Trop J Nat Prod Res, December 2024; 8(12): 9524 - 9528

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Insulin Resistance and Propolis in Polycystic Ovary Syndrome (PCOS) Model Rats

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ARTICLE INFO

Article history:
Received 19 August 2024
Revised 03 October 2024
Accepted 07 December 2024
Published online 01 January 2025

ABSTRACT

Administering propolis delays the liver's release into the bloodstream and stimulates insulin-sensitive glucose transporters.. The purpose of this study is to assess propolis' impact on insulin resistance in mice that are PCOS model users. The control group design was restricted to post-test in laboratory experimental research. Twenty-five female Wistar rats, three months old, weighing between 100 and 130 grams, were utilised as research subjects in this study. The rats were in good health, had normal activity levels, had normal vaginal swabs, were not pregnant, and had no anatomical abnormalities. Groups K1 (negative control), K2 (positive control PCOS), P1 (PCOS + propolis 50 mg/kgBW), P2 (PCOS + propolis 100 mg/kgBW), and P3 (PCOS + propolis 200 mg/kgBW) were the five groups into which the subjects were split. kgBB). After a 21-day High Fat, High Fructose (HFHF) diet and intramuscular testosterone propionate (1.8 mg/kgBW) injection, the treatment group received propolis interventions at doses of 50 mg/kgBW (P1), 100 mg/kgBW (P2), and 200 mg/kgBB (P3) for 14 days. On the 36th day GDP, insulin, HOMA-IR, and HOMA-B values were measured. The data obtained were analysed with One-way ANOVA and the Kruskal-Wallis test and $p<0.001$ values were regarded as statistically significant. Propolis treatment significantly ($p<0.001$) lowers the levels of FBS and HOMA-IR ($p<0.05$), raises insulin levels and dramatically ($p<0.001$) raises HOMA-β values. The highest effective dose of propolis that significantly reduced insulin resistance in PCOS mice was 100 mg/kgBW. The study concluded that in PCOS model mice, propolis significantly reduced insulin resistance.

Keywords: Insulin resistance, Polycystic Ovary, Propolis, Hyperglycaemia

Introduction

Endocrine disorders affect 6–15% of women who have polycystic ovarian syndrome, or PCOS. Amenorrhea, irregular periods, obesity, hirsutism, and infertility are a few of the symptoms. Insulin resistance frequently serves as the root cause of PCOS. One metabolic condition that leads to hyperinsulinemia is insulin resistance. Comparatively to ovulatory women with PCOS, anovulatory women had higher insulin resistance and hyperinsulinemic levels. Serum hormone binding globulin (SHBG), which is produced when insulin levels are high, is synthesised less frequently and is instead stimulated by androgens from the ovaries. In order to directly affect the hypothalamus, this hormone stimulates the production of androgen in the ovaries and adrenal glands. Decreased SHBG can block the synthesis of IGF-1 (Insulin-like Growth Factor 1) binding protein and raise blood levels of free testosterone. Growth Factor-1 mimics insulin acting as a trigger to produce androgens. This inhibition accelerates granulosa cell death and inhibits folliculogenesis by increasing androgen synthesis and lowering certain miRNAs.[1]

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Citation: Wahyuni A, Meida NS, Ramadhan AJ. Insulin Resistance and Propolis in Polycystic Ovary Syndrome (PCOS) Model Rats. Trop J Nat Prod Res. 2024; 8(12): 9524 – 9528 https://doi.org/10.26538/tjnpr/v8i12.25

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

By assessing insulin resistance and beta cell activity based on basal glucose and insulin concentrations, the Homeostasis Model Assessment Insulin Resistance (HOMA-IR) approach can be used to objectively evaluate insulin levels. The ELISA technique was used to measure the levels of insulin. Pancreatic beta cells have the ability to affect insulin levels, which in turn affect glucose concentration, which is regulated by insulin-mediated glucose synthesis in the liver. The sensitivity of beta cells to insulin release is diminished when beta cell activity is compromised. As a result, the clinical stage of insulin resistance is measured using HOMA-IR.

Follicle growth is halted by hyperinsulinemia, and this process is linked to anovulatory subfertility, irregular menstruation, and the buildup of immature follicles.[2] By stimulating the pituitary gland's LH release receptors and GnRH production, hyperinsulinemia actively contributes to PCOS. As a result, insulin resistance is a factor in the prevalence of PCOS. Results from earlier studies showing that PCOS participants have increased insulin resistance when compared to controls support the theory that up to 70% of women with PCOS have insulin resistance.[3] Insulin secretion is inhibited in insulin-resistant patients, necessitating the use of insulin-sensitizing medications like metformin. On the other hand, metformin side effects include diarrhoea, nausea, vomiting, and stomach pain might upset the digestive system.[4] It is envisaged that complementary therapies will reduce the possibility of adverse reactions to traditional therapies. Iranian propolis raises insulin receptor sensitivity by decreasing insulin levels and HOMA-IR, according to earlier studies.[5] Propolis is a resin derived from bee products that exhibit anti-inflammatory, anti-hyperglycemic, and antioxidant properties. Propolis administration slows release into circulation from the liver and activates insulin-sensitive glucose transporters. There is little information to explain how propolis helps PCOS patients' insulin resistance. The purpose of this study is to ascertain how propolis affects insulin resistance in mice with polycystic ovarian syndrome (PCOS).

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Materials and methods

The propolis has been collected from sub-district Kerjo, Karanganyar, Surakarta (lat:-7.5407351 long:111.0639245). It was collected in 2022. This is quantitative and experimental research conducted in a lab setting using a control group that is solely used for post-testing. The dependent variables were HOMA-IR and HOMA-B, and the independent research variable was Gunung Lawu propolis.

Animals and Ethical Approval

Twenty-five female white rats were collected from the Center for Food and Nutrition Studies (PSPG) UGM Yogyakarta and employed as research participants. Female Wistar strain mice, 3 months old, weighing between 100 and 130 grams, in good health, having normal activity levels and vaginal swabs, not being pregnant, and having no anatomical abnormalities met the inclusion criteria for this study. The rats were housed in an environment with enough light, a temperature range of 25 to 18 °C, and a humidity level of 40 to 60%. Each rat's cage was 20 x 30 x 20 cm. All procedures were approved by the Animal Ethical Committee of Muhammadiyah Yogyakarta Universitas ethical approval number No. 146 / EC-KEPK FKIK UMY / VI / 2022.

The study was conducted at the Center for Food and Nutrition Studies, Experimental Animal Laboratory, Gadjah Mada University, Yogyakarta, Inter-University Center (PAU). The participants were acclimated for seven days, during which time they were split into five groups of five white rats each, namely:

K1: Negative control in the absence of therapy
K2: Positive control (PCOS model without the use of propolis)
P1: Propolis 50 mg/kgBB/day with PCOS model
P2: Propolis 100 mg/kgBB/day plus PCOS model
P3: Propolis 200 mg/kgBB/day plus PCOS model

Experimental

Insulin and fasting blood glucose (GDP) levels were assessed after induction of PCOS in groups K2, P1, P2, and P3 by intramuscular injection of testosterone propionate (1.8 mg/kgBW) and HFHF diet, whilst group K1 served as a negative control. Groups P1, P2, and P3 received propolis intervention at varying doses for 14 days following a 21-day induction period. To get HOMA-IR and HOMA-B data, the insulin and fasting blood glucose (GDP) levels of each group were tested after the intervention was over.

Statistical Analysis

Data obtained from this experiment was subjected to ANOVA and Kruskal-Wallis test and $p<0.001$ or $p<0.05$ were considered statistically significant. Post-test analysis was used only for the control.

Results and Discussion

Following the intervention, fasting blood sugar levels (FBS) were measured in this study. The data were regularly distributed, as indicated by the Shapiro-Wilk test results (sig. 0.081; $p>0.05$), and differences in the test were subjected to One-way ANOVA analysis. The test evaluates differences between two additional groups, unpaired data, and regularly distributed data (Table 1). Data analysis indicates a significant difference ($p<0.001$) in the average FBS levels between the groups (Figure 1). Also, significant differences ($p<0.001$) were observed in all groups following post-hoc LSD testing. Compared to groups K2, P1, P2, and P3, group K1 showed a considerably lower mean ($p<0.001$) (Table 2). Also, the K2 showed a significant mean difference ($p<0.001$) when compared to those of P1, P2, and P3, with a higher mean value. Also, compared to P2 and P3, the P1 group's mean was noticeably higher, while P2 was noticeably lower than P3. According to the data, the K2, P1, P3, P2, and K1 groups had high average fasting blood sugar levels (FBS). This indicates that administering 100 mg/kgBW of propolis ethanol extract was more effective than 200 mg/kgBW in reducing FBS levels in PCOS model mice.

Table 1: Average FBS Levels (mg/dL)

Group	N	Mean ± SD	P
K1	5	67.1460 ± 1.8405	P<0.001
K2	5	149.9620 ± 2.87219	
P1	5	119.5680 ± 4.84498	
P2	5	93.2120 ± 0.93184	
P3	5	108.7360 ± 5.14675	

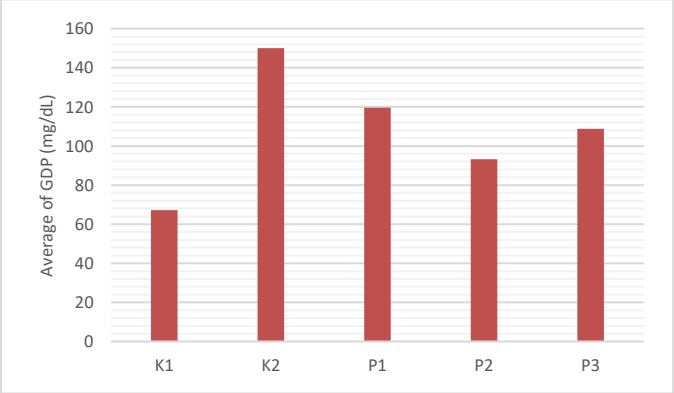

Figure 1: Average FBS Levels (mg/dL) between treatment groups and control

Table 2: Comparison of Average Differences in FBS Level Variables (mg/dL)

Between-group	Mean Difference	IK95%		p
		Minimum (mg/dL)	Maximum (mg/dL)	
K1 vs K2	-82.81600*	-86.5838	-79.0482	.000
K1 vs P1	-52.42200*	-56.1898	-48.6542	.000
K1 vs P2	-26.06600*	-29.8338	-22.2982	.000
K1 vs P3	-41.59000*	-45.3578	-37.8222	.000
K2 vs P1	30.39400*	26.6262	34.1618	.000
K2 vs P2	56.75000*	52.9822	60.5178	.000
K2 vs P3	41.22600*	37.4582	44.9938	.000
P1 vs P2	26.35600*	22.5882	30.1238	.000
P1 vs P3	10.83200*	7.0642	14.5998	.000
P2 vs P3	-15.52400*	-19.2918	-11.7562	.000

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Note: K1: Negative control (no treatment), K2: positive control (PCOS model without propolis intervention), P1: PCOS Model + propolis 50mg/kgW/day, P2: PCOS Model + propolis 100mg/kgW/day, P3: PCOS Model + propolis 200mg/kgW/day

Likewise, the insulin levels were determined post-treatment. The FBS data analysis showed varied distribution following the Shapiro-Wilk test (sig. 0.021, $p<0.05$). Therefore, the non-parametric Kruskal-Wallis test was used to evaluate mean differences. The Kruskal-Wallis test evaluates differences in data that are not regularly distributed, or unpaired, and involves more than two groups (Table 3). The average insulin levels showed a significant difference at $p<0.001$, from the Kruskal-Wallis difference test analysis, indicating that the average insulin levels were considerably different (Figure 2). When comparing the average insulin levels, the negative control group (K1) showed a considerable increase in insulin levels. The insulin levels in the positive control group (K2) dropped noticeably. After receiving propolis at doses of 50 mg/kgBW, 100 mg/kgBW, and 200 mg/kgBW, the average insulin level of groups P1, P2, and P3 increased or remained higher. Insulin levels may be suppressed by propolis when dosages of 50, 100, or 200 mg/kgBB are administered. The average insulin levels across the groups were also compared. The Post Hoc Mann-Whitney test was therefore used to evaluate differences between each group in non-parametric data with more than two groups that are not paired and are not normally distributed (Table 4). Post Hoc Mann-Whitney test analysis results revealed that there were significant variations in average insulin levels between groups K1 vs K2, K1 vs P1, K1 vs P2, K1 vs P3, P1 vs P2, and P2 vs P3. Compared to groups K2, P1, P2, and P3, group K1 showed a considerably higher ($p<0.05$) average insulin level. Comparing K2 to K1, the average insulin levels were lower. In both groups (K1 and K2), P1, P2, and P3, propolis intervention doses of 50 mg/kgBW, 100 mg/kgBW, and 200 mg/kgBW resulted in considerably better results ($p<0.05$). The average insulin levels across all groups were analysed, and the results showed substantial differences ($p<0.05$). These findings suggest that administering propolis to PCOS model mice can cause notable alterations in insulin levels.

Table 3. Average Insulin Levels (pg/mL)

Group	N	Median (Minimum – maximum)	p
K1	5	551.9800 (549.86 – 555.17)	P<0.001
K2	5	429.8200 (424.50 – 435.13)	
P1	5	487.1800 (482.93 – 495.68)	
P2	5	512.6800 (507.37 – 520.11)	
P3	5	498.8700 (493.56 – 506.30)	

Table 4: Comparison of Average Differences in Insulin Levels (pg/mL)

Between-group	Mean difference	p
K1 vs K2	20	.009
K1 vs P1	14.7	.009
K1 vs P2	5	.009
K1 vs P3	10.3	.009
K2 vs P1	-5.3	.009
K2 vs P2	-10	.009
K2 vs P3	-9.7	.009
P1 vs P2	-9.7	.009
P1 vs P3	-4.7	.021
P2 vs P3	5.3	.009

Note: K1: Negative control (no treatment), K2: positive control (PCOS model without propolis intervention), P1: PCOS Model + propolis 50mg/kgW/day, P2: PCOS Model + propolis 100mg/kgW/day, P3: PCOS Model + propolis 200mg/kgW/day

Furthermore, the study evaluated the impact of propolis administration on the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) levels in PCOS model mice. The data has a normal distribution of 0.06 ($p>0.05$) according to the Shapiro-Wilk test, hence One-way ANOVA was used to evaluate the differences in the values in the unpaired data in multiple groups (Table 5). The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) average analysis test results indicate a significant difference ($p<0.001$) in the average HOMA-IR between groups K1, K2, P1, P2, and P3 (Figure 3). Subsequent testing utilising the Post-Hoc LSD test following the intervention revealed a significant difference ($p<0.001$) in the average difference in HOMA-IR levels (Table 6). In comparison to groups K2, P1, P2, and P3, group K1's average Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) levels were considerably lower. Comparing group K2 to groups P1, P2, and P3, it was significantly higher. The outcomes demonstrate how seriously the hypothesis "There is an effect of giving propolis on insulin resistance in PCOS model mice" was examined. The results demonstrated that propolis doses of 50 mg/kgBB, 100 mg/kgBB, or 200 mg/kgBB effectively lower insulin resistance.

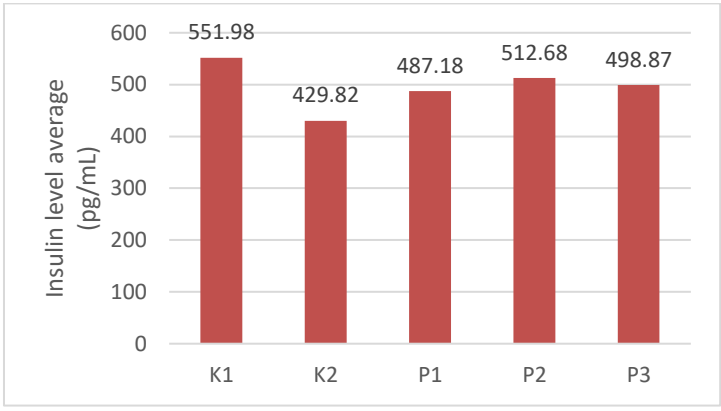

Figure 2: Average insulin levels (pg/mL) between treatment groups and control

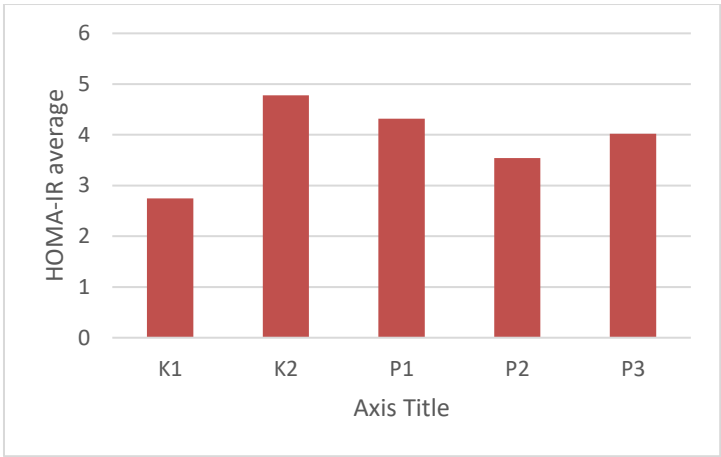

Figure 3: Average HOMA-IR values between treatment groups and control

Similarly, the Shapiro-Wilk test was used to compare differences in the average Homeostatic Model Assessment of Beta Cell Function (HOMA-B) levels following propolis administration to PCOS model mice. Since the data were not normally distributed at 0.000 ($p<0.05$), as indicated by the Shapiro-Wilk test results, the Kruskal-Wallis test was employed to evaluate the differences in the test (Table 7). Based on the analysis, each group's HOMA-B mean difference test results in Table 7 demonstrate substantial differences ($p<0.001$) (Figure 4). The results demonstrated that HOMA-B levels were significantly higher when compared to the negative control group (K1). When contrasted with the positive group (K2), the P1, P2, and P3 groups typically exhibit noticeably better outcomes. The Mann-Whitney Post-Hoc test was utilised to compare the aforementioned results using the mean

difference test. The Homeostatic Model Assessment of Beta Cell Function (HOMA-B) difference test revealed significant average differences between groups following the Mann-Whitney test. Group K1 demonstrated considerably higher HOMA-B test findings ($p<0.05$) in comparison to groups K2, P1, P2, and P3. Mice with PCOS models that were administered propolis at different levels, namely 50 mg/kg BW (P1), 100 mg/kg BW (P2), and 200 mg/kg BW (P3), tended to have higher average scores across all tests, with no substantial reduction in pancreatic beta cell activity ($p<0.05$). In contrast to treatment groups P1 and P3, group P2's propolis dose of 100 mg/kg BW had a noticeably greater average per treatment group. It follows that in PCOS model mice, P2, or 100 mg/kg BW of propolis, had the greatest effect on raising HOMA-B. According to the investigation, propolis influenced the PCOS model mice Homeostatic Model Assessment of Beta Cell Function (HOMA-B).

Table 5: Average Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) Levels

Group	N	Mean ± SD	p
K1	5	2.7480 ± 0.07950	
K2	5	4.7760 ± 0.11718	
P1	5	4.3200 ± 0.01732	
P2	5	3.5420 ± 0.05119	
P3	5	4.0220 ± 0.22399	

Table 6: Comparison of Average Differences in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)

Between group	Mean Difference	IK95%		p
		Minimum (mg/dL)	Maximum (md/dL)	
K1 vs K2	-2.02800*	-2.1876	-1.8684	.000
K1 vs P1	-1.57200*	-1.7316	-1.4124	.000
K1 vs P2	-.79400*	-.9536	-.6344	.000
K1 vs P3	-1.27400*	-1.4336	-1.1144	.000
K2 vs P1	.45600*	0.2964	0.6156	.000
K2 vs P2	1.23400*	1.0744	1.3936	.000
K2 vs P3	0.75400*	0.5944	0.9136	.000
P1 vs P2	0.77800*	0.6184	0.9376	.000
P1 vs P3	0.29800*	0.1384	0.4576	.001
P2 vs P3	-.48000*	-.6396	-.3204	.000

Note: K1: Negative control (no treatment), K2: positive control (PCOS model without propolis intervention), P1: PCOS Model + propolis 50mg/kgW/day, P2: PCOS Model + propolis 100mg/kgW/day, P3: PCOS Model + propolis 200mg/kgW/day

In this study, propolis showed a substantial ($p<0.001$) influence on fasting blood glucose (FBS) levels and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in PCOS model mice. Insulin levels increased significantly ($p<0.05$) in response to propolis, and the Homeostatic Model Assessment of Beta Cell Function (HOMA-B) value showed significant ($p<0.001$) values. From the research findings, it could be established that administering propolis to PCOS model mice can lower insulin resistance. The present study's findings are consistent with those of Anvarifard *et al*, who found that propolis can significantly lower fasting blood glucose (FBS), raise insulin levels, and significantly improve homeostatic model assessment of insulin resistance (HOMA-IR) and beta cell function (HOMA-B).[6] It appears from this research that propolis may help repair damaged kidney tissue and restore renal function. Using quantitative information on FBS, insulin, HOMA-IR, and HOMA-B levels, we evaluated insulin resistance in our study using PCOS model mice. Sameni[7] found that propolis doses of 100 mg/kgBB and 200 mg/kgBB significantly correlated with blood glucose levels, which explains why propolis extract administration produced FBS reductions. When glucose-producing glycosylation products auto-oxidise, more ROS and SO are produced, a situation known as hyperglycemia. By lowering oxidative stress and protecting vascular function from high FBS, propolis helps patients with hyperglycemia maintain a better antioxidant balance.[8] This study clarifies that elevated oxidative stress brought on by hyperglycemia in PCOS can result in ovarian anomalies. The reason for this is that compared to healthy women, fat accumulation doubles in hyperandrogenism.[9] Fertility frequently results from abnormalities in the ovaries, which alter their normal functioning. Every woman's quality of life is affected profoundly by infertility. Effective management is therefore something that needs to be considered. Our research's management involves examining how propolis usage affects insulin resistance in mice with PCOS. Taiwanese green propolis has demonstrated the potential benefits of propolis supplementation for improving insulin sensitivity and glucose intolerance. Propolis enhances remodelling and counteracts the detrimental metabolic effects of hyperglycemia by suppressing inflammatory signals and lowering reactive oxygen species (ROS). Propolis helps the body maintain proper glucose homeostasis.[10] In a study by Fukuda[11], it was stated that the HOMA-IR value with the administration of propolis decreased significantly. Reducing HOMA-IR can improve glucose homeostasis. Propolis can suppress insulin resistance in PCOS model mice. The study explains that propolis contains several compounds such as phononic acid and flavonoids. Propolis can prevent oxidative stress in brain tissue exposed to radiation by suppressing the formation of lipid peroxidation and increasing the activity of antioxidant enzymes and can inhibit the generation of free radicals.[12] Another study explained that propolis supplementation also affected glucose homeostasis in patients with non-alcoholic fatty liver disease (NAFLD). It was found that propolis reduced serum inflammation as well as liver enzymes and the severity of fatty liver.[13] Propolis administration increased HOMA-B significantly. These results are in accordance with previous research which states that the use of honey and propolis can significantly attenuate liver and kidney damage towards the normal range. These results are proven by an increase in the number of islets of Langerhans and a decrease in fasting blood glucose levels in cases of acute kidney injury (AKI), liver injury, and pancreatic injury.[14] According to Nna[15], pancreatic histopathology showed an increase in islet area and the number of beta cells in the treatment group comparable to normal controls. Insulin fails to be produced by pancreatic beta cells as a result of an increase in oxidants in the body (oxidative stress) and free radicals which cause inhibition of glucose uptake. High levels of oxidants can be reduced by consuming antioxidants. One of the ingredients with high antioxidant content is propolis.[16] Under hyperglycemia conditions, propolis exhibits both biological and therapeutic benefits, with insulin concentration characteristics ascertained through the use of HOMA-IR, the findings demonstrate a noteworthy decrease.[14] Propolis has an anti-hyperglycemic effect that lowers fasting blood glucose (FBS), stabilizes insulin levels to prevent HOMA-IR from increasing in PCOS mice,

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

raises HOMA-B in PCOS model mice to enhance the function of pancreatic beta cells and repair ovarian damage to aid in PCOS recovery. The propolis dosage that produced the highest results in this investigation was 100 mg/kgBB. According to Sapmaz, the best propolis dosage to improve zona pellucida and fibrous tissue degeneration in PCOS is 50 mg/kgBB propolis, as opposed to a high dose of 150 mg/kgBB propolis.[17] This study showed that higher doses of propolis do not produce more effective treatment outcomes.

Table 7: Average Homeostatic Model Assessment of Beta Cell Function (HOMA-B)

Group	N	Median (Minimum – maximum)	p
K1	5	1442.7100 (949.60 – 3002.07)	P<0.001
K2	5	53.2900 (51.73 – 55.79)	
P1	5	92.7400 (90.02 – 97.89)	
P2	5	181.5300 (178.29 – 190.94)	
P3	5	119.5700 (105.56 – 13.86)	

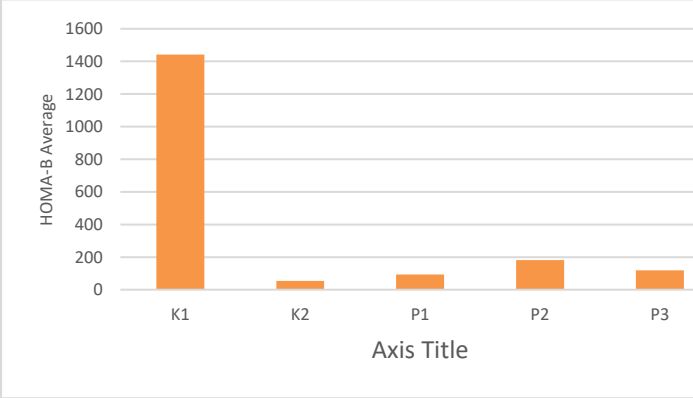

Figure 4: Average HOMA-B values between treatment groups and control

Conclusion

This study found that administration of propolis improves insulin resistance in Polycystic Ovary Syndrome (PCOS) mice, significantly reduces fasting blood glucose (FBS) levels in Polycystic Ovary Syndrome (PCOS) mice and increases insulin levels in Polycystic Ovary Syndrome (PCOS) mice. Also, treatment with Propolis administration at different doses significantly reduced Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) levels in Polycystic Ovary Syndrome (PCOS) mice and increased Homeostatic Model Assessment of Beta Cell Function (HOMA-B) levels in Polycystic Ovary Syndrome (PCOS) mice. The study concluded that Propolis at 100 mg/kg BW has the maximum effect in suppressing homeostasis model Assessment of Insulin Resistance (HOMA-IR) levels.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

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