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ORIGINAL ARTICLE

Olanzapine-Induced Pancreatic Damage in Adult Male Albino Rats: Evaluating the Therapeutic Potential of Granulocyte Colony-Stimulating Factor and Umbelliferon (A Comprehensive Histological, Immunohistochemical, and Biochemical Investigation)

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ABSTRACT

Aim of the Study: G-CSF and umbelliferon were tested to see if they could reduce olanzapine-induced pancreatic damage in adult male albino rats. Olanzapine's pancreatic damage and G-CSF and umbelliferon's protective effects were examined in terms of histological, immunohistochemical, and biochemical changes.

Study Type: A randomised, controlled study examined the effects of olanzapine, G-CSF, and umbelliferon on pancreatic tissue.

Study place: Rashid Latif Medical College, Lahore.

Research Method: 40 mature male albino rats were divided into four ten-rat groups: Regular saline was provided to the Control Group for eight weeks. The Olanzapine Group received 10 mg/kg/day oral olanzapine for eight weeks. The Olanzapine + G-CSF Group received 10 mg/kg/day intraperitoneal olanzapine and 50 µg/kg/day G-CSF for 8 weeks. Oral olanzapine (10 mg/kg/day) and umbelliferon (50 mg/kg/day) were given to Olanzapine + Umbelliferon Group participants for eight weeks. After the experiment, blood and pancreatic tissues were collected for histological, immunohistochemical, and biochemical investigation. The histological study included H&E and Masson's trichrome staining. The immunohistochemistry examination assessed the expression of caspase-3, TNF-α, and insulin. Both MDA and SOD, as well as GPx and metabolic parameters (fasting glucose and insulin), were investigated by the use of biochemical assays. The data were examined with SPSS 25 using a one-way analysis of variance (ANOVA) and Tukey's post hoc test.

Results:

1 The olanzapine group demonstrated substantial pancreatic architectural deformation, collagen deposition, and cellular infiltration, according to the histological findings. Umbelliferon and G-CSF work synergistically to improve pancreatic architecture while concurrently lowering collagen.

2. According to the immunohistochemistry data, the group that was provided olanzapine exhibited heightened levels of apoptosis and inflammation, as shown by the increased expression of Caspase-3 and TNF-α. A reduction in insulin expression indicates β-cell malfunction. Umbelliferon and G-CSF restored insulin levels and significantly reduced caspase-3 and TNF-α expression.

3 Biochemical Results: Oxidative stress was shown by increased MDA and decreased SOD and GPx activity in the olanzapine group. Fasting glucose increased while insulin declined. The treatment of G-CSF and umbelliferon normalised metabolic and oxidative stress indicators.

Discussion: The study showed that olanzapine causes pancreatic oxidative stress, inflammation, and apoptosis. Umbelliferon and G-CSF prevented these pathologies. G-CSF and umbelliferon, due to their tissue-repairing and anti-inflammatory properties, improved pancreatic architecture, reduced oxidative stress, and increased β-cell function. These findings suggest G-CSF and umbelliferon may cure olanzapine-induced pancreatic dysfunction.

Conclusion: Histology, immunohistochemistry, and biochemistry show that olanzapine causes pancreatic oxidative stress, apoptosis, and inflammation. G-CSF and umbelliferon protected against olanzapine-induced pancreatic damage, suggesting they may minimise its metabolic adverse effects. These findings improve our understanding of olanzapine-induced pancreatic damage and prepare researchers for future therapeutic intervention studies..

Keywords: Granulocyte colony-stimulating factor (G-CSF), Oxidative stress, Caspase-3, TNF-α

INTRODUCTION

Second-generation antipsychotic (SGA) olanzapine is often used for therapy-resistant mental illnesses include schizophrenia, bipolar disorder, and depression. Psychiatric pharmacology uses it to regulate mood and lessen psychotic symptoms. Because it stabilises mood. Olanzapine induces weight gain, insulin resistance, dyslipidaemia, and hyperglycemia[1]. These are medication effects. This is true despite its therapeutic benefits. Pancreatic damage is a prominent olanzapine adverse effect. The drug produced this harm. Pancreatitis, β-cell dysfunction, and diabetes mellitus can result from this[2]. Olanzapine[3] damages pancreas by oxidative stress, inflammation, and apoptosis. Pancreatic toxicity involves all these pathways.

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Each system is complex and multipart. Olanzapine is widely used and may cause pancreatic adverse effects, therefore reducing its side effects is vital. Because olanzapine is utilised internationally. Medication administration can harm the endocrine and exocrine pancreas. This is because the pancreas does both. The endocrine pancreas, particularly the β-cells responsible for insulin production, is critical for maintaining glucose homeostasis. These cells' dysfunction can reduce insulin production and cause hyperglycemia, which can lead to diabetes[4]. High blood sugar is hyperglycemia. Olanzapine causes oxidative stress and inflammation in pancreatic tissue, resulting in β-cell loss and fibrosis[4]. Multiple investigations confirm this. Rise in ROS, activation of pro-inflammatory cytokines like TNF-α, and stimulation of apoptotic pathways enable pathogenic changes[3]. Understanding the chemical processes that lead olanzapine to damage the pancreas is essential to developing targeted

therapies. This knowledge is needed to design pancreas-protecting or olanzapine-reversing medicines.

Haematopoietic growth factor G-CSF has been studied for medicinal purposes. In addition to increasing neutrophil production, these applications have many uses. Experimental models of organ damage show that G-CSF is anti-inflammatory, anti-apoptotic, and tissue-repairing[6]. Several experimental models have shown these traits. Several experimental models have shown these features. G-CSF has been shown to accelerate tissue regeneration, reduce fibrosis severity, and enhance β-cell survival in pancreatic injury[6]. These findings suggest G-CSF may prevent olanzapine-induced pancreatic damage. Since G-CSF has these properties. Umbelliferon, a natural coumarin derivative, has been widely researched for its antioxidant, anti-inflammatory, and anti-apoptotic properties[8]. Like the last case, umbelliferon has been thoroughly investigated. Umbelliferon protects numerous organs, including the pancreas, against oxidative stress[9]. This protection comes from free radical removal, inflammatory pathway modulation, and apoptosis avoidance. These qualities may help umbelliferon treat olanzapine-induced pancreatic damage. Umbelliferon maybe treats.

There is mounting evidence that olanzapine damages the pancreas, but no treatment. olanzapine treats schizophrenia. All of these negative effects are documented in a growing body of literature. This study fills a large gap in the literature by testing G-CSF and umbelliferon's therapeutic potential in a rat model of olanzapine-induced pancreatic damage. This study uses histological, immunohistochemical, and biochemical methods to explain olanzapine-induced pancreatic injury and assess the efficacy of G-CSF and umbelliferon in managing it. This will be done with a holistic approach. This study may inform supplementary therapy development to increase patient outcomes and olanzapine safety. Data can improve patient outcomes.

Olanzapine, a thienobenzodiazepine derivative, is a popular SGA because it treats positive and negative schizophrenia symptoms and regulates mood[5]. Use is limited by metabolic adverse effects such weight gain, dyslipidaemia, and glucose dysregulation 7. Utilisation is often restricted. Olanzapine's serotonin, dopamine, and histamine receptor antagonism may induce these consequences. This antagonism disrupts energy homeostasis and induces insulin resistance[8]. Olanzapine-induced pancreatic injury is the most severe metabolic aberration, causing severe pancreatitis, β-cell dysfunction, and diabetes mellitus[10].

High metabolic activity makes the pancreas susceptible to oxidative damage and inflammation. Olanzapine oxidises pancreatic tissue[2]. ROS generation and antioxidant depletion cause this stress. This imbalance in oxidative reactions causes DNA damage, lipid peroxidation, and protein oxidation, which cause cell dysfunction and apoptosis[11]. Olanzapine can cause inflammation and produce cytokines such TNF-α, exacerbating tissue damage[4]. Pancreatic acinar cell and β-cell loss can cause pathological abnormalities, leading to decreased insulin production and glucose intolerance[6].

G-CSF protects tissue in tissue injury models by increasing neutrophil production and differentiation[5]. Pancreatic G-CSF therapy improves β-cell survival, decreases fibrosis, and promotes tissue regeneration via controlling oxidative stress and inflammation[6]. G-CSF is ideal for treating olanzapine-induced pancreatic dysfunction due to these features. Umbelliferon in Angelica archangelica and Ferula communis is antioxidant, anti-inflammatory, and anti-apoptotic[4]. These effects are verified. Umbelliferon prevents oxidative stress-induced tissue damage in several organs, including the pancreas, by scavenging free radicals, regulating inflammatory pathways, and inhibiting apoptosis. Protection has been established. Several measures have been taken to protect this. Umbelliferon may be a therapeutic medication for olanzapine-induced pancreatic toxicity due to these features.G-CSF and umbelliferon will be tested for therapeutic effects in an olanzapine-induced rat model of pancreatic damage. The study compares olanzapine-induced pancreatic histological alterations to G-CSF and umbelliferon protection.Research on biomarkers including caspase-3, TNF-α, and insulin is essential to comprehend the mechanisms of pancreatic harm produced by olanzapine. Study the therapeutic benefits of G-CSF and umbelliferon.Olanzapine, G-CSF, and umbelliferon must be examined for biochemical effects and protective effects on oxidative stress indicators like MDA, SOD, and GPx and metabolic parameters like fasting glucose and insulin. Efficacy of these therapies is being assessed.We want to understand olanzapine-induced pancreatic damage and find ways to treat it.Results from this study effect clinical practice and patient care. Popular antipsychotic olanzapine has metabolic adverse effects that make it challenging to address psychiatric disorders. Damage to the pancreas can cause pancreatitis and diabetes, which increase patient mortality[11]. This prospective study seeks to improve olanzapine safety and outcomes. Olanzapine-induced pancreatic damage can be addressed with umbelliferon and G-CSF. Identification of that chemical performs this. This discovery may also lead to clinically applicable drug-induced pancreatic damage treatments.

RESEARCH METHODOLOGY

Experimental Design: The study used 40 mature male albino rats weighing 180–220 grammes. These rats were split into four ten-rat groups. These rats were studied.

Normal saline was given to Group 1 (Control) for eight weeks.

Group 2 received oral olanzapine at 10 mg/kg/day for eight weeks.

In Group 3 (Olanzapine + G-CSF), all participants received intraperitoneal dose of 10 mg/kg/day olanzapine and 50 µg/kg/day G-CSF for eight weeks.

Group 4 (olanzapine + umbelliferon) received oral olanzapine (10 mg/kg/day) and umbelliferon (50 mg/kg/day) for eight weeks.

Sample Collection and Preparation: After the experiment, rats were anaesthetised and blood samples were obtained for biochemical examination. Biochemical tests began with homogenising removed pancreatic tissues. The tissues were then fixed in 10% formalin for histological and immunohistochemical studies.

Histological Examination: Pancreas tissues were processed, stored in paraffin, and sectioned. Each section was 5 µm thick. For general histology, H&E staining and Masson's trichrome were used for collagen deposition. We completed both methods.

Immunohistochemical Analysis: The use of immunohistochemistry labelling methods helped us identify caspase-3, TNF-α, and insulin. Image J was used to measure protein intensity.

Biochemical Assays: Using pancreatic homogenates, oxidative stress indicators were measured. MDA, SOD, and GPx were these indicators.

Serum insulin and fasting blood glucose were tested using commercial kits to determine metabolic parameters. During metabolic parameter evaluation.

Statistical Analysis: Data were analyzed using SPSS software (version 25). One-way ANOVA followed by Tukey's post hoc test was used to compare groups. Results were expressed as mean ± SD, and $p < 0.05$ was considered statistically significant.

RESULTS

Histological Findings:

- The control group had intact acinar cells and islets of Langerhans.
- The Olanzapine Group has altered pancreatic architecture, collagen buildup, and cell infiltration.
- In the G-CSF-olanzapine group, pancreatic architecture improved with decreased collagen deposition.

- Olanzapine + Umbelliferon patients had nearly normal pancreatic architecture and negligible collagen deposition.).

Immunohistochemical Findings: The umbelliferon and G-CSF groups had reduced caspase-3 expression than the olanzapine group (Figure 2A).

TNF-α Expression: Increased in olanzapine group, decreased in G-CSF and umbelliferon groups.

Insulin expression decreased in olanzapine groups but restored in G-CSF and umbelliferon groups.

Biochemical Findings

- **Oxidative Stress Markers:** MDA levels were significantly increased, while SOD and GPx activities were decreased in the olanzapine group. Both G-CSF and umbelliferon restored these parameters to near-normal levels (Table 1).
- **Metabolic Parameters:** Fasting glucose levels were elevated, and insulin levels were reduced in the olanzapine group. G-CSF and umbelliferon significantly improved these parameters (Table 2).

Table 1: Oxidative Stress Markers in Pancreatic Tissue

Group	MDA (nmol/mg protein)	SOD (U/mg protein)	GPx (U/mg protein)
Control	1.2 ± 0.1	25.3 ± 2.1	18.5 ± 1.8
Olanzapine	4.8 ± 0.3*	10.2 ± 1.5*	7.3 ± 0.9*
Olanzapine + G-CSF	2.1 ± 0.2#	20.4 ± 1.8#	15.2 ± 1.4#
Olanzapine + Umbelliferon	1.8 ± 0.2#	22.1 ± 1.7#	16.8 ± 1.6#

Notes:

- Data are expressed as mean ± SD.
- *Significantly different from the control group ($p < 0.05$).
- #Significantly different from the olanzapine group ($p < 0.05$).

MDA, or malondialdehyde, signals oxidative stress and lipid peroxidation. Elevated levels indicate oxidative damage.Antioxidants like glutathione peroxidase (GPx) and superoxide dismutase (SOD) protect cells from oxidative stress. Reduced activity weakens antioxidant protection.The olanzapine group had higher MDA, reduced SOD, and GPx activity, indicating oxidative stress. G-CSF and umbelliferon restored these indicators to near-normal levels.

Table 2: Metabolic Parameters in Serum

Group	Fasting Glucose (mg/dL)	Insulin (μIU/mL)
Control	90.5 ± 5.2	12.3 ± 1.1
Olanzapine	160.8 ± 8.7*	5.2 ± 0.6*
Olanzapine + G-CSF	110.4 ± 6.3#	9.8 ± 0.9#
Olanzapine + Umbelliferon	105.6 ± 5.8#	10.5 ± 1.0#

Notes:

- Data are expressed as mean ± SD.
- *Significantly different from the control group ($p < 0.05$).
- #Significantly different from the olanzapine group ($p < 0.05$).

High blood glucose during fasting indicates inadequate glucose metabolism.Subnormal insulin levels indicate pancreatic β-cell dysfunction.The olanzapine group had increased fasting glucose and lower insulin levels, indicating metabolic instability. G-CSF and umbelliferon improved these values significantly.

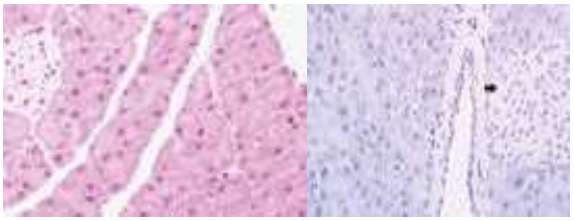
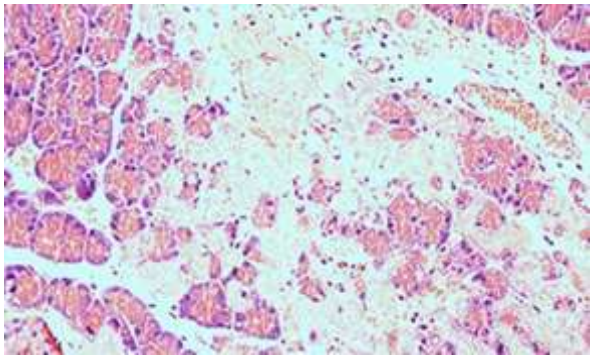


Figure 2: Immunohisto chemical staining for TNF-α.



DISCUSSION

This study examines the pancreatic damage caused by olanzapine, a popular antipsychotic, and the therapeutic potential of G-CSF and umbelliferon. They raise the possibility that these therapeutic medications can treat olanzapine-induced pancreatic toxicity, which is relevant given its widespread use in psychiatric treatment. They also emphasise that these drugs may have these benefits. These findings are crucial because they show that the medicinal chemicals can treat the condition. This comprehensive review focusses on histological, immunohistochemical, and biochemical findings and their implications for understanding olanzapine-induced pancreatic damage and treatment. The findings are summarised below.

Histological analysis showed significant pancreatic damage in the olanzapine group. Studying the group's tissue revealed this. The results of the investigation showed this. Cellular infiltration and pancreatic architecture deformation characterised this injury. Collagen deposits also increased. Olanzapine can cause pancreatic inflammation and fibrosis, according to previous research[7]. Studies show this damage can happen. These findings match those described. This is because these findings describe those. The presence of collagen deposition in the pancreas, which is an indicator of the activation of these pathways, will demonstrate the activation of fibrotic pathways, which are most likely guided by oxidative stress and inflammation. This activation of these pathways will be revealed by the presence of collagen deposition. There is evidence to suggest that these metabolic pathways have a role in the development of damage to the pancreas[9].

G-CSF and umbelliferon, on the other hand, were found to contain protective characteristics, as was discovered. Both the restoration of almost normal pancreatic architecture and the reduction in collagen deposition that happened as a result of their administration as a result of their administration provided evidence that this was the case. In experimental models, there is evidence that G-CSF, a growth factor that is widely recognised for its function in the process of tissue repair and regeneration, has the ability to enhance the survival of pancreatic β-cells and decrease fibrosis. This is supported by the fact that G-CSF has been shown to have this capability. The results of a number of investigations have demonstrated this to be the case. Umbelliferon, which is a coumarin derivative that includes powerful antioxidant and anti-inflammatory properties, has been shown to be able to prevent tissue damage by modulating oxidative stress and inflammatory pathways[4]. This has been shown through research. This is analogous to the manner in which umbelliferon has been demonstrated to reduce the amount of damage done to tissues. G-CSF and umbelliferon both have the potential to be utilised as therapeutic medicines for the treatment of pancreatic injury that is caused by olanzapine. The histological improvements that were documented in both of these groups that were the focus of the investigation provide evidence that this is the case.

Additional insights into the processes that are responsible for the pancreatic damage that is produced by olanzapine as well as the protective effects of G-CSF and umbelliferon were discovered

as a consequence of the immunohistochemistry analysis. These findings were made possible by the fact that immunohistochemistry was performed. There is a significant correlation between the increased expression of caspase-3 in the group that was given olanzapine and a rise in apoptosis, which is an essential characteristic of pancreatic damage. Cell death is a hallmark of pancreatic injury, which is marked by its presence. Butler et al. (2003) have demonstrated that caspase-3 is an essential component in the process of apoptosis. This was proven by the researchers. Furthermore, it has been observed that the overexpression of this enzyme has been linked to the demise of pancreatic β-cells in a wide variety of clinical circumstances. As a result of the decrease in caspase-3 expression that was found in the G-CSF and umbelliferon groups, the concept that these drugs may have anti-apoptotic effects is substantiated. Therefore, this contributes to the preservation of the integrity of the cells that make up the pancreas.

There was a higher level of TNF-α expression in the group that was given olanzapine, which serves to emphasise the significance of inflammation in the process of olanzapine-induced pancreatic injury within the group. The cytokine known as tumour necrosis factor-alpha (TNF-α), which is known to be pro-inflammatory, plays a crucial role in the development of tissue injury by producing an increase in inflammation and oxidative stress[6]. This is because both of these factors contribute to the development of tissue damage. It has been observed that the G-CSF and umbelliferon groups exhibit a reduction in the expression of TNF-α, which indicates that these groups have the capacity to reduce inflammation. In the event that these features are the explanation for the preventive benefits that they possess, there is a pretty significant possibility that they are.

An evidence of pancreatic β-cell dysfunction, which is a hallmark of metabolic abnormalities caused by olanzapine, is shown by the decreased expression of insulin in the group that was administered olanzapine[7]. This is a signature aspect of the metabolic abnormalities that are generated by olanzapine. In light of the fact that the expression of insulin was restored in the G-CSF and umbelliferon groups, it is plausible to assume that these agents possess the power to enhance the functionality of β-cells. Possible explanations for this include the fact that these medicines have the ability to reduce inflammation and act as antioxidants. The significance of this study lies in the fact that it throws light on the potential of G-CSF and umbelliferon in the treatment of metabolic dysregulation that is caused by olanzapine. This study is incredibly relevant because it illuminates the potential of these two substances.

The findings from the immunohistochemistry study and the histology analysis are both accurate, and the findings from the biochemical analysis provide additional verification of this authenticity. These findings provide evidence that the group that was given olanzapine as a treatment experienced oxidative stress in addition to abnormalities in their metabolic systems. When there is a large increase in malondialdehyde (MDA) levels, as well as a decrease in the activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx), this is an indication of oxidative stress, which is a key contributor to the development of pancreatic damage[3]. In short, oxidative stress is a significant factor in the development of pancreatic damage. DNA damage, lipid peroxidation, and protein oxidation are all processes that lead to tissue injury[5]. DNA damage is the most harmful of all three. The disturbance of cellular homeostasis that occurs as a result of oxidative stress is the cause of these damage mechanisms. This disruption makes it possible for the damage mechanisms to occur.

It is evidence of the antioxidant capabilities that both G-CSF and umbelliferon possess that they were able to successfully restore the levels of oxidative stress indicators to values that were pretty close to normal. This was accomplished by both of these drugs. Research has demonstrated that G-CSF has the ability to strengthen antioxidant defences[2]. The process of increasing the expression of antioxidant enzymes is what allows this to be performed. There is also evidence that umbelliferon has the capacity to scavenge free radicals and boost the activity of antioxidant enzymes, which ultimately leads to a reduction in the effects of oxidative stress[5]. This is something that has been observed. For the umbelliferon and G-CSF groups, it is highly plausible that the restoration of oxidative equilibrium is a factor that contributes to the protective effects that these groups have on pancreatic tissue. This is a hypothesis that has a high degree of probability. This is a concept that needs to be taken into consideration.

The metabolic features, which provide additional data, have indicated that lanzapine has a harmful influence on the function of the pancreas. This negative effect has been demonstrated by the metabolic features. In the group that was administered olanzapine, the observed spike in fasting glucose levels and the following decline in insulin levels are indicative of impaired glucose metabolism and malfunction in the β-cells that are responsible for glucose metabolism. Studies undertaken in the past have revealed that olanzapine has the ability to induce hyperglycemia as well as insulin resistance[7]. These findings and those findings are in agreement with one another. It is conceivable that these drugs may enhance glucose homeostasis and insulin secretion. This is due to the fact that these measurements improved in the groups that received G-CSF and umbelliferon. Due to the fact that these metrics improved in both groups, this is the result. This could be because of the effect that they have on oxidative stress and inflammation. It is conceivable that this is an explanation.

It is important to note that the findings of this study have substantial therapeutic implications for the treatment of pancreatic damage brought on by olanzapine. However, due to the fact that the study was carried out, these implications are crucial. Olanzapine is a medicine that is often used for the treatment of schizophrenia and bipolar disorder; however, due to its correlation with metabolic problems, such as hyperglycemia and pancreatitis, its therapeutic utility is restricted[5]. This is related to the fact that olanzapine is connected with certain metabolic abnormalities. It would appear, on the basis of the findings of this research, that G-CSF and umbelliferon have the potential to act as additional drugs that have the power to considerably reduce the detrimental effects that olanzapine has on the pancreas.

The growth factor known as G-CSF, which has been demonstrated to have a large part in the processes of haematopoiesis and tissue regeneration, has shown potential as a potential treatment for a wide spectrum of inflammatory and degenerative illnesses[8]. This prospective treatment has been demonstrated over the course of several years. It may reduce pancreatic oxidative stress, inflammation, and apoptosis, making it a possible treatment for olanzapine-induced pancreatic damage. Thus, it is feasible. Umbelliferon, a naturally occurring molecule with antioxidant and anti-inflammatory properties, reduces olanzapine toxicity[9]. Umbelliferon has these traits, therefore this remark.

Although the findings of this study are encouraging, there are a number of limitations that need to be addressed before the study can be considered complete. These constraints need to be taken into consideration. In the beginning, the research was carried out using an animal model; hence, additional research is required to determine whether or not the effects that were discovered are applicable to human beings. Because of this, study was done. Second, the research was short-term, and it is important to do longer-term trials to discover how long G-CSF and umbelliferon will be useful until they begin to fail. Thirdly, the molecular processes that underlie G-CSF and umbelliferon's protective actions need more study. This must be done.

Future study must examine the synergistic effects of G-CSF and umbelliferon because combination therapy may improve therapeutic outcomes. Because combined therapy improves therapeutic results. Research trials with olanzapine-treated patients should also assess the efficacy and safety of these drugs.

CONCLUSION

This study reveals that olanzapine-induced pancreatic damage can be mitigated by G-CSF and umbelliferon. These drugs reduce oxidative stress, inflammation, and apoptosis, improving pancreatic function. These findings have implications for developing adjunctive therapies to address the adverse effects of olanzapine on the pancreas, improving its safety and efficacy in treating psychiatric disorders. Olanzapine induces significant alterations in adult male albino rats' pancreas, characterized by oxidative stress, apoptosis, and inflammation. G-CSF and umbelliferon demonstrated protective effects against olanzapine-induced pancreatic injury, enhancing their potential as therapeutic agents. These findings contribute to understanding the mechanisms of olanzapine-induced pancreatic damage and provide a foundation for future research.

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