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Ameliorative effect of cinnamon and rosemary against acrylamide–induced renal injury in rats

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ABSTRACT

Acrylamide (ACR) is a contaminant found in heated food products. The exposure of humans and animals to ACR through their diet has become a serious issue. In response, natural dietary antioxidants have emerged as potential protective agents and health supplements to counteract the toxicity caused by dietary contaminants. The study objective is to examine the side-effect of acrylamide on rats' kidneys and investigate whether the use of cinnamon oil, rosemary oil, or a combination of both can reduce these negative effects while acrylamide is being induced. A total of 70 rats that were accustomed to the environment were randomly allocated into seven groups, each consisting of 10 rats, and were exposed to different treatments. These treatments were orally administered once daily for 28 consecutive days, then blood and kidney tissue samples were gathered. The results of the study demonstrated that both rosemary and cinnamon offered some degree of protection to the kidneys. This was evidenced by the nearly normalized levels of parameters such as urea and creatinine. The observed nephroprotection provided by cinnamon and rosemary can be attributed to their ability to inhibit the oxidative stress induced by acrylamide. This was indicated by the reduction in renal lipid peroxidation product Malondialdehyde-(MDA) and the enhancement of antioxidative enzymes, specifically Glutathione-(GSH), and Catalase-(CAT), in the renal homogenate. In conclusion, natural dietary antioxidants such as cinnamon and rosemary show promise in mitigating the adverse effects of acrylamide on the kidneys and could be explored further as potential therapeutic options for renal protection.

1. INTRODUCTION

The prevalence of nephropathies, particularly nephrotoxicity, has emerged as a significant contributor to life-threatening conditions due to excessive exposure to xenobiotics, whether through environmental pollution or drug abuse. The kidneys, vital organs within the human body, are highly susceptible to the harmful effects of toxins. This acute damage to the kidneys has the potential to develop into chronic renal disease (Venkatachalam et al 2010). Acrylamide (ACR) is a food process toxicant, that develops during cooking at temperatures above 120 °C (kumar et al., 2018), It also occurs in fried potato, French fries, savory snacks, starchy extruded products, and coffee.

The International Agency for Research on Cancer has classified ACR as potentially carcinogenic to humans due to the lack of epidemiological evidence indicating its carcinogenicity in humans. Extensive research has been dedicated to investigate the harmful consequences linked to the consumption of ACR, primarily based on experimental findings from studies conducted on rats and mice. These studies have shown evidence of detrimental effects like liver damage (hepatotoxicity) and kidney damage (nephrotoxicity). Detectable amounts of ACR have been found in baked goods, particularly in bread and similar products, which can contribute significantly to dietary exposure for consumers due to their frequent consumption. Factors such as moisture content, pH, temperature, and baking time can influence the formation of ACR during the bread baking process. (Andačić et al., 2020). In the process of Maillard reactions, numerous desirable compounds are formed that greatly influence and enhance the flavor and taste of baked goods. However, the drawback lies in the inevitable formation of ACR in these products due to the high temperatures involved. (Komoike et al., 2020).

Cinnamon is a commonly used ingredient in the food industry, where it is frequently utilized as a flavoring and additive spice. Its components are essential in the production of various food additives like seasoning for baked goods and chili sauce. Cinnamon and its derivatives have been found to possess numerous beneficial properties, such as being antioxidants, anti-inflammatory, anti-cancer, antimicrobial, and antidiabetic (Tuzcu et al., 2017). Rosemary essential oil, leaf extracts, and isolated substances have been credited with a variety of biological effects and health advantages, including antibacterial properties, due to the extensive use of Rosmarinus officinalis as a medicinal plant, antifungal, anti-inflammatory,

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antiatherogenic, antiangiogenic, antihypertensive, antiulcer, anti-diabetic and other effects. In addition to these effects, this plant is also well known for its powerful antioxidant activity, upon conducting phytochemical analyses on rosemary extracts and essential oils, it has been identified that various substances, including flavonoids and phenolic compounds Dorta et al., 2008, possess established antioxidant properties. These antioxidant activities of Rosmarinus officinalis may contribute to elucidating certain biological effects associated with it. The administration of cinnamon, rosemary, or a combination of both to nephrotoxic rats resulted in a notable reduction in the average value of MDA, accompanied by a significant increase in renal GSH levels (Zohrabi et al., 2012).
In light of the ongoing research into the toxic effects of acrylamide on animal renal tissue, the primary objective of this study was to evaluate the potential ameliorative effects of cinnamon and rosemary in mitigating acrylamide-induced nephrotoxicity in adult male albino rats.

2. MATERIAL AND METHODS

Ethics statement

Conducting this study followed rigorous adherence to the guidelines provided in the 8th edition of the Guide for the Care and Use of Laboratory Animals from the National Institutes of Health, as well as the principles established by the International Council for Laboratory Animal Science (ICLAS). The study was also approved by the Benha University Animal Care and Use Committee under number (03-03-23).

2.1. Drugs and chemicals

The white crystalline powder form of acrylamide was obtained as (Acrylamide LR for synthesis) from Fine-Chem Limited Company-Mumbai, India with a powder purity of approximately 98.5%. Prior to administration, the powder was freshly dissolved in distilled water. Acrylamide was utilized at a dose of 20 mg/kg body weight (Bedir et al., 2021).
El-captain Company, based in El Obour City, Cairo, Egypt, supplied the cinnamon and rosemary oils used in the study. Cinnamon oil was employed at a dose of 200 mg/kg body weight (Prajapati et al., 2019), while rosemary oil was utilized at a dose of 250 mg/kg body weight.
Bio-Diagnostic Company, situated in Dokki, Giza, Egypt, provided the diagnostic kits required for estimating markers such as urea and creatinine, as well as oxidative stress markers including Malondialdehyde (MDA), Glutathione (GSH), and Catalase (CAT) in renal tissue homogenate.

2.2. Experimental design
The current study included a total of 70 male Wister rats, which were white albino and weighed between 180-200 grams. These rats were obtained from the Center of Laboratory Animals at the Faculty of Veterinary Medicine, Benha University, Egypt. Before starting the experiment, the rats were given a one-week period to adapt to their new environment. Throughout the study, the rats were freely provided with a standard laboratory balanced commercial diet and water. The research followed the guidelines for experimental animal care and procedures set by the Faculty of Veterinary Medicine, Benha University, Benha, Egypt. The basal diet given to the rats was formulated according to the recommended nutrient requirements for rat maintenance specified by the National Research Council (1995). Acclimatized rats were distributed into seven groups, each comprising 10 rats, to fulfill the objectives of the present study.
The treatment of each group was as follows:
Group 1: Rats in this control group were orally administered distilled water once daily for 28 consecutive days.
Group 2: Rats in this group were taken acrylamide orally administering at a dose of 20 mg/kg body weight once daily for 28 consecutive days.
Group 3: Rats in this group received oral administration of cinnamon oil at a dose of 200 mg/kg body weight once daily for 28 consecutive days.
Group 4: Rats in this group were orally administered rosemary oil at a dose of 250 mg/kg body weight once daily for 28 consecutive days.
Group 5: Rats in this group received acrylamide at a dose of 20 mg/kg body weight followed by oral administration of cinnamon oil at a dose of 200 mg/kg body weight once daily for 28 consecutive days.
Group 6: Rats in this group received acrylamide at a dose of 20 mg/kg body weight followed by oral administration of rosemary oil at a dose of 250 mg/kg body weight once daily for 28 consecutive days.
Group 7: Rats in this group received acrylamide at a dose of 20 mg/kg body weight followed by oral administration of cinnamon oil at a dose of 200 mg/kg body weight, and then rosemary oil at a dose of 250 mg/kg body weight once daily for 28 consecutive days.

2.3. Sampling

After the end of 28 days, treatment period, all rats were euthanized and blood samples, kidney tissue were collected for biochemical and histopathological examinations.

2.3.1. Blood samples
After 28 days of treatment, blood samples were obtained from each group of 10 rats. The samples were collected from the retroorbital plexus, located at the inner corner of the eye, using capillary tubes. An anticoagulant was added to each sampling tube to prevent clotting at room temperature. The collected samples were then centrifuged at a speed of 900Xg for 10 minutes to separate the clear plasma which was subsequently transferred to Eppendorf's tubes using automatic pipettes. The plasma samples were stored in a deep freezer at -20 °C for analysis.

2.3.2. Tissue specimens
At the end of the experiment the kidney was dissected out, and then washed with normal saline to separate the surrounding blood, fats and connective tissue. Samples from kidney of about (1 gm) of 10 rats in each group were collected in dry, clean, tightly closed and labeled Eppendorf tubed Tissues were

homogenated with phosphate buffer solution PH 7.4 and centrifuged at 10000 rpm for 10 minutes then stored at -20°C for determination of oxidative cascade in tissues. Other tissue samples of kidney were collected and fixed in 10% formalin for histopathological studies.

2.4. Serum and tissues analysis

The assessment of various biochemical parameters, including enzyme activities in blood, tissues, and body fluids, plays a crucial role in evaluating the safety of drugs. Creatinine and urea activities in plasma were measured using specific kits and determined spectrophotometrically, Kaplan, L.A. and Pesce, A.J. (1984); Murray, R.L (1984). The manufacturer's instructions were followed for the assay procedures.
The oxidative and antioxidative parameters in kidney homogenate, such as MDA, GSH, and Catalase, were also determined spectrophotometrically using specific kits. The methods described by Aebi (1984) were followed for the respective assays. The manufacturer's instructions were followed during the analysis.
For the histopathological examination, the protocols outlined by Banchroft et al. (1996) were followed.

2.5. Statistical analysis

One-way analysis of variance (ANOVA) was used to analyze the collected data. Post hoc testing was performed using Duncan's test. The analysis was conducted using SPSS 25 for Windows. The results were presented as mean ± standard error (SEM) and statistical significance was determined at P values of ≤0.05.

3. RESULTS

3.1. Serum Biochemical parameters
Rats administered Acrylamide exhibited a significant ($p<0.05$) increase in serum creatinine and urea levels compared to the control group. However, notable improvement in these parameters was observed following administration of cinnamon and/or rosemary oil, as indicated in Table (1).

Table 1: The serum creatinine and urea levels in control and treated groups

Experimental Group	Creatinine (mg/dL)	Urea (mg/dL)
Control group	0.87±0.03^{e}	34.70±2.00^{e}
Acrylamide group	2.01±0.08^{a}	75.87±1.26^{a}
Cinnamon group	0.86±0.03^{e}	33.95±0.86^{e}
Rosemary group	0.83±0.02^{e}	36.69±0.68^{e}
Acrylamide + Cinnamon group	1.55±0.03^{b}	63.91±1.93^{b}
Acrylamide + Rosemary group	1.39±0.05^{c}	54.28±1.14^{c}
Acrylamide + Mix group	1.16±0.05^{d}	47.21±1.16^{d}

The data is presented as (Mean ± S.E), with S.E representing the standard error. Mean values with distinct superscript letters within the same column indicate a statistically significant difference at ($P<0.05$).

3.2. Oxidative stress
As in Figure 1 (A, B, and C), rats treated with acrylamide displayed a considerable elevation in MDA levels and a significant reduction in CAT and GSH levels in renal tissues compared to the control group. However, significant improvement in these parameters was observed following cinnamon and/or rosemary administration.

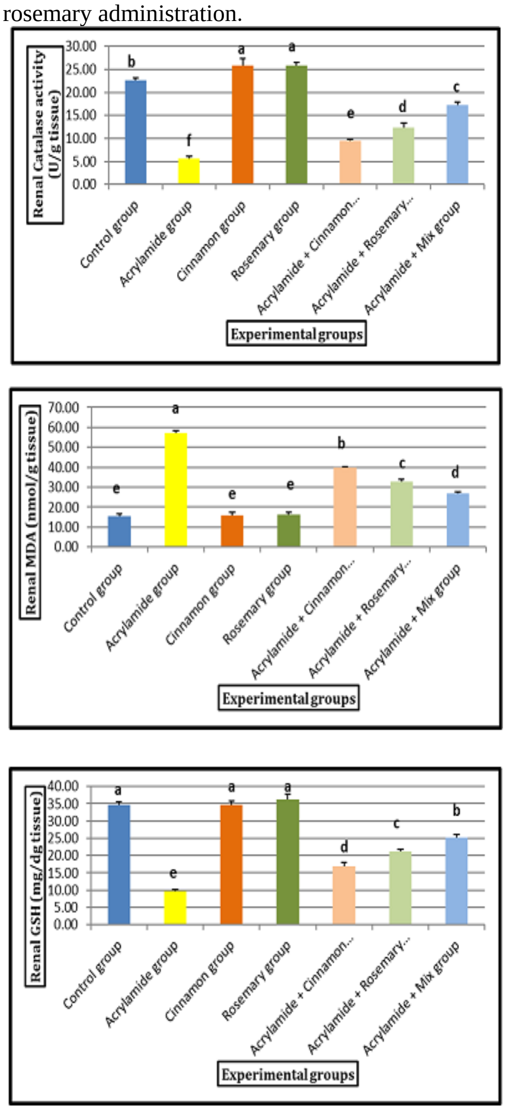

Figure (1): Renal CAT, MDA and GSH levels of rats in control and treated groups

3.3. Histopathological changes
The microscopic examination of the kidneys in control, cinnamon and rosemary groups revealed normal glomeruli made up of glomerular tufts surrounded by Bowman's capsules and convoluted renal tubules lined by a simple cuboidal epithelium (Fig. 2 A). In contrast, nearly all of the examined kidneys in the acrylamide group showed severe disruption of renal histoarchitecture, including glomeruli and renal tubules. Severe degeneration and even necrosis of renal tubular epithelium were commonly seen (Fig. 2 B). Desquamation of some of renal tubular epithelium and presence of hyaline casts in the lumen of certain renal tubules were detected. In addition, there was significant glomerular damage, including shrinking of the glomerular tufts with widening of Bowman's spaces (Fig. 2 C). Pretreatment with cinnamon attenuated the acrylamide induced renal damage. Almost all examined kidney sections revealed more or less typical histological structures of the glomeruli and renal tubules with only pyknosis of nuclei of some renal tubules and presence of eosinophilic debris

inside lumens of few renal tubules (Fig. 2 D). Similarly, administration of rosemary reduced the kidney impairment especially the glomerular damage caused by acrylamide. The only microscopic abnormalities seen in the kidneys of rats in acrylamide + rosemary group were multifocal renal tubular degenerative changes and pyknosis of the nuclei of some tubular epithelium with the presence of eosinophilic debris in the lumens of some renal tubules (Fig. 2 E). Furthermore, combination of cinnamon and rosemary provided greater protection against acrylamide -induced renal damage where the majority of the examined kidneys revealed improvement in the renal histoarchitectures. Almost all the examined kidney sections displayed more or less normal renal corpuscles and only pyknosis of the nuclei of renal tubules was occasionally seen in few examined kidneys (Fig. 2 F).

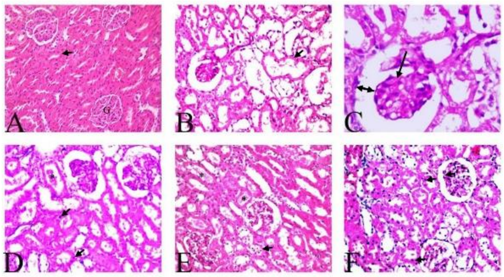

Figure (2): Representative photomicrographs of H&E stained kidney sections showing (A) normal glomeruli and renal tubules X200 (B) extensive degeneration and necrosis of renal tubular epithelium X200 (B), shrinkage of the glomerular tuft with widening of Bowman's space X400 (C), pyknosis of nuclei of some renal tubules and eosinophilic debris in lumen of renal tubule X200 (D), degeneration of few renal tubular epithelium and pyknosis of some nuclei with eosinophilic debris in the tubular lumens X200 (E) pyknosis of nuclei of few renal tubules X200 (F). (A: Control, B&C: Acrylamide group, D: Acrylamide + Cinnamon, E: Acrylamide + Rosemary F: Acrylamide + Cinnamon + Rosemary)

4. DISCUSSION

The serum levels of creatinine in the current experiment on ACR-exposed animals showed a significant increase, indicating renal impairment. This finding is consistent with previous studies conducted by Karimani et al. (2019), which also reported that creatinine is a byproduct of muscle activity that circulates in the blood and is eliminated solely by the kidneys. Therefore, there is a direct link between creatinine levels and renal function. Most of the creatinine eliminated by the kidneys is freely filtered in the renal glomeruli, with only a small fraction being filtered by the tubular component, making it a good indicator of renal-glomerular function. Blood urea and serum creatinine levels in the blood are commonly used as markers for kidney impairment.

Ghorbel et al. (2016) conducted a study that found a significant increase in serum urea and creatinine levels in acrylamide-induced nephrotoxicity compared to the control group.

Renal damage induced by ACR primarily occurs through the main pathogenic mechanism of oxidative stress. Oxidative stress refers to an imbalance between oxidants and antioxidants, with an increase in oxidants, according to the research conducted by Birben et al. (2012). The role of oxidative stress in ACR-induced kidney damage has been supported by various researchers. Acrylamide has been found to cause significant decreases in the activities of GSH and CAT, while also leading to significant increases in MDA concentration in kidney tissues. Our findings align with those of numerous other studies, such as Akbaribazm et al. (2021), which also observed similar alterations in oxidative stress markers in relation to acrylamide.

An elevation in lipid peroxidation is a key process underlying the oxidative damage to the kidneys caused by acrylamide, and this damage can be mitigated by antioxidants. MDA, a harmful byproduct of lipid peroxidation, has been demonstrated to be involved in this process, as noted by Elhelaly et al. (2019). Our experimental results reflect a reduced level of GSH in the acrylamide group, accompanied by an increased level of MDA. This finding is supported by the research conducted by Alturfan et al.(2012) .

The histopathological changes observed in the present study indicate that animals exposed to ACR exhibited various alterations in the renal tissue. These alterations included congestion of the glomerular capillary tuft, and presence of infiltrating inflammatory cells, focal hemorrhages, renal tubular degeneration and necrosis. These findings align with previous studies conducted by Karimani et al.(2019) .

Antioxidants play a role in protecting the kidneys by inducing apoptosis of myofibroblasts and promoting the regeneration of epithelial cells. Cinnamon, a widely used herbal medication, is commonly found in Asia and Australia. The medicinal properties of this plant are attributed to its active components, including coumarin, cinnamaldehyde, and cinnamic acid, as identified through cinnamon analyses conducted by Lim and Ko (2022). Cinnamon possesses several beneficial effects, such as being antiallergic, antiviral, antimicrobial, anti-inflammatory, and antioxidant. It has also been associated with potential benefits in treatments for heart disease and diabetes. Recent studies have provided evidence of cinnamon's therapeutic and preventive potential against various infections associated with oxidative stress, as documented by Salman et al.(2021) .

Cinnamon, an herb commonly used in various applications, possesses antioxidative properties that can protect the kidneys from damage induced by diabetes and various toxins .

The nephroprotective effects of cinnamon have been attributed to the presence of cinnamaldehyde and eugenol. Several studies have reported the beneficial nephroprotective action of cinnamon as an antioxidant in different models, such as paracetamol-induced nephrotoxicity in rats (Quamuddin et al., 2021), gentamicin-induced nephrotoxicity (Elkomy et al., 2020), cypermethrin-induced nephrotic disorders (Sakr and Albarakai, 2014), and the negative impact of fluoxetine drug on renal tissue (Hashem et al., 2022). These researchers reported significant reductions in creatinine and urea levels, along with an improvement in the histological structure of the kidney.

Cinnamon extract has a protective effect against renal oxidative injury, which can be attributed to its ability to enhance antioxidant enzymes and inhibit the synthesis of reactive oxygen species (ROS). The study also indicated that Cinnamon extract contains a high concentration of polyphenolic compounds, making it suitable as a natural nutritional supplement with antioxidant properties. Similar findings have been reported by previous researchers, both in vitro and in vivo, such as Eidi et al. (2012), who also observed the antioxidant action of Cinnamon.

Cinnamon has been shown to possess antioxidant activity through the neutralization of free radicals and inhibition of the 5-lipoxygenase enzyme. Additionally, it has been found to decrease lipid peroxidation and increase the total antioxidant power, as demonstrated by Roussel et al.(2009) .

Mishra et al. (2010) reported that cinnamon provides kidney protection by reducing glomerular expansion and decreasing tubular dilations.

Rosemary (Rosmarinus officinalis L., Lamiaceae) is a perennial herb with a woody structure and is originally from the Mediterranean region.

Rosemary leaves are widely recognized for their common use as a food condiment to enhance flavors. However, this plant has also gained significant attention for its diverse medicinal purposes. In traditional medicine, rosemary has been valued as a stimulant and mild analgesic, often regarded as an effective remedy for ailments such as headaches, poor circulation, inflammatory disorders, and both physical and mental fatigue. Additionally, rosemary has been empirically utilized in folk medicine as a choleretic and hepatoprotective agent (Yu et al., 2013).

The pharmacological effects of rosemary can largely be attributed to the remarkable antioxidant activity of its primary chemical constituents. The potent antioxidant properties of rosemary are primarily associated with its major diterpenes, carnosol and carnosic acid, as well as the components found in its essential oil (Ngo et al., 2011).

Rosemary essential oil possesses antioxidant and antimicrobial properties, as demonstrated by Bozin et al. (2007). These qualities enable it to prolong the shelf life of food products and maintain their overall quality during storage. Consequently, rosemary essential oil has been utilized as a biopreservative in the food industry, as noted by Ojeda et al.(2013) .

Virk et al. (2013) found that co-treatment with rosemary leaf extract as an antioxidant effectively reduced malondialdehyde (MDA) levels, increased the activities of superoxide dismutase (SOD) and catalase (CAT), and restored cellular disorganization induced by cadmium in the liver and kidney.

The potential of rosemary extract treatment as a supportive therapy for lead-induced hepatotoxicity and nephrotoxicity in rabbits was investigated by Mohamed et al. (2016). Their study revealed that pretreatment with rosemary extract had the ability to safeguard the liver and kidney from lead-related damage through its radical-scavenging and antioxidant activities.

Rosemary was found to improve the nephrotoxicity of gentamicin in guinea pigs and alleviate the structural changes observed in the kidney, resulting in decreased levels of blood urea, creatinine, and uric acid, as observed by Azab et al.(2014) .

The potent antioxidant and anti-apoptotic properties of carnosic acid were associated with enhancements in glutathione (GSH) levels and the activities of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), as highlighted by Sahu et al , (2011) .

The nephrotoxic effects of CCl_4 in mice were suppressed by rosemary through the prevention of lipid peroxidation, as demonstrated by Hamed et al . (2020).

Tavafi et al. (2011) observed a significant reduction in glomerular hypertrophy and glomerulosclerosis, accompanied by attenuated levels of urea and creatinine.

Rosemary was also found to protect against histopathological lesions and oxidative stress induced by doxorubicin in the liver, kidney, and heart of mice, according to Ahmed and Abdella.(2010)

According to Mwaheb et al. (2016), the use of Rosmarinus officinalis was effective in averting histopathological lesions and oxidative stress that were caused by (Li_2CO_3) in the kidneys and testis tissues.

According to Sakr et al. (2012), the use of rosemary aqueous extract was found to alleviate the nephrotoxicity caused by CCL_4 in albino rats. The protective effect of rosemary can be attributed to its high capacity to scavenge various reactive oxygen and nitrogen species, particularly free radicals, which is believed to be one of the primary mechanisms behind the antioxidant properties of phenolic phytochemicals. Additionally, Abdelkader et al. (2012) demonstrated that the rosemary aqueous extract can mitigate lead-induced kidney toxicity by stimulating the endogenous antioxidant defense system.

5. CONCLUSIONS

The results of biochemical and histopathological analysis revealed that administration of cinnamon and/or rosemary oils to acrylamide-treated rats significantly decreased serum creatinine and urea and efficiently reduced renal MDA level, they also increased GSH, and CAT activity in kidney tissue. Cinnamon and/or rosemary oils treatment mitigated renal damage associated with acrylamide treatment and this is attributed to their potent antioxidant activities. Cinnamon and rosemary oils are recommended to people with high risk of acrylamide exposure.

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