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Original Article

Impact of Ruthan date extract in alleviation of cypermethrin induced pancreatic toxicity via SiRT-1 and Cyto-c in rats

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Abstract

Cypermethrin (CYPn) is a commonly used pesticide in agriculture and houses for insect's control. We evaluated the pancreatic toxicity in rats exposed to CYPn and the protective efficacy of *Ruthana* date extract (RDE) as against toxicity. In the current study, male *Wister* albino rats were allocated into five groups; (8 rats/group). Group I: Control, while rats in groups II-V were daily given 100 mg/ kg CYPn (1/10 LD_{50}) orally for 4 weeks. Groups III, IV and V; rats were supplemented in the same time 100, 200 and 300 mg RDE/kg respectively. Data obtained showed that, phytochemical analysis of RDE showed its high content of catechin, naringenin and apigenin as major flavonoids content. Also, rats given CYPn showed a significant elevation in fasting blood glucose, glycated hemoglobin (HA1c), malondialdehyde (MDA) and interleukin-6 (IL-6) levels while the insulin and GSH levels were significantly reduced ($p< 0.001$) compared with control. On the other hand, the activities of antioxidant enzymes (GST, GSPx and SOD) were increased in rats injected with CYPn versus control. In addition, CYPn increased HOMA-IR, cytochrome c (Cyto-c), and reduced Sirtuin 1 level. Rats treated with RDE restored these abnormalities with dose-dependent. Flavonoids (catechin, naringenin and apigenin) from RDE showed a protective effect against toxicity induced by CYPn via reduction of antioxidants activities, sirtuin 1, insulin sensitivity, reduction Cyto-c release and inflammatory mediators. It was concluded that, the active ingredients of RDE is promising in developing a safe protective agent against pancreatic toxicity and incidence of diabetogenesis induced by CYPn.

Keywords: *Ruthana* date, Cypermethrin, Insulin resistance, SIRT-1, Cytochrome c, Diabetes, Antioxidant, Rats

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Introduction

Pesticides were used on a large scale to protect commercial crops from insects for increasing field productivity to cover the national and international requirements. The contamination of plants and animals caused by pesticides are considered as a major challenge problem in ecosystem (Guo et al., 2019). In human, it can causes disturbance in hormonal , neurologic and fertility (Roknil et al., 2023).

Cypermethrin (CYPn) is one of the commonly used pesticide in different fields as agriculture and control of house insects (Rezania et al., 2022; Khormi et al., 2025). It was reported that, If CYPn taken by inhalation it causes respiratory distress and irritation of the GIT if taken by orally. In addition, it can cause allergic reactions for skin and eyes (Scheepers et al., 2023).

Sirtuin 1 (SIRT1) is deacetylase enzyme that plays a role in cell cycle and induce DNA repair, reduce apoptosis and aging. In addition, it enhances fat mobilization and insulin sensitivity (Zhang et al., 2025). Polymorphism of *SIRT1* was associated with obesity, diabetogenesis and cardiovascular disease CVD (Tao et al., 2022). The damage of pancreatic β-cells and development of diabetes can be induced by release inflammatory mediators (Berbudi et al., 2020). Insulin resistance characterized by hyper-secretion of insulin is an early step in diabetogenesis (Janssen, 2024). The pancreatic Islets of Langerhans composed of β -cells that produce insulin that contributed in metabolism of nutrients (Cuenco and Dalmas, 2022). Exposure to chemicals can release reactive oxygen species (ROS) that damage β- cells and affect metabolism.

The Phoenix dactylifera L. (date palm) fruit is being a good energy source of high and due to its high nutrients, it is recommended in traditional medicine for health and disease prevention since it contains several micronutrients. 400 cultivars of date palm were identified (Courts and Williamson, 2015). Phytochemical analysis indicated presence of include fibers, sugar, fat, protein, and active polyphenols (Michael et al., 2013). The polyphenols showed different biological activities as hypoglycemic, analgesic, dyslipidemic and hepatoprotective (Zhang et al., 2013). Saudi Arabia are famous with special production of date as *Khodry*, *Khalas, Ruthana, Sukkari, Sefri*.

Previous study reported that, due to its high content of vitamins, minerals, and many biologically active gradients Ruthana dates revealed a high nutritional value. In addition, its high carbohydrates content is the main source of energy (Al-Farsi et al., 2007). Also, its phenolic content showed a potent antioxidant power (El-Mergawi et al., 2019). It was reported that, Ruthana date exert cytotoxicity against different cell lines (Al Alawi et al., 2020), but studies in this scope are still limited. To decrease incidence of diabetes due to environmental pollution, the rational of current study to evaluate the protective role of *Ruthana* date extract (RDE) against pancreatic toxicity by CYPn in rats.

Material and Methods

All solvents used are HPLC grade with high purity >99%, Fluka, Germany. CYPn was purchased from Sigma Company with purity (99.93%).

Preparation of Ruthana date extract (RDE) and identification of *Ruthana* date flavonoids by GC–MS

Fresh *Ruthana* dates were procured from Saudi Arabia Dates center. The fruit part was separated from the seeds , then 100 g of sample was homogenized in 80% ethanol 1:1 (w/v) and left for 6 hours. The homogenate was centrifuged at 10000 rpm for 10 min. The solvent was removed and dried by lypholization. The sticky solution was stored at -20 ^{o}C until use in experiments (Saleh et al., 2011). About10 mg of homogenates was dissolved 1mL acetonitrile. The sample was injected into GC/MS with an Agilent 6530 mass spectrometer.

Experimental design

Forty male *Wister* rats, aging 4 weeks, weighed 120–150 g were supplied by animal house at KAU, Jeddah. All rats were housed for 12-hrs light/dark cycle. Animals were treated in accordance with guide for the care and use of laboratory animals. CYPn was dissolved in DMSO to (100 mg/1 mL DMSO). The rats were randomly allocated to five groups (8 rats/group). Group I; Control received 0.1 mL DMSO. Rats in groups (II -V) were received CYPn orally at doses (100mg /kg) respectively for 4 weeks, the dose of CYPn was given based on study by Seven et al. (2022). Rats in groups (III-V) were received RDE at 100, 200, 300 mg /kg respectively for four weeks. The doses indicated for the administration groups were selected according Salah et al. (2012).

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Methods

Assay of biochemical markers

Fasting blood glucose by colorimetric method using BIORAD kit. The glycated hemoglobin (HA1c) was quantified by Latex Enhanced Immunoturbidimetry Method assay kit from Abbexa, UK. Insulin, and TNF-α were quantified by ELISA technique (ABCAM, USA).

Assay of serum amylase and lipase activities

The activities of serum lipase and amylase were determined by kits from My BioSource, Cat# MBS2570530 , MBS044269. San Diego, CA 92195-3308, USA.

Preparation of pancreatic homogenate and biochemical evaluation

About 10 mg of pancreatic tissue was homogenized in 2 mL of PBS contain 1mM EDTA, using Teflon glass pestle, then centrifuged at 10,000 RPM at -4°C for 15 min. The supernatant was stored at - 40 ° C.

The total protein in homogenate was quantified by Bradford reagent (BIO-RAD, England). The MDA level was determined by the method described (Randox Ltd., UK).

The GST activity was determined according to (Habig et al., 1974), the activity of GSH-Px (Paglia and Valentine, 1967). The catalase and SOD activities by available kit (R&D System, Inc.).

Assay of SIRT1 and Cyto-c in pancreatic homogenate

The level of SIRT1 in tissue was determined by ELISA Kit; a single-wash 90-min by quantitative measurement CAT# ab206983.The level of Cyto-c was evaluated by ELISA Kit, ELABSCIENCE, Cat # E-EL-R0006.

Statistical analysis

All data were expressed as mean ± S.D. The data were statistically analyzed using student tests. One-way ANOVA test was applied. If the p-value < 0.05, it was considered as statistically significant. The Data was evaluated for normality and homogeneity of variances; group differences were evaluated using one-way ANOVA followed by Tukey's HSD for post-hoc comparisons.

Results

The active components of *Ruthana* date extract (RDE) identified by GC/MS revealed its high content of apigenin, naringenin, catechin as major flavonoids content with retention times (10.29,12.54 and 14.80 mins) respectively (table 1). Data obtained showed that, rats injected with CYPn for four weeks showed a statistical increased in the levels of FBG, HA1c, TNF-α and insulin versus control ($p < 0.001$) (Figures 1-4). However, rats injected with CYPn and treated with RDE at a dose 100, 200 or 300 mg/kg showed a significant reduction in fasting blood glucose, HA1c, TNF-α, and insulin with dose-dependent versus untreated.

Table-1. Flavonoids from RDE with relative retention times.

#	Compounds	RT (mins)	Height	Area	Area %	Molecular mass
1	Catechin	14.80	570,33	43,36	0.911	290.26
2	Naringenin	12.54	354,38	29,45	0.541	272.25
3	Apigenin	10.29	550,36	32,52	0.721	270.24

Inst. (Perkin Elmer model: clarus 580/560S), Inj=°C, Volume=1 µL, split=:1, Carrier Gas=, Solvent Delay=6.00 min, Transfer Temp=150°C, Source Temp=180°C, Scan: 50 to 620Da, Column (Elite-5MS, 30m 0.25mmID 0.25um df).

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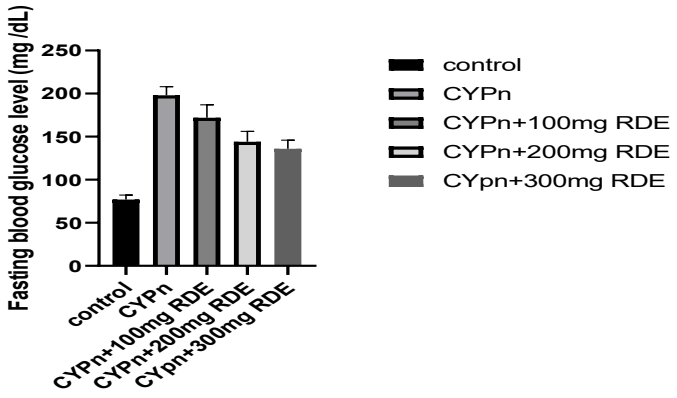

Figure-1. Fasting blood glucose level in all studied groups.

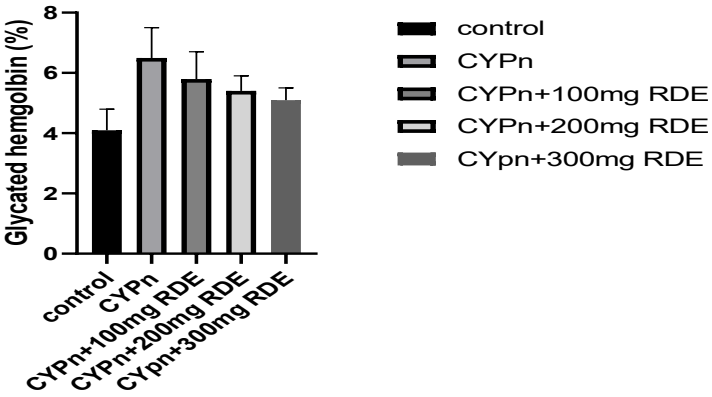

Figure-2. Glycated hemoglobin in all studied groups.

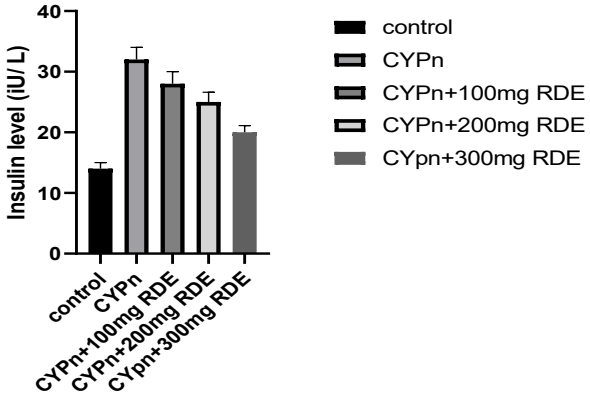

Figure-3. Insulin level in all studied groups.

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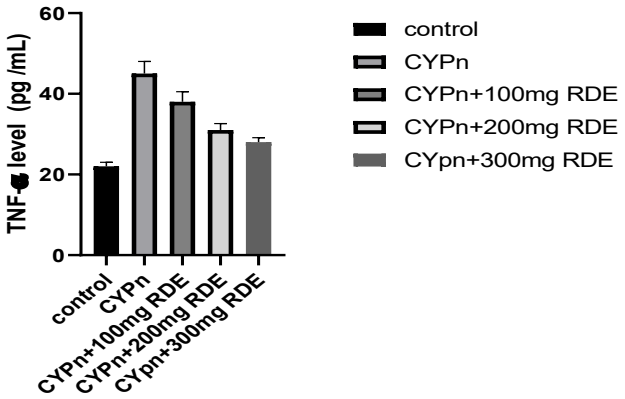

Figure-4. TNF α-level in all studied groups.

Rats injected with CYPn for four weeks showed a significant elevation (p<0.01) in the activities of serum lipase and amylase compared with control (figures 5,6). Treatment with RDE at the different doses reduced the activities of amylase and lipase with dose-dependent versus untreated (p<0.001). Data presented in figures (7-10) revealed the oxidant/ antioxidant balance. It was found that, rats exposed to CYPn showed a significant elevation of MDA level (p<0.001) concomitant with elevation of antioxidant enzymes activities (GST, GPX and SOD) compared with control. Treatment with RDE at a dose 100,200 or 300 mg/kg showed significant reduction in the MDA and antioxidant enzymes activities compared with untreated. Figures (11,12) showed a significant reduction in levels of SIRT1 and Cyto-c in rats exposed to CYPn compared with normal control. However, treatment with RDE at a dose 100, 200 or 300 mg/kg showed significant elevation in SIRT1 and Cyto-c versus untreated.

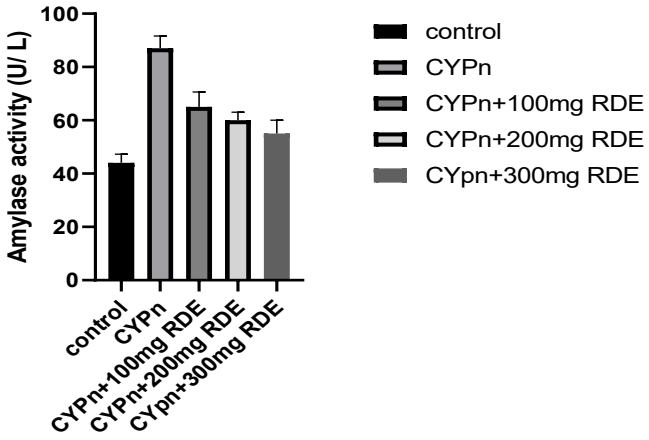

Figure-5. Serum amylase activity in all studied groups.

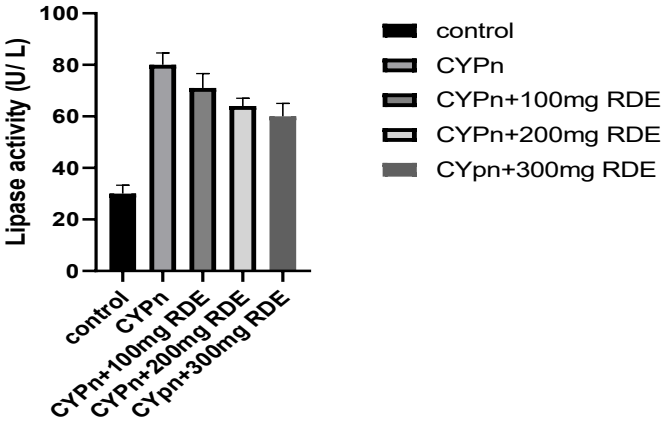

Figure-6. Serum lipase activity in all studied groups.

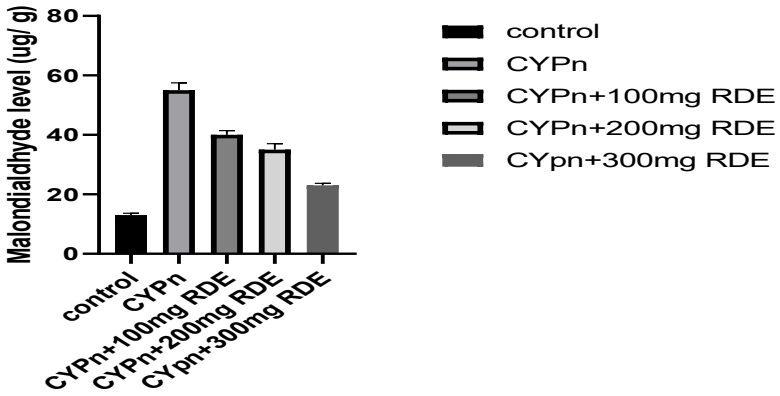

Figure-7. Pancreatic MDA level in all studied groups.

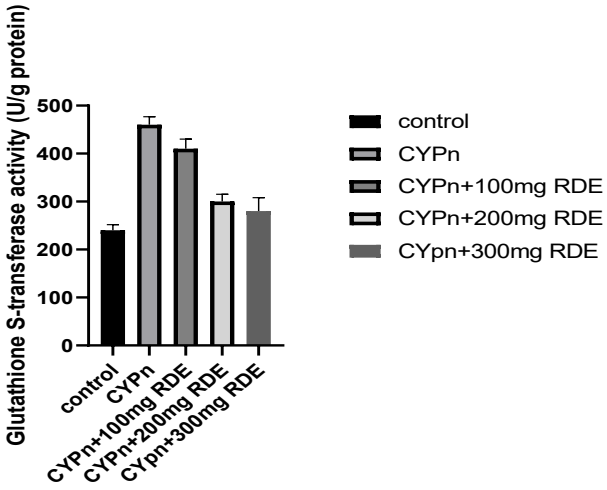

Figure-8. Pancreatic Glutathione S-transferase activity in all studied groups.

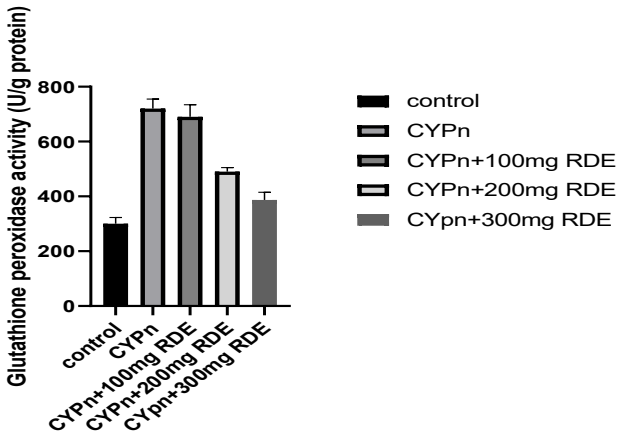

Figure-9. Pancreatic Glutathione peroxidase activity in all studied groups.

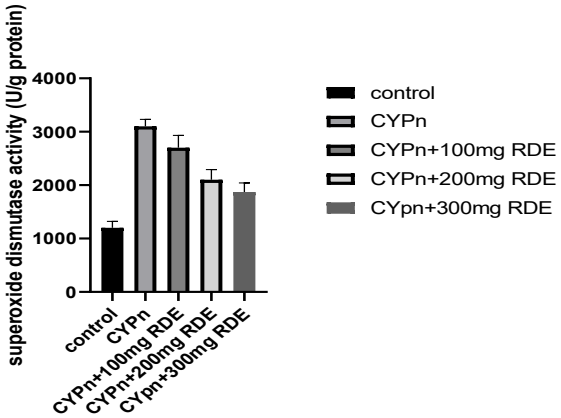

Figure-10. Pancreatic superoxide dismutase activity in all studied groups.

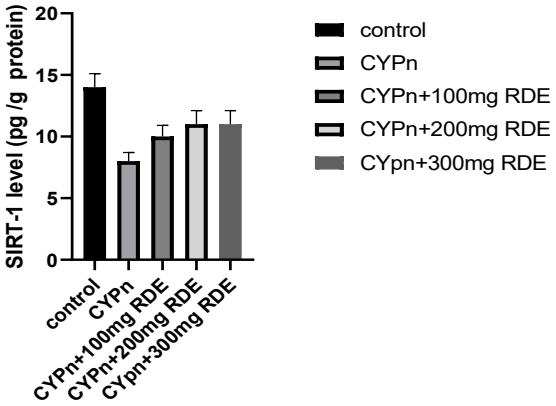

Figure-11. Level of SIRT-1 in Pancreatic tissue in all studied groups.

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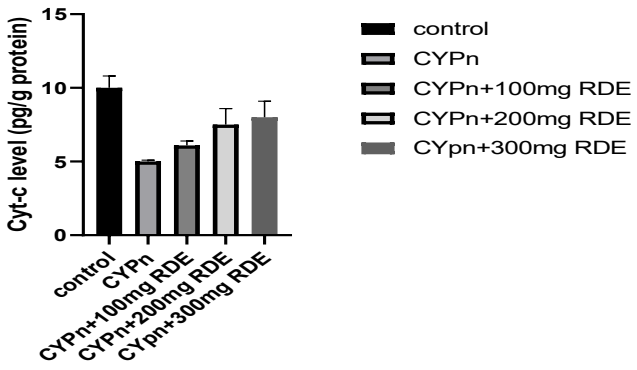

Figure-12. Level of Cyt-c in Pancreatic tissue in all studied groups.

Discussion

Environmental pollution due to pesticides exposure can causes disruption of the physiological pathway due to endocrine system affection and development of some cancer (Uwamahoro et al., 2024). There is no specific antidote to manage its toxicity. CYPn induced neurotoxicity depends on dose, duration and age (Mohammadi et al., 2019). This study investigated the protective effect of *Ruthana* date extract (RDE) against pancreatic toxicity and risk of diabetogenesis in rats injected with CYPn.

In current study, ethanolic date extract showed its high content of apigenin, naringenin, catechin as major flavonoids content. This is in accordance with study of Alsarayrah et al. (2022), who found that, the Ruthana dates contain a high phenols and flavonoids (119.2 %, and 55.6 %) respectively. Rats given CYPn at dose 100 mg/kg showed that, the levels of FBG, HA1c and insulin were significantly higher than control group. However, rats treated with RDE ameliorated CYPn induced these changes. This is in accordance with study of (Acker and Nogueira, 2012), who found that, diabetic rats treated with date seed extract caused hypoglycemic action (El Fouhil et al., 2010). Wei et al. (2023), reported that, fasting insulin was elevated in CYPn-treated high-calorie diet fed mice. Also, CYPn exposure decreased glucose uptake in insulin-sensitive tissues in high-calorie diet fed mice whether skeletal muscle is insulin-mediated glucose uptake (Honka et al., 2018). In addition, study by Pournourmohammadi et al. (2007) reported that, chlorpyrifos can cause mitochondrial dysfunction of islets of Langerhans. Panda et al. (2015) reported that, organophosphate exposure was associated with insulin resistance and elevated HA1c. This effect was may be due to reduced key regulatory enzymes of glycolysis as PFK1 and HK after exposure of organophosphate (Sarin and Gill, 1999). Hagar and Fahmy (2002) reported that, chronic administration of dimethoate showed a significant reduction in plasma insulin level and elevation of blood glucose level and was accompanied by histological and histochemical changes with destruction of the β-cells.

In this study, CYPn given rats caused a generation of inflammatory mediator generation as TNF-α, which may cause damage of pancreatic β- cells. Treatment with RDE reduced these mediators versus untreated rats with dose dependent. Flavonoids rich in RDE inhibited inflammatory release as a protection mechanism. Afolabi et al. (2019) revealed that, CYP induced the expression of the proinflammatory cytokines IL-6 and TNF- α in rats. In addition, Yang et al. (2015), reported that, epicatechin can alleviate the production of inflammatory mediators as IL-6 and TNF- α. Ince et al. (2017), OPs-injected rats showed higher proinflammatory mediators, as ɤ-interferon, IL1 β, TNF- α, versus normal rats, thus reduced the action of insulin.

In current study, CYPn induced a significant elevation of serum α-amylase and lipase activities compared with control rats. However, RDE caused a significant reduction of these enzymes compared with untreated. Serum α-amylase and lipase activity are good markers for pancreatitis toxicity with organophosphates (Adhil and Sudharsan, 2015; Moussa et al., 2018). Acute pancreatitis occurred after OPs poisoning is caused by release of acetylcholine from pancreatic nerves (Singh et al., 2007). This explained the elevation of α-amylase and lipase activities after CYPn injection in this study. Previous work reported that OPs stimulated pancreatitis and higher of serum amylase (Yoshida et

al., 2015). This confirmed that, Ops mediated pancreatic damage.

Imbalance between oxidant and antioxidant is considered as the pathogenesis of many diseases .Free radicals released during metabolism or pollution is removed by antioxidant components (Kemal et al., 2022; El Arem et al., 2017). CYPn caused increased oxidative stress by increasing malondialdehyde and this peroxidation is counteracted by stimulation of antioxidant activities (GST, SOD and GSPx) while the level of reduced glutathione (GSH) decreased compared with control. RDE showed a reduction in MDA, antioxidant enzymes activities (GST, SOD and GSPx) and elevation of GSH compared with untreated rats.

CYPn was reported to be associated with an increase in lipid peroxidation. It was reported that, Khalas, Sukkari, and Ajwa dates showed high phenolic contents. This reflects its antioxidant and anti-inflammatory activities (Franklin et al., 2011; Saleh et al., 2011; Hamad, 2014).

The study by Afolabi et al. (2019) mentioned that, GSH decreased in rats' liver and kidney tissues after CYP exposure. Anitha et al. (2019) found that, the GSH content was directly decreased with oxidative stress progression and making cells more susceptible to radical generation. Also, RDE keep normal GSH level because it contains phenolic compounds. The elevation of antioxidant enzymes helps to combat free radical formation. The combined effect of SOD and CAT help for removal H_2O_2 (Ghazouani et al., 2020). While GST conjugates toxic substances with GSH thiol group to form less toxic easily eliminated. Our results are in agreement with (Soliman et al., 2021; AlKahtane et al., 2018; Khan et al., 2017) who reported that, SOD, CAT and GST activities were elevated in rats exposed to OPs versus control rats.

SIRT1 was found to exert different physiological processes such as metabolism, inflammation, oxidative stress, signaling transduction, and apoptosis (Farghali et al., 2019). The reduced values of Sirtuin 1 and elevated Cyto-c levels in response to CYPn administration revealed its toxicity via increased cell death and apoptosis. However, RDE ameliorated these changes that reflect its efficacy in protection against CYpn toxicity. Previous research reported that the level of SIRT1 gene expression was significantly decreased in the rat after Bisphenol A exposure (Santoro et al., 2021). Our data are in agreement with previous study which reported that, the content of cytochrome-c in tissues of male rats was decreased, under the effect of malathion either in case of formulation or technical form. It was supported by succinate-cytochrome-c-reductase, which stimulated by the organophosphorus insecticide treatment. SIRT1 was found to be a possible target to modulate cytokine-induced β-cell damage (Lee et al., 2009).

Poovala et al. (1999) reported that, the oxidative stress mediated by OPs caused proximal tubular damage in an in vitro study performed via the activation of the MAPK signaling pathway within nephron after activating JNK and caspase-3 (Ren et al., 2012).

Xu et al. (2024) demonstrated that, kaempferol treated mice was rescued from diet-induced obesity by promoting white adipose browning which correlated with AMPK/SIRT1/PGC-1α pathway modulation. However, the insulin resistant mice (HFAT) supplemented with RSV for 12 weeks showed improved insulin action (Khamis et al., 2025), along with increased AMPK phosphorylation and PGC1a expression but not SIRT1 (Um et al., 2010).

Conclusion

It was concluded that, CYPn exposure can induced production of free radicals and inflammatory mediators that affect efficacy of pancreas. This will increase risk of diabetes. RDE attenuated the CYPn induced pancreatic toxicity via anti-inflammatory, antioxidant, SIRT1 and Cyto-C and protect against diabetogenesis.

Study Limitations

The study was carried out on male rats not female to avoid any hormonal disturbances changes. In addition, due to high cost fee of antibodies for detection signals by immunohistochemistry. no histological validation, no measurement of CYPn plasma levels.

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Disclaimer: None.

Conflict of Interest: None.

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Ethical Approval Statement

The study protocol was approved by the Ethics Committee of King Abdulaziz University, Jeddah, Saudi Arabia. The protocol was done according to the ethical guidelines of the 1975 Declaration of Helsinki.

Contribution of Authors

Kumosani TA, Huwait E & Moselhy SS: Conceived idea, designed research methodology, reviewed literature and edited the manuscript.
Alsunusi S & Yaghmoor SS: Conducted experiments, collected data and edited the manuscript.
Huwait E: Analyzed and interpreted data and edited the manuscript
Kumosani TA & Moselhy SS: Interpreted data, reviewed literature and wrote and revised the manuscript.

All authors read, revised and approved the final draft of the manuscript.

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