Anti-diabetic Effect of *Syzygium cumini* leaves on Induced diabetic Rats

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ABSTRACT

The effect of different concentrations 1.5, 3, 4.5, 6 and 7.5% *Syzygium cumini* leaves as powder of *Syzygium cumini* on diabetes rats were evaluated. Thirty five male rats was purchased from Vaccine and Immunity Organization, and kept for 7 days on basal diet (Adaptation period). After adaptation period, the 35 rats were classified into two main groups; 5 rats in a normal group and 30 rats in a treated group. Diabetes was induced via injection of the infected rats with alloxan (150 mg/kg BW). To ascertain the induction of diabetes mellitus blood samples, were obtained from rats and blood glucose was determined. All diabetic rats were classified into the following group (5 rat each group): The control negative and control positive were fed on basal diet, as well as, the third, fourth, fifth, sixth and seventh groups fed standard diet had contained 1.5, 3.0, 4.5, 6.0 and 7.5% *Syzygium cumini* leaves powder respectively for 28 day after injection. At the end of experimental period, the results showed that the lowest value glucose recorded for sixth group fed on *Syzygium cumini* powder (6%) with significant difference. The highest cholesterol and triglycerides levels recorded for third group fed on *Syzygium cumini* powder (1.5%) while, the lowest value recorded for Seventh group fed on *Syzygium cumini* powder (7.5%) with significant difference. From the results, it could be recommended that leaves of *Syzygium cumini* is effective in improving lipid metabolism and preventing diabetic in diabetic rats.

Keywords: *Syzygium cumini*, Rats, Anti-diabetes and Biochemical analysis.

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia due to defects in insulin secretion, action, or both (Nathan, 1993). In 2019, 463 million people were estimated to have diabetes worldwide, 8.8% of them are of adult population while 90% of the cases are with type 2 diabetes (Harding et al., 2019). Women and men have similar rates of getting DM and that rates is expected to be in a continual rise, DM is classified as the 7th leading cause of death globally, it at least doubles a person's risk of early death. In 2019, approximately 4.2 million deaths were recorded due to DM (Falk and Zekanowski, 2018). Moreover latest studies reviewed that the susceptibility for COVID-19 as well as risk of morbidity and mortality of it, is increased in patients with DM. Higher affinity cellular binding, efficient virus entry, reduced viral clearance, T cell malfunction as well as high susceptibility to hyper inflammation may be the potential mechanisms by which the susceptibility for COVID-19 is increased in patients with DM (Alireza et al., 2020). Furthermore DM has negative impact on the global economy as the cost of diabetes-related health expenditure in 2017 was estimated at US$727 billion (IDF Diabetes atlas, 2019). Also diabetes cost nearly US$327 billion in the United States, in 2017 (Falk and Zekanowski, 2018). Furthermore average medical expenditures are increased to about 2.3 times among people with diabetes (Shaw et al., 2010). *Syzygium cumini* (Myrtaceae) is a well known medicinal plant commonly used in herbal medicines. It contains vital compounds such as phenols, flavonoids, and tannins in different parts of the plant that provide it with attractive and desired properties against cardio metabolic disorders, including: antihyperglycemic, hypolipemiant, anti-inflammatory, cardio protective, and antioxidant activities (Shanmugam, 2001).

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The aim of this study was to determine whether dietary supplementation of *Syzygium cumini* treat diabetes rat.

2. Material and Methods

2.1. Materials

*Syzygium cumini* was purchased from the Agricultural Research Center, Giza, Egypt. Kits were purchased from (Alkan Medical Company, St. El Doky, Cairo, Egypt). All other chemicals and reagents were obtained from El-Gomhoreya Company, Cairo, Egypt.

I. The induction of experimental diabetes

Diabetes was induced in normal healthy male albino rats with weight ranging from 190-210g, the rats were injected with alloxan (150 mg / kg of body weight) according to method described by NDDG (1994).

2.2. Methods

I. Preparation of leaves *Syzygium cumini*

The *Syzygium cumini* leaves were hand cleaned to render them free of dust, washed by soaking in distilled water for 5 minutes, skinthen dried at 50 °C for 6 hour using vacuum oven. The leaves were ground to pass through 1.6 mm sieve then packed in polyethylene bags and stored in a freezer until used.

2.3. Experimental design

Male albino rats (35 rats) with weight ranging from 190-210g were purchased from Pharmacy Vaccine and Immunity Organization. Rats were housed in individual cages with screen bottoms and fed ad libitum on a basal diet for one-week for acclimatization, which containing casein (20 %), corn oil (8%), corn starch (31%), sucrose (32%), cellulose (4%), salt mixture (4%) and vitamin mixture (1%) according to the method Pell et al., (1992).

Experimental rats were fed on basal diet for 7 days and randomly divided into seven groups five rats for each. The 1st main group was fed on basal diet for another four weeks and considered as control negative rats.

The six rat groups (30 rats) were injected with alloxan (150 mg/kg BW) to induce diabetes. To ascertain the induction of diabetes mellitus blood samples, were obtained from rats and blood glucose was determined. These groups were reclassified into control positive as a second group fed on basal diet. The third, fourth, fifth, sixth and seventh groups were fed on basal diet had contained 1.5, 3.0, 4.5, 6.0 and 7.5% *Syzygium cumini* leaves powder for four experimental period.

At the end of experimental period, rats were anesthetized with diethyl ether after fasting for 12h and blood samples were collected, and serum was separated by centrifugation. Serum were frozen and kept at −20°C for later analysis.

2.4. Blood sampling

After fasting for 12 hours, blood samples in initial times were obtained from retro-orbital vein, while it obtained from a hepatic portal vein at the end of each experiment. Blood samples were collected into dry clean centrifuge glass tubes and left to clot in a water bath (37°C) for 30 minutes, then centrifuged for 10 minutes at 4000 rpm to separate the serum, which was carefully aspirated and transferred into clean cuvette tube and stored frozen in deep freezer till analysis according to method described by Schermer (1967).

2.5. Body weight gain (BWG), feed intake (FI), and feed efficiency ratio (FER)

During the experimental period (28 days) the net feed intake was daily recorded, while body weight was weekly recorded. The net feed intake and gained body weight was used for the calculation of feed efficiency ratios (FER) according to Chapman *et al.*, (1959) as follow:

\[
FER \% = \frac{Body \ weight \ gain \ (g)}{Food \ intake \ (g)} \times 100
\]
2.6. Biochemical analysis

Determination of plasma glucose was carried out calorimetrically according to the method of Tinder and Ann, (1969). Serum triglyceride was determined by enzymatic method using kits according to the Fossati and Prencipe, (1982). Serum total cholesterol and HDL-c were determined according to the method described by Thomas (1992) and Gordon (1977). VLDL-c was calculated in mg/dl according to the equation with Lee and Nieman (1996) as follows:

\[
\text{VLDL-c (mg/dl)} = \frac{\text{Triglycerides}}{5}
\]  

(1)

The low density lipoprotein cholesterol LDL-c was calculated in mg/dl according to the equation with Lee and Nieman (1996) as follows:

\[
\text{LDL-c (mg/dl)} = \text{Total cholesterol} - \text{HDL-c} - \text{VLDL-c}
\]  

(2)

Kidney functions as Serum urea and serum creatinin were determined by the method according to Henry (1974) and Patton & Crouch (1977).

2.7. Statistical analysis

The data were analyzed using a completely randomized factorial design (SAS, 2000) when a significant main effect was detected; the means were separated with the Student-Newman-Keuls Test. Differences between treatments of (P ≤0.05) were considered significant using Costat Program. Biological results were analyzed by One Way ANOVA.

3. Results and Discussion

3.1. Effect of Syzygium on body weight gain, feed intake and feed efficiency ratio of diabetic rats

Data presented in Table (1) show the effect of Syzygium on body weight gain (BWG), feed intake (FI) and feed efficiency ratio (FER) of diabetic rats. The results showed that the highest value was recorded for the body weight gain (BWG) % of negative control when compared with positive control with significant difference. They were 25 and 18%, respectively. From diabetic groups, it is clear to notice that the highest (BWG) % recorded for fourth group fed on 3% Syzygium cumini powder, while the lowest BWG% recorded for Seventh group fed on Syzygium cumini powder (7.5%) with significant difference (P≤0.05). The mean values were 25 and 13%, respectively. In case of feed intake; it could be noticed that the highest value of the feed intake (FI) % was recorded for negative control when compared with positive control with significant difference. The mean values were 19 and 13 %, respectively while, 3% Syzygium recorded the highest FI while the lowest value recorded for 7.5 % Syzygium with significant difference (P≤0.05). The mean values were 19 and 10 %, respectively.

Table 1: Effect of Syzygium on body weight gain, feed intake and feed efficiency ratio of diabetic rats

| Parameter     | BWG (g) | FI (g/day) | FER (%) |
|---------------|---------|------------|---------|
|               | M ± SD  | M ± SD     | M±SD    |
| Control group (-) | 25±0    | 19±0       | 0.74±0  |
| Control group (+) | 18±0    | 13±12.7    | 0.7±12.7|
| Syzygium1.5%    | 17±16.26| 13±0       | 0.64±0  |
| Syzygium3%      | 25±0    | 19±0       | 0.7±0   |
| Syzygium4.5%    | 23±1.0  | 17±0       | 0.7±0   |
| Syzygium6%      | 15±0    | 11±0       | 0.7±0   |
| Syzygium7.5%    | 13±0    | 10±0       | 0.6±0   |

Each value is represented as mean ± standard deviation (n = 3).Mean under the same column bearing different superscript letters are different significantly (p < 0.05).
On the other hand, feed efficiency ratio (FER) of negative control recorded the highest value when compared with positive control with no significant difference (P ≤ 0.05). The mean values were 0.74 and 0.7 %, respectively. In case of treated rat groups, it clear to mention that 3% Syzygium recorded the highest FER while, the lowest value recorded for 7.5 % Syzygium with significant difference. The mean values were 0.7 and 0.6 %, respectively. Syzygium cumini powder supplementation showed decreased body weight gain. These results are in agreement with Ulla et al., (2017) who study the effect on body weight, food intake and the body weight of each rat that noted every day during the experimental period. The study stated a significant body weight gain in high carbohydrate high fat diet rats compared to the control rats. Syzygium cumini powder supplementation showed decreased body weight gain in high carbohydrate high fat diet fed rats. Food intake were also decreased in high carbohydrate high fat diet Syzygium cumini rats compared to control and Control + Syzygium cumini rats respectively. Syzygium consumption improve nutrient intakes and reduce body weight and possibly decrease the risk of metabolic syndrome. Moreover, the feed efficiency ratio of treated groups fed on diet with Syzygium at (6% or 7.5%) recorded significant decreased (P< 0.05), as compared to control positive group.

3.2. Effect of Syzygium on glucose of diabetic rats.

The effect of Syzygium on the serum glucose of diabetic rats are shown in Table (2) and the results indicated that the highest glucose level recorded for positive control group (232±7.5mg/dl), while the lowest level recorded for negative control was (150±0.54mg/dl). On the other hand, rats the lowest value glucose recorded for sixth group fed on Syzygium cumini powder (6%) The mean value was (152±0.83 mg/dl) with significant difference. These results are in agreement with Kaur and Meena, (2012) who reported that Syzygium cumini powder supplemented diet significantly lowered the effect of blood glucose, estimation of blood glucose concentration and plasma There is a significant increase in blood glucose concentration ( p < 0.05) in alloxan diabetic rats compared to the control (-). Syzygium cumini supplementation intended to lower the increased blood glucose concentration and return the circulating insulin level in blood plasma in to normal levels. Syzygium cumini has chemo preventive, radio protective, antioxidant and antineoplastic properties that confer medicinal benefits, it recognized for their anti-hyperglycemic activity 3 and are shown to reduce fasting plasma glucose levels in type 2 diabetes, it was concluded that Syzygiumcumini provided momentous decrease in blood glucose level in diabetic rats according to Tripathi and Kohli (2014) who observed the effect of Syzygium cumini of jamun on normal and streptozotocin-induced diabetic rats when Syzygium cumini extract was given to rats at two different concentrations (200 & 400 mg/kg) for 15 days in comparison to glibenclamide; an antidiabetic drug.

| Parameter | Glucose level (mg/dl) |
|-----------|-----------------------|
| Treatment | M±SD                  |
| Control group (-) | 150±0.54             |
| Control group (+)  | 232±7.5               |
| Syzygium 1.5%     | 173 b±0.54            |
| Syzygium 3%       | 170a±0.83             |
| Syzygium 4.5%     | 152.5bc±0.83          |
| Syzygium 6.0%     | 152.0bc±0.83          |
| Syzygium 7.5%     | 152.1bc±0.83          |

Each value is represented as mean ± standard deviation (n = 3). Mean under the same column bearing different superscript letters are different significantly (p < 0.05).

It was concluded that Syzygium cumini extract resulted in a significant reduction in serum glucose. The results of the present study are consistent with the reports of Shankar et al., (2007) who stated 65% decrease in glucose level of Syzygium cumini fed rats. They inferred that jamun enhanced the insulin secretion from the pancreatic β-cells and hence reduced the glucose levels. Sharma et al., (2011) used ethanolic extract on the alloxan-induced diabetic rabbits and evaluated the hypoglycemic
potential of jamun seed. On the provision of Syzygium cumini to the diabetic rabbits, 42.85% decline in the blood sugar concentration was observed.

Findings from Safdar et al., (2006) are similar to the current results. They estimated the hypoglycemic effects of jamun pulp on diabetic individuals for 12 days. A positive relationship between the intake of Syzygium cumini with a consequent decline in the abnormal glucose levels of the individuals was noticed. Decline up to 9.1% was recorded in serum glucose level. The current findings are also in accordance with Sharma et al., (2011), they explored that providing diabetic rabbits with Syzygium cumini and water extract for 15 days resulted in 14.8% and 37.1% decline in serum glucose, respectively.

3.3. Effect of Syzygium on total cholesterol and triglycerides level of diabetic rats

The effect of Syzygium on the serum total cholesterol and triglycerides of diabetic rats are shown in Table (3). The obtained results indicated that the highest value of cholesterol levels was recorded for positive control group when compared with negative control group with significant difference (p < 0.05). The mean values were 135.50 and 95.50 mg/dl, respectively, the lowest cholesterol levels recorded for group fed on 7.5% Syzygium cumini, while the highest value recorded for 1.5 % Syzygium cumini with significant difference (P< 0.05). The mean values were 94.50 and 104.50 mg/dl, respectively. On the other hand, the highest value of triglyceride was recorded for positive control group when compared with negative control group with significant difference (P<0.05). The mean values were 133.0and 63.00mg/dl, respectively. While, the lowest triglyceride recorded for group fed on 7.5% Syzygium cumini while the highest value recorded for 1.5 % Syzygium cumini with significant difference (P<0.05). The mean values were 70.50 and 97.50mg/dl, respectively.

Table 3: Effect of Syzygium on serum total cholesterol and triglycerides of diabetic rats.

| Treatment          | Total cholesterol (mg/dl) | Triglycerides (mg/dl) |
|--------------------|---------------------------|-----------------------|
|                    | M ± SD                    | M ± SD                |
| Control group (-)  | 95.50±1.16<sup>e</sup>    | 63.00±1.10<sup>f</sup>|
| Control group (+)  | 135.50±1.17<sup>a</sup>   | 133.0±1.16<sup>a</sup>|
| Syzygium 1.5%      | 104.50±1.13<sup>c</sup>   | 97.50±1.15<sup>c</sup>|
| Syzygium 3%        | 98.50±1.14<sup>d</sup>    | 83.50±1.13<sup>e</sup>|
| Syzygium 4.5%      | 96.50± 0.5<sup>d</sup>    | 87.50± 0.5<sup>c</sup>|
| Syzygium 6%        | 94.50± 0.5<sup>f</sup>    | 71.40± 0.5<sup>e</sup>|
| Syzygium 7.5%      | 94.50±1.12<sup>g</sup>    | 70.50±1.11<sup>f</sup>|

Each value is represented as mean ± standard deviation (n = 3). Mean under the same column bearing different superscript letters are different significantly (p < 0.05).

These results are in agreement with Howard et al., (2000) study in which the diabetic condition, high levels of TC, TG as well as lowered level of HDL along with the different composition of LDL particles have been commonly reported. The previous study is compatible with this study, the use of Syzygium cumini changed the normal lipid profiles. It was realized that TC, TG, LDL and VLDL levels were elevated while HDL level was reduced when compared to normal control rats. A similar findings have been reported in high-fat diet diabetic rats by Ghozhdi et al. (2021). They revealed that lipid profiles were turned around to close normal levels after the treatment with both Syzygium cumini. This decline of lipids may be attributed to stabilized glucose level and elevated insulin level after the administration of Syzygium cumini, which may returned the disturbed lipid metabolism in to normal levels in diabetic rats. The decline of TC level can be attributed to the inhibition of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase by the action of Syzygium cumini (Sartorius et al., 2014). Therefore, Syzygium has a hypolipidemic effect on diabetic rats which protect them against cardiovascular diseases associated with diabetes. Moreover a decrease of liver triglyceride content along with elevated glycogen storage by the effect of Syzygium cumini administration has been noticed (Sartorius et al., 2014).
3.4. Effect of *Syzygium* on lipid profile level of diabetic rats

The effect of *Syzygium cumini* on serum lipid profile (HDL-c, LDL-c and VLDL-c) level of *Syzygium cumini* rats was shown in Table (4). The results indicated the highest value of HDL-c for negative control rats group when compared with positive control group with significant difference (P<0.05). The mean values were 45.00 and 26.50 mg/dl, respectively. While, the highest HDL-c of treated group recorded for group fed on 7.5% *Syzygium cumini* but, the lowest value recorded for group fed on 1.5% *Syzygium cumini* with significant difference (P<0.05). The mean values were 45.00 and 32.00 mg/dl, respectively.

On the other hand, the LDL-c of positive control rats group recorded the highest value when compared with negative control group with significant difference (P<0.05). The mean values were 82.40 and 37.90 mg/dl, respectively. While, the highest LDL-c of treated group recorded for group fed on 1.5% *Syzygium cumini* but, the lowest value recorded for group fed on 6% *Syzygium cumini* with significant difference (P<0.05). The mean values were 57.7 and 35±0 mg/dl, respectively. In case of VLDL-c, the positive control rats group recorded the highest value when compared with negative control group with significant difference (P<0.05). The mean values were 26.60 and 12.60 mg/dl, respectively. While, the highest VLDL-c of treated group recorded for group fed on 1.5% *Syzygium cumini* but, the lowest value recorded for group fed on 6% *Syzygium cumini* with significant difference (P<0.05). The mean values were 19.50 and 14.3 mg/dl, respectively. These results are in agreement with Kasetti et al., (2010) they found that *Syzygium cumini* of diabetic has a positive effect on the level of cholesterol. Similarly, treatment with fruit extracts and *L. fermentum* were found to successfully affect the levels of LDL, HDL and triglycerides of diabetic mice. It is in accordance with previous studies which stated that the hypoglycemic as well as hypolipidemic activity of fermentum could be helpful in the control of diabetes mellitus and related complications (Sanches et al., 2016).

| Parameter (HDL-c) | (LDL-c) | (VLDL-c) |
|-------------------|---------|---------|
| (g/dl) M ± SD     | (g/dl) M ± SD | (g/dl) M ± SD |
| Control group (+) | 45.00±1.15<sup>a</sup> | 37.90±1.10<sup>a</sup> | 12.60±1.12<sup>d</sup> |
| Control group (+) | 26.50±1.13<sup>c</sup> | 82.40±1.16<sup>a</sup> | 26.60±1.15<sup>b</sup> |
| Syzygium 3%       | 32±1.10<sup>c</sup> | 57.70±1.14<sup>b</sup> | 19.50±1.13<sup>b</sup> |
| Syzygium 4.5%     | 36±1.13<sup>c</sup> | 47.50±1.14<sup>c</sup> | 16.70±1.12<sup>c</sup> |
| Syzygium 6%       | 39± 2<sup>d</sup> | 32.5± 0.5<sup>b</sup> | 17.5± 0.5<sup>b</sup> |
| Syzygium 7.5%     | 42± 1<sup>a</sup> | 35± 0<sup>b</sup> | 14.3± 0.3<sup>c</sup> |
|                  | 45±1.14<sup>b</sup> | 37±1.15<sup>c</sup> | 14.40±1.11<sup>c</sup> |

Each value is represented as mean ± standard deviation (n = 3). Mean under the same column bearing different superscript letters are different significantly (p < 0.05).

3.5. Effect of *Syzygium* on kidney functions level of diabetes rats

Data presented in Table (5) show the effect of *Syzygium* powder and on uric acid, urea and creatinine of diabetic rats. The obtained results indicated that highest value of creatinine level was recorded for positive control rats group when compared with negative control group with significant difference. The mean values were 1.33 and 0.95 mg/dl, respectively. While, the highest creatinine recorded for group fed on 1.5% *Syzygium* but, the lowest value recorded for group fed on 7.5% *Syzygium* powder with significant difference (P≤0.05). The mean values were 1.22 and 0.95 mg/dl, respectively.

On the other hand, the highest value of urea level was recorded for positive control rats group when compared with negative control group with significant difference. The mean values were 31.50 and 20.80 mg/dl, respectively. While, the highest urea levels recorded for group fed on 1.5% *Syzygium* powder but, the lowest value recorded for group fed on 7.5% *Syzygium* with significant difference (P≤0.05). The mean values were 29.60 and 22.10 mg/dl, respectively. In case of uric acid level, the highest value was recorded for positive control rats group when compared with negative control group with significant difference. The mean values were 8.50 and 4.40 mg/dl, respectively. While, the highest uric acid levels recorded for group fed on 1.5% *Syzygium* powder but, the lowest
value recorded for group fed on 7.5% Syzygium powder with significant difference (P≤0.05). The mean values were 7.76 and 5.2 mg/dl, respectively. Syzygium cumini powder supplementation showed decreased uric acid these results are in agreement with (Santhan et al., 2013) they stated the effect on control rats showed less creatine and urea levels compared to standard and test groups. Syzygium administered group showed maximum increase in creatine and urea levels compared to other groups. Syzygium treated groups showed significant difference compared to Gliben clamide and aqueous extract of S. cumini seed powder (500 mg/kg). Graded doses of plant extract do not show any significant difference. Administration high dose of seed extract showed equality with standard drug. Administration of standard and high dose plant extract significantly cells. The study results suggest that the aqueous extract of S. cumini seed powder showed nephron protective activity and the dose level. Extensive and multiple animal studies required to elucidate the exact mechanism of action on active ingredients in plant extract (Sampath Kumar et al., 2012).

### Table 5: Effect of Syzygium on uric acid, urea and creatinine of diabetic rats

| Treatment               | Creatinine (mg/dl) | Urea (mg/dl) | Uric acid (mg/dl) |
|-------------------------|--------------------|--------------|-------------------|
|                         | M ± SD             | M ± SD       | M ± SD            |
| Control group (-)       | 0.95± 0.01d        | 20.80± 1e    | 4.40± 0.2f        |
| Control group (+)       | 1.33 ± 0.1a        | 31.50± 0.5a  | 8.50± 1a          |
| Syzygium 1.5%           | 1.22± 0.01b        | 29.60± 0.5b  | 7.76± 1b          |
| Syzygium 3%             | 1.14± 0.05b        | 25.50± 0.5b  | 7.12±0.02bc       |
| Syzygium 4.5%           | 1.05± 0.01c        | 24.60± 0.5d  | 7.00±0.01c,d      |
| Syzygium 6%             | 0.98± 0.01d        | 23.40± 0.5d  | 5.55± 0.01d       |
| Syzygium 7.5%           | 0.95± 0.01d        | 22.10± 1e    | 5.2± 0.1e         |

Each value is represented as mean ± standard deviation (n = 3). Mean under the same column bearing different superscript letters are different significantly (p < 0.05).

### 4. Conclusion

Syzygium cumini leaves showed potentially beneficial effects on diabetics and on serum lipids in diabetic rats. Therefore, it could be recommended that the diabetics rat groups fed on Syzygium cumini leaves until 7% were lowering blood glucose and improving lipids profile and kidney function.

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