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**Artikel Asli/*Original Articles***

# Antihyperglycemic Activity of Oil Palm *Elaeis guineensis* Fruit Extract on Streptozotocin-induced Diabetic Rats

(Aktiviti Antihiperglisemik Minyak Ekstrak Buah Kelapa Sawit *Elaeis guineensis* ke atas Tikus Diabetik Teraruh Streptozotocin)

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ABSTRACT

*Hypoglycaemic and antihyperglycemic activity of oil palm Elaeis guineensis fruit extract on normal and Streptozotocin-induced diabetic rats was studied. The oil palm fruit extract (OPF) were administered orally at different concentrations (100, 200 and 500 mg kg$^{-1}$ b.w.) in fasting and post-prandial rats. Hypoglycaemia was not observed in the group of normal rats treated with OPF. In fasting rats, OPF (500 mg kg$^{-1}$ b.w.) has caused the blood glucose level (BGL) to reduce significantly. For post-prandial diabetic rats, the antihyperglycemic activity was observed after OPF treatment at concentrations 200 and 500 mg kg$^{-1}$. Chronic OPF treatments (for 28 days) had increased the diabetic rat's body weight and reduced BGL as well as improved plasma insulin secretion. The result of this study suggests E. guineensis palm fruit extract show evidence of antihyperglycemic properties from the reduction of the BGL in diabetic rats.*

*Keywords: Elaeis guineensis; oil palm fruit extract; blood glucose level; hypoglycaemic; antihyperglycemic*

ABSTRAK

*Aktiviti hipoglisemik dan antihiperglisemik ekstrak buah kelapa sawit Elaeis guineensis terhadap tikus normal dan tikus diabetik aruhan- Streptozotocin dikaji. Ekstrak minyak buah kelapa sawit (OPF) diberi secara oral pada kepekatan berbeza (100, 200 dan 500 mg kg$^{-1}$ b.w.) kepada tikus puasa dan posprandial. Hipoglisemia tidak berlaku dalam kumpulan tikus normal yang dirawat dengan OPF. Dalam tikus puasa, OPF (500 mg kg$^{-1}$ b.w.) telah menyebabkan aras glukosa darah (BGL) turun secara bererti. Bagi tikus diabetik posprandial, aktiviti anti hiperglisemik telah diperhatikan selepas rawatan OPF pada kepekatan 200 dan 500 mg kg$^{-1}$. Rawatan OPF secara kronik (selama 28 hari) meningkatkan berat badan tikus diabetik dan menurunkan BGL secara bererti serta memperbaiki rembesan plasma insulin. Keputusan kajian ini mencadangkan, ekstrak buah kelapa sawit E. guineensis menunjukkan sifat antihiperglisemik dengan penurunan BGL tikus diabetik.*

*Kata kunci: Elaeis guineensis; ekstrak buah kelapa sawit; aras glukosa darah; hipoglisemik; antihiperglisemik*

## INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder which affects more than 300 million people worldwide. The main characteristic of this disease includes hyperglycemia, polydipsia, polyphagia, polyurea, muscle weakness, weight loss and dyslipidemia. Major factors contributing to diabetes are imbalance diet, high sugar intake, less healthy lifestyle as well as family genetic history. Despite these major factors, the role of oxidative stress in causing diabetics had also been reported (West 2000). Oxygen free radicals such as superoxide anion ($O_2^{\cdot-}$), hydroxyl radical ($OH^{\cdot}$), hydrogen peroxide and singlet oxygen are among the first damaging species generated in islet cell. High concentration of oxygen free radicals may result in significant damage to pancreatic ß-cell structures and further disrupting its ability to produce insulin. This phenomenon is known as oxidative stress (West 2000).

Phenolic compounds are ubiquitous in all plant organs. Human consume various type of plants as their diet hence making the phenolic compounds as integral part of human's life. Recent interests in phenolics are due to its antioxidants activities and radical scavenging capabilities which create potential benefits on human health (Gallagher et al. 2003; Xia & Wang 2006). Oil palm (*Elaeis Guineensis*) was the number one oil producing crop in Malaysia. It is the major source of edible oils. The utilisation of oil palm as potential source of polyphenols and antioxidant compounds have been reported widely (Nagendran et al. 2005; Neo et al. 2010).

Previously much attention has focused on oil palm fruits carotenes and vitamin E (tocopherols and tocotrienols) for their anti-proliferative effects on tumor cells (Kausar et al. 2003). To date, the attention has switched to the use of various types of phenolic compounds found in oil palm including ferulic, hydroxybenzoic, coumaric, chlorogenic, protocatechuic and gallic acid as well as narirutin,

hesperidin and catechin for their possibility in treating chronic diseases (Neo et al. 2010; Sundram et al. 2003). Nevertheless, the antidiabetic effects of oil palm fruits on blood glucose regulation are yet to be known. Hence this report in general was undertaken to determine the effects of oil palm fruits phenolic extract on glucometabolism of STZ-induced diabetic rats.

## MATERIALS AND METHODS

### SAMPLES PREPARATION

Ripe palm fruits were collected from Universiti Putra Malaysia (UPM) plantation. The fruits were cut into slices to remove the mesocarp from the nut. Then the mesocarps were dried at 40°C overnight. This temperature is sufficient to remove the water from the mesocarps without compromising its texture. The next day the dried flesh were grind into small pieces and subject to Soxhlet extraction using n-hexane to remove the oil.

### EXTRACTION

The oil palm fruit extract (OPF) preparation was conducted by adapting the procedure highlighted by Wang & Halliwell (2001). Briefly one gram of dried oil palm mesocarp was mixed with 40 ml of 60% aqueous ethanol (Merck). Next 5 ml of 6 M HCl was added into the mixture prior reflux. After refluxing for 2 h, the extract was cooled, filtered and made up to 50 ml with 60% ethanol.

### ANIMAL STUDY AND DIABETES INDUCTION

Male Sprague-Dawley rats (weighed 170-220 g) were used in the present study. The rats were housed in clean cages covered with stainless steel cover and kept in well ventilated room with 12-h light/12-h dark cycle. Prior to the examination all rats were acclimatized for one week where standard rat pellets (Gold Coin, Selangor, Malaysia) and water was supplied ad libitum during acclimatization. This study was conducted in accordance to the Animal Care and Use Committee (ACUC) Faculty of Medicine and Health Sciences, Universiti Putra Malaysia guidelines and have received unconditional ethical approval from the same committee (ACUC No: UPM/FPSK/PADS/BR-UUH/00406).

The rats were induced for diabetes using Streptozotocin, STZ (Sigma). At day 7 the rats were injected intraperitoneally (i.p) with 60 mg $kg^{-1}$ body weight (b.w) of STZ dissolved in water after an overnight fasting. Three days later the rat's BGL was checked and rats with a fasting BGL higher than 7.8 mmol $L^{-1}$ were considered as having diabetic and therefore selected for further study. The rats were divided into seven different groups ($n$ = 6 per group) as follows:

1. Group 1 – Normal control rats (NC)
2. Group 2 – Diabetic control rats (DC)
3. Group 3 – Diabetic rats receiving 100 mg $kg^{-1}$ b.w of OPF (OPF100)
4. Group 4 – Diabetic rats receiving 200 mg $kg^{-1}$ b.w of OPF (OPF200)
5. Group 5 – Diabetic rats receiving 500 mg $kg^{-1}$ b.w of OPF (OPF500)
6. Group 6 – Diabetic rats receiving 500 mg $kg^{-1}$ b.w of Metformin (Met)
7. Group 7 – Diabetic rats receiving 30 mg $kg^{-1}$ b.w of Glibenclamide (Gb)

### EFFECTS OF OPF ON RATS BGL

The rats were examined for their fasting and post-prandial BGL. For the fasting BGL, the rats were fasted overnight prior to the examination. In contrast, for the post-prandial BGL, rats had free access to water and pellet diet but were fasted for 1 h prior to the examination. The BGL was determined before and after 2, 4 and 6 hours of OPF administration. The blood was collected from the rat's tail tip and the glucose level was determined using a glucometer (Accu-check advantage, Roche Diagnostic, Germany).

### CHRONIC TREATMENT

For chronic treatment, the rats were given OPF orally using intragastric gavage for 28 days. Body weight and BGL were monitored at day 7 and 28 along the treatment period. At the end of the study, the rats were sacrificed after blood collection and the blood were used to determine the insulin level using radioimmunoassay (RIA) kit (GE Healthcare, Uppsala, Sweden).

### STATISTICAL ANALYSIS

The main variables were analysed descriptively using mean and 1 standard deviation. One-way ANOVA (GraphPad Prism 5) at 5% significance level ($p < 0.05$) was used to compare the mean differences in OPF extract treated groups and control group. To further investigate the significant results between pairs, Dunnet post hoc test was also conducted.

## RESULTS

### EFFECTS OF OPF ON NORMAL, FASTING AND POST-PRANDIAL RATS BGL

The hypoglycemic effects of OPF extract on BGL in normal rats are shown in Table 1. BGL of normal rats was not significantly increased or decreased in all groups. In contrast, rats treated with metformin showed significant reduction of blood glucose level after 2, 4 and 6 hours of administration. The same result was observed in glybenclamide treated group where the BGL was significantly reduced after 2, 4 and 6 hours of drug administration. The results suggest that hypoglycaemia was not present in the OPF treated group.

Table 2 shows the effects of different doses of OPF extract on fasting BGL of STZ-induced diabetic rats. The

TABLE 1. Effects of oil palm fruit extracts on normal rats BGL

| Treatment | Dose/ mg kg$^{-1}$ b.w. | BGL/mmol.l$^{-1}$ | | | |
|---|---|---|---|---|---|
| | | 0 hr | 2 hrs | 4 hrs | 6 hrs |
| Normal control | - | 3.91 ± 0.25 | 3.73 ± 0.27 | 4.25 ± 0.28 | 3.80 ± 0.16 |
| Extract | 100 | 4.01 ± 0.33 | 3.54 ± 0.10 | 3.50 ± 0.33 | 3.71 ± 0.25 |
| | 200 | 3.86 ± 0.25 | 3.58 ± 0.22 | 3.79 ± 0.13 | 3.69 ± 0.15 |
| | 500 | 4.20 ± 0.26 | 3.95 ± 0.34 | 3.75 ± 0.29 | 3.74 ± 0.18 |
| Metformin | 500 | 3.84 ± 0.21 | 2.78 ± 0.11** | 1.73 ± 0.12** | 2.40 ± 0.16** |
| Glybenclamide | 30 | 3.95 ± 0.18 | 3.20 ± 0.15* | 2.68 ± 0.14** | 3.14 ± 0.13** |

*$p < 0.05$, **$p < 0.01$ as compared to pre-treatment hour (0 hr)

TABLE 2. Effects of oil palm fruit extract on fasting diabetic rats BGL

| Treatment | Dose/ mg kg$^{-1}$ b.w. | BGL/mmol.l$^{-1}$ | | | |
|---|---|---|---|---|---|
| | | 0 hr | 2 hrs | 4 hrs | 6 hrs |
| Diabetic control | - | 19.17 ± 0.75 | 25.37 ± 0.65 | 24.55 ± 0.27 | 23.90 ± 0.68 |
| Extract | 100 | 19.47 ± 0.47 | 20.25 ± 0.85 | 19.50 ± 0.76 | 20.17 ± 0.79 |
| | 200 | 19.32 ± 0.80 | 21.02 ± 0.91 | 18.05 ± 0.50 | 18.33 ± 0.71 |
| | 500 | 19.22 ± 0.91 | 16.82 ± 0.48* | 11.12 ± 0.35*** | 8.03 ± 0.44*** |
| Metformin | 500 | 19.45 ± 0.90 | 15.28 ± 0.45* | 9.83 ± 2.14*** | 6.05 ± 0.40*** |
| Glybenclamide | 30 | 19.13 ± 0.59 | 19.18 ± 0.68 | 20.27 ± 1.12 | 20.17 ± 0.88 |

*$p < 0.05$, ***$p < 0.001$ as compared to pre-treatment hour (0 hr)

BGL was significantly reduced at the highest concentration of OPF (500 mg kg$^{-1}$ b.w) after 2, 4 and 6 hours of extract administration. The results in OPF groups receiving 500 mg kg$^{-1}$ b.w were comparable to metformin group in which a significant BGL reduction was observed after 2, 4 and 6 hours of administration. The glybenclamide treated group however did not show any significant fall in their BGL.

The effects of OPF extract on postprandial BGL of diabetic rats are shown in Table 3. The OPF treatment showed a significant BGL reduction in 200 and 500 mg kg$^{-1}$ b.w OPF treated groups. Group treated with 200 mg kg$^{-1}$ b.w OPF showed a significant BGL reduction after 4 and 6 hours of OPF treatment while 500 mg kg$^{-1}$ b.w OPF treated group showed a significant BGL reduction

TABLE 3. The effect of oil palm fruit extract on post-prandial diabetic rats BGL

| Treatment | Dose/ mg kg$^{-1}$ b.w. | BGL/mmol.l$^{-1}$ | | | |
|---|---|---|---|---|---|
| | | 0 hr | 2 hrs | 4 hrs | 6 hrs |
| Diabetic control | - | 26.05 ± 0.70 | 27.90 ± 0.77 | 26.52 ± 0.68 | 25.53 ± 0.73 |
| Extract | 100 | 26.63 ± 1.31 | 23.22 ± 1.47 | 26.35 ± 0.68 | 25.87 ± 0.89 |
| | 200 | 26.13 ± 0.52 | 24.98 ± 1.13 | 20.33 ± 1.49* | 18.38 ± 0.61*** |
| | 500 | 26.10 ± 1.04 | 21.22 ± 0.79* | 19.98 ± 1.32* | 12.52 ± 0.89*** |
| Metformin | 500 | 26.72 ± 0.84 | 25.35 ± 0.68 | 15.48 ± 1.34*** | 6.90 ± 0.69*** |
| Glybenclamide | 30 | 26.60 ± 1.30 | 27.75 ± 0.51 | 24.62 ± 1.65 | 24.30 ± 0.57 |

*$p < 0.05$, ***$p < 0.001$ as compared to pre-treatment hour (0 hr)

after 2, 4 and 6 hours of OPF administration. Both treatment groups showed a comparable result with metformin treated group in which the BGL reduced significantly after 4 and 6 hours of metformin administration. The glybenclamide treated group on the other hand did not show any significant result along the treatment period.

### EFFECTS OF CHRONIC TREATMENT ON BODY WEIGHT, BGL AND INSULIN SECRETION

Figure 1 shows the chronic effects (28 days) of OPF treatment on body weight of normal and STZ-induced diabetic rats. The body weight of normal control rats increased significantly ($p < 0.001$) during the treatment

with 32.5% increment at day 28. On the other hand, a significant fall was observed in body weight of diabetic control group (26.9%, $p < 0.001$) as well as the group receiving 100 (25.5%, $p < 0.001$) and 200 (9.9%, $p < 0.05$) mg kg$^{-1}$ b.w of OPF extract. In contrast, a significant increase in body weight was observed in group treated with 500 mg kg$^{-1}$ b.w OPF (22.9%, $p < 0.001$). In metformin treated group, there was no significant difference in body weight observed along the treatment period.

The antihyperglycemic activity of OPF extract on the BGL of normal and STZ-induced diabetic rats are shown in Figure 2. The normal control as well as the metformin and 200 mg kg$^{-1}$ b.w OPF treated groups showed no significant differences in fasting BGL along the treatment period. Meanwhile, a significant increase in BGL was observed in diabetic control and 100 mg kg$^{-1}$ b.w OPF treated groups in which the differences were 45.5% ($p < 0.001$) and 19.0% ($p < 0.001$) respectively. In contrast, the group treated with 500 mg kg$^{-1}$ b.w of OPF showed a significant decline in BGL by 31.5% ($p < 0.001$) at the end of experiment.

Figure 3 shows the chronic effect of OPF treatment on the plasma insulin level of normal and STZ-induced diabetic

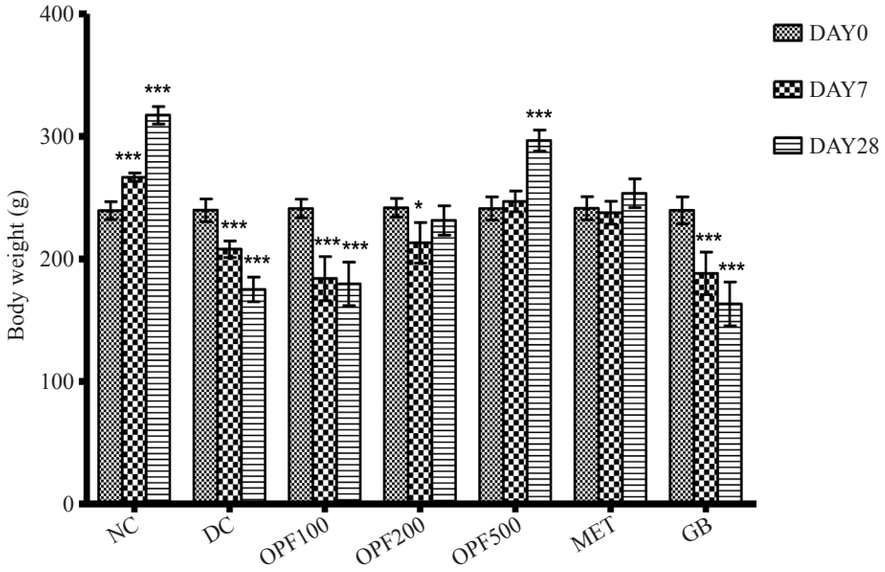


FIGURE 1. Body weight changes of rats over 28 day's chronic treatment. NC = normal control rats, DC = diabetic control rats, OPF100 = rats receiving 100 mg kg$^{-1}$ b.w of OPF extract, OPF200 = rats receiving 200 mg kg$^{-1}$ b.w of OPF extract, OPF500 = rats receiving 500 mg kg$^{-1}$ b.w of OPF extract, MET = rats receiving metformin and GB = rats receiving glybenclamide. Values represent mean ± SD. *$p < 0.05$, ***$p < 0.001$ as compared to day 0

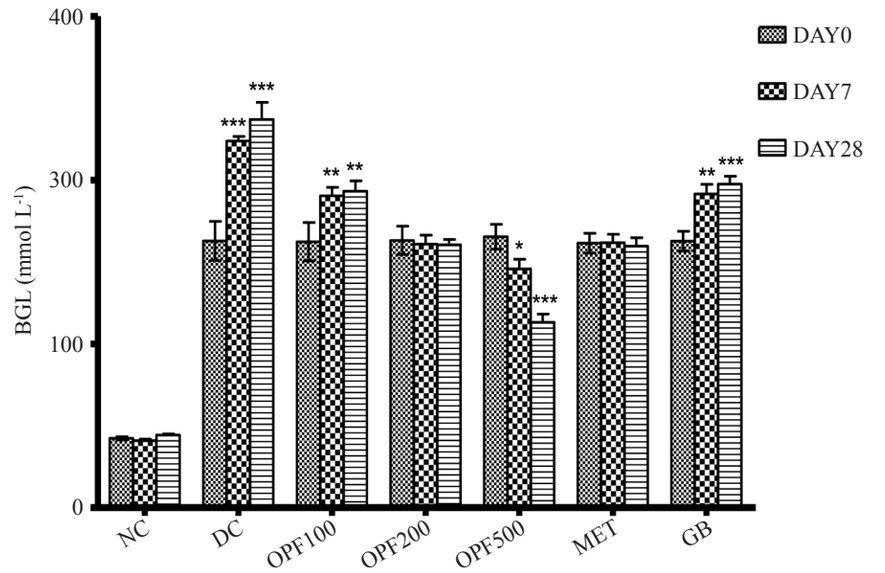


FIGURE 2. Blood glucose level changes of rats over 28 day's chronic treatment. NC = normal control rats, DC = diabetic control rats, OPF100 = rats receiving 100 mg kg$^{-1}$ b.w of OPF extract, OPF200 = rats receiving 200 mg kg$^{-1}$ b.w of OPF extract, OPF500 = rats receiving 500 mg kg$^{-1}$ b.w of OPF extract, MET = rats receiving metformin and GB = rats receiving glybenclamide. Values represent mean ± SD. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ as compared to day 0

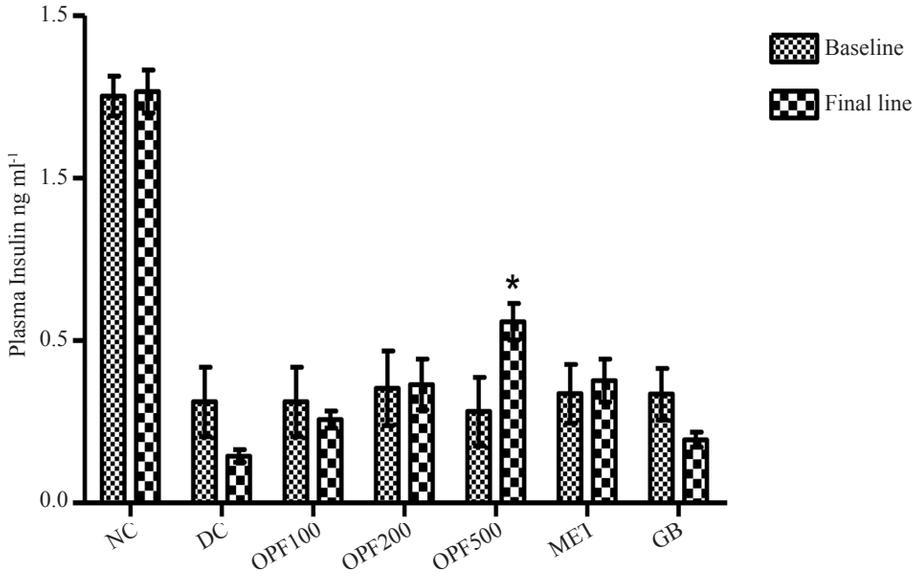


FIGURE 3. Plasma insulin level of rats over 28 day's chronic treatment. NC = normal control rats, DC = diabetic control rats, OPF100 = rats receiving 100 mg kg$^{-1}$ b.w of OPF extract, OPF200 = rats receiving 200 mg kg$^{-1}$ b.w of OPF extract, OPF500 = rats receiving 500 mg kg$^{-1}$ b.w of OPF extract, MET = rats receiving metformin and GB = rats receiving glybenclamide. Values represent mean ± SD. *$p < 0.05$, as compared to baseline.

rats. Almost all experimental groups showed no significance differences in their plasma insulin levels except for groups receiving 500 mg kg$^{-1}$ b.w of OPF extract. The extract was shown to increase the plasma insulin level significantly by 74.1% ($p < 0.05$) when compared to its baseline.

## DISCUSSION

### EFFECTS OF OPF ON NORMAL, FASTING AND POST-PRANDIAL RATS BGL

STZ has been used to chemically induce hyperglycemia in rats and mice (Rosalina et al. 2011; Sachdewa et al. 2003). It is taken up by pancreatic ß-cells through glucose transporter (GLUT2). It generates reactive oxygen species, causing alkylation of deoxyribonucleic acid (DNA) and evokes other deleterious changes in cells. DNA damage induces activation of poly adenosine diphosphate (ADP)-ribosylation which leads to the depletion of cellular nicotinamide adenine dinucleotide ($NAD^+$) and further reduction of the adenosine triphosphate (ATP) (Pieper et al. 1999). Enhanced ATP dephosphorylation supplies a substrate for xanthine oxidase (XOD), resulting in the formation of superoxide anion. As a result of superoxide anion generation, hydrogen peroxide and hydroxyl radicals are formed. Furthermore, STZ also liberates toxic amount of nitric oxide (NO). NO inhibits aconitase activity and participates in DNA damage. As the result, ß-cells undergo destruction and inhibit insulin synthesis and secretion.

In our study the rats were injected with 60 mg kg$^{-1}$ b.w STZ. It was reported that STZ dose of 40-60 mg kg$^{-1}$ b.w on a single intravenous injection produced an IDDM type of rats due to the damage of ß-cells of pancreatic islet (Szkudelski 2001). Glybenclamide and metformin were used as positive control in this study to evaluate the possible mechanism of action in reducing the hyperglycemia. Metformin is a common drug prescribed to a diabetic patient. Its main mechanism of action is through enhancement of glucose uptake in muscle and reducing hepatic gluconeogenesis, thereby reducing glucose level in blood stream (Chehad & Mooradian 2000). Glybenclamide on the other hand is classified into sulphonylurea group of drug. Its mode of action is by stimulation of $Ca^{2+}$ influx into pancreatic ß-cells which later results in synthesis and secretion of insulin (Malaisse 1999). Our data showed no significant decrease in hyperglycemia in all diabetic rat groups treated with glybenclamide (Table 1, 2 and 3). This may be resulted from the damaged ß-cells due to STZ action. As the ß-cells are destroyed they lose ability to produce enough amount of insulin to tackle down hyperglycemia.

In normal rats, the results showed no significance hypoglycaemic activity in all rat groups treated with the oil palm fruit extract; whereas metformin and glybenclamide has a significant hypoglycaemic activity after 2 h of drug administration (Table 1). The results indicated that all doses of oil palm fruit extract did not have hypoglycaemic activity in normal rats. This finding shows a bright potential of OPF as future antidiabetic agents as the current conventional drugs treatment exhibit hypoglycaemic activity and it is considered as a major limitation for the conventional drugs. In fasting and post-prandial diabetic rat groups, the results showed a decreasing pattern in hyperglycemia for rats treated with the OPF and metformin. In fasting diabetic rats the OPF exhibited a significant antihypergylcemic

activity after 2 ($p < 0.05$), 4 ($p < 0.001$) and 6 ($p < 0.001$) h of administration of 500 mg $kg^{-1}$ OPF (Table 2). The same results were observed with metformin after 2 ($p < 0.05$), 4 ($p < 0.001$) and 6 (0.001) h of administration. In post-prandial diabetic rats, OPF extract started to show a significant antihyperglycemic activity at a lower concentration of 200 mg $kg^{-1}$ b.w after 4 ($p < 0.05$) h of administration (Table 3). The results were also observed in metformin treatment in which a significant antihyperglycemic activity were observed after 4 ($p < 0.001$) and 6 ($p < 0.001$) h of administration. The glybenclamide treated groups however did not show any significant antihyperglycemic activity in both fasting and post-prandial diabetic rats. From this observation, we suggest that the OPF extract is able to lower BGL and the mechanism of action of OPF to reduce hyperglycemia may be the same as metformin via the enhancement of glucose uptake in muscle and reduction of hepatic gluconeogenesis. However further evaluations at the cellular level are required to confirm this speculation and to better understand the mechanisms involved.

### CHRONIC TREATMENT

Evaluation of chronic effects of OPF extract on STZ-induced diabetic rats was carried out for 28 days period. The diabetic rats exhibited a significant loss in body weight during the treatment. This could possibly due to the excessive catabolism of fats and proteins to produce glucose as insulin was not able to utilize the blood glucose as an energy source. Furthermore protein content is also decreased in muscular tissue due to insulin deficiency in diabetic rats (Vats et al. 2004). Treatment with OPF at 500 mg $kg^{-1}$ b.w not only significantly prevented weight loss but also caused significant weight gain as well as BGL reduction in the final week (Figure 1 & 2). This could be possibly due to the regeneration and revitalisation of the beta cells by OPF extract (Bolkent et al. 2004). Administration of 500 mg $kg^{-1}$ b.w OPF was shown to significantly increase the plasma insulin level after four weeks of chronic treatment (Figure 3). The phytochemicals that exert hypoglycaemic activity can be classified as flavonoids, alkaloids, glycosides, polysaccharides and saponin. It has been reported that certain flavonoids exhibit effective antidiabetic activity (Sharma et al. 2000). Therefore it can be suggested that flavonoids are present in OPF extract and may be responsible for its antihyperglycemic activity in this study. However further evaluation is needed to investigate the actual bioactive components in OPF to prove this deduction and to evaluate the actual mechanisms underlying its antihyperglycemic potential.

## CONCLUSION

Regulation of BGL to the normal level is the most important in managing diabetes mellitus (Kim et al. 2005). This can be achieved through medical nutrition therapy, oral hypoglycaemic agents and insulin therapy. Besides, the use of antihyperglycaemic plants may also benefit diabetic patients in controlling hyperglycemia (Rosalina et al. 2011). Based on the results of the present study, OPF extract exhibited antihyperglycaemic activity in STZ-induced diabetic rats at fasting and postprandial states as well as during chronic treatment. Therefore it is suggested that the OPF extracts have the potential to be developed as a new oral antihyperglycemic agent for the treatment of diabetes mellitus.

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