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Relationship Between Silymarin, Resveratrol And Blood Glucose Levels In Depression Rats

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Abstract

Depression is among the most common psychiatric disorders worldwide and causes widespread public health problems. Individuals diagnosed with depression are at risk of developing serious diseases such as coronary artery disease and diabetes. Research shows that depression disrupts glucose metabolism and can lead to cellular damage through mechanisms involving oxidative stress. Furthermore, these disruptions have been associated with depressive symptoms in individuals with impaired glucose regulation. In recent years, natural compounds such as resveratrol and silymarin have gained increasing attention in alternative medicine for the treatment of various diseases. This study aims to investigate the effects of silymarin and resveratrol on blood glucose levels in male Wistar rats subjected to reserpine-induced depression. The study was designed in four groups with six rats in each group. The groups were determined as follows: Control, Reserpine, Reserpine + Resveratrol and Reserpine + Silymarin. According to the findings, blood glucose levels in the Reserpine group were found to be statistically significantly higher compared to the control group ($p < 0.05$). It was found that glucose levels were lower in the Silymarin group than in the Reserpine and Resveratrol groups, and that silymarin had a stronger blood glucose-lowering effect than resveratrol. In conclusion, knowledge on the physiopathology of depression is still limited and despite current treatment approaches, it is difficult to achieve satisfactory therapeutic outcomes in depressed individuals. Therefore, the therapeutic potential of plant-derived compounds should be evaluated in more effective and large-sample studies. Our study reveals that silymarin can be used as a therapeutic agent especially against glucose dysregulation that may be caused by depression.

Keywords: Depression, Glucose, Reserpine, Silymarin, Resveratrol

Introduction

With an estimated lifetime prevalence of around 20%, depression is a highly common psychiatric disorder. It is associated with significant rates of morbidity and mortality. Individuals suffering from depression are more susceptible to major physical health issues, including coronary artery disease and diabetes. Additionally, depression has been shown to adversely influence the course of chronic illnesses(1). Increased activity in the hypothalamic-pituitary-adrenal axis has been found in approximately 20% to 80% of individuals with depression. This dysregulation is

considered a key mechanism underlying both the pathophysiology of depression and its link to comorbid conditions such as obesity and diabetes(2). Although the relationship between depression, anxiety and disorders of glucose metabolism is widely recognized, it is still not clear which of these disorders causes the other (3).

Depression is thought to contribute to impairments in glucose metabolism, central obesity and ultimately type 2 diabetes. Activation of the HPA axis may underlie this process (4). Glucose metabolism is important in depression because it increases the severity of diabetes and significantly reduces quality of life. Both depression and diabetes reduce an individual's quality of life; however, this effect becomes even more negative when they occur together (5).

Individuals with depression often present with symptoms such as fatigue, loss of appetite, and sad depressed mood. These clinical manifestations may reflect underlying alterations in glucose metabolism(6). Depression has been shown to alter glucose metabolism, which can lead to cellular damage through oxidative stress (7). Functional brain imaging studies have found abnormalities in glucose metabolism in the hippocampus and related brain regions in individuals with depression(8). Recent research suggests that irregularities in glucose levels are associated with many mental illnesses such as depression(9).

Resveratrol (RSV), a naturally occurring polyphenol present in grapes and various plant-derived foods, has attracted significant attention from the scientific community. Major natural sources of RSV include peanuts, grapes (especially red wine), and mulberries(10). It is called the “magic molecule” because it acts on multiple targets within the cell, reduces inflammation, prevents oxidative stress and has anti-cancer effects(11). RSV is a plant-derived dietary supplement shown to have antidiabetic properties in many animal models (12). By reducing glucose absorption from intestinal cells, RSV prevents spikes in blood glucose levels and prevents insulin resistance (13). RSV has also been shown to increase insulin secretion. Proper secretion of this hormone allows muscle and fat cells to utilize glucose, keeping blood sugar levels stable (14).

Silymarin is a herbal extract obtained from milk thistle seeds that has been used in the treatment of various diseases since ancient times and is widely used in alternative medicine today (15). Silymarin has shown suppressive effects on many types of cancer such as prostate, lung, colon, skin, bladder and liver cancer (16). However, the effects of silymarin on blood glucose in animal studies are not clear. These differences may be due to the doses used; antidiabetic benefits have been observed at low doses with antioxidant-like effects (16, 17).

In this study, our aim was to investigate the effects of resveratrol and silymarin on blood glucose in rats depressed with reserpine.

Materıals And Methods

This experimental study was carried out after ethical approval was obtained from Dicle University Animal Experiments Local Ethics Committee with protocol number 2023/35 dated 31/02/2024. The study was conducted at Dicle University Health Sciences Application and Research Center (DÜSAM) between January-February 2025. A total of 24 8-12 week old male Wistar rats with an average weight of 240-310 grams were included in the study. The subjects were divided into 4 groups. Rats;

1-Control group (n=6): Rats in this group received intraperitoneal (IP) injections of isotonic solution (0.1 mg/kg/day) for 14 consecutive days, followed by IP injections of isotonic solution every other day until the conclusion of the experiment.

2- Depression group (n=6): Rats in this group were treated with Reserpine (0.1 mg/kg/day, IP) for 14 days. The solution was prepared by dissolving Reserpine in sterile distilled water with a small amount of acetic acid. "To maintain the depressive state, injections were continued every second day from day 14 until the experiment was completed (18).

3- Depression Resveratrol group (n=6): Rats in this group were also injected with Reserpine solution (0.1 mg/kg/day) IP for 14 days. Starting from day 15, rats in this group were injected with Resveratrol (30 mg/kg) IP daily for 2 weeks. Additionally, IP injection of Reserpine solution (0.1 mg/kg) was administered every 2 days until the end of the experiment(19).

4- Depression Silymarin group (n=6): The animals in this group were also injected with IP Reserpine solution (0.1 mg/kg/day) for 14 days. Starting from the 15th day, the rats in this group were injected with Silymarin (100 mg/kg/day) every day for 2 weeks. In addition, IP injection of Reserpine solution (0.1 mg/kg) was administered every 2 days until the end of the experiment (20).

The weight of the rats was monitored weekly for four weeks and blood glucose was measured from the tail vein with a glucometer device.

Statistical Methods

The IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA) program was used to analyze the data obtained in the study. Continuous variables were defined with mean ± standard deviation (SD), correlation coefficient (r), coefficient of variation (CV%), 95% confidence interval (CI), consistency ratio and weighted kappa coefficient (κ). Categorical data were reported as number (n) and percentage (%). The distribution properties of the data were analyzed with the Shapiro-Wilk test to test the assumption of normality. The Kruskal-Wallis test was used to compare the four groups that did not show normal distribution and pairwise comparisons between groups were made with the Mann-Whitney U test with Bonferroni correction. All hypotheses were evaluated pairwise and $p<0.05$ was accepted as the statistical significance limit.

Results

The experimental animals were examined in 4 groups. In the 4-week experiment, weekly glucose levels were measured as med (min-max) and the measurements are given in Table 1.

Group	Mean	Min	Max
Control	124.13	108.4	137.4
Reserpine	128.47	114.8	138.8
Resveratrol	133.97	127.6	144.4
Silymarin	126.93	116.6	141.2

Table 1: Comparison of glucose levels between groups

Kruskal-Wallis Test was performed for glucose differences between the groups. A statistically significant difference was found between the groups in terms of glucose averages ($p < 0.05$). No statistically significant difference was found in the glucose averages of Reserpine and Resveratrol groups ($p > 0.05$). It shows a higher mean value when compared with the control and Silymarin groups ($p < 0.05$).

Mann-Whitney U test was performed to compare the control group and other groups separately. A significant difference was found between the control group and the other three groups ($p<0.05$). Glucose levels of the reserpine group were significantly higher than the control group ($p < 0.05$). Glucose levels of the Reserpine and Resveratrol groups were similar and no statistically significant difference was found($p > 0.05$). However, glucose levels of the Resveratrol group were statistically significantly higher than the control group ($p<0.05$).Glucose levels of Silymarin group were statistically significantly lower than Reserpine group ($p < 0.05$). Glucose levels of silymarin and control groups were similar, no statistically significant difference was found ($p > 0.05$).

Conclusion and Future Perspective

Depression ranks as one of the most significant psychiatric mood disorders worldwide, with a lifetime prevalence of approximately 17%. Common symptoms and associated comorbidities include social isolation, disturbances in sleep, persistent sadness, apathy, anxiety, changes in food intake, psychomotor slowing, and cognitive impairments such as memory deficits. It is widely accepted that depression arises through the intricate interaction of psychological, social, and epigenetic influences (21).

The relationship between depression and disorders of glucose metabolism has been extensively investigated for years. As early as 1931, McCowan and colleagues observed that depressed patients had abnormalities of glucose tolerance concomitant with decreased depressive symptoms (22).

To date, results from observational studies investigating the relationship between glucose levels and depression have been mixed (6). While some studies have found elevated glucose levels in depressed individuals (6, 23). In some studies, lower blood glucose levels were found (24, 25). In our study, higher glucose levels were obtained in the depression group compared to the control group in parallel with previous studies.

Some studies have reported that silymarin has the ability to lower and balance blood glucose (26). Another study showed that silymarin had no apparent significant effect on blood glucose regulation (17). Our study found that silymarin had a significant effect on glucose levels. Glucose levels in the silymarin group were much lower than those in the resveratrol and reserpine groups, suggesting that silymarin has a regulatory aspect

Although resveratrol has been reported to reduce dysglycemic adverse effects by improving mitochondrial function and energy expenditure in various studies (27, 28). No significant difference was observed in our study. The reason for this may be our small sample size, as well

as differences in other studies such as the region where the study was conducted, ethnicity, and sample size. Keeping blood glucose concentrations within the normal range has the potential to reduce both the frequency and severity of dysglycemia-related diseases. As shown in this study, silymarin can be used as a regulatory agent in glycemic disorders. Pathophysiological changes in glucose metabolism in patients with depression have become increasingly interesting. There is a need to investigate these mechanisms in a more comprehensive and broad-based manner.

Compliance with Ethical Standard

Conflict of Interest

The authors declare that there is no conflict of interest.

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Ethical Declaration

Prior to the study, ethical approval was obtained from the Animal Experiments Ethics Committee of Dicle University Health Sciences Application and Research Center under protocol number 2023/35 and date 31/02/2024.

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