Original Article

The Protective Role of Parsley extract on Carbimazole Induced Histopathological Alterations in The Exocrine Pancreas of Adult Male albino Rat

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ABSTRACT

Introduction: Carbimazole is used in the treatment of hyperthyroidism. Parsley is a common herb used in various types of industries such as food, cosmetics, and pharmaceuticals.

Aim of the Work: The current experiment is aimed to assess the harmful effect of carbimazole on the exocrine part of the pancreas of adult male albino rats and to analyze the protective role of parsley extract.

Material and Methods: Twenty-eight rats were used and divided equally into control group, parsley group that was administered 1 ml of parsley extract /150 g/day for 8 weeks, carbimazole group that was treated with 1.35 mg of carbimazole/ Kg/day for 8 weeks, and carbimazole and parsley extract-treated group that received both carbimazole and parsley extract in the same doses and durations as the previous groups. The pancreatic specimens were dissected out and prepared for light and electron microscopic examination.

Results: Carbimazole induced clear histopathological alterations in the rat pancreas compared to the control group. There was degeneration in the epithelial cells of pancreatic acini with cytoplasmic vacuolation and a marked decrease in apical acidophilia. Widening in the intercellular space with mononuclear cellular infiltration and blood vessel congestion were also noticed. Morphological analysis showed a significant increase in collagen fibers in-between the pancreatic acini, around the blood vessels, and the interlobular ducts. Ultrastructure analysis also revealed dilatation in the rough endoplasmic reticulum, ballooning mitochondria with disturbed cristae as well as less electron-dense secretory granules. However, carbimazole and parsley extract co-treated showed major improvement in the histology and ultrastructure of pancreatic tissue.

Conclusion: The results verified the protective role of parsley against the toxic effect of carbimazole which could belong to the antioxidant properties of parsley.

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Key Words: Carbimazole; histopathology; pancreas; parsley; ultrastructure.

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INTRODUCTION

Carbimazole is generally recommended for the treatment of hyperthyroidism brought about by various illnesses as nodular goiter and Graves' disease[1]. It incites a decline in the level of thyroid-stimulating hormone, serum thyroxin, and thyrotropin-binding inhibitory immunoglobulins following two, four, and six weeks of its intake[2]. Carbimazole is a 3-carbethoxy methimazole derivative, processed in the liver to methimazole. Methimazole prevents the thyroid peroxidase protein from coupling and iodinating the tyrosine stores on thyroglobulin, thereby lowering thyroid hormones (T3 and T4) synthesis[3].

Previous studies stated that the use of carbimazole is associated with a wide range of side effects varying from minor symptoms such as pruritus, rash, fever, and joint pain to life-threatening conditions as, agranulocytosis and hepatotoxicity with fatal cholestasis jaundice[4]. Other adverse effects in the form of nausea, gastrointestinal pain, and an impaired sense of smell or taste have also been observed during carbimazole therapy[5]. Other studies have indicated that carbimazole can seriously affect the thyroid function of newborns, even at its therapeutic dosage, if taken by pregnant or lactating women[6].

It has been reported that carbimazole therapy can affect different body organs. It can cause mild renal tubular necrosis in rats and was also related to pulmonary hemorrhage and necrotizing glomerulonephritis[7]. Different testicular alterations including vein clog degenerated interstitial tissue and spermatogenic cells with apoptotic and necrotic changes have been seen in rats treated with carbimazole[8].

Parsley (Petroselinum crispum), a member of the Apiaceous family is a bright green annual herb that is historically commonly used as a food additive and treatment for several illnesses. Parsley is commonly used in various types of industries such as food, cosmetics, and pharmaceuticals[9]. Parsley is considered as an important dietary source of essential metals as zinc, iron, calcium, phosphorous and important vitamins such as vitamins A, B, C, β-carotene, when supplemented at sufficient levels. parsley is a popular herb used in the conventional treatment of urinary tract infection, nephritis, cystitis,

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and the prevention of renal stone development due to its anti-inflammatory and possibly immune-boosting properties[10,11].

Many compounds such as flavonoids, carotenoids, ascorbic acid, and tocopherol have been detected upon phytochemical screening of parsley[12]. The latter components are present in fresh parsley leaves and have the capacity of in *vitro* scavenging of superoxide anion. Additionally, methanol extracts of parsley scavenge hydroxyl radical and can protect against membrane oxidation induced by ascorbic acid[13]. Moreover, ethanol and aqueous extracts of fresh parsley Leaves effectively inhibit linoleic acid oxidation and lipid oxidation[14]. Parsley has large amounts of an antioxidant called arsenal which contains luteolin, a flavonoid that can eradicate free radicals in the body which cause oxidative stress in different cells[15,16]. So, it was reported that the addition of fresh parsley leaves to daily diets can elevate the antioxidant capacity of rat plasma and decrease oxidative stress in humans[17].

Parsley extract was used in previous research as protective against pancreatic changes induced by valproate[9]. Moreover, Carbimazole is widely prescribed as a treatment in different conditions of hyperthyroidism. Taken together, this work is aimed to detect if parsley can ameliorate the changes caused by carbimazole in the exocrine pancreas of the adult male albino rat.

MATERIALS AND METHODS

Chemicals

- Carbimazole (Catalog Number, C1080) was purchased from Chemical Industries Development Company (CID), that present in Giza, Egypt in the form of tablets. Carbimazole (5 mg) was present in each tablet.
- Aqueous extract of parsley was prepared as described by[18]. The leaves of parsley were collected from the vegetable market and were washed under a tap running water then they were cut into small pieces and then kept at room temperature away from light and left to dry. 100 mg of dried parsley leaves were soaked in 1000 ml of distilled water, then the mixture was boiled for 30 minutes. The resultant extract was filtered by a filter paper to remove fibers and other insoluble materials. The filtrate was given to rats in a dose of 1 mL/150 g body weight.

The experimental animals

Twenty-eight adult male albino rats (16 weeks of age) weighing between 180 and 200 grams were used, which were collected from the animal house., Tanta University, Egypt. All the animals were housed in clean, well-ventilated cages under similar conditions (22 ± 1°C, and relative humidity of 60 ± 5%) and have been fed the same commercial lab diet as well as water. Additionally, animals are exposed to a twelve-hour light/dark cycle. Before beginning the experiment, the experimental animals were acclimatized to their surroundings for at least one week. The experiment was carried out in Tanta University, Faculty of Medicine, Egypt, following the guidelines for the treatment and use of laboratory animals and was authorized by the Faculty's Local Ethics Committee (approval code: 34680/5/21).

The experimental groups and the experimental design:

Rats were divided equally into the following experimental groups:

- Control group: The animals of this group were given 1 mL distilled water, daily, using an intragastric tube for 8 weeks.
- Parsley extract-treated group: The rats of this group were given an aqueous extract of parsley using the intragastric tube in a dose of 1 mL/150 g/ day for 8 weeks[19].
- Carbimazole treated group: The rats of this group were given carbimazole using the intragastric tube in a dose of 1.35 mg/Kg/day dissolved in I ml distilled water (this dose is equivalent to the human therapeutic dose) for 8 weeks[1].
- Carbimazole and Parsley extract-treated group: These animals were given both Parsley extract and Carbimazole at the same doses and durations of group II and group III respectively (the parsley extract was given about one hour before administration of carbimazole).

By the end of the experiment, all experimental animals had been anesthetized with pentobarbital (40 mg/kg) intraperitoneally[20]. Then, the pancreatic tissues were dissected and processed for light and electron microscopic examination.

Processing for histological examination

Pancreatic specimens were fixed in 10% formalin buffered saline then, dehydrated in ascending grades of alcohol, cleared in two changes of xylene, and finally, the specimens were embedded in hard paraffin. Next, 5 µm thick sections were cut using a rotatory microtome (Leica, US)[21].

Hematoxylin & Eosin (H&E) stained sections

Pancreatic sections were stained by Hematoxylin & Eosin to study the general histological structure of the pancreatic tissue. The nuclei were stained blue by Hematoxylin, and the cytoplasm and connective tissue fibers were stained pink by eosin[22].

Masson trichrome stained sections

Pancreatic sections were stained by Masson trichrome stain for detection of collagen fibers within the pancreatic tissue[23].

Processing for transmission electron microscopy examination

The pancreatic samples were cut into very small pieces about 1mm3, then they were fixed in phosphate-buffered 2.5% glutaraldehyde at 4C for 2 hours. The samples were then rinsed in 0.1 moll/l phosphate buffer, post-fixed in phosphate-buffered 1% osmium tetroxide for 1 hour, and dehydrated in ascending grades of ethanol and acetone for 30 minutes each. The specimens were immersed in propylene oxide and finally embedded in an epoxy resin mixture. Semithin sections (1 μm thick) were cut and stained with 1% toluidine before being examined under a light microscope[24]. Finally, ultrathin sections (80–90nm) were cut, stained with uranyl acetate, and counterstained with lead citrate. The ultrathin sections were examined and photographed by JEOL-JEM-100 SX transmission electron microscope (Tokyo, Japan) at the Electron Microscopic Unit, Faculty of Medicine, Tanta University, Egypt.

Morphometric study and analysis

The area percentage (%) of collagen fibers (Estimation of the bluish coloration) was evaluated by using Ten different non-overlapping fields from each Masson trichrome slide at a magnification of x 400. The software "ImageJ" (version 1.48v National Institute of Health, Bethesda, Maryland, USA) was used for image analysis.

Statistical analysis

Graph pad prism 9 was used for statistical analysis and the data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey posthoc test to compare the differences between the groups. Results were expressed as mean ± SEM and $P < 0.05$ was considered significant.

RESULTS

In the present work, all rats survived and no mortality was observed.

H&E staining

Histological examination of the control group and parsley-treated group revealed the same results and revealed the normal histological structure of the exocrine pancreas. It consists of pancreatic lobules containing closely packed pancreatic acini. Each acinus consists of pyramidal cells with basal rounded nuclei, some cells appear binucleated. The pyramidal cells show characteristic basal basophilia and apical acidophilia. Centro-acinar cells are present in the center of the acini which appeared small with oval euchromatic nuclei and pale staining cytoplasm. Narrow interlobular septa are seen in between acini and containing blood vessels and ducts (Figures 1,2).

On the other hand, histological examination of specimens obtained from carbimazole-treated animals revealed serious affection of the exocrine pancreas. Thickening and fatty infiltration of the interlobular septum were observed (Figure 3). Some acini appeared with a marked decrease in the apical acidophilia with vacuolation of the cytoplasm of some acinar cells (Figure 4). Some sections exhibited loss of pancreatic acinar architecture (Figures 5,6). Some acinar cells appeared with completely basophilic cytoplasm (Figures 3,5). A lot of acinar cells appeared well demarcated with the widening of intercellular space and wide separation of acinar cells (Figure 6). Some pancreatic ducts appeared dilated with irregular outlines and hyaline material in their lumens. Ducts were also lined by crowded nuclei. Many acinar cells showed perinuclear halos around their nuclei (Figure 7). Some blood vessels appeared dilated and congested while other vessels appeared dilated and contained hyaline material. Moreover, some blood vessels appeared dilated with perivascular cellular infiltration along their sides (Figure 8).

Examination of sections from the carbimazole and parsley-treated group revealed marked improvement of the state of the exocrine pancreas. The reappearance of normal pancreatic architecture was observed, most of the acini appeared normal. There were minimal changes in some acini in the form of a few separations between pancreatic acinar cells as well as some acinar cells appeared completely basophilic with thickening of the interlobular septum (Figures 9,10).

Masson trichrome staining

Masson trichrome stained pancreatic sections from control and parsley treated groups showed the scanty amount of blue-stained collagen fibers in the capsule, around blood vessels, and in between pancreatic acini (Figure 11). On the contrary, the Masson trichrome stained pancreatic sections from carbimazole treated group showing massive deposition of blue-stained collagen fibers in the interlobular septum, in-between pancreatic acini, around blood vessels and the interlobular duct (Figures 12,13). on the other hand, carbimazole and parsley treated group revealed relatively few amounts of blue-stained collagen fibers in between pancreatic acini (Figure 14). These observations were confirmed by the morphometric analysis of the area percentage of the collagen fibers in the experimental groups. There is a highly significant increase in the area percentage of collagen fibers of the carbimazole treated group (38.55± 2.838) compared to the control (5.947± 0.7561) and the parsley extract administered group (5.841± 0.6711). While the co-administered carbimazole and parsley treated group revealed a highly significant decrease (10.28±1.340) in collagen fibers area percentage in comparison to the carbimazole treated group with no significant difference between the control and the group treated with both carbimazole and parsley extract (Histogram 1).

Transmission electron microscopic results

Electron micrographs analysis of pancreatic tissue from the control group and the parsley extract-treated group showed the same normal structure of pancreatic acini which consists of pyramidal acinar cells with basal euchromatic nuclei and prominent nucleolus. The nuclei

are surrounded by basal well-developed cisternae of rough endoplasmic reticulum, mitochondria with apical electron-dense secretory granules. The lumen is lined with microvilli with the presence of a centroacinar cell near the lumen of the acinus (Figure 15).

On the other hand, carbimazole treated group showing pancreatic acinar cells with dilatation of RER cisternae (Figures 16,18), rarefaction of cytoplasm, and perinuclear dilatation (Figure 16) as well as less electron-dense secretory granules (Figures 16,17,18). Carbimazole treated group also revealed many pancreatic acinar cells with a small dense nucleus which some have irregular outlines, while the other showed indentation of its nuclear membrane (Figures 17,18). Cytoplasmic vacuolation was noted in some acinar cells (Figure 17) and elongated balloon-shaped mitochondria with partially disrupted cristae were also noticed (Figures 17,18).

However, electron microscopic analysis of pancreatic sections from the carbimazole and parsley co-treated group showed normal pancreatic acini with few microvilli in their lumen. The acinar cells have normal euchromatic nuclei with minimal localized perinuclear dilatation. Normal mitochondria, rough endoplasmic reticulum, and electron-dense secretory granules are demonstrated in most pancreatic acinar cells. Though, the presence of some cytoplasmic vacuolation in few cells with minimal dilatation of only a few RER cisternae was observed (Figures 19,20).

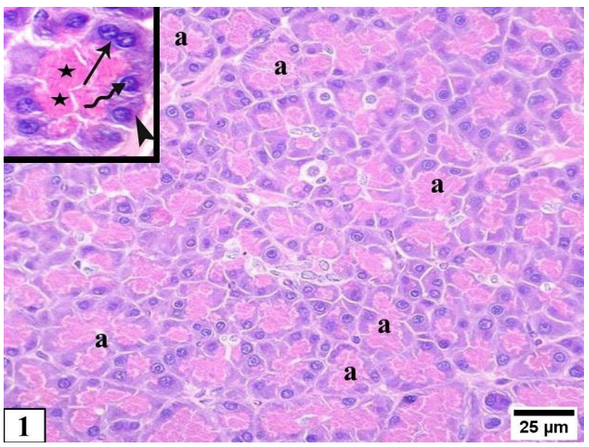


Fig. 1: A photomicrograph of a pancreatic section from the control group showing pancreatic lobules containing normal pancreatic acini (a), each acinus consists of pyramidal cells with basal rounded nuclei (wavy arrow), some cells appear binucleated (arrow). The pyramidal cells show basal basophilia (arrowhead) and apical acidophilia (star). (H&E. x400, inset x1000; Scale bar:25µm).

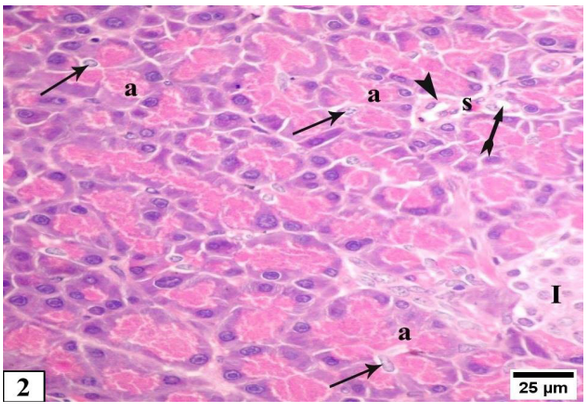


Fig. 2: A photomicrograph of a pancreatic section from the control group showing normal pancreatic acini (a), some acini contain centroacinar cells in their lumens (arrows). Blood vessels (notched arrow) and interlobular ducts (arrowhead) are present in the interlobular septum (S) which is present separating pancreatic acini. Notice the presence of islets of Langerhans (I). (H&E. x 400; Scale bar:25µm).

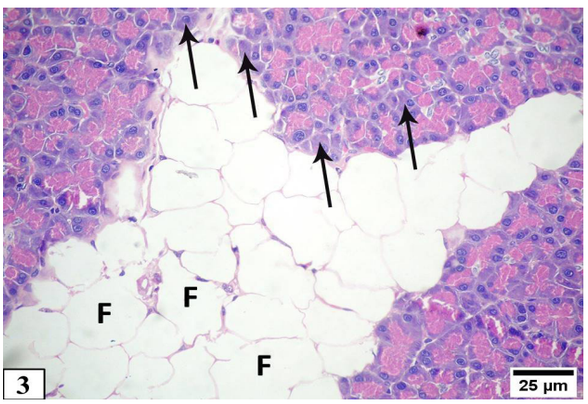


Fig. 3: A photomicrograph of a pancreatic section from the carbimazole treated group showing thickening and fatty infiltration (F) of the interlobular septum. Notice some acinar cells with completely basophilic cytoplasm (arrows). (H&E.x 400; Scale bar:25µm).

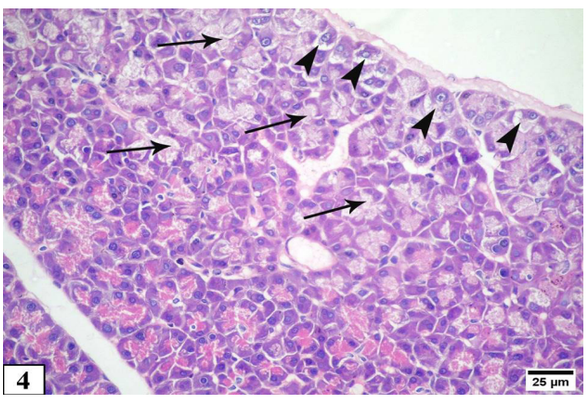


Fig. 4: A photomicrograph of a pancreatic section from the carbimazole treated group showing some acini with a marked decrease in the apical acidophilia (arrows), some acinar cells with vacuolated cytoplasm (arrowheads). (H&E. x 400; Scale bar:25µm).

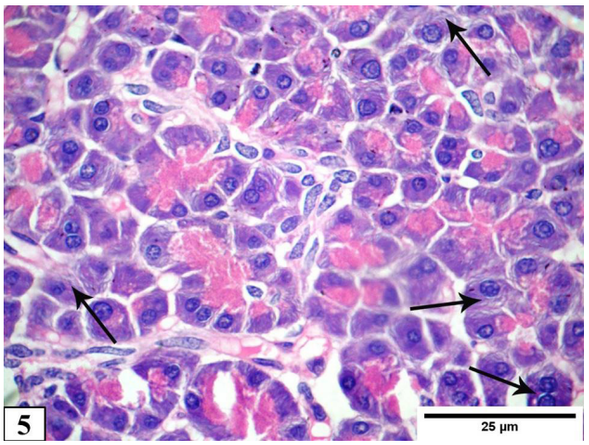
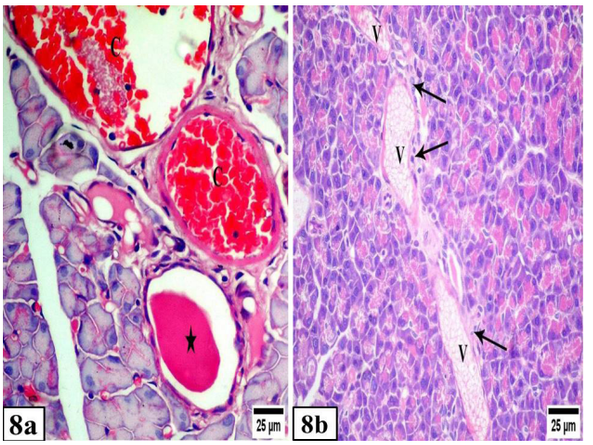


Fig. 5: A photomicrograph of a pancreatic section from the carbimazole treated group showing loss of pancreatic acinar architecture. Notice some acinar cells with completely basophilic cytoplasm (arrow). (H&E. x 1000; Scale bar : 25µm).



Figs. 8 (a&b): Photomicrographs of pancreatic sections from the carbimazole treated group showing some dilated congested blood vessels (C), while other vessels appear dilated and contain hyaline material (star). Notice perivascular cellular infiltration (arrows) alongside dilated blood vessels (V). (H&E. x 400; Scale bar :25µm).

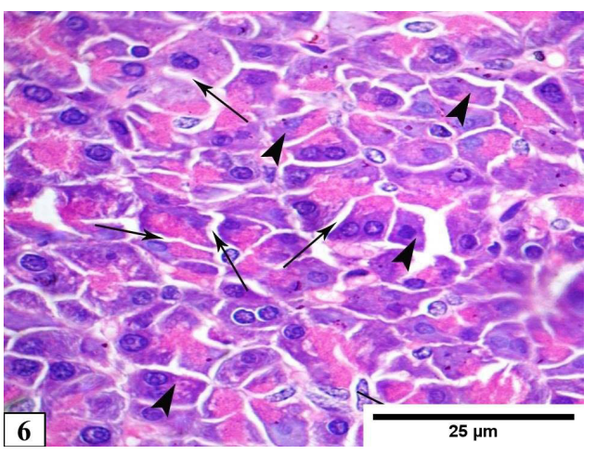


Fig. 6: A photomicrograph of a pancreatic section from the carbimazole treated group showing disruption of normal pancreatic architecture. Some acinar cells appear well-demarcated (arrowheads) with the widening of intercellular spaces (arrows) and separation of acinar cells. (H&E x 1000; Scale bar : 25µm).

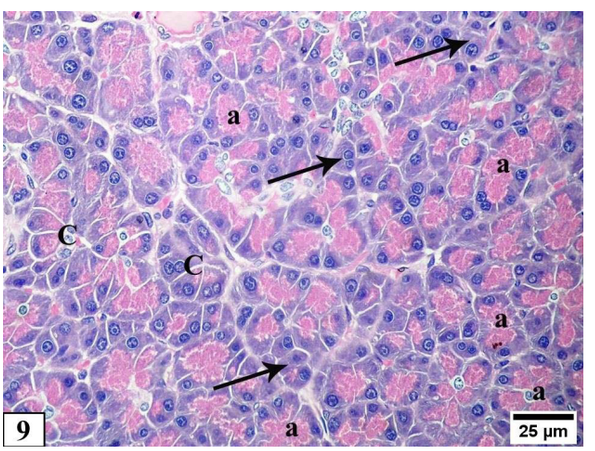


Fig. 9: A photomicrograph of pancreatic sections from the carbimazole and parsley treated group showing most of the acini appearing normal (a), however, some acini (C) appearing with minimal separation between pancreatic acinar cells. Notice some acinar cells with completely basophilic cytoplasm (arrow). (H&E. x 400; Scale bar : 25µm).

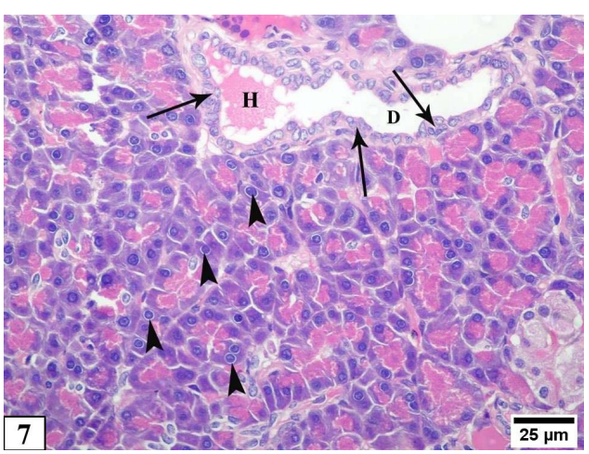


Fig. 7: A photomicrograph of a pancreatic section from the carbimazole treated group showing dilated pancreatic duct with irregular outlines (D), contains hyaline material (H) and lined by crowded nuclei (arrows). Notice perinuclear halos around acinar cells nuclei (arrowheads). (H&E. x 400; Scale bar : 25µm).

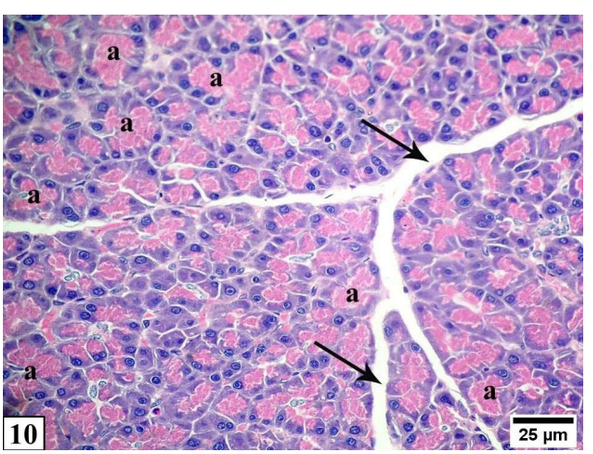
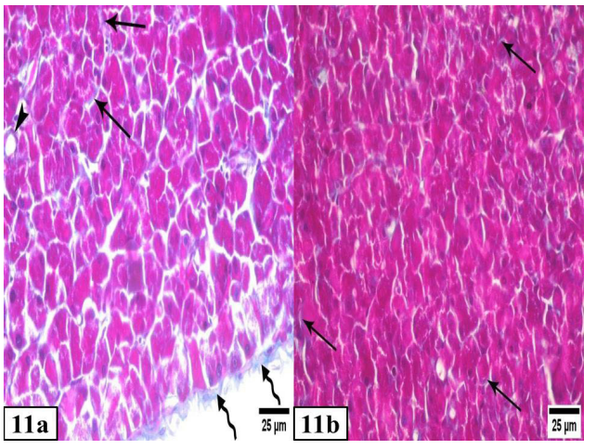
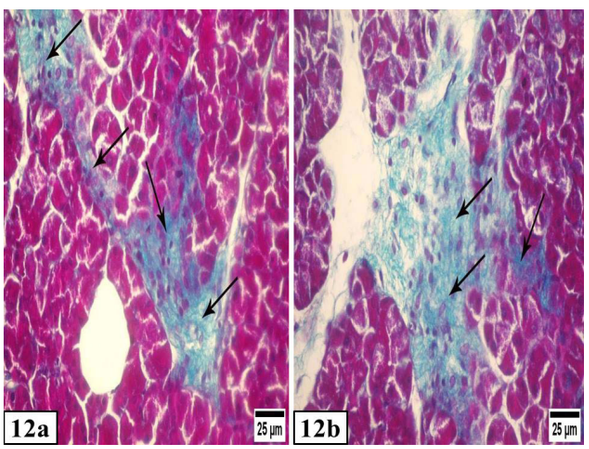


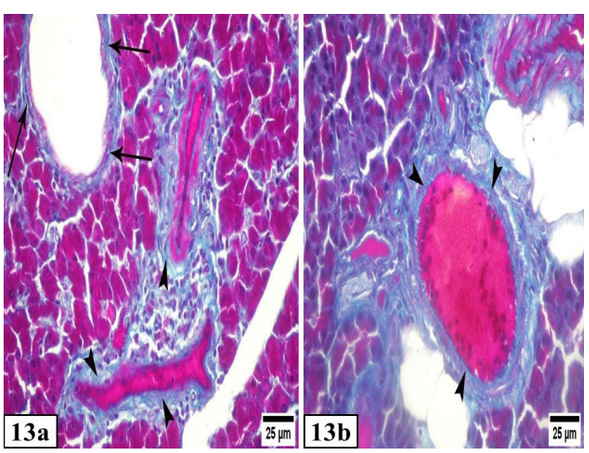
Fig. 10: A photomicrograph of a pancreatic section from the carbimazole and parsley treated group showing nearly normal pancreatic architecture with normal pancreatic acini (a). Notice thickening of the interlobular septum (arrow). (H&E. x 400; Scale bar : 25µm).



Figs. 11 (a & b): photomicrographs of pancreatic sections from the control group showing a scanty amount of collagen fibers in the capsule (wavy arrows), around blood vessels (arrowhead), and in between pancreatic acini (arrows). (Masson trichrome X 400; Scale bar : 25µm).



Figs. 12 (a & b): Photomicrographs of pancreatic sections from the carbimazole treated group showing massive deposition of collagen fibers in the interlobular septum (arrows). (Masson trichrome X 400; Scale bar : 25µm).



Figs. 13 (a & b): Photomicrographs of pancreatic sections from the carbimazole treated group showing excessive deposition of collagen fibers around blood vessels (arrowheads) and interlobular duct (arrows). (Masson trichrome X 400; Scale bar : 25µm).

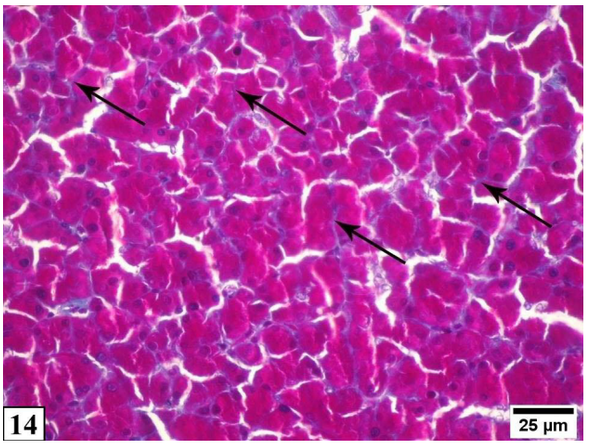
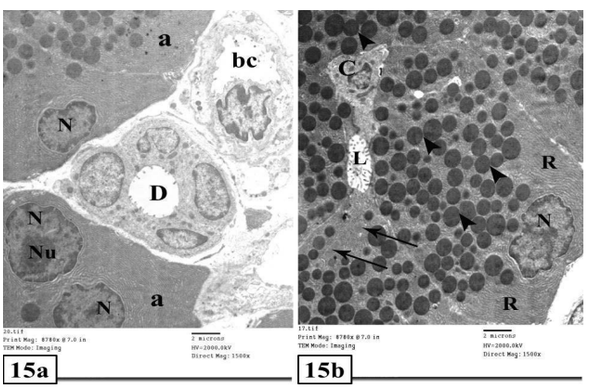
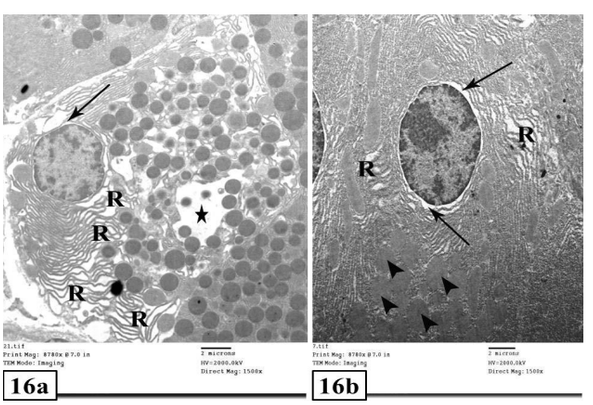


Fig. 14: A photomicrograph of pancreatic sections from the carbimazole and parsley treated group showing relatively few amounts of collagen fibers in between pancreatic acini (arrows). (Masson trichrome X 400; Scale bar : 25µm).



Figs. 15 (a & b): Electron micrographs from the control group (a): Showing two normal pancreatic acini (a) consisting of pyramidal acinar cells with basal euchromatic nuclei (N) containing prominent nucleolus (Nu). Notice the presence of interlobular duct (D) and blood capillary (bc). (b): Showing acinar cells with basal nuclei (N), basal well-developed cisternae of RER (R), mitochondria (arrows), apical electron-dense secretory granules (arrowheads), and lumen with few microvilli (L). Notice the presence of centroacinar cell (C) near the lumen of the acinus. (TEM X 1500, scale bar: 2 µm).



Figs. 16 (a & b): Electron micrographs from the carbimazole-treated group showing pancreatic acinar cells with dilatation of RER cisternae (R), rarefaction of cytoplasm (star), and perinuclear dilatation (arrows). Some secretory granules with less electron density (arrowheads) are noticed. (TEM X 1500, scale bar: 2 µm).

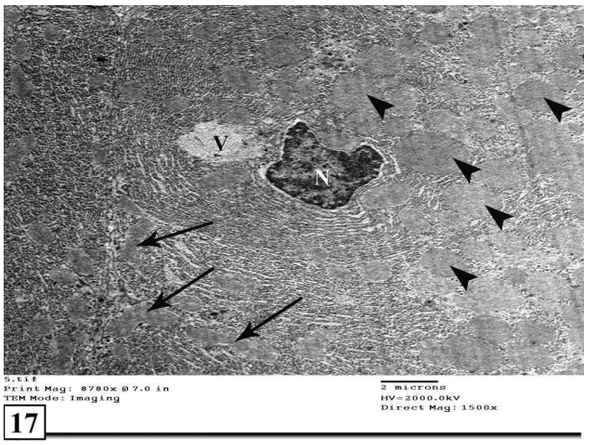
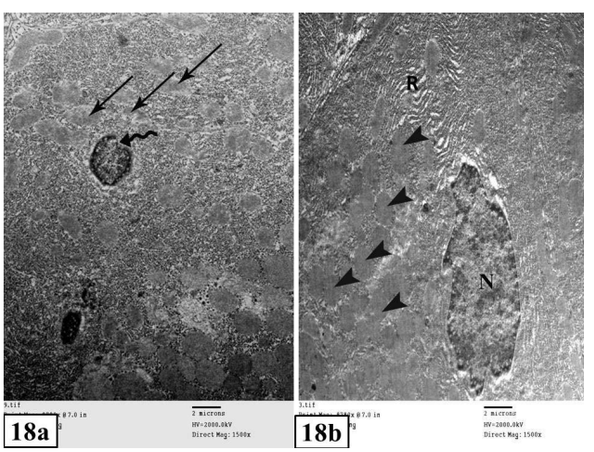


Fig. 17: An electron micrograph from the carbimazole treated group showing a pancreatic acinar cell with a small dense nucleus with irregular outlines (N), cytoplasmic vacuole (V), and elongated balloon-shaped mitochondria with partially disrupted cristae (arrows). Almost all secretory granules appear to be less electron-dense (arrowheads). (TEM X 1500, scale bar: 2 µm).



Figs. 18 (a & b): Electron micrographs from the carbimazole treated group. (a): Showing pancreatic acinar cell with small dense nucleus with indentation of its nuclear membrane (wavy arrow) and swollen partially disrupted mitochondria (arrows). (b): Showing pancreatic acinar cell with irregular nuclear outlines (N), less electron-dense secretory granules (arrowheads), and dilated RER cisternae (R). (TEM X 1500, scale bar: 2 µm).

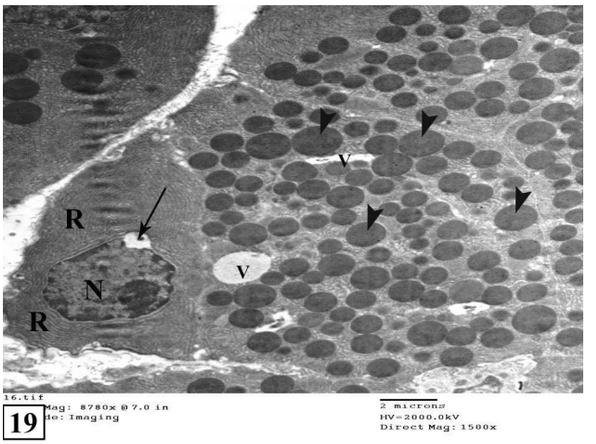


Fig. 19: An electron micrograph from the carbimazole and parsley treated group (group IV) showing apparently normal pancreatic acinar cells, one of them reveals euchromatic nucleus (N) with minimal localized perinuclear dilatation (arrow), normal RER (R), and normal electron-dense secretory granules (arrowheads). Notice the presence of cytoplasmic vacuolation (V). (TEM X 1500, scale bar: 2 µm).

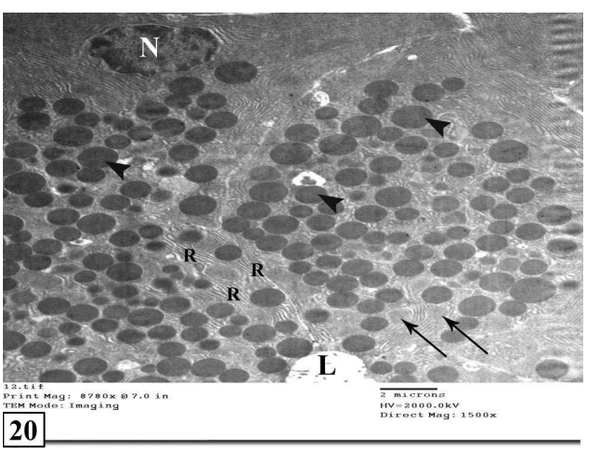
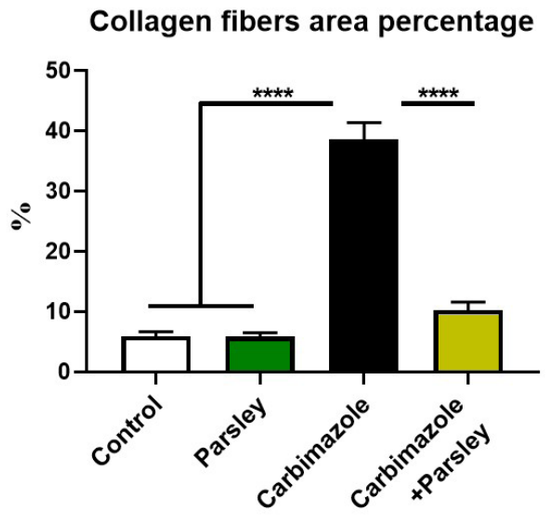


Fig. 20: An electron micrograph from the carbimazole and parsley treated group showing normal pancreatic acinus with a lumen (L) containing a few microvilli. Acinar cells show normal euchromatic nucleus (N), normal mitochondria (arrows) and normal secretory granules (arrowheads). Minimal dilatation of only a few RER cisternae (R) is observed. (TEM X 1500, scale bar: 2 µm).



Histogram 1: Area percentage of collagen fibers between the experimental groups showing a highly significant increase in collagen fibers in the carbimazole treated group compared to the control and the co-administered of carbimazole and parsley groups. Data are represented as mean ±SEM. ****P<0.0001.

DISCUSSION

Carbimazole is the most used antithyroid drug that is usually used as the first-line therapy in the case of the overactive thyroid gland which is known as hyperthyroidism or thyrotoxicosis[25]. Along with the valuable effects of carbimazole, it can also cause undesirable side effects and alterations in the structure and functions of different cells and organs such as the liver, kidney, prostate, testes, and blood vessels[26]. So, this study aimed to clarify the histopathological alterations that possibly occurred in the pancreas as a result of carbimazole administration and the role of parsley extract in the reduction of these changes.

The results of this study revealed different histopathological alterations in the exocrine part of the rat pancreas associated with carbimazole administration. The most obvious histological changes in the acinar cells were vacuolation of the cytoplasm with the absence of apical acidophelia. In addition to congestion and dilatation of blood vessels with dilatation of pancreatic ducts. These results agreed with the cellular degeneration reported after oral carbimazole administration. Earlier studies revealed degeneration and cytoplasmic vacuolation in prostatic epithelial cells and seminiferous tubules, with congestion and dilatation of interlobular blood vessels[1,3]. In addition to, necrosis of renal tubules and interstitial degeneration with increase in serum creatinine, urea and potassium levels of experimental rats induced by carbimazole[27]. The decline in apical acidophelia, completely basophilic cells, and cytoplasmic vacuolation of pancreatic acinar cells may belong to a decrease in the thyroid hormones following impairment in the synthesis of a submembranous matrix of zymogen granules and subsequent drop in secretory protein synthesis in the pancreas[28]. While the dilation and congestion of blood vessels that were described with carbimazole in the pancreas as well as in different organs may be attributed to extra production of nitric oxide (NO) that play a key role in local, systemic, and homodynamic disturbances[29].

The results also revealed mononuclear cellular infiltration around the blood vessels in the carbimazole treated group, which was in agreement with the diagnosis of different cases of acute pancreatitis[30,31] and a case of cholestatic hepatitis within the first three months of carbimazole treatment[32]. Which may belong to dysregulation of the secretion of digestive enzymes with early activation of both intrapancreatic trypsinogen and necrotic factor. Consequently, proinflammatory cytokines are upregulated, and inflammatory cellular infiltrate occurs[33].

Carbimazole administered group also showed widened the spaces between pancreatic lobules and acini, which may account for tissue edema due to increased production of hyaluronic acid with its hydrophilic property[34]. This study also showed thickening and fatty infiltration in some interlobular septa, which was also described in the pancreas of hypothyroidism and diabetic animal models, which may belong to the compensatory mechanism of adipocytes in the case of tissue atrophy[35].

Masson trichrome-stained pancreatic sections of the carbimazole treated group demonstrated a significant increase of collagen fibers in the septa around the pancreatic lobules and blood vessels compared to the control group. This agreed with a previous report that stated increase deposition of connective tissue around the pancreatic acini as well as around blood vessels and ducts with carbimazole[36], with subsequent insufficient tissue oxygenation which induced degenerative changes in these tissues[37].

Electron microscopic findings of this study reinforced the light microscopic results and revealed disturbance in the cellular structure of pancreatic acini induced by carbimazole. There was cytoplasmic vacuolation with less electron-dense secretory granules. Comparable findings were described previously in cases of acute pancreatitis[36,38]. That could be related to a reduction in the synthesis of thyroid hormones with a consequence decline in the synthesis of secretory proteins[39].

The pancreatic acinar cells of the carbimazole group also showed dilatation of RER, elongated, and ballooning of mitochondria with partially disrupted cristae. That could be explained by a deficiency in adenosine triphosphate (ATP) with insufficient energy supply as in the case of acute pancreatitis that makes possible dilatation in RER[40]. An irregular nucleus with widening in peri-nuclear space was also demonstrated with carbimazole. These findings could be a sign of trypsinogen activation inside acinar cells instead of intestinal activation with subsequent cellular damage that induces free radical production and DNA damage[41].

The mechanism of the damaging effect of carbimazole on the pancreas was unclear. It was reported that acute pancreatitis was not cumulative dose-related for carbimazole administration[42]. However, a previous study related the pancreatic damaging effect of carbimazole to an idiosyncratic mechanism depending on the early onset of pancreatitis, besides its reoccurrence shortly after rechallenging even though a direct toxic effect of the drug or its metabolites. The genetic background may likely be applicable, as recently reported for methimazole-induced agranulocytosis[43].

Oxidative stress was also described as one of the main mechanisms through which carbimazole induces structural alterations in the pancreas. In which carbimazole delivers increasing in free radicals and superoxide production that induce the inflammatory reaction within the pancreas[44,45]. Carbimazole administration was also associated with an increase in the level of lipid peroxidation as well as a decrease in the level of catalase, glutathione, and enzymatic antioxidant status as reported previously in some investigations[3].

The current study was also aimed to explore the defending role of parsley juice extract against carbimazole damaging effect on the exocrine pancreas. Parsley (Petroselinum crispum) is one of the famous herbs, that is widely used in the preparation of different food in the whole world. Parsley contains a variety of vitamins such as vitamins A, C, and E. In addition to its content of calcium, iron, manganese, and phosphorus that give it the ability to be used in the management of different sicknesses such as diabetes and cardiovascular diseases[46].

The existing results demonstrated great improvement in the structure of rat pancreas with the coadministration of parsley and carbimazole compared to the group treated with carbimazole only. These outcomes agreed with the protective properties of parsley aqueous extract against different body toxicants that were stated previously in experimental animals. Previous studies proved the efficacy of parsley aqueous extract against the cadmium neurotoxicity and nephrotoxicity induced by carbon tetrachloride[11,12]. They have stated the significant effect of parsley in reducing the level of hydroperoxide and reactive oxygen species production with increasing glutathione synthesis that enhances cellular antioxidant defense mechanism[47]. The previous study has also reported the effective role of parsley administration in the decline of lipid peroxidation and Malondialdehyde concentration which could be attributed to the adequate clearance of free radicals[48].

CONCLUSION

Our findings provide clear evidence that oral administration of carbimazole induced histopathological alterations in rat exocrine pancreas, which confirm the risk of pancreatic damage with carbimazole. So, great cautions are needed during carbimazole prescriptions and administration. The results have also revealed the effective role of parsley aqueous extract in the protection of the exocrine pancreas against carbimazole toxicity.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

الدور الوقائي لمستخلص البقدونس على التغيرات النسيجية التي يسببها الكاربيمازول في الجزء الافرازي من البنكرياس لذكر الجرذ الأمهق البالغ

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مقدمة: الكاربيمازول هو دواء يستخدم في علاج فرط نشاط الغدة الدرقية. يعتبر البقدونس عشب شائع يستخدم في أنواع مختلفة من الصناعات مثل الأغذية ومستحضرات التجميل والمستحضرات الصيدلانية.

الهدف من البحث: تهدف التجربة الحالية إلى تقييم التأثير الضار للكاربيمازول على الجزء الافرازى من بنكرياس الجرذ الأمهق البالغ وتحليل الدور الوقائي لمستخلص البقدونس

مواد و طرق البحث: تم استخدام ثمانية وعشرين من الجرذان المهق البالغة وقسمت بالتساوي إلى مجموعة ضابطة ، مجموعة البقدونس التي تم إعطاؤها ١ مل من مستخلص البقدونس لكل ١٥٠ جم عن طريق الفم يوميا لمدة ثمانية أسابيع ، مجموعة الكاربيمازول التي عولجت بـ ١,٣٥ مجم كاربيمازول لكل كجم عن طريق الفم يوميا لمدة ثمانية أسابيع ، و المجموعة التي تلقت كلا من كاربيمازول و خلاصة البقدونس بنفس الجرعات و المدد مثل المجموعات السابقة. تم تحضير عينات البنكرياس ومعالجتها للدراسة النسيجية (المجهرية الضوئية والمجهرية الإلكترونية).

النتائج: لقد تسبب الكاربيمازول في تغيرات نسيجية مرضية واضحة في بنكرياس الجرذان مقارنة بالمجموعة الضابطه. كان هناك تنكس في خلايا حويصلات البنكرياس مع فجوات سيتوبلازميه وانخفاض ملحوظ في الحمضية القمية. كما لوحظ اتساع في الفراغ بين الخلايا مع تسلل خلوي وحيد النواة واحتقان في الأوعية الدموية. أظهر التحليل المورفولوجي زيادة ذو دلاله احصائيه في ألياف الكولاجين بين حويصلات البنكرياس وحول الأوعية الدموية والقنوات بين الفصوص. و قد كشف التركيب الدقيق أيضًا عن توسع في الشبكة الإندوبلازمية الخشنة ، وتضخم الميتوكوندريا مع تلف في الأعراف بالإضافة إلى حبيبات إفرازية أقل كثافة. ومع ذلك ، أظهر استخدام مستخلص البقدونس مع الكاربيمازول تحسنًا كبيرًا في التركيب الهستولوجى والتركيب الدقيق للبنكرياس.

الإستنتاج: أكدت النتائج على الدور الوقائي للبقدونس ضد التأثير السام لمادة الكاربيمازول والتي يمكن أن تكون مرتبطة بخصائص البقدونس المضادة للأكسدة.