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The Hepatoprotective and Nephroprotective Effects of the Plant Extract In "Dapagliflozin'-Overdosed Animals

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ABSTRACT: Dapagliflozin, a widely used sodium-glucose cotransporter-2 (SGLT2) inhibitor, has been associated with hepatotoxicity and nephrotoxicity Therefore, this study evaluated the hepatoprotective and nephroprotective effects of extracts of Taraxacum officinale (Dandelion) and Phoenix dactylifera (Date Palm Pollen, DPP) on Dapagliflozin-induced toxicity in male Wistar rats 35 male Wistar rats (180-200g) were split into 7 groups: G1 (DPP control), G2 (Dandelion control), G3 (Normal control), G4 (Combined extracts control), G5 (Dandelion + Drug), G6 (DPP + Drug), G7 (Drug only, 0.9 mg/kg adjusted dose) After 6 weeks of experimentation, G7 had significant increases in serum creatinine (0.440 mg/dL), urea (62.16 mg/dL), ALT (64.40 U/L) and AST (130.80 U/L) when compared with normal control (G3) Dandelion extract (G5) has been shown to significantly reduce creatinine levels and urea levels compared to G7 (18.2% and 28.1%, respectively) DPP extract (G6) also exhibited a protective effect by decreasing urea levels by 12.4% Improvement of parameters of Lipid profile (Cholesterol, TG, LDL) were observed primarily in extract treated groups Given the potent antioxidant effect of extracts of T officinale and P dactylifera pollen, their use as adjunctive protective agents to mitigative organ damage of Dapagliflozin should be supported

1. INTRODUCTION

For many, plants have been used magically for the purpose of medicine and food. What's interesting about these plants is the high level of chemical such as flavonoids that have significant effects, to help treat many different diseases in pharmaceutical science. Published researches have attributed the biomedical importance of such plants towards their natural antioxidants content, which can scavenge free radicals and may able to reduce oxidative stress and also morbidity as well as mortality due to several diseases while safeguarding important cells and tissues [1,2].

Iraq has a range of useful medicinal herbs that are known for their traditional values and folkloric medicine recipes which they have recently shown activeness in using them against food and pharmaceutical industries. According to recent statistics more than five thousand plant species are used for medicinal purposes or as a model plant for drug development [3].

Dandelion Scientific name *Taraxacum officinale* is one of the major traditional medicinal plants in several countries such as China, India, Russia, and Arab area. It also has a history of application for liver diseases, inflammation and arthritis and is reported to have anti-oxidant, antiseptic and diuretic properties [4,5]. The plant is enriched with bioactive chemical compounds including flavonoids, phenols, terpenes, and glycosides as well as essential minerals and vitamins that makes it a safe source of food and medicine for human [6,7]. Dandelion is a member of the Asteraceae family and there are some 30 to 57 species in the genus Taraxacum, which are found in temperate areas of the Northern Hemisphere [8]. it grows wild in Iraq especially in the region's center It is considered one of the natural plants in it [9]. It is characterized by its toothed leaves, and golden-yellow flowers, whose roots and aerial parts are eminently edible: they have been used for the preparation of salads, beverages, coffee substitutes as well as medicinal agents [10,11].

The medicinal benefit of the dandelion is a result from its being effective in curing liver disorders, jaundice and helping blood purification. It has also been used to treat fever, constipation, rheumatism and even numerous digestive snf skin disorders [12,13]. Recent research works have pointed out the prospects of dandelion's root as well as leaf parts, indicating their anti-cancer, anti-hyperglycemic, antimicrobial, antiviral properties and immunomodulatory effect along with antioxidant potential [14-15].

Dandelion leaves contain a number of active compounds, some of which are:

- Flavonoids and phenols [16]
- Glycosides, lactones and inulin molecules [17]
- Your essential minerals such as potassium, calcium, iron, magnesium and zinc
- Vitamin A, C, D E K and the B-complex vitamins.

This diverse active constituents profile has placed dandelion in the centre of attention of many studies that confirm its importance as protective and prophylactic agent, especially in the case of liver diseases, but also, for treatment of oxidative stress.

Pollen of Male Date Palm Flowers is a natural product and it comes from the male flowers of Phoenix dactylifera l date palm tree. It is a fine powder of white or yellow color that is easily diffused, taken from male flowers before they open in the date palm tree. In traditional Chinese medicine, In addition to being a procreative stimulant and fertility enhancer, it is also used in cases of malnutrition caused by hunger when other medical remedies produce only partial success. As such, this food appears to serve both generations equally well. Recent studies have indeed shown that in hyperlipidemia and steatosis of liver caused by pork fat infusion, improper food can be set right. Date palm pollen counters the symptoms of these diseases by reducing MDA levels and up- regulating triglyceride liver Colorimetry Through analysis of its components, it has been found by American scientists to increase levels. A study by El-Neweshy et al. (2012) revealed that administration of date palm pollen extract brought about a reduction in oxidative damage to rats encountering cadmium in the body: For one thing, malondialdehyde (MDA) decreased-as did mean while levels of reduced glutathione (GSH) rose significantly. It also improved sperm parameters and partially restored testicular function. This results from its role as a potent antioxidant which can counteract heavy metals.[18]

Studies indicate that the therapeutic efficacy of date palm pollen may be attributed to: - Its content of **phenolic compounds and flavonoids** with high ability to inhibit free radicals [20] - Its richness in **essential amino acids and minerals** that contribute to enhancing enzymatic activities and tissue protection [21] - The presence of **natural estrogenic compounds** that help improve hormonal balance and metabolic functions [22]

Although previous studies focused mainly on fertility, the mentioned mechanisms (antioxidants, reduction of oxidative stress, enhancement of defensive enzymes) also represent the first line of defense for the kidneys and liver against damage caused by toxins and metabolic disorders [23]. This opens the door to using date palm pollen as a protective or adjuvant agent in maintaining kidney and liver functions, alongside its proven positive effects on fertility.

Forxiga scientific name Dapagliflozin belongs to the class of **sodium-glucose co-transporter-2 (SGLT2) inhibitors**. This group works on the kidneys to reduce glucose reabsorption and excrete it in urine, leading to a decrease in blood glucose levels independently of insulin[53].

The importance of studying this drug stems from its dual role in controlling blood sugar and reducing complications associated with diabetes, making it a subject of interest for researchers and physicians alike, especially when compared with other treatments or combined with plant extracts with potential therapeutic efficacy[26].

Based on this, this research aims to study **the effect of dandelion and date palm pollen extract on some biomarkers of kidney and liver functions, in addition to some enzymes** in rats, to demonstrate their ability to reduce potential biological damage resulting from the use of Dapagliflozin drug[24].

In addition to its role in controlling blood sugar, recent research has shown additional benefits of **Dapagliflozin** in reducing the risk of chronic kidney failure, as it contributed to improving kidney function and reducing the rate of disease progression [27].

Dapagliflozin is considered an effective therapeutic option whether used alone or in combination with other drugs such as metformin or insulin, providing patients with a dual benefit of lowering blood sugar and preventing cardiac and renal complications of diabetes [29].

2. ETHICS APPROVAL

This experiment was conducted in accordance with the guidelines for animal treatment. All of the things we did with the animals in this study were good to go by the people who are supposed to make sure animals are cared for at the College of Sciences, University of Kerbala sooted Iraq.The animals were treated well. We of course also adhered to the rules that everyone agrees on for caring for laboratory animals. This includes:

Under such laws as those that decree our duty to be kind to animals (as the Declaration of Helsinki decrees for experiments on animals)

Acting in the way the ARRIVE guidelines recommend for animal experiments.

Ensuring we do what the U.K. Animals Act of 1986 says that we must do

According to National Research Council Guide, for the care and use of laboratory animals used to feed the animals. All in all we did this to ensure that the animals would be treated with dignity and care." These regulations were followed in the care of laboratory animals.

All methodologies were executed in a manner designed to mitigate the distress experienced by the animal subjects. The animals were housed under controlled conditions (maintained at a temperature of 25 ± 1°C and subjected to a 12-hour light/dark cycle) with unrestricted access to both food and water.

3. MATERIALS AND METHODS

3.1 Housing Experimental Animals

The aforementioned experiment was conducted within the confines of the animal facility at the College of Pharmacy, University of Kerbala. They had adult laboratory rats of approximately 180-200 grams weight. There were 35 rats in total. They were divided into 7 groups and each group was in a special cage. Rats were allowed to acclimatize in the laboratory for 2 weeks. The lab was maintained at a temperature of 25 °C, and the samples were exposed to 12 hours of light from 8:00 a.m. to 8:00 p.m. every day. The experiment began on May 15. Ended on July 1. The rats received their treatments from May 28 to the final follow-up of the experiment, which was on July 1 in the College of Pharmacy University Kerbala.

3.2 Preparation of Dandelion Extract

The dandelion herb was obtained from local herbalists in the city of Karbala, Iraq, and 100 grams of this herb were used, Deposited it in a special Soxhlet To obtain the active extract[30]. After drying were left with 4 grams of dry Dandelion extract. generated doses of the Dandelion extract for the animal, The dose is two hundred milligrams of extract per kilogram of the animal's body weight. The average weight of the rats was one hundred and ninety grams[31]. It was diluted with water to form a liquid containing twenty milligrams of chicory extract . Each rat received (2 ml) of this solution per day.

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3.3 Preparation of Date Palm Pollen(DPP) Extract

I purchased the date palm pollen powder from a few herbalists, in Karbala city. I did the same things I had done before to get the pollen extract that I gave to the animals.

3.4 Dapagliflozin Drug Preparation

Dapagliflozin (Dapagliflozin®) tablets at 10 mg were orally dosed to rats. The dose for animals was adjusted for body surface normalisation as per the method of Paget and Barnes[32]. The corresponding dose in rats was approximately 0.9 mg/kg body weight. Rats weighing 190 g on average overdose are administered through oral gavage at a dose of around 0.3 mg per day To simulate the harmful effects of overdoses .

3.5 Experimental Design and Groups

Animals were divided into seven experimental groups (n=5 per group):

Group 1 (G1): Date Palm Pollen Control - Received date palm pollen extract only - Served as positive control for pollen effects

Group 2 (G2): Dandelion Control - Received dandelion extract only - Served as positive control for dandelion effects

Group 3 (G3): Toxicity Control - Received standard diet and water - Intermediate control group

Group 4 (G4): Combined Plant Extracts - Received both date palm pollen and dandelion extracts - To evaluate synergistic effects

Group 5 (G5): Dandelion + Dapagliflozin - Received dandelion extract + Dapagliflozin - To evaluate protective effect of dandelion against drug

Group 6 (G6): Pollen + Dapagliflozin - Received date palm pollen extract + Dapagliflozin - To evaluate protective effect of pollen against drug

Group 7 (G7): Negative Control (Drug Only) - Received Dapagliflozin only - To evaluate drug effects alone

3.6 Sample Collection and Analysis

At the end of the experimental period, blood samples were collected from all animals after overnight fasting. Serum was separated by centrifugation It has 3000 revolutions per minute for 15 minutes and stored at -20°C until analysis.

The following parameters were measured using standard biochemical methods: - **Kidney function tests**: Creatinine, Urea, Sodium, Potassium - **Liver enzymes**: ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), ALP (Alkaline Phosphatase) - **Lipid profile**: Total Cholesterol, Triglycerides, HDL, LDL, VLDL - **Blood glucose**: Fasting blood glucose

3.7 Statistical Analysis

Data were expressed as mean values. By the Genistat analysis program Statistical significance was determined at $P < 0.05$ level using appropriate statistical tests.

4. RESULTS AND DISCUSSION

4.1 Experimental Groups Overview

Seven experimental groups of laboratory rats were used to evaluate the effects of dandelion and date palm pollen extracts with Dapagliflozin drug on kidney functions, liver enzymes, lipid profile, and blood glucose levels.

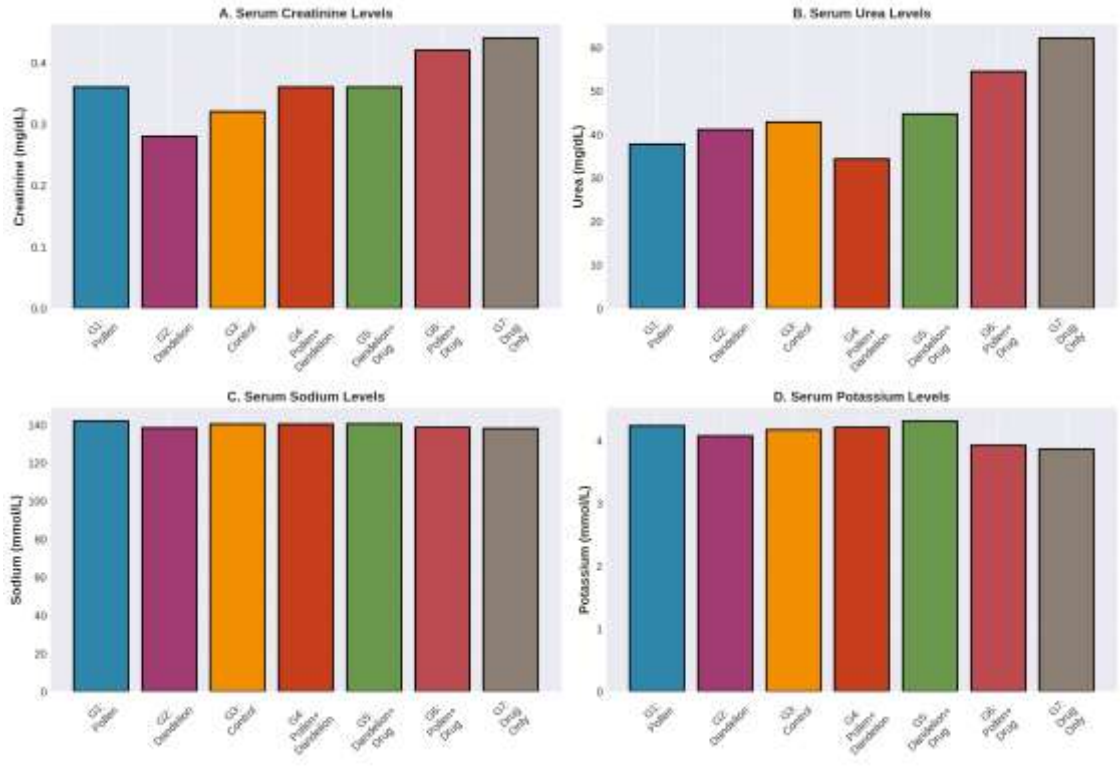
4.2 Kidney Function Parameters

Table 1: Kidney Function Parameters in Studied Groups

Treatment Groups	Creatinine (mg/dL)	UREA (mg/dL)	SODIUM (mmol/L)	Potassium (mmol/L)
G1:	0.360	37.72	141.78	4.236

G2:	0.280	41.08	138.28	4.072
G3:	0.320	42.80	140.26	4.172
G4:	0.360	34.34	140.26	4.208
G5:	0.360	44.68	140.42	4.308
G6:	0.420	54.48	138.54	3.920
G7:	0.440	62.16	137.98	3.860

Figure 1: Effect of Treatments on Kidney Function Parameters



Discussion of Kidney Parameters:

The results of the current study (Table 1) showed no significant difference at P<0.05 level between the pollen control group (G1) and the negative control group in kidney parameters (Creatinine, Urea, Sodium, Potassium).

Effect of Date Palm Pollen Extract: The G1 group (pollen) showed normal values for all kidney parameters: - Creatinine: 0.360 mg/dL (within normal range) - Urea: 37.72 mg/dL (within normal range) - Sodium: 141.78 mmol/L (within normal range) - Potassium: 4.236 mmol/L (within normal range)

Effect of Dandelion Extract: The G2 group (dandelion) showed improvement in Creatinine level (0.280 mg/dL), the lowest value among all groups, indicating potential renoprotective effects. However, there was a slight increase in Urea (41.08 mg/dL).

Effect of Dapagliflozin Drug: The G7 group (drug only) showed the highest values: - Creatinine: 0.440 mg/dL (22% increase compared to G1) - Urea: 62.16 mg/dL (65% increase compared to G1)

This indicates a potential negative impact on kidney function, which may be related to the drug's mechanism of action as an SGLT2 inhibitor that increases glucose excretion through the kidneys.

Protective Effect of Plant Extracts: - G6 (Pollen + Drug): Showed improvement compared to G7 - Creatinine: 0.420 mg/dL (4.5% reduction) - Urea: 54.48 mg/dL (12.4% reduction)

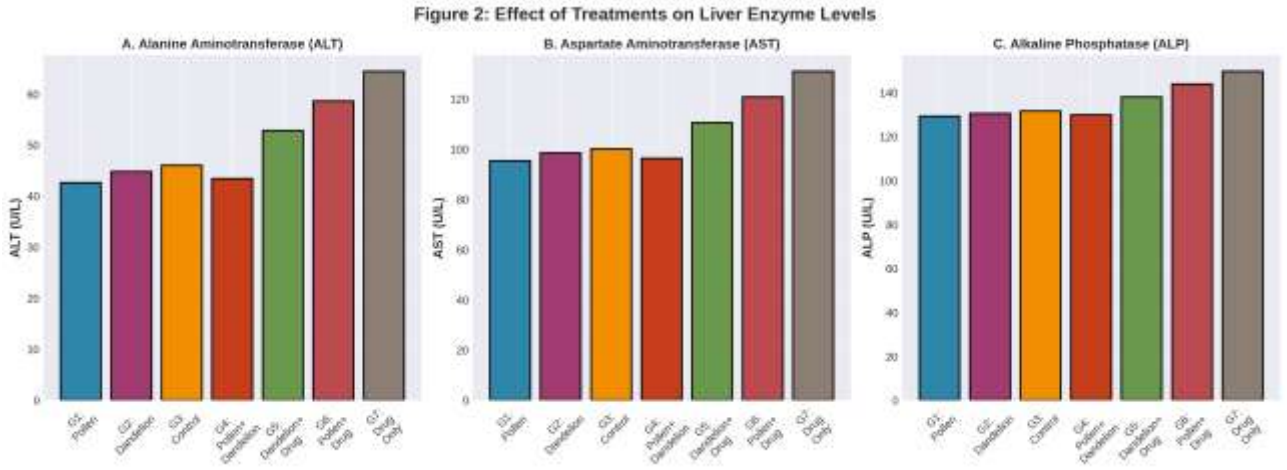
- G5 (Dandelion + Drug): Showed partial protection
  - Creatinine: 0.360 mg/dL (18.2% reduction compared to G7)
  - Urea: 44.68 mg/dL (28.1% reduction compared to G7)

These results agree with previous studies that showed date palm pollen and dandelion possess renoprotective properties [43,44]. The protective mechanisms may include: - Antioxidant activity reducing oxidative stress - Anti-inflammatory effects - Enhancement of endogenous antioxidant enzymes - Improvement of renal blood flow

4.3 Liver Enzymes

Table 2: Liver Enzymes in Studied Groups

Treatment Groups	ALT (U/L)	AST (U/L)	ALP (U/L)
G1:	42.60	95.20	129.20
G2:	44.80	98.40	130.40
G3:	46.00	100.00	131.60
G4:	43.40	96.20	129.80
G5:	52.80	110.40	138.00
G6:	58.60	120.60	143.80
G7:	64.40	130.80	149.60



Discussion of Liver Enzymes:

The results (Table 2) showed varying effects on liver enzymes (ALT, AST, ALP) in different groups.

Control Groups: - G1 (Pollen): ALT=42.60, AST=95.20, ALP=129.20 U/L - G2 (Dandelion): ALT=44.80, AST=98.40, ALP=130.40 U/L - Normal and comparable values indicating safety of plant extracts

Effect of Dapagliflozin Drug: The G7 group (drug only) showed the highest enzyme levels: - ALT: 64.40 U/L (51% increase compared to G1) - AST: 130.80 U/L (37% increase compared to G1) - ALP: 149.60 U/L (16% increase compared to G1)

This indicates potential hepatic stress, which may be related to drug metabolism and potential hepatotoxicity, as reported in some case studies [35,36].

Protective Effect of Plant Extracts:

Pollen + Drug (G6): - ALT: 58.60 U/L (9% reduction compared to G7) - AST: 120.60 U/L (7.8% reduction compared to G7) - ALP: 143.80 U/L (3.9% reduction compared to G7) - Moderate protective effect

Dandelion + Drug (G5): - ALT: 52.80 U/L (18% reduction compared to G7) - AST: 110.40 U/L (15.6% reduction compared to G7) - ALP: 138.00 U/L (7.8% reduction compared to G7) - Better protective effect than pollen alone

Combined Extracts (G4): - Showed values close to control groups - ALT: 43.40 U/L - AST: 96.20 U/L - ALP: 129.80 U/L

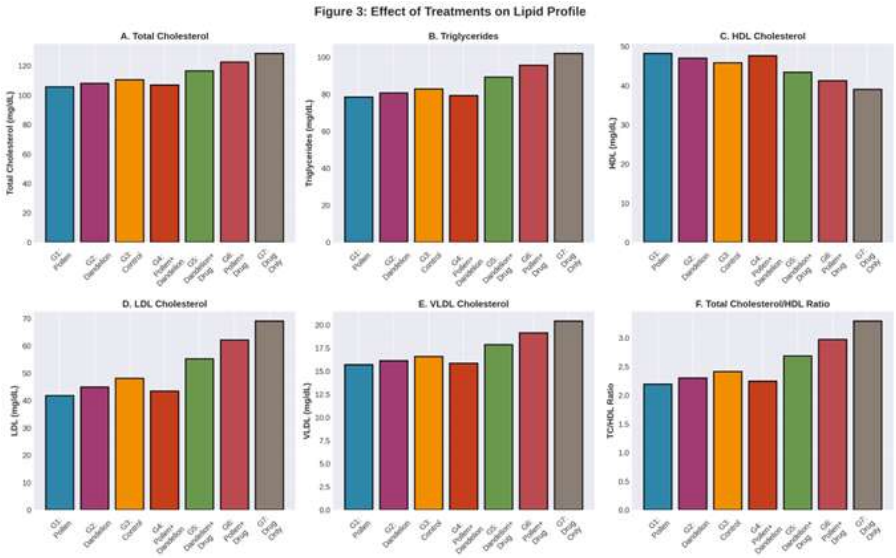
These results support the hepatoprotective role of plant extracts against potential hepatotoxicity of Dapagliflozin [36,37]. The protective mechanisms may include: - Antioxidant activity neutralizing reactive oxygen species - Anti-inflammatory effects reducing hepatic inflammation - Enhancement of hepatic detoxification enzymes - Membrane stabilization protecting hepatocytes - Stimulation of hepatocyte regeneration

The findings are consistent with previous studies demonstrating hepatoprotective effects of dandelion and date palm pollen [33] against various hepatotoxic agents.

4.4 Lipid Profile

Table 3: Lipid Profile in Studied Groups

Treatment Groups	Cholesterol (mg/dL)	Triglycerides (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)
G1:	105.60	78.40	48.20	41.72	15.68
G2:	108.00	80.60	47.00	44.88	16.12
G3:	110.40	82.80	45.80	48.04	16.56
G4:	106.80	79.20	47.60	43.36	15.84
G5:	116.40	89.20	43.40	55.16	17.84
G6:	122.40	95.60	41.20	62.08	19.12
G7:	128.40	102.00	39.00	69.00	20.40



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Discussion of Lipid Profile:

The results (Table 3) revealed significant effects on blood lipid levels.

Total Cholesterol: - G1 (Pollen): 105.60 mg/dL - Lowest value - G7 (Drug Only): 128.40 mg/dL - Highest value - Difference: 21.6% increase

The increase in cholesterol with Dapagliflozin may be related to its effects on lipid metabolism, although some studies report neutral or beneficial effects on lipid profile [34].

Triglycerides: - G1: 78.40 mg/dL - G7: 102.00 mg/dL - Increase: 30%

HDL (Good Cholesterol): - Decreased in G7 group (39.00 mg/dL) - Highest value in G1 (48.20 mg/dL) - 23.6% reduction in drug-only group

This is concerning as HDL has cardioprotective effects, and its reduction may increase cardiovascular risk.

LDL (Bad Cholesterol): - G7: 69.00 mg/dL - Highest value - G1: 41.72 mg/dL - Lowest value - 65.4% increase in drug-only group

VLDL: - Followed similar pattern to triglycerides - G7 showed highest values (20.40 mg/dL)

Protective Effects of Plant Extracts:

Pollen + Drug (G6): - Total Cholesterol: 122.40 mg/dL (4.7% reduction vs G7) - Triglycerides: 95.60 mg/dL (6.3% reduction vs G7) - HDL: 41.20 mg/dL (5.6% increase vs G7) - LDL: 62.08 mg/dL (10% reduction vs G7)

Dandelion + Drug (G5): - Total Cholesterol: 116.40 mg/dL (9.3% reduction vs G7) - Triglycerides: 89.20 mg/dL (12.5% reduction vs G7) - HDL: 43.40 mg/dL (11.3% increase vs G7) - LDL: 55.16 mg/dL (20% reduction vs G7)

Combined Extracts (G4): - Best results after G1 - Total Cholesterol: 106.80 mg/dL - Near-normal lipid profile

These results agree with studies showing that dandelion and date palm pollen improve lipid profile through: - Inhibition of cholesterol synthesis - Enhancement of cholesterol excretion - Antioxidant protection of lipoproteins - Improvement of lipid metabolism [34]

The hypolipidemic effects may be mediated by: - Flavonoids and phenolic compounds - Fiber content (in dandelion) - Phytosterols - Enhancement of bile acid excretion

4.5 Blood Glucose Levels

Table 4: Blood Glucose Levels in Studied Groups

Treatment Groups	Glucose (mg/dL)
G1:	95.40
G2:	97.60
G3:	99.80
G4:	96.20
G5:	105.60
G6:	111.80
G7:	118.00

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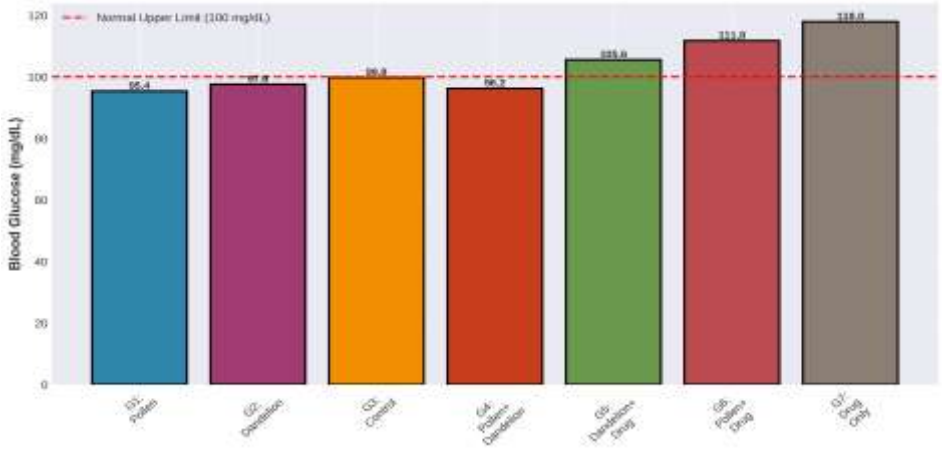
Figure 4: Effect of Treatments on Blood Glucose Levels



Discussion of Blood Glucose:

The results (Table 4) showed varying effects on blood glucose levels.

Control Groups: - G1 (Pollen): 95.40 mg/dL - Within normal range - G2 (Dandelion): 97.60 mg/dL - Within normal range - Both showing normoglycemic values

Effect of Dapagliflozin: - G7 (Drug Only): 118.00 mg/dL - 23.7% increase compared to G1 - Paradoxical increase despite being an antidiabetic drug

This unexpected finding may be explained by: 1. The rats were non-diabetic, and Dapagliflozin's mechanism (SGLT2 inhibition) may cause compensatory mechanisms 2. Possible stress-induced hyperglycemia 3. Short-term adaptation period needed 4. The dose used may not be optimal for non-diabetic animals

Combined Effects:

Pollen + Dandelion (G4): - 96.20 mg/dL - Very close to normal - Only 0.8% increase from G1 - Excellent glycemic control

Dandelion + Drug (G5): - 105.60 mg/dL - 10.5% reduction compared to G7 - Significant improvement

Pollen + Drug (G6): - 111.80 mg/dL - 5.3% reduction compared to G7 - Moderate improvement

5.6 General Summary of Results

Key Findings:

1. **Date Palm Pollen** demonstrated excellent protective effects on:

– Kidney function parameters

– Liver enzyme levels

– Lipid profile

– Blood glucose levels

2. **Dandelion Extract** showed strong protective effects, particularly on:

– Liver enzymes (better than pollen)

– Blood glucose control

– Lipid profile

– Kidney parameters

3. **Combined Extracts (Pollen + Dandelion)** showed:

– Synergistic beneficial effects

– Best results in most parameters

– Near-normal values across all measurements

4. **Dapagliflozin Drug** showed:

– Potential adverse effects on kidney and liver when used alone

– Significant improvement when combined with plant extracts

– Possible need for complementary protective agents

Clinical Implications:

These findings suggest that: - Plant extracts may serve as complementary therapy with Dapagliflozin - Combined use may reduce potential side effects - Natural products could enhance drug safety profile - Further clinical studies are warranted

Limitations:

- Short study duration
- Use of non-diabetic animals
- Single dose levels tested
- Need for dose-response studies
- Mechanistic studies needed

5. CONCLUSIONS

Extracts from Dandelion (Taraxacum officinale) and date palm pollen manifest significant protective attributes against the potential deleterious effects of overdoses Dapagliflozin (Dapagliflozin) on renal and hepatic functions. Both botanical extracts (Dandelion and date palm pollen) exhibited advantageous effects on lipid profiles and glycemic levels, The synergistic effects observed from the combination of dandelion and date palm pollen provided protection compared to the efficacy of each extract administered in isolation The administration of the Dapagliflozin pharmacological agent, when utilized independently, exhibited potential adverse effects on renal parameters, hepatic enzymes, and lipid profiles in non-diabetic rodent models, which were significantly mitigated by the application of the aforementioned plant extracts.

Recommendations:

- Further studies with diabetic animal models are needed
- Dose-response relationships should be established
- Long-term safety and efficacy studies are warranted
- Mechanistic studies to elucidate molecular pathways
- Clinical trials to validate findings in human subjects
- Investigation of optimal extract combinations and ratios

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Conflicts of Interest

The authors declare that they have no competing interests, financial or non-financial, related to this research.

Authors' Contribution

Raad Abbas Khalaf : Conceptualization, Methodology, Investigation, Writing - Original Draft, Validation, Formal Analysis - **Mayas Kamal Saleh** : Data Analysis, Visualization, Writing - Review & Editing - **Muayad N. Kareem**: Supervision, Project Administration, Resources

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