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Protective effects of *Saussurea lappa* root aqueous extract against Tamoxifen-induced pancreatic injury in female rats

Eman Ali Farag Hamouda[1]*, Abdulkarem A. Ilfergane[2]
[1]Department of Zoology, Faculty of Humanities and Applied Sciences, University of Benghazi, Tocra, Libya
[2]Department of Zoology, Faculty of Science, University of Benghazi, Benghazi, Libya
*Corresponding author: eali40411@gmail.com

Abstract

Tamoxifen (TAM), a selective estrogen receptor modulator (SERM) widely used in breast cancer therapy, is associated with oxidative stress, dyslipidemia, and pancreatic toxicity. *Saussurea lappa* (*S. lappa*), a traditional medicinal plant, possesses antioxidant, anti-inflammatory, and metabolic regulatory properties. This study aimed to evaluate the protective effects of an aqueous extract of *S. lappa* root (AESL) against tamoxifen-induced pancreatic injury in female rats. Twenty-four female rats were divided into four groups: Control, AESL (200 mg/kg), tamoxifen (TMX, 40 mg/kg), and TMX + AESL, with oral administration for 28 days. Serum levels of amylase, lipase, triglycerides, free fatty acids, glucose, and insulin were measured, and pancreatic tissues were examined histologically. Tamoxifen treatment significantly increased serum amylase, lipase, triglycerides, free fatty acids, and glucose, while decreasing insulin levels compared to controls ($p < 0.001$). Co-treatment with AESL significantly reversed these biochemical alterations and improved pancreatic histology. These findings suggest that AESL exerts potent protective effects against TMX-induced pancreatic damage, potentially through antioxidant and insulin-sensitizing mechanisms, highlighting its potential as a phytotherapeutic agent for pancreatic protection.

Keywords*:* Pancreatic injury; Rat; *Saussurea lappa* roots aqueous.

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التأثير الوقائي للمستخلص المائي لجذور نبات القسط الهندي ضد الإصابة البنكرياسية المستحثة بعقار التاموكسيفين في إناث الجرذان

إيمان علي فرج حموده[1]*، عبد الكريم عبدالله عمر الفرجاني[2]

[1]قسم علم الحيوان، كلية العلوم الإنسانية والتطبيقية، جامعة بنغازي، توكرة، ليبيا.

[2]قسم علم الحيوان، كلية العلوم، جامعة بنغازي، بنغازي، ليبيا.

*البريد الإلكتروني للمؤلف المسؤول eali40411@gmail.com

الملخص

يُعد التاموكسيفين من معدِّلات مستقبلات الإستروجين الانتقائية(SERM) ، ويُستخدم على نطاق واسع في علاج سرطان الثدي. ومع ذلك، قد يؤدي استخدامه إلى الإجهاد التأكسدي، واضطرابات الدهون في الدم، وسمّية في البنكرياس. يُعرف نبات القسط الهندي (*Saussurea lappa*)، وهو نبات طبي تقليدي، بخصائصه المضادة للأكسدة، والمضادة للالتهاب، والمنظِّمة للأيض. هدفت هذه الدراسة إلى تقييم التأثير الوقائي للمستخلص المائي لجذورنبات القسط الهندي (AESL) ضد إصابة البنكرياس المستحثة بالتاموكسيفين (TMX) في إناث الجرذان. تم تقسيم أربع وعشرين أنثى جرذ بشكل عشوائي إلى أربع مجموعات: مجموعة ضابطة، ومجموعة المستخلص المائي النباتيAESL (200 ملغ/كغ) ، ومجموعةTMX (40 ملغ/كغ)، ومجموعة (TMX + AESL) تم إعطاء جميع المواد عن طريق الفم لمدة 28 يومًا. تم قياس إنزيمات الأميلاز والليباز، والدهون الثلاثية، والأحماض الدهنية الحرة، والجلوكوز، والأنسولين في المصل. كما تم تجهيز أنسجة البنكرياس للفحص النسيجي. تسبب علاج التاموكسيفين في زيادات معنوية في مستويات الأميلاز، والليباز، والدهون الثلاثية، والأحماض الدهنية الحرة، والجلوكوز، بالإضافة إلى انخفاض في مستويات الأنسولين مقارنةً بالمجموعة الضابطة (p< 0.001)أدى العلاج المصاحب بالمستخلص المائي النباتي (AESL) إلى عكس هذه التغيرات البيوكيميائية بشكل ملحوظ وتحسين التركيب النسيجي للبنكرياس. أظهر المستخلص النباتي تأثيرات وقائية قوية ضد الضرر البنكرياسي الناجم عن التاموكسيفين، ويرجح أن يكون ذلك من خلال آليات مضادة للأكسدة ومحفزة لحساسية الأنسولين. وتشير هذه النتائج إلى إمكانية استخدامه كعامل علاجي نباتي ضد تلف أنسجة البنكرياس.

الكلمات المفتاحية :تلف البنكرياس؛ جرذ؛ مستخلص مائي لجذور *Saussurea lappa*؛ تاموكسيفين

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Introduction

Tamoxifen is a chemotherapeutic agent widely used for the treatment and prevention of breast cancer (Lumachi et al., 2015). TMX has tissue-specific agonistic and antagonistic effects on the estrogen receptor (ER) (Singh et al., 2016). It mainly inhibits the estrogenic activity in ER-positive breast cancer cells, thereby; preventing cancer development (Xiong et al., 2017). Despite its effectiveness, TMX is associated with many side effects and organ toxicities, including blood clotting, stroke. Endometrial cancer, thyroid toxicity, ocular toxicity and hepatotoxicity (Yang et al., 2013). In addition, TMX elicits Estrogenic effects on the fat tissue including hypertriglyceridemia, which is a risk factor for acute pancreatitis in patients treated with TMX (Singh et al., 2016; Sakhri et al., 2010). Recently, TMX was found to inhibit the proliferation of pancreatic β-cells in non-diabetic mice and was associated with modest changes in glucose homeostasis (Ahn et al., 2019). Considering the fact that obesity, diabetes, and breast cancer may occur con comitantly (Barone et al., 2008), and in view of the widespread use of TMX to manage breast cancer, the deleterious effects of TMX on the pancreas, particularly in diabetic patients, have attracted attention. The principle mechanism underlying TMX-induced organ toxicity is oxidative and nitrosative stress(Owumi et al., 2021; El-Dessouki et al., 2018; Parvez et al., 2008; Nazarewicz et al., 2007) . . TMX- has many deleterious effects on mitochondria which include the impairment of mitochondrial membrane integrity leading to increased production of reactive oxygen species (ROS) (Repero et al., 2014). TMX-also increases the expression of nitric oxide synthase which generates nitric oxide NO (Nazarewicz et al., 2007). NO combines with superoxide to form peroxynitrite which causes peroxidation of unsaturated fatty acids in the cell membrane leading to its damage (Nazarewicz et al., 2007; Radi et al., 1991)

Furthermore, tamoxifen triggers an inflammatory response in various body tissues (Owumi et al., 2021; El-Dessouki et al., 2018; Zhou et al., 2019). Zhou et al. (2019) demonstrated that TMX activates the p38 component of the mitogen-activated protein kinase (MAPK) inflammatory pathway, and that inhibition of p38 significantly attenuates TMX-induced oxidative stress in the liver. Considering these findings, supplements with antioxidant and anti-inflammatory properties may be effective in protecting against TMX-induced toxicity. Natural antioxidants play a critical role in

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reducing oxidative stress by scavenging excess free radicals (Ahmad et al., 2012).

Saussurea lappa, a perennial herb native to Kashmir and known as Kushta in Sanskrit, is rich in antioxidants and has been traditionally used in folk medicine. The hot water extract of its roots has long been employed to treat asthma, inflammation, and rheumatism (Shah, 1982; Lechner-Knecht, 1982; Sircar, 1984). The roots are characterized by hot, bitter, sweetish, pungent, and warming properties, and are utilized as an analgesic, digestive, aphrodisiac, and diuretic. Numerous studies have reported that *S. lappa* roots possess cortisol-modulating, bronchodilator, antiulcer, anticancer, anti-inflammatory, antiviral, and hepatoprotective effects (Chen et al., 1995; Ambavade et al., 2009). Traditionally, the aqueous extract of *S. lappa* root was used for its anti-anginal effect (Khare, 2008).

Therefore, given the beneficial properties of the aqueous extract of *Saussurea lappa* (AESL), this study was conducted to evaluate the injurious effects of TMX on the pancreas of female rats and to investigate the potential protective role of AESL in these animals.

Material and methods

Chemicals

Tamoxifen (tamoxifen citrate), marketed as Nolvadex® and produced by AstraZeneca UK, was administered orally to experimental animals at a dose of 40 mg/kg body weight, equivalent to the human therapeutic dose, for 28 consecutive days (Bacharach, 1964).

Plant material and extraction method for *Saussurea lappa*

Dried *Saussurea lappa* roots were purchased from a medicinal plant market in Benghazi, Libya. For extract preparation, 1 kg of powdered root was boiled in 5 liters of distilled water for 30 minutes, filtered, and lyophilized. The resulting freeze-dried extract (≈35 g) was reconstituted in distilled water to a final concentration of 50 mg/ml (Saleem et al., 2013).

Animals and Treatment

Twenty-four female albino rats (8 weeks old, 180–190 g) were obtained from the animal house of the University of Benghazi, Faculty of Medicine. They were housed under standard conditions (23–25 °C, 50–65% humidity, 12 h light/dark cycle), with free access to standard diet and water. After a 7-day acclimatization period, the animals were randomly divided into four groups (n = 6 each):

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Group I– Control rats received oral normal saline.
Group II –Rats received AESL (200 mg/kg/day) orally for 28 days (Saleem et al., 2013).
Group III – Rats received TMX (40 mg/kg/day) orally for 28days (Bacharach, 1964).
Group IV – Rats co-treated with TMX (40 mg/kg/day) and AESL (200 mg/kg/day) orally for 28 days.

Assessment of serum levels of pancreatic enzymes, TG, FFAs, glucose and insulin

Serum activities of α-amylase and pancreatic lipase and the levels of glucose and TG were measured using commercial spectrophotometric diagnostic kits. Serum levels of FFAs and insulin were determined using ELISA, following the instructions in the manual provided with the commercial kit.

Histological examination

A portion of the excised pancreatic tissue was fixed in 10% phosphate-buffered formalin for 24 hours, followed by dehydration in graded alcohol, paraffin embedding, and sectioning at 5 µm thickness using a microtome. Sections were then deparaffinized, rehydrated, and stained with hematoxylin and eosin (H&E) for histological examination under a light microscope to assess structural alterations (Longnecker, 2021).

Statistical analysis

Data were analyzed by comparing the mean values of the TMX-treated groups to the control group. Results are presented as mean ± standard deviation (SD). Statistical significance was assessed using one-way ANOVA followed by Bonferroni's post hoc test, with $p < 0.05$ considered significant. Analyses were performed using SPSS version 27.

Results

Serum amylase

The impact of AESL on serum amylase activity as a biomarker of pancreas in different animal groups is shown in Figure1. Marked decrease in amylase activity in rats treated with S. *lappa* extract only when compared with control ones (P=0.001), while significant elevation in this pancreatic marker in serum of TMX intoxicated rats in comparison to control animals (P=0.001). Administration of *S. lappa* extract concurrently with TMX markedly ameliorated serum amylase activity in TMX- *S. lappa* extract treated group with respect to TMX intoxicated group (P=0.001).

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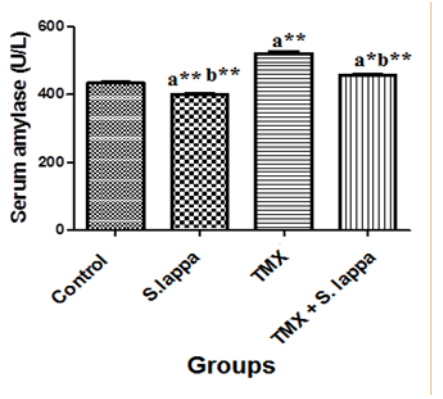

Figure1. Effect of AESL on serum amylase activity in TMX induced pancreas damage in rats. Values are expressed as mean ± SD of 6 rats, $a^{**}P$=0.001, $^{a*}P$ =0.006 compared control, $^{b**}P$= 0.001 compared with TMX.

Serum lipase

The serum lipase activity level in different experimental rat groups as another index of pancreas function is demonstrated in Figure 2. The data revealed that treatment of normal rats with AESL only significantly reduced the serum lipase activity level with respect to control (P = 0.003). Oral ingestion of female rats with TMX for 28 successive days, significantly boosted the serum activity level of lipase versus control rats (P=0.001). Co administration of AESL with TMX markedly down regulated the serum lipase activity in TMX -AESL treated group relative to TMX intoxicated group (*P*=0.001).

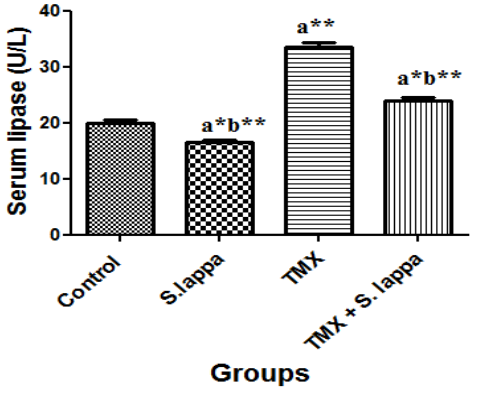

Figure2. Effect of AESL on serum lipase activity in TMX induced pancreas damage in rats. Values are expressed as mean ± SD of 6 rats, $a^{**}P$=0.001, $^{a*}P$ < 0.01 compared control, $^{b**}P$= 0.001 compared with TMX.

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Histopathological observations

Histological evaluation (Figure 3) demonstrated that control rats (Figure 3A) and those treated with *S. lappa* extract alone (Figure 3B) exhibited normal pancreatic architecture characterized by intact islets of Langerhans and healthy exocrine acini. Tamoxifen treatment resulted in significant pancreatic damage, including shrinkage of islets, cellular degeneration, necrosis, and apoptotic changes affecting both endocrine and exocrine cells (Figure 3C). However, co-administration of AESL with tamoxifen preserved the pancreatic structure, maintaining normal integrity of both endocrine and exocrine compartments (Figure 3D) (H&E staining, ×400.

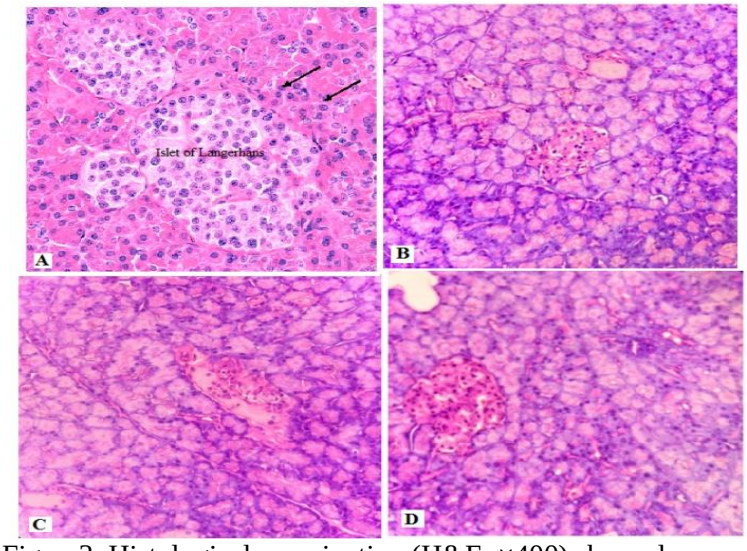

Figure3. Histological examination (H&E, ×400) showed normal pancreatic structure in control rats (A) and those treated with *S. lappa* extract (B). Tamoxifen caused significant damage, including islet shrinkage and cell degeneration (C). Co-treatment with AESL preserved pancreatic integrity, maintaining both endocrine and exocrine structures (D).

Serum triglycerides (TG)

Figure4 Shows the impact of *S.lappa* extract on serum TG concentration in TMX intoxicated rats. Relative to control rats, remarkable depletion in TG level in *S.lappa* extract treated rats was recorded (P=0.001). Meanwhile significant increase in this lipid in TMX intoxicated rats versus control ones (P=0.001). Administration of *S.lappa* extract concurrently with TMX, significantly reduced the serum TG level in TMX- *S.lappa* treated rats compared to TMX intoxicated animals (P=0.001).

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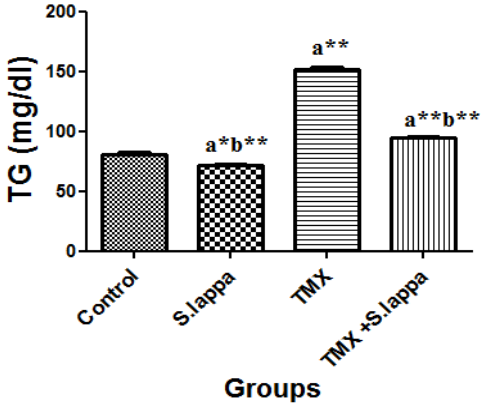

Figure4. Influence of AESL on serum TG concentration in TMX induced pancreatic damage in rats. Values are expressed as mean ± SD of 6 rats, $a^{**}P$=0.001, $^{a*}P$ < 0.01 relative to control, $^{b**}P$= 0.001 relative to TMX.

Serum free fatty acids (FFAs)

The influence of *S. lappa* root extract on serum free fatty acids (FFAs) concentrations in TMX intoxicated rats is illustrated Figure **5.** Remarkable depletion in serum FFAs was noticed in rats treated with *S. lappa* root extract only relative to control counterparts (P= 0.004). Marked increase in FFAs was found in TMX intoxicated rats with relation to control animals (*P*=0.001). Administration of the plant extract to TMX group, markedly down modulated the serum FFAs levels versus TMX intoxicated group (*P*= 0.001).

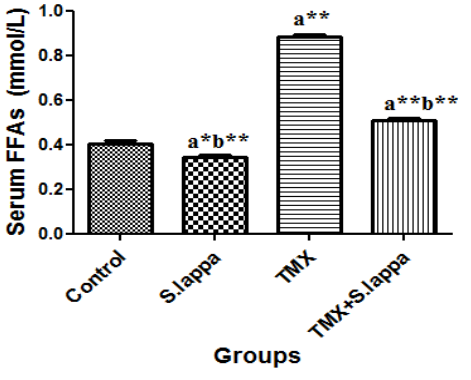

Figure5. Effect of AESL on serum FFAs concentrations in TMX induced pancreatic damage in rats. Values are expressed as mean ± SD of 6 rats, $a^{**}P$=0.001, $^{a*}P$ < 0.01 compared control, $^{b**}P$= 0.001 compared with TMX.

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Serum glucose

Figure6. Demonstrates the level of serum glucose in different animal groups. Marked depletion in serum glucose level in animals ingested *S.lappa* extract only versus control counterparts (*P*=0.001), while elevation in this glycemic index in TMX intoxicated rats in comparison to control ones (*P*=0.001). Administration of *S.lappa* extract along with TMX markedly ameliorated serum glucose concentration in TMX- *S.lappa* extract treated group with respect to TMX intoxicated group (*P*=0.001).

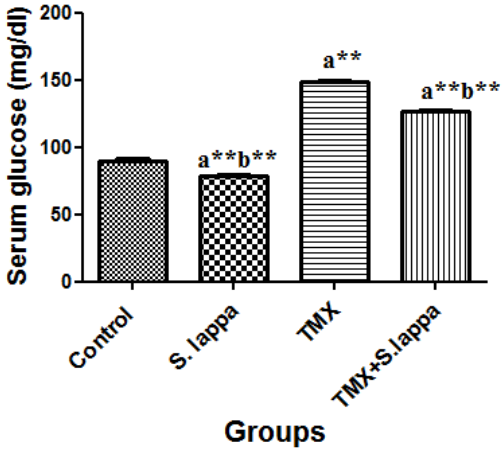

Figure6. Effect of AESL on serum glucose in TMX induced pancreatic damage in rats. Values are expressed as mean ± SD of 6 rats. $^{a**}P$=0.001, relative to control, $^{b**}P$= 0.001 relative to TMX

Serum insulin

The serum insulin levels in different experimental groups are shown in Figure 7**.** *S.lappa* extract treated rats showed high insulin level versus control ones (*P*=0.001). Oral intake of TMX markedly reduced the insulin level in TMX intoxicated rats with respect to control counterparts (*P*=0.001). Administration of *S. lappa* extract along with TMX potentially up modulated the serum insulin level in TMX- *S.lappa* extract treated group relative to TMX intoxicated group (*P*=0.001).

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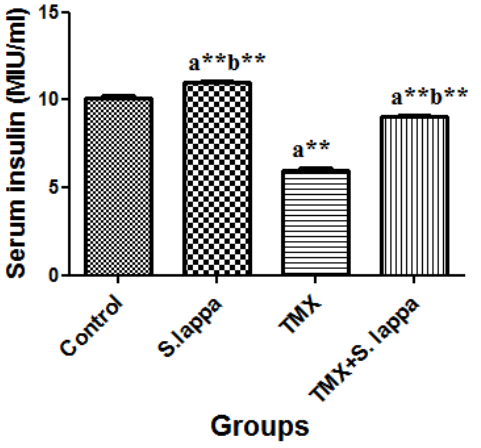

Figure7. Effect of AESL on serum insulin levels in TMX induced pancreatic damage in rats. Values are expressed as mean ± SD of 6 rats. $^{a**}P$=0.001, relative to control, $^{b**}P$= 0.001 relative to TMX

Discussion

Pancreatitis is a serious disease of the digestive system and is associated with significant morbidity and mortality (Wall et al., 2011). Previous published data have been shown that endocrine therapy with tamoxifen in breast cancer patients can cause severe pancreatitis. So searching for an agent to prevent or reduce this undesirable side effect of Tamoxifen is becoming an urgent need for patients with breast cancer. In the current investigation, the protective effect of aqueous extract of *Saussurea lappa* (AESL) against TMX induced pancreatic injury in female rats was studied.

The results of the current work revealed that administration of TMX induced pancreatic tissue injury as indicated by significant increases in serum pancreatic enzymes, namely lipase and α-amylase (biomarkers of pancreatic cell injury) in rats intoxicated with Tamoxifen relative to TMX untreated intoxicated ones. The damaging impact of TMX was further confirmed by severe disorganization of histo -morphological pictures of pancreatic tissue as observed by shrinkage of islets of Langerhans with degeneration and necrosis of components cells. In addition, apoptotic degeneration of exocrine acinar cells was also noticed. Many factors may have contributed to these changes. Among these factors could be the ability of TMX to induce peroxidation of unsaturated fatty acids in the pancreatic cell membrane, leading to pancreatic cell membrane rupture and tissue destruction. This can, result in enzymatic leakage into circulation (Owumi et al., 2021). In addition,

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TMX promotes the release of inflammatory cytokines which cause tissue necrosis, resulting in further damage to pancreatic cells. Protective oral administration of AESL significantly prevented the enzymatic elevation of both lipase and α-amylase. The plant extract also greatly protected the pancreatic architecture from damaging influence of TMX as observed by normal pancreatic architecture with normal endocrine and exocrine cells. The prophylactic beneficial impact of AESL may correlate to its phytochemical constituents. *S. lappa* plant contains phenolic acids and flavonoids with antioxidant properties. These compounds can prevent oxidation of polyunsaturated fatty acids and preserve membrane integrity (Hassan & Masoodi, 2020).
In the present study, marked elevations in the serum TG and free fatty acids (FFAs) were recorded in rats administered TMX for 28 successive days with respect to control rats. This result is coped with a previous study report that TMX treatment induced hypertriglyceridemia (Liu & Yang, 2003). This hypertriglyceridemia may be attributed to two main mechanisms: first, TMX acts as an estrogen receptor (ER) agonist, stimulating hepatic synthesis of TG-rich lipoproteins such as chylomicrons and very low-density lipoproteins (VLDL); second, it suppresses lipoprotein lipase activity, thereby impairing TG clearance from the circulation (Filippatos et al., 2009). Elevated TG levels may contribute to pancreatic tissue damage by obstructing capillaries, impairing pancreatic blood f low and causing pancreatic ischemia and cell death (Singh et al., 2016) .Pancreatic lipase released from damaged cells further hydrolyzes excess TG into FFAs, which accumulate and block microvasculature, depriving tissues of oxygen and thereby exacerbating cellular damage (Singh et al., 2016; Ewald et al., 2009) . This may explain the elevation of serum level of FFAs presented in the current study in TMX intoxicated rats. Co-treatment of TMX intoxicated rats with AESL (200 mg/kg) significantly reduced the serum levels of TG and FFAs which may relate to its hypolipidemic activity. Bioactive compounds in AESL, including flavonoids such as quercetin and catechins, have been shown to downregulate enzymes involved in TG synthesis and improve lipid metabolism (Musdalifah et al., 2024). Furthermore, Kumar et al.(2020) Demonstrated that AESL inhibits pancreatic lipase, contributing to its anti-obesity and TG-lowering effects Pancreatic damage can disrupt glucose metabolism, leading to hyperglycemia (Wynne et al., 2019) In this study, TMX intoxication

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caused a significant increase in serum glucose and a decrease in insulin levels, likely due to TMX -induced damage to pancreatic beta cells in the islets of Langerhans, impairing insulin secretion (Wynne et al., 2019) AESL treatment significantly reversed these effects, suggesting its beneficial role in glycemic control and pancreatic protection. Notably, the protective impact of the current plant extract against TMX induced islets of Langerhans damage may contribute to improved insulin secretion and enhanced glucose uptake. The hypoglycemic effects of *S. lappa* have also been reported by (Chaturvedi et al., 1993)

Conclusion

Overall, the present findings provide strong evidence AESL exerts a protective effect against TMX -induced pancreatic injury, likely through its combined antioxidant, anti-inflammatory, and hypolipidemic properties. These results support the potential therapeutic utility of AESL in mitigating pancreatic dysfunction associated with TMX toxicity

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