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Submission date: 04-Oct-2022 04:34PM (UTC+0800)
Submission ID: 1916285958
File name: Glucose_Levels_and_Diameter_of_Langerhans_Pancreatic_Islats.pdf (1.02M)
Word count: 4671
Character count: 24195

Hypoglycemic Effects of *Rosa damascena* Mill. Ethanolic Extract on Blood Glucose Levels and Diameter of Langerhans Pancreatic Islets

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Abstract

Background: Diabetes mellitus is a chronic disorder caused by elevated levels of high blood glucose (hyperglycemia). This chronic hyperglycemia causes ROS to accumulate and oxidative stress to increase. *Rosa damascena* is a plant that contains high levels of antioxidants and polyphenols, but this is not widely known to the public. **Purpose**: The aim of this study is to understand the hypoglycemic effects from *Rosa damascena* on blood glucose levels and diameter of Langerhans pancreatic islets. **Method:** Thirty Wistar albino rats (200-225gr) were divided into 6 groups. Group 1 was a normal control (KN), group 2 was hyperglycemic (KD), group 3 was metformin 250 mg/kg BW (KM), group 4 was treatment extract 250 mg/kg BW (P1), group 5 was treatment extract 500 mg/kg BW (P2) group 6 was treatment extract 1000 mg/kg BW (P3). All animals in the group were injected with STZ 50 mg/kg BW, except for group 1. **Result:** Data were analyzed statistically using SPSS- 22 software with the Kruskall-Wallis test ($p<0.05$). The result showed that ethanolic extract of *Rosa damascena* has decreased blood glucose levels in days-14 (382 ±21,97) with 250 mg/kg BW (P1) compare with another treatment group. In histological observed there are no significant different between group ($p>0.05$). This is showing that ethanolic extract of *Rosa damascena* has inability to repaired the diameter of Langerhans pancreatic islets. **Conclusion:** Ethanolic extract of *Rosa damascena* decreased blood glucose levels but did not repaired the diameter of Langerhans pancreatic islets.

Key words: *hyperglycemic, Rosa damascena, Langerhans islets.*

Introduction

Diabetes is a group of metabolic diseases characterized by increased blood glucose levels (hyperglycemia) due to impaired insulin secretion, insulin resistance or both[1]. Diabetes is classified into type 1 diabetes which results from failure of insulin secretion, type 2 diabetes occurs due to insulin resistance, gestational diabetes that occurs during pregnancy and other types of diabetes that occur due to autoimmunity[2]. According to data from the International Diabetes Federation, 382 million people worldwide suffer from diabetes, and this figure will increase to 592 million sufferers in less than 25 years[3]. Diabetes can lead to complications of micro vascular and macro vascular damage. Macro-vascular damage can be in the form of heart failure, stroke, peripheral vascular disorders, while microvascular damage can result in retinopathy, neuropathy and nephropathy in diabetic patients[4]. Hyperglycemia in diabetes can lead to increased production of ROS in various cell types. For example, there was an increase in AGEs in Type-2 DM in a diabetic mouse model. Increase in 8-hydroxydeoxyguanosine and modification

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of hydroxynonenal protein in pancreatic beta cells. This study shows that increased glucose levels and chronic hyperglycemia can further exacerbate oxidative stress during Type-2 DM[5].

Treatment of diabetes mellitus with herbal ingredients has been widely researched, especially in relation to its effectiveness, safety and low side effects. One of the herbs that can be used for diabetes treatment is rose flower (*Rosa damascena*). The rose (*Rosa damascena*) is a family of Rosaceae or commonly referred to as damask rose. Rose is a plant that is found almost all over the world, this plant is found in many areas including Europe, the Middle East, especially Iran and Turkey[6]. In Indonesia, this plant can be found in almost all regions, in East Java, this plant is found in many mountainous areas such as Batu Aji, Batu, Malang. Roses have many phenolic contents including flavonoids, glycosides, terpenes and anthocyanins isolated from various parts of *R. damascena* flowers[7]. The highest content of phenolic compounds is glycosides and quercetin which are obtained from methanol extract. Both of these compounds have high antioxidant abilities and are DNA protective agents. Based on the DPPH test conducted by Kumar[8] It is known that roses have the ability to free radical-binding by 43.6 ± 0.25% at every 100mg/ml. Study conducted by Gholamhoseinian[9] showed that *R. damascena* methanol extract with a dose between 100-1000 mg/kg BW can reduce blood glucose levels through inhibition of α-glucosidase activity by 98% compared to acarbose which only achieves 51%.

This study aims to determine the effect of giving different doses of rose flowers extract (*Rosa damascena*) on fasting blood glucose levels and the diameter of Langerhans islets in male albino Wistar rats (*Rattus norvegiccus*) after being induced with low doses of streptozotocin. The results of this study are expected to be useful for the development of plant effectiveness as an innovation in diabetes therapy.

Method

Animal

This study used experimental 30 animals Wistar white rat (*Rattus norvegiccus*) 3-4 months old male with a body weight of 200-225 grams. The maintenance and surgery of experimental animals was carried out in the Pharmacology Laboratory, Faculty of Medicine, Universitas Airlangga. Rats were acclimatized for 7 days at room temperature 25-30°C with a relative humidity of 55-65%. During the adaptation period, the experimental animals were fed a standard diet and drank clean water ad libitum. This research was conducted based on the letter of ethics no: 150/HRECC.FODM/III/2020.

Extraction Proses

Roses are obtained from rose plantations in the Batu Aji area, Batu, Malang, East Java. 800 grams of rose flowers that have been dried and soaked in 5 Liters of 96% ethanol solution for 3 x 24 hours, closed tightly and kept out of the sun. The liquid extract obtained was then removed from the moisture using the evaporation method with a rotary evaporator machine at a temperature of 50°C so that a thick extract was obtained. The extract obtained is then diluted and calculated according to doses of 250 mg/kg BW, 500 mg/kg BW, and 1000 mg/kg BW[10].

Animals Treatmenet

The experimental animals were divided into 6 groups, KN (control group), KD (hyperglycemic group), KM (metformin 250 mg / kg BW), P1 (RD 250 mg / kg BW extract), P2 (RD 500 mg / kg BW extract), P3 (extract RD 1000 mg / kg BW). The experimental animals were injected with a single dose of STZ 50 mg/kg BW. After 5 days of measurement of fasting blood glucose levels, the rats were considered diabetic if their glucose levels reached >200 mg/dL. Treatment according to each category was then given to the experimental animals for 14 days. Glucometers and glucostrip (*Easy Touch Blood Glucose*) were used to measure GDP levels[11], The animals were fasted for 8 hours, then slightly wounded at the tip of their tail, then dripped at the tip of the strip as the blood came out. Blood glucose fasting rate testing was performed on the 0th, 7th and 14th days.

Preparation of Histological staining Pancreas

The experimental animals were euthanized using 0.67 ml chloroform / experimental animal for 60 seconds until the experimental animals did not move[12]. Furthermore, surgery and removal of the pancreas are performed. The pancreas wad washed with normal saline solution and then immediately put into a 10% *neutral*

buffer formalin solution. The preparation of HE staining slides was carried out at the Laboratory of Anatomical Pathology, Faculty of Medicine, Universitas Airlangga. The pancreas organ that has been inserted into the 10% NBF is made paraffin blocks, then cut using a microtome knife to produce a thickness 4-5m. The results of the slices were transferred with a brush into warm water 38˚-40˚C to straighten any fine wrinkles. Perfectly stretched slices are taken with a slide. The pieces that have been taken are then dried and placed on a hot plate 38˚- 40˚C until dry. Subsequently, counterstaining was carried out with *Mayer haematoxylin* for 10 minutes and washed with tap water. The final step is to dry the preparations in the mounting using an entellan and cover with a glass cover[13].

Data Analysis

The data obtained were in the form of average fasting blood glucose levels and the average diameter of the pancreatic islets of Langerhans. In the process of determining the diameter of the Langerhans pancreatic islets, a qualitative observational study was carried out using an Olympus BX-50 light microscope combined with the *Olympus cellSens* Entry software with 4 fields of view. Data processing was performed with the help of SPSS version 22 software. Data were analyzed using the *Kruskall-Wallis* and *Mann-Whitney* tests with significance ($p < 0.05$).

Result

Testing of Blood Glucose Levels

Data on the results of blood glucose levels were tested for normality with Shapiro-Wilk with an abnormal distribution ($p > 0.05$) so that it was followed by the *Kruskall-wallis* test, it was obtained that the GDP data had differences between groups. The data then performed the *Mann-Whitney* test to determine significant differences between groups. GDP rate data is presented in Table 1.

Table 1. Fasting Blood Glucose levels before and after treatment

Treatment	N	Blood Glucose level 0 days treatment (mg/dL)	Blood Glucose levels 7 days after treatment (mg/dL)	Blood Glucose levels 14 days aftertreatment (mg/dL)
Control (KN)	5	103.8 ± 5,72a	106,20 ± 12,25a	98 ± 5,86a
Hyperglycemia (KD)	5	393.4 ± 101,37b	404,80 ± 91,75b	437,20 ± 75,96bc
Metformin 250 mg/kg BW (KM)	5	418 ± 102,39b	407 ± 149,39b	388 ± 166,12b
Extract RD 250 mg/kg BW (P1)	5	433.2 ± 43,67b	408,80 ± 21,97b	382 ± 21,97b
Extract RD 500 mg/kg BW (P2)	5	430 ± 20,71b	552,40 ± 46,94bc	402,40 ± 78,20bc
Extract RD 1000 mg/kg BW (P3)	5	417.6 ± 87,26b	491,20 ± 61,26bc	454 ± 75,80bc

Noted: *significant $\alpha = 0.05$

[a,b] Different superscript showed the difference between group significantly

From these data, it can be seen that the treatment group experienced a decrease in fasting blood glucose compared to the hyperglycemic group although it was not statistically significant. There can be seen that in the hyperglycemic group, which was only given STZ injection without extract, there was an increase in GDP levels on day 7 with a value of 404.8 ± 91,75 mg/dL and on day 14 to 437.2 ± 75,96 mg/dL. In the KM treatment group that was given metformin 250 mg/kg BW, there was a decrease in GDP on day 7 with a value of 407 ± 149,39 mg/dL and on day 14 to 388 ± 166,12 mg/dL. In the P1 treatment group given RD 250 mg/kg BW ethanol extract, there was a decrease in GDP on day 7 with a value of 408.8 ± 21,97 mg/dL and on day 14 it became 382 ± 21,97 mg/dL. In the P2 treatment group given RD ethanol extract 500 mg/kg BW, there was an increase in GDP on day 7 with a value of 522.5 ± 46,94 mg/dL and a decrease on day 14 to 402.4 ± 78,20 mg/dL. In the P3 treatment group given RD ethanol extract 1000 mg/kg BW, there was an increase in GDP on day 7 with a value of 491.2 ± 61,26 mg/dL and a decrease on day 14 to 454 ± 75,80 mg/dL.

Measurement of Pancreatic Langerhans Islet

The average results from the Langerhans islets diameter measurement results was checked using *Shapiro-Wilk* and reported that the data was normally distributed. The *Brown-Forsythe* test was then carried out and found a value ($p > 0.05$), which implies that there is no substantial difference between classes. Table 2 presents the data from the measurement results of the Langerhans islets diameter measurement.

Table 2. Diameter of Langerhans Pancreatic Islets

Treatment	N	Average Diameter of Langerhans Pancreatic Islets (mm)	0,592 p
KN (Normal)	5	124.01 ± 10.82	
KD (Diabetes)	5	107.96 ± 19.65	
KM (Metformin 250 mg/kg BW)	5	114.02 ± 7.95	
P1 (Extract RD 250 mg/kg BW)	5	111.27 ± 32.94	
P2 (Extract RD 500 mg/kg BW)	5	120.92 ± 15.00	
P3 (Extract RD 1000 mg/kg BW)	5	112.89 ± 16.21	

Noted: *significant $\alpha = 0.05$

From the data above, it can be seen that there are increase in the average diameter of the pancreatic islets of Langerhans although statistically there are no significant difference between groups. The histological of the pancreatic islets of Langerhans diameter showed that the hyperglycemic group (KD) had the least value (107.96 ± 19.65mm) compared to the all treatment group. The P2 group had the best value compared to other treatment groups (120.92 ± 15.00mm) almost the same as the control group.

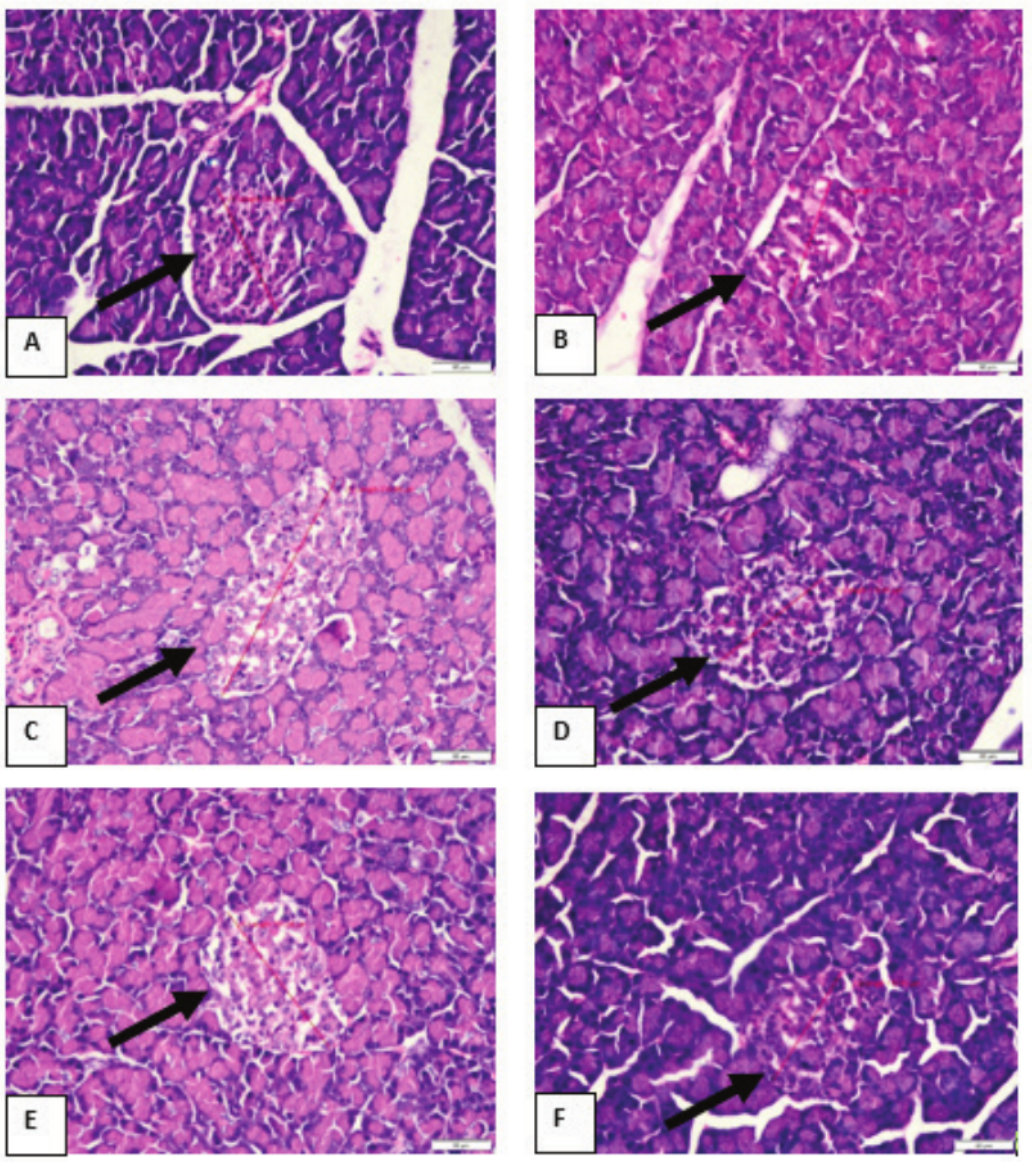

Figure 1. Histology Image of Langerhans Pancreatic Islets with 40x magnification.

A: Control group (KN), **B**: Hyperglycemic group (KD), **C**: Metformin group (KM) 250 mg/kg BW, **D**: (P1) Extract RD group 250 mg/kg BW, **E**: (P2) Extract RD group 500 mg/kg BW, **F:** (P3) Extract RD group 1000 mg/kg BW

Discussion

In normal rats, blood glucose levels can vary. According to research conducted by Gutierrez[14] normal fasting glucose rats levels ranged from 91.19 to 95.41 mg/dL. In this study, the fasting blood glucose levels in the control group showed 98-103 mg/dL. Meanwhile, the hyperglycemic group showed an increase in GDP after being injected with STZ 50 mg/kg BW with a range of 390-500 mg/dL. This shows that giving STZ at a dose of 50 mg/kg BW can increase fasting blood glucose levels in experimental animals. As already mentioned by Jinzi[15] the STZ mechanism enters pancreatic β cells

through the GLUT 2 receptor found on the pancreatic β cell membrane. Pancreatic β cells are specific target cells for STZ. As a glucose analog, via the GLUT2 transporter, STZ reaches β-cells and accumulates intracellularly. An alkylating agent, diazomethane (DAM), which induces DNA methylation and elicits diabetogenic action, forms STZ inside the cells. STZ also induces diabetes through various mechanisms, such as increased NADPH levels either through the development of glucose auto-oxidation or *diacylglycerol* (DAG) and increased free radical generation of O^2, activation of the protein kinase C pathway, glucose flux through the metabolic pathway of polyol, accumulation of *Advanced Glycation End products* (AGEs) and secretion of cytokine[16]. STZ selectively destroys β cells, allowing STZ to be considered a special compound in animals with an appropriate build and face validity for modeling diabetes.

From this research, it can be seen that the hyperglycemic group and the treatment group before and after being given the treatment showed different results. In the metformin group, the value of blood glucose levels on day 7 was 404.8 mg/dL and on day 14 it decreased to 388 mg/dL. This is in accordance with the research conducted by Shahlah[10] that metformin at a dose of 250 mg/kg BW can reduce fasting blood glucose levels. According to Ikeda[17] the mechanism action of metformin is related to the absorption process that occurs in the small intestine. The accumulation of metformin in the small intestine tissue after oral administration indicates that metformin increases the work of glucose absorption in the small intestine in rats in vivo, and this is believed to be a form of efforts to lower blood glucose levels. This maximum absorption of glucose cannot occur if metformin is given intravascularly or intraduodenal.

Another study suggested that metformin could decrease blood glucose levels through the (*Glucagon Like Peptide*) GLP-1 pathway. The gastrointestinal tract is the body's largest endocrine organ and accountable for the release of several hormones essential for homeostasis of blood glucose[18]. GLP-1 and *Glucose-dependent Insulinotropic Polypeptide* (GIP) which when compared to "isoglycaemic" intravenous glucose infusion, account for substantially greater insulin secretion in response to oral or enteral glucose, a phenomenon known as the "incretin effect." GLP-1 also inhibits gastric emptying, suppresses the secretion of glucagon and food intake and can minimize gluconeogenesis irrespective of insulin or glucagon shifts[19]. This study showed a decrease in fasting blood glucose levels in the KM group but the decrease was only slightly. This can be affected by the duration of metformin administration which is only given for 14 days. In an acute experimental study (850 mg/kg and 1500 mg/kg BW) it was found that metformin could increase postprandial GLP-1 in several groups. Another study states that giving metformin for 4 weeks and 18 months can consistently increase GLP-1 levels[20].

Based on report by Gholamhosseinian[21] *Rosa damacena* extract at doses of 250, 500, and 1000 mg/kg BW can reduce post prandial sugar levels in the 60th minute. In our study, there was a decrease in blood glucose levels in the P1 and P2 groups (250 and 500 mg/kg BW) compared to the hyperglycemic group, this is in accordance with the research conducted by Abbas [21] that methanol extract of *Rosa damascena* dose of 100 mg / kg BW can reduce fasting blood glucose levels in 2 weeks. From these studies it is known that *Rosa damascena* is able to reduce blood glucose levels and the HOMA-IR index on insulin resistance. *Rosa damascena* also increases sensitivity to insulin but has not been able to increase insulin secretion.

Study by Gholamhosseinian [9] *Rosa damascena* extract has been shown could reduce glucose levels by inhibiting the α-glucosidase enzyme, which slows down the absorption of carbohydrates from the small intestine and results in an antidiabetic effect by reducing the postprandial glucose level effect. In vitro inhibitory effect on lipid oxidation and antioxidant effect of *R. damascene*. Another study *R. damascena* has been shown to have a tocopherol-like effect and causes a strong antioxidant and lipid peroxidation inhibitor effect. This plant is proposed for the treatment and prevention of free radical diseases[22]. The study that did by Kumar [8] total phenolic contents of *Rosa damascena* methanolic extracts by DPPH-scavenging activity 43.6 ± 0.25 at 100mg/mL. The IC50 value for the methanolic extract of *R. damascena* was found relatively at 21.4 mg/mL. Thus, rose extracts displayed strong antioxidant activity due to the high content of polyphenols. These phenolic antioxidants play an important role as bioactive concepts in the conventional medicines used in rose flowers. In *Rosa damascena*, the flavonoid content is indicated to induce hypoglycemia and hypolidemia. A 16 percent

rise in insulin secretion from pancreatic β - cells is also induced by flavonoids. The action is activated by the *peroxisome proliferator receptor* (PPAR dan PPAR γ) arrangement[21]. Another study showed that the hypoglycemic effects of flavonoids can be partially due to increased hexokinase and glucokinase activity in the liver and their insulin-like effect, thus reducing the indications of diabetes mellitus[23].

In this study, the effect of decreasing fasting blood glucose occurred at doses of 250 mg/kg BW and 500 mg/kg BW, but at doses of 1000 mg/kg BW, the decrease in fasting blood glucose was not very visible. This is not in line with research conducted by Gholamhosseinian[9] at doses 1000 mg/kg BW, *R. damascena* was able to reduce post-prandial blood glucose levels. Several things that extract compounds are not well absorbed such as; because the doses used are non-toxic, the substances may not have been absorbed by oral gavage due to the presence of some materials in this plant, or they have been metabolized by the liver and produced inactive metabolite. Many things may affect the extract's ability to lower glucose, among others; Another potential reason is that, as shown in the present analysis, the small decrease in blood glucose achieved by obtaining the extract is neutralized due to the presence of absorbable carbohydrates usually found in extracts. It is also likely that there were substances that decreased blood glucose along with their additive in *R. damascena* extract to prevent blood glucose in rats[11].

The statistical analysis result showed that histological observations of the diameter Langerhans pancreatic islets there are no differences between groups. However, when seen from Figure 2, it shows that the hyperglycemic group has the smallest average value (107.96 ± 19.65mm) compared with the control and treatment groups, the P2 treatment group has the highest value (120.92 ± 15.00 mm) compared with other treatment groups. Figure 3 shows an overview of Langerhans islet cells in the hyperglycemic group that experienced the most severe damage due to STZ induction compared to the control and treatment groups. Pancreatic β cell damage can result in an inability to produce normal amounts of insulin; consequently, the size of Langerhans islets will be affected by a degree of damage. According to the number of their constituent cells, the Langerhans islets differ in size. These islets are responsible for the pancreatic β-cells' secretion of insulin. Under normal conditions, the presence of diabetic agents would not affect insulin secretion[24]. Histologically, the diameter of Langerhans islets in mice has a diameter approximately 2 times greater (116±80 μm) than human islets (50±29 μm)[25]. Pancreatic islets will experience a change in diameter under the condition of hyperglycemia.

In the KM, P1, P2, and P3 treatment groups, there was an increase in the diameter of Langerhans islets but it was not significantly different ($p>0.05$). This shows that the administration of metformin 250 mg/kg BW and *R. damascena* extract at a dose of 250 mg/kg BW, 500 mg/kg BW, 1000 mg/kg BW has not been able to increase the diameter of the pancreatic islets of Langerhans. This is due to the mechanism of action of metformin which increases the effectiveness of GLP-1 and *R. damascena* extract which inhibits α-glucosidase activity by inhibiting carbohydrate absorption in the intestines without stimulating the β cells of the pancreas so that there is no significant change in the histological cross section of Langerhans islets.

Conclusion

Based on the results of this study, it can be concluded that *Rosa damascena* ethanol extract can reduce blood glucose levels at doses of 250 mg/kg BW and 500 mg/kg BW. The ethanol extract of *Rosa damascena* has not been able to improve the diameter of the islets of Langerhans Pancreas in Wistar rats injected with STZ.

Funding: None

Conflict of Interest: None

Ethical Permission: 150/HRECC.FODM/III/2020

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