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ORIGINAL ARTICLE

# The Effect of Strawberry Juice on Homa-IR Level in Rat Model of Type 2 Diabetes Mellitus

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ABSTRACT

**Background:** Strawberries contain high level of antioxidants and polyphenols, especially anthocyanins as powerful antioxidants. These ingredients can recover insulin resistance, oxidative stress, and pancreatic beta-cell function, which can affect blood sugar levels. This study aimed to evaluate the effect of strawberry juice in recovering insulin resistance in rat model of type 2 diabetes mellitus (T2DM) by homeostatic model assessment of insulin resistance (HOMA-IR) indicators.

**Methods:** In an experimental study, 21 male rats (*Rattus norvegicus*) of Wistar strain were enrolled and received streptozotocin and nicotinamide to induce DM. They were divided into groups of P1 as negative control group in absence of any treatment, P2 as positive control group that were given metformin HCl (0.9 mg/Kg BW/day), and P3 as intervention group receiving strawberry juice (3.6 mL/200 g BW/day) for 14 days. The HOMA-IR level was determined for all groups and compared.

**Results:** HOMA-IR level in P1 was 8.32±0.26, in P2 was 4.89±0.29, and in P3 was 5.16±0.20. Among groups, prior to treatment, there were no significant differences ($p$=0.66). A significant decrease was noted in HOMA-IR in P2 group (-3.75±0.09; $p$<0.001) and P3 group (-3.26±0.12; $p$<0.001), while in P1 group was not significant (0.03±0.12; $p$=0.46).

**Conclusion:** Strawberry fruit like metformin was effective in reducing HOMA-IR in rat model of T2DM, when administered alone.

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## Introduction

The antioxidant content of strawberries has been shown to have a positive impact on people with type 2 diabetes mellitus (T2DM) (1-4). The main antioxidant content in strawberries is anthocyanins that can stabilize glucose levels (5) and increase insulin sensitivity (6). Anthocyanins as the dominant polyphenolic compounds in strawberries range from 150 to 800 mg/kg-1 of net weight (7). The hypoglycemic effect of anthocyanins is facilitating of insulin-mediated glucose absorption by cells. The strawberry extract can facilitate the secretion of insulin in a bound form in order to reverse the low insulin levels (8). In T2DM patients, hyperglycemia is caused by the inability of insulin to mobilize blood glucose into cells due to insulin receptor resistance (9). Hyperglycemia increases the auto-oxidation of glucose to form free radicals and free radicals or Reactive Oxygen Species (ROS) are formed from glucose oxidation, non-enzymatic proteins, and oxidative degradation of glycolyzed proteins (10).

The increase in intracellular glucose causes an abundance of electron donors to be generated during the Krebs cycle, thereby pushing the potential of the

inner mitochondrial membrane upward, a condition that is associated with mitochondrial dysfunction and an increased production of ROS (11). ROS will increase the expression of tumor necrosis factor-α (TNF-α) and exacerbate the level of oxidative stress and TNF-α can lead to insulin resistance through a decrease in auto-phosphorylation of insulin receptors (12, 13). Insulin resistance in turn impairs the ability of muscle cells to take up and store glucose and triglycerides, which results in high circulating glucose and triglycerides levels in the blood (14). One of the biomarkers used to measure insulin resistance is the homeostatic model assessment of insulin resistance (HOMA-IR), based on fasting blood glucose (FBG) and plasma insulin levels (15).

The content of anthocyanins in strawberries can increase glucose metabolism and peripheral glucose uptake in insulin-sensitive tissues by increasing the translocation and activity of insulin-regulated glucose transporter-4 (GLUT4) and reducing oxidative stress and inflammation (16, 17). A meta-analysis study has proved that consumption of 100% fruit juice is not associated with an increased risk of diabetes (18). So this study aimed to analyze the effect of strawberry juice on reducing levels of HOMA-IR in rat model of T2DM.

Several studies have examined the effects of insulin resistance using strawberries, but this is a new study that uses pure strawberry juice in different dosage. In this study, the author has used 100% pure strawberry juice to get the natural antioxidant, especially anthocyanins. As the antioxidant content of strawberries in each region will certainly be different, so the researchers used strawberries obtained from Tawangmangu, because this is a strawberry supplier area in Central Java, Indonesia.

## Materials and Methods

The Strawberry (*Fragaria x ananassa*) was obtained from Tawangmangu as the same plantation with similar variety. The maintenance and treatment of experimental animals was carried out at the Laboratory of the Center for Food and Nutrition Studies, Gadjah Mada University, Yogyakarta, Indonesia. The antioxidant test was conducted at the Universitas Sebelas Maret Nutrition and Food Laboratory, Yogyakarta, Indonesia. Assessment of fasting blood glucose and serum insulin levels was carried out at the Integrated Research and Testing Institute of Gajah Mada University. All chemicals used in this study have met the lab analysis standards. This study was approved by the Ethics Committee of The Health Research of Faculty of Medicine, Universitas Sebelas Maret (protocol number 465/UN27.06/KEPK/EC/2019). Working with laboratory animals was based on general principles and practical considerations of Helsinki declaration. Rats were obtained from Inter University Center (IUC) Nutrition of Gadjah Mada University in the field of pre-clinical service and experimental animal development. Animal breeding was attempted based on the modification procedures by Nain *et al.* (19). Rats were kept in a special room placed in hygienic polypropylene cages enrolling 7 rats per cage with transparent dividers, so that one rat occupied one small compartment. The food given to animals was a Comfeed standard feed consisted of 70% corn starch, 10% casein corn oil, 4% salt mixture, 1% vitamin mixture and 5% cellulose. The research was started by preparing 21 male Wistar rats aged 8-10 weeks with body weight of 180 grams that were adapted for 7 days.

This study had a pre-posttest control group design enrolling 21 male Wistar rats (*Ratus norvegicus*), divided into 3 groups of P1 as negative control group, P2 as positive control group and P3 as treatment group. The sample size was determined based on the provisions of the Institutional Animal Care and Use Committee (IACUC) (2002), while at least 6 rats in each group were included (20% for the probability of dropping out were added to reach 7 rats). The sampling technique was undertaken by simple random sampling method in order to obtain a total of 7 rats in each group. The therapeutic dose of fruit juice as described in a previous research was 3.6 mL/200 g BW/day for 14 days (20). The reference material of metformin HCl has been a single dose of 500-1700 mg per day orally in order to reduce the blood glucose level in humans of 70 kg body weight (21). Metformin is a biguanide compound that is used as an oral hypoglycemic drug in Indonesia to reduce blood glucose by improving glucose transport to muscle cells. This drug can improve glucose uptake by 10-40%. The therapeutic dose of metformin in male white rats (*Rattus norvegicus*) has been defined 0.9 mg in a previous study using red dragon fruit (22). In our study, there are 3 groups of P1 as negative control group (streptozotocin+nicotinamide induction), P2 as positive control group (streptozotocin+nicotinamide induction and metformin HCl at a dose of 0.9 mg/kgBW, and P3 as strawberry group (streptozotocin+nicotinamide induction and strawberry juice of 3.6 mL/200 gBW/day for 14 days).

Diabetes in rats was induced by administration of 230 mg/kg nicotinamide and after 15 minutes, administration of 65 mg/kg streptozotocin in cold citrate buffer, and pH of 4.5, intraperitoneally (23). Hyperglycemia was confirmed after 48 hours of streptozotocin-nicotinamide administration. Rats

with blood glucose levels of 180 mg/dL were considered diabetic and were included in the study. Sampling of animal blood was part of our *in vivo* study using the Plexus Retro-Orbital method from the eyes (24). Measurement of plasma insulin levels from blood samples was quantitatively. Rat Enzyme-Linked Immunosorbent Assay (ELISA) was by Insulin DRG kit brand (no EIA catalog 2048.r). The amount of blood glucose was assessed quantitatively by Enzymatic Colorimetric Test of Glucose Oxidase Phenol 4-Aminophenazone (GOD-PAP) method which was carried out before treatments (pre-test) and after treatment (day 14$^{th}$). The homeostasis model assessment-insulin resistance (HOMA-IR) as a validated and widely used method measured the insulin resistance from fasting glucose and insulin (25).

**HOMA-IR**:

$$\frac{Fasting\ blood\ glucose\ levels\ \left(\frac{mg}{dL}\right) x\ insulin\ level\ \left(\frac{ng}{mL}\right)}{405}$$

Paired t-test was used to compare before and after treatments, while one way-ANOVA test was utilized to analyze the effect of treatments among the 3 groups followed by the Post-Hoc test.

## Results

Table 1 shows the mean difference for FBG, tested with One Way-ANOVA and Paired T-Test. Prior to the intervention (day 0), comparison of the mean of FBG levels among groups did not show any statistically significant difference, indicating that randomization had been achieved for the objective. Both the P2 and the P3 groups had lower FBG levels than the P1 group, and the mean difference was statistically significant ($p$<0.001).

Table 2 demonstrates the same result as Table 1. Prior to the intervention, there were not significant differences for plasma insulin levels among the groups, indicating that randomization was achieved for the goal. Both the P2 and the P3 groups illustrated higher insulin levels than the P1 group, and the mean difference between them was statistically significant ($p$<0.001).

Table 3 displays the mean difference for HOMA-IR after being tested with One Way-ANOVA and Paired T-Test. Among groups prior to treatment, there were not any significant differences, indicating that randomization was achieved for our objective. In each group, if compared before and after treatment; there was a significant decrease for HOMA-IR in P2 and P3 groups, while in P1 group was not seen.

Table 4 reveals a significant difference for strawberry juice effect on FGB, insulin and HOMA-IR when comparing the positive control group and negative control group ($p$<0.001). There was a significant difference for the mean in P1 and P3 groups ($p$<0.001). Both the metformin group (P2) and the strawberry fruit group (P3) were shown to reduce levels of FBG, HOMA-IR and increase insulin levels in comparison to the control group (P1).

## Discussion

This study illustrated that the administration of 3.6 mL/200 g BW/day of strawberry juice can reduce insulin resistance levels. In 3.6 mL strawberry juice contain, there are 194.35 ppm anthocyanin, 5.24% wb antioxidant and 0.129% wb total phenolic compounds (5) which can effect on fasting blood

**Table 1:** Effect of strawberry juice on fasting blood glucose level.

| Group | Duration | | Δ Fasting Blood Glucose (mg/dL) | $p^a$ |
|---|---|---|---|---|
| | Day 0 (mean±SD) mg/dL | Day 14 (mean±SD) mg/dL | | |
| P1 | 272.69±9.53 | 275.03±8.69 | 2.33±2.92 | 0.080 |
| P2 | 282.49±7.35 | 116.95±7.32 | -165.54±8.89 | <0.001* |
| P3 | 272.79±4.92 | 134.78±5.71 | -138.00±0.93 | <0.001* |
| $p^b$ | 0.090 | <0.001* | <0.001* | |

Primary Data (2019), *There is a significant difference, [a]($p$<0.05) Paired T-Test, [b]($p$< 0.05) One Way ANOVA

**Table 2:** Effect of Plasma insulin level juice.

| Group | Duration | | Δ Plasma Insulin (pg/mL) | $p^a$ |
|---|---|---|---|---|
| | Day 0 (mean±SD) pg/mL | Day 14 (mean±SD) pg/mL | | |
| P1 | 414.01±6.07 | 409.90±2.92 | -4.10±5.47 | 0.095 |
| P2 | 413.55±2.97 | 549.88±4.90 | 136.32±6.48 | <0.001* |
| P3 | 417.35±4.19 | 517.35±6.91 | 100.00±6.75 | <0.001* |
| $p^b$ | 0.160 | <0.001* | <0.001* | |

Primary Data (2019), *There is a significant difference, [a]($p$<0.05) Paired T-Test, [b]($p$<0.05) One Way ANOVA

**Table 3:** Effect of strawberry juice administration on HOMA-IR level.

| Group | Duration | | Δ HOMA-IR | $p^a$ |
|---|---|---|---|---|
| | Day 0 (mean±SD) | Day 14 (mean±SD) | | |
| P1 | 8.35±0.19 | 8.32±0.26 | -0.03±0.12 | 0.460 |
| P2 | 8.65±0.25 | 4.89±0.29 | -3.75±0.09 | <0.001* |
| P3 | 8.43±0.12 | 5.16±0.20 | -3.26±0.12 | <0.001* |
| $p^b$ | 0.658 | <0.001* | <0.001* | |

Primary Data (2019), *There is a significant difference, [a]($p$<0.05) Paired T-Test, [b]($p$<0.05) One Way ANOVA, HOMA-IR: homeostatic model assessment of insulin resistance.

**Table 4:** The mean difference of FGB, Insulin and HOMA-IR levels.

| Group | | Mean difference | | |
|---|---|---|---|---|
| | | FBG | Insulin | HOMA-IR |
| P1 | P3 | <0.001* | <0.001* | <0.001* |
| P2 | | <0.001* | <0.001* | <0.001* |

Primary data (2019), *There is a significant difference ($p$<0.01 Post-Hoc test), FBG: Fasting blood glucose, HOMA-IR: homeostatic model assessment of insulin resistance.

glucose and insulin plasma level. In table 1, we showed that the levels of FBG increased above 200 mg/dL in all groups revealing that the condition of hyperglycemia due to the effect of streptozotocin and damage to Langerhans pancreatic β cells resulted in a decrease in insulin secretion, thereby causing T2DM (26); While nicotinamide which is a vitamin B3 (niacin) derivative with an antioxidant capacity decreased the cytotoxic action of streptozotocin and protected β cells against it. The streptozotocin is transported into B-cells via the glucose transporter 2 (GLUT2) and causes DNA damage which leads to an increase in activity of Poly(ADP-ribose) Polymerase (PARP-1) and DNA repair (27). However, the overactivity of this enzyme results in depletion of intracellular NAD (+) and ATP, and the insulin-secreting cells undergo necrosis. The protective action of nicotinamide is to inhibit PARP-1 activity and prevents the activity of this enzyme and depletion of NAD (+) and ATP in cells exposed to streptozotocin (23).

The decrease in FBG levels in rats is due to the high content of antioxidants, especially anthocyanins in strawberries. Strawberry anthocyanins can reduce glycemia and increase insulin sensitivity in diabetic rats (28). This is also due to anthocyanins effect to increase insulin signaling by stimulating tyrosine phosphorylation from insulin receptors and by increasing GLUT4 expression in muscle streptozotocin-diabetic rats (16). This study is in line with the research of Abdulazeez and Ponnusamy (2016) where oral administration of strawberry extract (at a dose of 50 mg/kg body weight for 45 days) in diabetic mice could reduce blood sugar levels in T2DM mice model (8). Antihyperglycemic effects of anthocyanins can also inhibit the activity of the α-glucosidase enzyme in producing glucose.

In Table 2, it was shown that after administration of streptozotocin and nicotinamide, the insulin level decreased. Insulin deficiency can be caused by a decrease in insulin ability in peripheral tissues (insulin resistance) and beta cell dysfunction resulting in absence of enough insulin production in the pancreas to compensate the insulin resistance indicating an increase in reactive oxygen species (ROS) level. Increased blood glucose (hyperglycemia) and free fatty acids can stimulate the formation of ROS, reactive nitrogen species (RNS), and oxidative stress (29). The increasing insulin levels in the P2 and the P3 groups after treatment with strawberry juices verified that strawberry can increase plasma insulin levels in rat model of T2DM. This study is in line with a research conducted by Aranaz *et al.* (2017) revealed that administration of freeze-dried strawberry and blueberry powder could lower the insulin resistance index (HOMA-IR) in rats along with a decrease in plasma concentrations of the inflammatory marker MCP-1 (30). This study is also in agreement with a previous research carried out by Abdulazeez and Ponmurugan (2016) stating that strawberry extract has effective hypoglycemic activity against alloxan diabetes animal (8).

The increase in plasma insulin levels is due to high levels of antioxidants in strawberries. Anthocyanins can increase insulin sensitivity and glucose uptake in vital organs such as muscle and adipose tissue and therefore can improve insulin resistance in diabetes (31). In addition, anthocyanins have a positive effect on adipocyte cell culture by suppressing lipogenic factors targeting carbohydrate digestion

in the intestine, thereby limiting the availability of glucose release into the blood (32, 33). Anthocyanins regulate carbohydrate metabolism in the body due to upregulation of translocation of insulin-regulated GLUT4, increased activation of peroxisome proliferator-activated receptors (PPARγ) in adipose tissue and skeletal muscle and increased secretion of adiponectin and leptin. This compound can reduce the inflammatory status in the body by increasing the expression of the GLUT4 gene, activating AMP-activated protein kinase and downregulating the expression of retinol binding protein (RBP4). Anthocyanins also enhance the tissue uptake and utilization of glucose in streptozotocin-induced diabetic rats, and also protect pancreatic cells against necrosis caused by streptozotocin (34, 35).

Insulin resistance is an abnormal physiological condition that occurs when insulin from pancreatic β cells is unable to trigger signal transduction pathways in target organs such as liver, muscle, and adipose tissue. Loss of insulin sensitivity is generally associated with persistent hyperglycemia (diabetes) (36). The HOMA-IR value is inversely related to plasma insulin levels and is directly proportional to FBG levels. The results in Table 3 indicate the value of insulin resistance (HOMA-IR), so the uptake and use of glucose by the body's cells was disrupted, as a result, the blood glucose level increased. The most relevant mechanism of decreasing insulin resistance levels by anthocyanins is because these compounds can increase GLUT-4 translocation, activate AMPK and lipolytic enzymes, reduce insulin receptor substrate 1 (IRS-1), serine phosphorylation, decrease regulation of binding to retinol 4 expression, sterol regulation of element-binding protein 1 (SREBP-1) mRNA levels and inhibit fatty acid and diglycerol synthesis enzymes and lipogenic activity. These all play an effective role in increasing insulin sensitivity and reversing the condition of diabetes (28, 37, 38). Furthermore, Table 4 displays that the administration of strawberry juice at a dose of 3.6 mL/200 g BW/day is effective in increasing insulin resistance levels.

## Conclusion

T2DM is becoming a worldwide health problem that reiterats an importance for alternative therapies to tackle the disease progression. Berries have received great scientific interest due to their high nutritive composition and their wide range of polyphenolic phytochemicals. Among them, strawberries (*Fragaria x ananassa*) are popularly consumed and became very popular due to their wide range of health benefits, mainly attributed to their content of anthocyanins. The whole strawberry and its bio-constituents can act on various pathophysiological targets of T2DM. The present research revealed that the treatment using strawberry juice could increase plasma insulin and results in a decrease in HOMA-IR index. This research demonstrated that supplementation of 3.6 mL/200 g BW/day of strawberry juice had beneficial effects on blood glucose maintenance, insulin sensitivity that can be due to upregulation of translocation of GLUT4. Further researches seem necessary to suggest the possible application of strawberry juice as a potential therapeutic factor for T2DM.

## Conflict of Interest

None declared.

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