegetables and fruit is still recommended as a healthy habit to prevent or inhibit various diseases. Further research is needed with a larger number of subjects and limiting the variety of vegetables that have been shown to contain glutathione.

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To each sample and standard solution (50 mol/L standard GSH) was added 100 L of reagent 1 and 10 L of reagent 2. Furthermore, the working solution of reagent 3 was added and the absorbance was recorded at the same time, at the 30th (A1) and 630th (A2) seconds.

Data Analysis

The data obtained were analyzed using the Statistical Package for the Social Sciences (SPPS). Demographic data (age and sex) and consumption habits of vegetables and fruit in T2DM patients were analyzed using a descriptive test presented in the form of frequency. Then the homogeneity and normality tests were carried out using the explore of descriptive tests and the Kolmogorov-Smirnov Test to determine the type of further analysis.

The test results showed that the data obtained were homogeneous ($p > 0.05$) but not normally distributed ($p < 0.05$) so the further test was to determine the relationship between the differences between the independent variables (age, gender and consumption of vegetables and fruit) and the dependent variable. (T-GSH levels in blood plasma of DMT2 patients) using a nonparametric test, namely the Mann Whitney Test. Results were considered to be statistically significant at $P < 0.05$.

RESULT AND DISCUSSION

Demographic Profile and Lifestyle of T2DM Patients

Table 1 Demographic Profile and Lifestyle of T2DM Patients at Jetis 1 Public Health Center, Bantul, Yogyakarta (statistical test: frequency distribution)

Variable				∑ (n=85)	Percentage (%)
Demographics	1.	Age	< 55	32	37,6
			≥ 55	53	62,4
			Mean ± SD	57,6 ± 9,1	
	2.	Sex	Male	33	38,8
			Female	52	61,2
Lifestyle	3	Consumption habits of vegetables and fruit	Yes	70	82,4
			No	15	17,6

This study involved 85 patients with the average age of the patients was 57.6 ± 9.1 years. The proportion of female 61.2% and male 38.8% and there were 82.4% of patients who had habit of consuming vegetables and fruit.

Table 2 The relationship between differences in characteristics and lifestyle of patients with T-GSH levels in blood plasma of DMT2 patients at Jetis 1 Health Center Bantul Yogyakarta (Statistical test: Mann Whitney Test, significant (p<0.05))

	Variabel		N	T-GSH (µmol/L)		
				Mean ± SD	(min-max)	*p*
Demographics	1. Age	<55	32	13,28 ± 3,47	(6,82-22,73)	0,884
		>=55	53	13,46 ± 2,88	(6,82-20,45)	
	2. Sex	Male	33	13,84 ± 3,08	(6,82-20,45)	0,153
		Female	52	13,11 ±3,10	(6,82-22,73)	
Lifestyle	3. Consumption habits of vegetables and fruit	Yes	70	13,54 ± 3,34	(6,82-22,73)	0,222
		No	15	12,73 ± 1,44	(9,09-13,64)	
Kadar T-GSH				13,39 ± 3,10	(6,82-22,73)	

Association of plasma T-GSH levels with age in diabetes patients

The mean plasma T-GSH level in T2DM patients with age less than 55 years (13.28 ± 3.47 µmol/L) was slightly lower than plasma T-GSH levels in T2DM patients aged more than or equal to 55 years (13.46 ± 2.88 µmol/L). There was no significant relationship between age difference in T2DM patients and plasma T-GSH levels (p > 0.05).

Association of plasma T-GSH levels with gender in diabetes patients

The mean plasma GSH levels in male patients were (13.84 ± 3.08 µmol/L) higher than female (13.11 ± 3.10 µmol/L). There was no significant relationship between gender differences and plasma T-GSH levels (p > 0.05) (table IV).

Association between plasma T-GSH levels with consumption habits of vegetables and fruit and non in diabetes patients

The mean T-GSH levels in patients who consumed vegetables and fruit (13.54 ± 3.34 µmol/L) were lower than those who did not consume vegetables and fruit (12.73 ± 1.44 µmol/L). No significant relationship was found between differences in vegetable and fruit consumption habits and T-GSH levels (p > 0.05). The results obtained are contrary to the hypothesis of this study. However, a similar pattern was found in the study of Rohim et al, who did not find a significant difference in cholesterol levels after consuming foods rich in glutathione (Rohim Tualeka' et al., n.d.).

Many factors can affect the level of GSH consumed, including how to cook it. Peeling and chopping vegetables before cooking can remove the epidermis and have a protective effect when cooked. Cooking duration, especially the baking and frying method, can significantly affect GSH levels. In addition, although not significant, cooking at high temperatures (baking, frying, and grilling) can reduce GSH levels by as much as 40% (Drinkwater et al., 2015). Any form of food processing will reduce the content of phytochemicals, including CItrus plants (Zou et al., 2016).

Another influencing factor is the characteristics of the vegetables and fruits themselves in terms of their phytonutrient content. In line with this, Zou et al's research stated that citrus plants contain very diverse and varied phytochemicals that can affect antioxidant capacity (Zou et al.,

2016). Other supporting research shows that Se supplementation significantly increases blood glutathione (Sedighi et al., 2014), the selection of vegetables and fruits consumed with greater Se content will also have a greater chance of increasing glutathione levels. The amount of vegetables and fruit consumed also affects the increase in glutathione peroxidase activity (Hermsdorff et al., 2012). However, it is recommended that a variety of vegetables be consumed daily to obtain health benefits, including reducing the risk of diabetes (Dias, 2012).

It is known that type 2 diabetic patients have lower plasma glutathione concentrations than non-diabetic controls. This is probably due to reduced synthesis and increased irreversible utilization by non-glycemic mechanisms (Lutchmansingh et al., 2018). The habit of consuming vegetables and fruit regularly can improve antioxidant status. Research shows that consuming one serving of broccoli has significantly increased GST activity in plasma (Bahadoran et al., 2011) (Riso et al., 2014). The same thing was seen in type 2 diabetes patients who did a low-calorie diet of 2 pieces per day, the results obtained were significantly increased glutathione reduction (Hegde et al., 2013).

Our study has several limitations. First, we did not compare plasma glutathione concentrations in the group of patients with T2DM with that of a healthy control group. Second, the number of samples used was not so large and many confounding factors were not excluded in this study, including the method of preparation and cooking. However, despite the aforementioned challenges it is apparent that optimizing dietary intake of glutathione precursors, co-factors, and whole foods that have been shown to enhance glutathione status or are a source of glutathione would be a relatively simple, low cost, and safe approach that could improve health by optimizing glutathione status in an individual (Minich & Brown, 2019).

CONCLUSION

The relationship between lifestyle and degenerative diseases has been widely recognized. In this study, differences in lifestyle associations in the form of habits of consuming vegetables and fruit on T-GSH levels were assessed, because they will provide an overview of the influence of nutrition on disease development. In conclusion, this study did not show that lifestyle habits in consuming vegetables and fruit did not significantly affect plasma T-GSH levels. However, consuming vegetables and fruit is still recommended as a healthy habit to prevent or inhibit various diseases. Further research is needed with a larger number of subjects and limiting the variety of vegetables that have been shown to contain glutathione.

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Section Editor
2022-02-12 04:30 AM

Subject: [Pharmaciana] Editor Decision DELETE

Prita Anggraini Kartika Sari:

We have reached a decision regarding your submission to Pharmaciana, "Effect of Consumption of Vegetables and Fruit on T-glutathione Levels in Patients with Type 2 Diabetes Mellitus".

Our decision is to: Revision Required
Please follow the reviewer suggestion's to revise your manusccript. Your revision must be uploded at least February 14, 2022.

apt. Susan Fitria Candradewi, M.Sc
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Susanfitria2@gmail.com

Best regards,

Susan Fitria Candradewi, M.Sc., Apt.
Faculty of Pharmacy Ahmad Dahlan University

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Author
2022-02-13 11:59 PM

Subject: Effect of Consumption of Vegetables and Fruit on T-glutathione Levels in Patients with Type 2 Diabetes Mellitus DELETE

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Section Editor
2022-03-18 04:05 AM

Subject: [Pharmaciana] Editor Decision DELETE

Prita Anggraini Kartika Sari:

We have reached a decision regarding your submission to Pharmaciana, "Effect of Consumption of Vegetables and Fruit on T-glutathione Levels in Patients with Type 2 Diabetes Mellitus".

Our decision is to: REVISION REQUIRED
please add 1 more variables for the analysis.

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Susanfitria2@gmail.com

Best regards,

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Faculty of Pharmacy Ahmad Dahlan University

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Section Editor
2022-05-25 09:14 AM

Subject: [Pharmaciana] Editor Decision DELETE

Prita Anggraini Kartika Sari:

We have reached a decision regarding your submission to Pharmaciana, "Effect of Consumption of Vegetables and Fruit on T-glutathione Levels in Patients with Type 2 Diabetes Mellitus".

Our decision is to: ACCEPT SUBMISSION

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Best regards,

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Editor
2022-06-07 10:14 AM

Subject: [Pharmaciana] Editor Decision DELETE

Prita Anggraini Kartika Sari:

We have reached a decision regarding your submission to Pharmaciana, "Effect of Consumption

We have reached a decision regarding your submission to Pharmaciana, "Effect of Consumption of Vegetables and Fruit on T-glutathione Levels in Patients with Type 2 Diabetes Mellitus".

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