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Pancreatic Protective role of resveratrol extracted from peanut skin under Toxic Influence of Alloxan in Mice

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Abstract

Background: Oxidative stress plays an important role in the pathogenesis of a wide range of diseases, many of the plant chemicals (phytochemicals) in the foods are antioxidants. These nutrients the decrease free radicals and may reduce the damage they would cause in the body. **Aim:** The objective of this study is to assess the activity of resveratrol derived from peanuts (*Arachis hypogaea* L.) in male albino mice given alloxan to create a diabetic model with pancreatic damage and elevated blood glucose. **Methods:** raw peanut pods were gathered from Iraqi markets, and then the Soxhlet equipment was used to prepare a 95% ethanol extract of resveratrol from peanut skin using reflux extraction. Numerous studies were carried out, such as biochemical assays and total phenolic content. By measuring blood glucose levels, the protective effects of resveratrol extract against Alloxan toxicity were assessed. Thirty mice were randomly assigned to five groups, each including six animals. Mice included in the experiment were given an alloxan injection on day one and were given resveratrol extracts at doses of 50 and 100 mg/kg for 42 days. **Results:** Treatment with resveratrol extract 50 mg/kg resulted in a significant decrease in serum glucose concentrations (126 mg/dl). The greatest effect was observed with resveratrol extract 100 mg/kg (111.67 mg/dl), which also showed a significant decrease when compared to the control group. Additionally, pancreatic tissue from animals given 150 mg/kg of Alloxan treatment exhibited histological deformation of the outline structure together with scattered necrotic endocrine cells. On the other hand, endocrine cell therapy with a 100 mg/kg resveratrol extract exhibited almost normal histological structure appearance. **Conclusion:** According to this study, resveratrol extract helped to decrease blood glucose levels in diabetic mice

Keywords: Alloxan, Pancreatic, resveratrol, *Arachis hypogaea*, Diabetic, Total phenol.
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Introduction

A metabolic disease with several underlying causes is diabetes mellitus. Diabetes is a disorder in which there is insufficient insulin production or action. It is caused by a number of causes, including ageing, genetics, lifestyle choices, obesity, hypertension, and other risk factors. Hyperglycemia and dysfunctional protein, lipid, and electrolyte metabolism accompany diabetes (1). Diabetes can cause mortality if ignored. It can also cause difficulties with the kidneys, heart, and nervous system (2).

Globally, the prevalence of diabetes is increasing, and by 2035, there will likely be 592 million adults with the disease (1). With the right diet, regular exercise, and prescription medication, this illness can be effectively treated (3). Oxidative stress is linked to diabetes, and glucose autoxidation is a common cause of it (4).

Prolonged high blood sugar levels disrupt antioxidant balance, resulting in oxidative damage and inflammation, perhaps leading to the demise of pancreatic β-cells (5). If the cells in the pancreas are exposed to harmful chemicals on a regular or frequent basis, their antioxidant defence is often compromised. As a result, oxidative stress causes damage to the

cells. The pancreas secretes exocrine substances from its acinar cells in addition to endocrine secretions produced by the Langerhans islets. Digestive enzymes such as lipase, amylase, and proteases are secreted by these cells (6).

As a result, safer and more potent medications are required for the treatment of diabetes (1). Traditional medicine is increasingly being used these days to treat a wide range of chronic illnesses, including diabetes. Approximately two thirds of people worldwide seek medical treatment through traditional means, with its use being most prevalent in underdeveloped nations (7). Patients tolerate traditional medications better, they are more affordable, and they are easier to obtain (8). Their antioxidant qualities may allow them to affect diabetes more effectively and beneficially (9). Many compounds possessing anti-oxidant qualities have been found in different plant components, including fruits, stems, roots, leaves, flowers, and seeds (10).

Among the various fruits and vegetables, including peanut sprouts, grapes, and peanuts, resveratrol is the most compelling polyphenolic compound. Since its initial extraction from *Veratrum grandiflorum*, also known as white hellebore plants (11), it has garnered considerable interest from medical chemists, dietitians, and other health professionals due to its numerous advantageous properties, which include immunomodulatory, antimicrobial, neurological, anticancer, antidiabetic, and prevention of cardiovascular diseases (CVD) (12). It helps in reducing inflammation along considering oxidative stress, which helps creatures of many kinds live longer (13).

Materials and Methods

Collection of *Arachis hypogaea* L.

Raw peanut pods were acquired from a local market and identified as (*Arachis hypogaea* L.) by an expert at the Department of Biology, College of Science, University of Baghdad. Pods were manually shelled, and skins were removed from raw peanut kernels. The skins were powdered with a grinder and kept at -20 °C for future investigation.

Procedures for the preparation of resveratrol from peanut skin

Based on the chemical characteristics of the components in the 95% ethanol extract of peanut skin, resveratrol was prepared by filtering, hydrolyzing, reflux extraction, liquid-liquid extraction, and eluting (14).

Preparation of an ethanol extract

The procedure described was followed in order to prepare the 95% ethanol extract of resveratrol from peanut skin utilising reflux extraction and the Soxhlet equipment (15). One hundred grammes of powder were added to a distillation flask for this procedure. The mixture was kept between 40 and 60 degrees Celsius for six hours after adding 95% ethanol (95 ml Absolute ethanol: 5 ml Distil water) at a ratio of 1:7 (Peanut skin powder: 95% ethanol, g/ml). This extraction process was carried out several occasions. The resulting extract solutions were mixed and dried in a rotary evaporator operating under vacuum at 40 degrees Celsius.

By dividing the mass of recovered dry extract (P_1) by the original mass of powdered peanut skin (P_2), the yield was computed. The product's yield was determined using the equation below.

Yield (%) = $P_1/ P_2 \times 100\%$

Filtering and hydrolyzing

The 95% ethanol extract was ground into a powder. After a milled sample and water were sealed in a vessel in a ratio of 1:30 (w/v, g/ml), the mixture formed a homogenous suspension solution, which was then filtered right away at a reduced pressure. The aqueous solution was brought to pH=1 using hydrochloric acid, and the polydatin was hydrolysed to resveratrol by refluxing it in a water bath for eight hours at 70 degrees Celsius (14).

Liquid–liquid extraction

The extraction of liquid from liquid was done in a separating funnel. Gravitational sedimentation was used to separate the aqueous and organic phases after the aqueous solution described in the previous paragraph (Filtering and Hydrolysing) was combined with an equal amount of extraction solvents. Three extractions were conducted in order to attain a high

recovery rate. The resveratrol concentration was determined using the following equation.

Extraction recovery of resveratrol (%) = ($V_1 C_1$ / $V_2 C_2$) × 100%

Where V_1 and C_1 are the volume and concentration of resveratrol in organic phase after extraction respectively, V_2 and C_2 are the initial volume and initial concentration of resveratrol in aqueous solution before solvent extraction (14).

Determination of total phenolic contents

Using the Folin Ciocalteu technique as reported by Jayaprakasha *et al*. (16), the total phenolic content of resveratrol was measured spectrophotometrically. 1.6 ml of 7.5% sodium carbonate solution, 2.0 ml of the diluted Folin-Ciocalteu reagent, and 0.4 ml of various resveratrol concentrations (50, 25, and 12.5 mg/ml) were combined. The amount of distilled water was added to get the total volume down to 5 ml. The absorbance at 760 nm was measured after the tubes were wrapped in parafilm and left to stand at room temperature for half an hour.

Experimental animals

A total of thirty male albino mice weighing 30±5 g was acquired from AL-Nahrain University's Biotechnology Research Centre. Standard circumstances were maintained for them, with a 12-hour light/dark cycle and a temperature of around 22 °C. They were given a two-week period to become used to the experimental setup. Water and a normal pellet diet were given every day.

Prior to the treatments, baseline blood glucose levels were measured. All mice (except from the normal control group) were given intraperitoneal injections of alloxan (150 mg/kg body weight) dissolved in normal saline to develop diabetes mellitus. Following a 72-hour alloxan administration, blood was drawn from the mice's tail vein and quantified using a glucometer. For the investigation, mice with fasting blood glucose levels more than 250 mg/dl were chosen. From the start to the last day of the experiment (six weeks), a glucometer was used to assess the mice's fasting blood glucose levels once a week using their lateral tail veins.

Thirty mice were used in this experiment, and they were split into five groups of six mice each at random.

Group 1: For 42 days, the mice in this group were given regular food and purified water as a negative control.

Group 2: This group served as an alloxan positive control.

Group 3: This group of diabetic mice received resveratrol treatment (50 mg/kg BW/day) for 42 days.

Group 4: This group of diabetic mice received resveratrol treatment (100 mg/kg BW/day) for 42 days.

Group 5: This group of diabetic mice received oral metformin (100 mg/kg BW/day) for 42 days.

Resveratrol was dissolved in 10 millilitres of tween 80 to yield concentrations of 50 and 100 mg/kg BW, respectively.

Collection of blood

Three mice from each group had their blood samples taken at the end of each week after they were given an injection of 200 µl of anaesthesia agent (160 µl ketamine 10% + 40 µl xylazine) to make them unconscious. Following the opening of their abdomen regions, blood samples were drawn straight from their hearts. After a brief 5 minutes of centrifuging at 3000 rpm, the blood sample was gently shaken. After that, the serum was kept in the freezer at -21°C until it was examined (17).

Histopathological Examination

Pancreatic tissue samples were generated for the following histopathological investigations:

1. **Fixation*:*** Prior to fixation, all tissue samples are typically sliced into tiny pieces of two to three centimeters to allow the fixative to penetrate and preserve the tissue. A 10% formaldehyde buffered isotonic solution is one of the best fixatives for regular light microscopy; leave it on for 24 hours.
2. **Embedding:** Prior to paraffin embedding, also known as tissue impregnation, there are often two primary stages involved:

- **Dehydration*:*** The water is initially removed from the embedding pieces by immersing them in a graded series of ethanol and water combinations (often ranging from 70 to 100% ethanol) for one to two hours at a time.

- **Clearing:** After that, the ethanol is swapped out for a solvent that is miscible with the embedding media; typically, xylene is used for one to two hours.

  For one to two hours, the tissue is submerged in melting paraffin in an oven, usually set to 60 to 65°C. After that, the tissues' hard blocks are placed on a microtome and sectioned to a thickness of 5 µm. The pieces are placed on glass slides to be stained with haematoxylin and eosin after floating in warm water.

Procedure:

1. Xylene was used to dewaxe the tissue slice on the slides.
2. Quickly wash in three increments of 100% alcohol, followed by 95% and 70% alcohol.
3. Soaked for five minutes in water.
4. Use hemotoxylin for a duration of 5 to 10 minutes.
5. Rinse for five minutes in water.
6. After that, the slides spent ten to fifteen seconds in eosin.
7. Soak in water for a couple of minutes.
8. Following that, the sections were dehydrated for two shifts in absolute alcohol percentage (70, 80, and 95) in a few seconds each.
9. The last process was covering the slides with Canada balsam-covered slip and putting them in xylene once they had dried (18).

Statistical Analysis

The application SAS (19) from the Statistical Analysis System was utilised to determine how different factors affected the research parameters. In this investigation, the means were significantly compared using the ANOVA method of the least significant difference (LSD) test.

Results

Extraction of resveratrol from *Arachis hypogaea*

The resveratrol concentration of the 95% ethanol extract obtained from *Arachis hypogaea* was 2.9%, while the yield was 12.8%.

Total phenolic content of resveratrol

Resveratrol's total phenolic content was 11.633, 18.360, and 25.723 mg/g at 10, 25, and 50 mg/ml, respectively, with significant variations between concentrations ($P < 0.01$) (Table 1).

Table (1): Total Phenolic content of Resveratrol

Compound	Concentration (mg/ml)	Total Phenol (µg/ml)
Resveratrol	10	11.633 ± 0.015
	25	18.360 ± 0.011
	50	25.723 ± 0.015
LSD value		0.042**
**(P<0.01)		

Experiment Diabetic mice (Protective and therapeutic role of the resveratrol extract on glucose level)

Alloxan was employed in a diabetic model with respect to blood glucose level. The current study's findings clarify why the Alloxan-treated group of mice (group 2) had substantially higher serum glucose concentrations ($p < 0.01$) than the control group (group 1) (88.6 ± 0.88 mg/dl), indicating elevated blood glucose levels (diabetic mice).

The highest effect was seen in resveratrol extract 100 mg/kg (Group 4) with a significant decrease in serum glucose concentrations (111.67 ± 0.33 mg/dl) when compared with the control group, while treatment with resveratrol extract 50 mg/kg (Group 3) showed a significant decrease ($p \leq 0.01$) in concentrations of serum glucose (126.67 ± 0.88 mg/dl) when compared with the Alloxan treated group. This outcome was comparable to that of (Group 5) received metformin treatment and attained (107.33 ± 0.88 mg/dl) after 42 days (6 Weeks), as shown in Table (2).

Table (2): Effect of resveratrol extract on serum glucose (mg/dl) level

Groups	Mean ± SE							
	Baseline	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Group 1	88.67±0.33	89.00±0.58	86.33±2.03	88.67±0.88	90.33±1.45	88.3±0.33	87.67±1.45	88.6 ±0.88
Group 2	88.67±0.88	409.00±0.58	401.67±2.33	395.33±2.40	391.67±1.76	365.3±34.18	401.67±2.91	394.33±1.20
Group 3	89.00±0.58	399.33±1.20	331.00±0.58	288.33±0.88	221.00±0.58	190.7±0.88	143.67±0.33	126.67±0.88
Group 4	88.33±0.33	399.67±1.20	310.67±0.88	253.00±1.53	189.00±0.58	167.3±1.20	121.67±0.88	111.67±0.33
Group 5	89.67±0.88	400.33±1.86	301.00±0.58	200.00±2.89	166.00±2.08	141.0±0.58	117.67±0.88	107.33±0.88
LSD value	2.912	5.303**	6.648**	8.504**	6.409**	68.580**	7.008**	3.953**
P-value	0.668	<.001	<.001	<.001	<.001	<.001	<.001	<.001

** (P<0.01).

Means having with the different letters in same column differed significantly

Group 1: Normal control, **Group 2:** Alloxan (150 mg/kg/BW), **Group 3:** Diabetic mice + resveratrol (50 mg/kg/BW/day), **Group 4:** Diabetic mice + resveratrol (100 mg/kg/ BW/day), **Group 5:** Diabetic mice + metformin (100 mg/kg/BW/day).

Effect of resveratrol extract on body weight

Diabetes is an important metabolic illness that affects a sizable portion of the world's population. Social structural differences, psychological stress, obesity, hormone imbalances, and inheritance are all contributing factors to the pandemic's optimal growth. Currently, the primary goal of treating diabetes is to consistently lower blood sugar levels through the use of hypoglycemic medications in addition to insulin. Furthermore, a wide variety of therapeutic herbs appear to have promising antioxidant and hypoglycemic effects (31).

The results of this study showed that the end body weight of the diabetes induction positive control group was considerably lower (23.97 ± 0.23) than that of the control negative group (30.26 ± 0.18; group 1). In contrast to the control positive group, resveratrol extract treatment at dosages of 50 and 100 mg/kg (groups 3 and 4) resulted in a partial restoration or improvement of the reduction in body weight, as indicated by Table (3).

Histological examination of the Pancreatic

The pancreatic tissues of normal mice were given normal diet and distilled water for 42 days. The pancreatic tissues in group 1 control tissues were stained specifically to demonstrate normal histological structural appearance, consisting of alpha and beta cells, under a light microscope (Figure 1).

Sections of the pancreas taken from mice (group 2) subjected to 150 ml/kg of alloxan revealed a deformation of the outline structure together with scattered necrotic endocrine cells (Figure 2).

The mice were given 150 ml/kg of alloxan intraperitoneally and given resveratrol extracts orally for 42 days (daily oral dosage). After 42 days, the pancreatic segment revealed degenerative endocrine cell alterations together with a rare but persistent apoptotic cell (group 3) (Figure, 3). Treatments with 100 mg/kg of resveratrol extract (Group 4) on the other hand, produced endocrine cells that almost resembled normal histological structures (Figure 4).

The pancreatic histological sections of mice in group 5 that received a dosage of metformin (100 mg/kg) similarly exhibit the typical Langerhans cell histological structure (Figure 5).

Table (3): Effect of resveratrol extract on body weight

Groups	Initial weight (g)	Final weight (g) after 6 weeks
Group 1	28.00 ± 0.58	30.67 ± 0.33
Group 2	31.33 ± 0.33	23.33 ± 0.33
Group 3	29.67 ± 0.33	27.67 ± 0.33
Group 4	30.33 ± 0.33	29.33 ± 0.33
Group 5	30.00 ± 0.58	28.67 ± 0.33
LSD value	2.004	1.494**
** (P<0.01): Means having with the different letters in same column differed significantly		

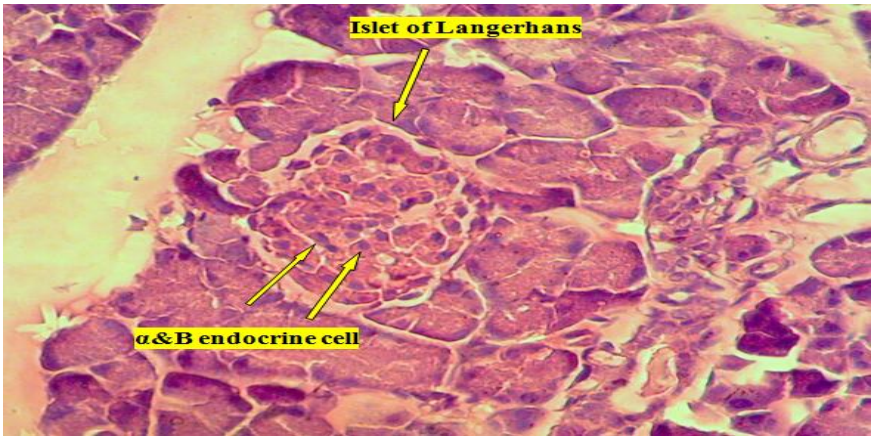

Figure (1): Section of pancreas in normal mice received normal feed and distilled water for 42 days showing normal histological structure appearance in which consist alpha and Beta cells (H&E) (X 40).

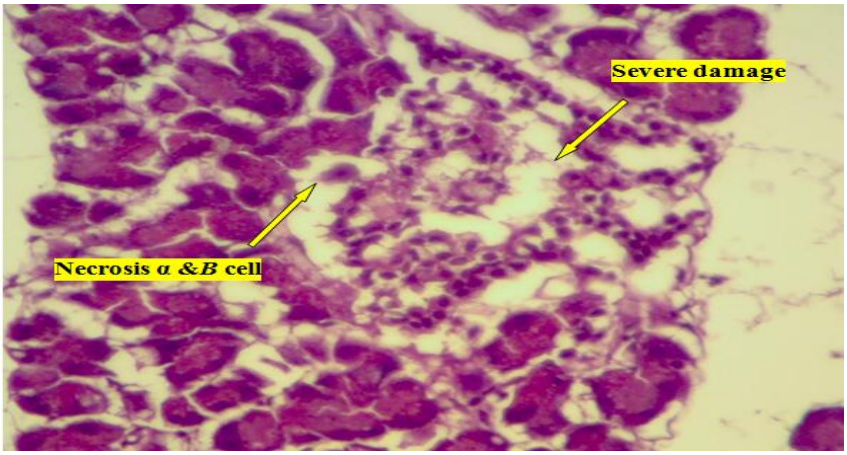

Figure (2): Section of pancreas in mice treated by alloxan (150 mg/kg/ BW) showing distortion of the outline structure with dispersed necrotic endocrine cell (H&E) (X 40).

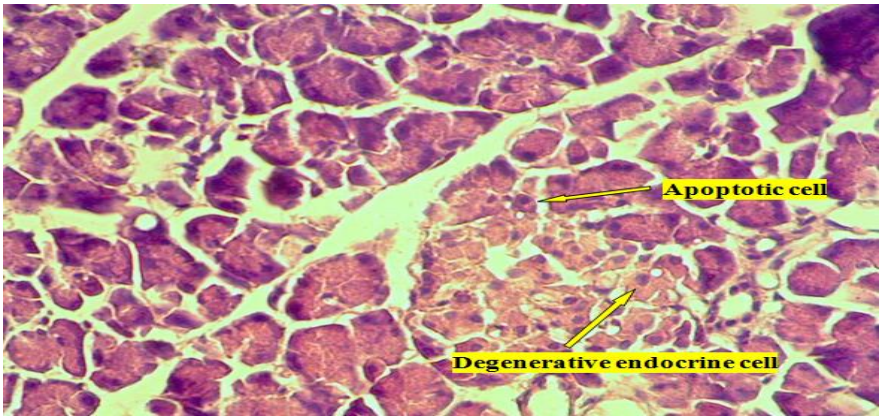

Figure (3): Section of the pancreas in diabetic mice group treated by resveratrol (50 mg/kg/B.W/day) for 42 days showing degenerative endocrine cell changes with still rare apoptotic cell (H&E) (X 40).

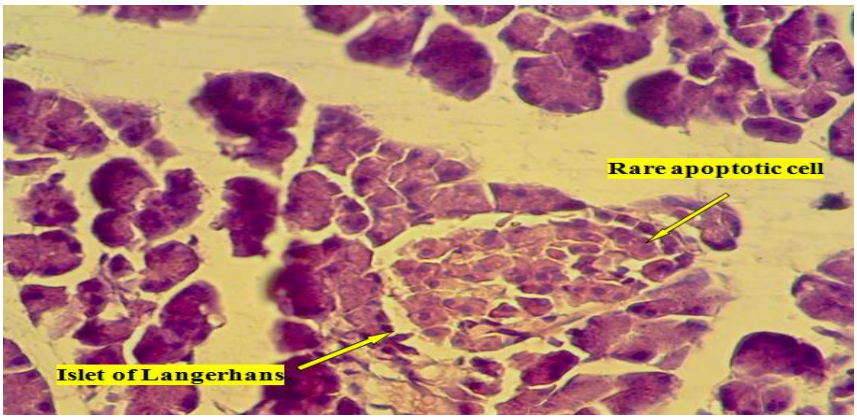

Figure (4-20): Section of pancreas in diabetic mice group treated by resveratrol (100 mg/kg/B.W/day) for 42 days showing near look like normal histological structure appearance of endocrine cells (H&E) (X 40).

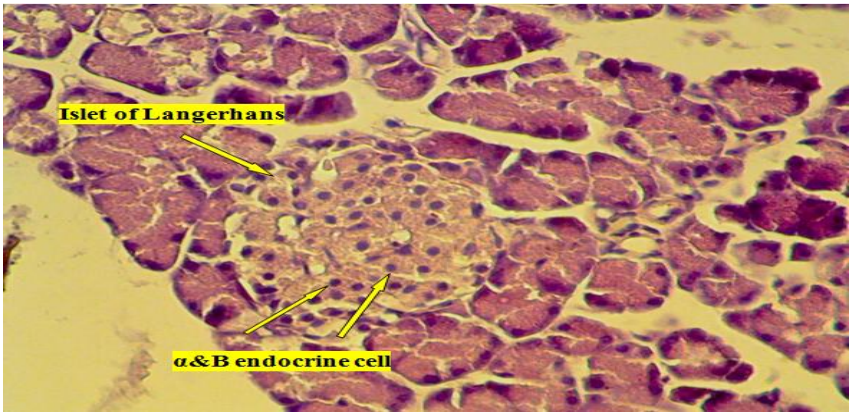

Figure (5): Section of pancreas in diabetic mice treated by metformin (100 mg/kg/B.W/day) orally for 42 days showing look like normal histological structure appearance of Langerhans cells (H&E) (X 40).

Discussion

The yield of resveratrol was 12.8%. The outcome was comparable to that of Wang *et al*. (14) who discovered that *Arachis hypogaea* yielded 3.3% resveratrol and 13.3% ethanol extract. Additionally, Jitrangsri *et al*. (20) found that using 20% and 80% ethanol, respectively, resulted in resveratrol concentrations of 1.72 and 2.73%.

Plant polyphenols are extracted using methanol, ethanol, ethyl acetate, and other organic solvents (21). Moreover, the strong polarity of water molecules allows for a significant degree of component extraction (22). Furthermore, the extraction of phenols and other physiologically active chemicals from plant raw material depends on a number of factors, including preparation temperature, time, and the ratio of dry herbal material to solvent (23).

Given its possible health advantages, such as its anti-inflammatory, anti-cancer, and antioxidant qualities, resveratrol a naturally occurring organic polyhydroxyphenolic compound has attracted a lot of interest recently (24).

Treatment with plants is often associated with antihyperglycemic effects because it can enhance pancreatic tissue function, either by raising insulin releases or by decreasing intestinal glucose absorption. These days, it is advised to treat illnesses like diabetes using medicinal plants since they contain a variety of phytoconstituents with potential antidiabetic properties, including flavonoids, terpenoids, saponins, carotenoids, alkaloids, and glycosides (24).

According to some research conducted on animal models, phenolic compounds may have a synergistic effect with anti-hyperglycemic commercial medications. This implies that patients with type 2 diabetes may be able to reduce their dosage of these medications by using these natural compounds instead of the full amount (25).

It has been demonstrated that resveratrol increases the amount of glycogen in the liver, decreases the amount of glycogen phosphorylase, and increases glycogen synthase. These actions all work together to change the metabolic pathways such that the amount of glucose produced by the liver is lowered. Increases in blood insulin concentrations coincide with the effects of resveratrol in the liver and are, at least partially, accountable for these alterations (26).

Resveratrol lowers insulin resistance in skeletal muscle via a variety of processes, such as changes in metabolism and lipid accumulation. Furthermore, in rats with diet-induced insulin resistance in their skeletal muscles, resveratrol enhances mitochondrial β-oxidation and promotes mitochondrial biogenesis (27).

Patients with type 1 diabetes were found to benefit from resveratrol as well. A two-month study using 500 mg twice-daily resveratrol capsules showed positive outcomes, including a decrease in fasting blood sugar (FBS), oxidative stress marker levels, and HbA1c (glycosylated haemoglobin) (28). Resveratrol has even been shown in a recent meta-analysis to lower C-reactive protein (CRP) levels in diabetes individuals (29).

The impacts on the gut microbiota have been the main focus of current research on the actions of food product components. Using a mouse model, peanut skin extracts have been studied for this effect; significant alterations in the microorganisms found in the stomach were noted. Most notably, there was an increase in those involved in sugar metabolism and fatty acid production. Positive implications arise from this, as chemicals isolated from peanut skins may have antidiabetic properties (30).

This conclusion is consistent with earlier research on the use of glibenclamide in the treatment of diabetes conducted by Muhammad *et al*. (32) and Okon *et al*. (33). Daye *et al*. (34) found that glibenclamide inhibited the reduction in body weight, whereas polyherbal extracts were used in this investigation to reduce the reduction in body weight.

According to Chinwe *et al*. (35) in rats with diabetes produced by alloxan, garcinia kola extract may be used as a therapeutic agent to cure diabetes mellitus and restore body weight loss. Additionally, Shahadat *et al*. (36) reported that there was a substantial rise in the end body weights of various treatments

including plant extracts compared to the beginning body weight.

Numerous writers have examined resveratrol's impact on obesity and metabolic syndrome in recent years, and they have shown that it improves glucose homeostasis and lowers the risk of cardiovascular disease linked to obesity. Nevertheless, it is still unclear how precisely resveratrol achieves its beneficial effects. Resveratrol has the potential to impact the activity of multiple intracellular targets, including the deacetylating enzyme sirtuin-1 (SIRT-1), the peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), and adenosine monophosphate-activated protein kinase (AMPK), which are all altered in metabolic abnormalities found in obese patients (37). Specifically, resveratrol can affect gene expression by causing alterations that resemble those that occur when one is calorie-restricted (38).

Resveratrol considerably lowers body weight in animal models, according to experiments; these effects are comparable to those brought on by a calorie-restrictive diet. Additionally, in mice given a high-energy diet, it enhances cellular sensitivity to insulin and mitochondrial activity, which is weakened in many metabolic disorders (39).

In many investigations, a mix of various substances was used instead of only the specific polyphenol (resveratrol combined with epigallocatechin, for example). Furthermore, the evaluations that were chosen only took weight into account as a primary result, although the majority of research examining resveratrol's impact on overall health evaluated weight status as a secondary outcome (40).

Resveratrol has been shown in studies to decrease blood insulin levels in animals that are insulin resistant and hyperinsulinemia. This effect was seen in rats that had been given a diet that caused hyperinsulinemia (41).

As a result of improved insulin action, blood glucose levels are lowered and glucotoxicity the detrimental consequences of hyperglycemia on β-cells is avoided (42). Resveratrol also reduces hepatic lipid accumulation and steatosis. These effects are associated with decreased levels of fatty acid synthase and acetyl-CoA carboxylase (43). Furthermore, it lowers fatty acid synthase expression (44).

Polyphenols play a significant role in the treatment of diabetes through insulin-dependent mechanisms, including the preservation of pancreatic islet cells, the inhibition of cell apoptosis, the enhancement of islet cell proliferation, the reduction of oxidative stress, the activation of insulin signalling, and the stimulation of insulin secretion (28). This is supported by an increasing body of evidence from both in vivo and in vitro studies. Additionally, insulin-independent strategies such as altering the inflammatory response, inhibiting digesting enzymes, controlling the gut flora, and preventing the formation of advanced glycation end products can accomplish this (43).

Additionally, resveratrol lowers inflammatory indicators, shielding pancreatic β-cells from damage. Additionally, research showed that resveratrol attenuates other deteriorating alterations, minimises oxidative stress, decreases islet fibrosis and destruction, restores islet architecture, and improves islet structure and function (28).

Conclusion

According to this study, using resveratrol extract helped to reduce the toxicity of alloxan by potentially modifying blood glucose levels. Additionally, studies conducted on animal models have demonstrated that resveratrol significantly lowers body weight because it improves glucose homeostasis and lowers the cardiovascular risk linked to obesity. Additionally, pancreatic tissues in male albino mice treated with resveratrol extracts show promise as a novel therapeutic agent which approaches the normal histological structure appearance of endocrine cells.

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