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Original Research Article

Effect of taxifolin on acrylamide-induced oxidative and proinflammatory lung injury in rats: Biochemical and histopathological studies

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Abstract

Purpose: *To examine the probable beneficial effects of taxifolin against acrylamide damage in lung tissue.*

Methods: *18 male albino Wistar rats were divided into healthy (HG), acrylamide (AG) and taxifolin + acrylamide (TAG) groups. Once a day for 30 days, acrylamide was orally administered to the AG group (50 mg/kg), while ACL (50 mg/kg) and TAX (20 mg/kg) were orally administered to TAG group. Protein concentration, malondialdehyde (MDA), and total glutathione (tGSH) levels as well as oxidant and antioxidant molecules concentrations of the rat lung tissues were measured. In addition, degree of mononuclear (MN) cell infiltration and bronchial-associated lymphoid tissue (BALT) hyperplasia was evaluated by the degree of hyperplasia (absent, mild, moderate, severe). The histopathological and biochemical data the groups were compared.*

Results: *When compared in terms of MDA levels, it was found that the AG group had high MDA levels, and the TAG group had low MDA levels. ($p < 0.001$). TAG group was found to have a higher tGSH level than the AG group ($p < 0.001$). Compared to the AG group, lower TOS and higher TAS levels were obtained in the TAG group ($p < 0.001$). In addition, when TOS levels of TAG and HG groups were compared, the TOS levels between the two groups were statistically insignificant ($p = 0.213$). It has been observed that TAX administration prevents the increase in NF-KB level. When the NF-KB levels of the AG and TAG groups were compared with each other, there was a statistically significant difference ($p = 0.001$). In the AG group, severe MN cell hyperplasia and BALT hyperplasia were observed histopathologically. It was determined that these findings were alleviated in the TAG group. A histopathologically significant difference was found between AG and TAG groups ($p < 0.05$).*

Conclusion: *Taxifolin has beneficial effects against lung injury caused by acrylamide, a health-damaging environmental factor. Regular use of taxifolin can be recommended, especially in people who are known to have intense contact with acrylamide. There is a need for research studies on this subject.*

Keywords: *Acrylamide, Taxifolin, Lung injury, Oxidative stress, Inflammatory response*

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INTRODUCTION

Acrylamide (ACL; CH_2=$CHCONH_2$) is a commonly used chemical compound. ACL can be found in two different forms: a monomer and a polymer (polyacrylamide). It has been mentioned that ACL monomers exhibit toxic properties while ACL polymers do not [1]. ACL has been used in many industries as an industrial product. These industrial fields include water treatment processes, papermaking, polyester resin production, gel chromatography and electrophoresis. ACL is also produced in foods exposed to high temperatures, called the Maillard reaction. According to a study conducted in Sweden, 85% of ACL consumed daily is found in carbohydrate-rich foods [2].

Furthermore, ACL is produced during the burning of cigarette tobacco and is inhaled into the body like smoke. It has been determined that extreme fatigue, ataxia and peripheral neuropathy have appeared in individuals who deal with ACL-containing products. Alturfan *et al.* reported that ACL causes oxidative organ damage in the lung, liver, kidney and testicular tissues [3]. According to Batoryna *et al.*, the inflammation and alveolar epithelium changes observed in the lungs of animals exposed to ACL are believed to be caused by a change in oxidant-antioxidant parameter levels [4]. Ghorbel *et al.* showed that ACL could cause inflammatory damage and oxidative damage in tissues [5]. All this information in the literature suggests that antioxidant and anti-inflammatory agents may help prevent or reduce ACL-induced lung injury.

Flavonoids are phytochemicals that have been discussed in many studies because of their antioxidant and anti-inflammatory properties. Taxifolin (TAX), a flavonoid, has been reported to have antioxidant, anti-inflammatory, antiviral, antibacterial, anticancer and neuroprotective effects [6]. TAX is known to inhibit the production of reactive oxygen species (ROS). However, no information was found in the literature regarding the therapeutic or protective effects of TAX against ACL-induced lung injury. In this study, oxidative stress was created in the lungs of rats by using ACL and lung damage was caused. The effect of TAX on this damage was investigated biochemically and histopathologically.

EXPERIMENTAL

Animals

The experiment involved 18 male albino Wistar rats weighing between 275 g and 287 g. The animals were kept and fed in the experimental environment to adapt to the environmental conditions: at room temperature (22 °C) for one week. The rats subjected to the experiment were taken from Ataturk University Medical Experimental Application and Research Center. The 'Ataturk University Animal Experiments Ethics Committee (AÜHADYEK)' approved the stages of this study for ethical principles in a letter dated 16/04/2020 and numbered 75296309-050.01.04-E.2000106271.

Chemical and reagents

Thiopental sodium (IE Ulagay, Turkey), taxifolia eva (Russia), and ACL (Sigma-Aldrich Chemical Company, USA) were used in the experiment.

Animal grouping and treatments

The albino Wistar male rats used in the experiment were categorised into three groups: those that were healthy (HG), those that received only ACL (AG) and those that received TAX + ACL (TAG).

The TAG group of rats (n = 6) was gavaged with a 50 mg/kg dose of TAX. The AG (n = 6) and HG (n = 6) groups received 0.5 mL distilled water (0.5 mL) orally as a solvent. The AG and TAG groups were gavaged with a 20 mg/kg dose of ACL 1 h later. These doses were administered to the groups every day for 30 days. At the end of this period, the animals were sacrificed using 50 mg/kg of thiopental sodium. Lung tissues of animals were removed, and samples were prepared. The evaluation was carried out by comparing the biochemical and histopathological results of the AG group to those of the TAG and HG groups.

Preparation of samples

At this study stage, 0.2 g of lung tissue was taken from each rat. Tissues were homogenised in 1.15% potassium chloride solution for malondialdehyde (MDA) on ice. Tissue homogenisation was performed with 2 mL phosphate buffer to determine protein, nuclear factor kappa B (NF-ƘB), total glutathione (tGSH), total oxidant status (TOS) and total antioxidant status (TAS). It was then centrifuged at +4 °C and 10000 rpm for 15 minutes.

Protein evaluation

The protein concentration was measured using the Bradford method [7]. This method involves measuring the absorbance of a coloured complex formed by the Coomassie Brilliant Blue G-250 dye binding to proteins at 595 nm. The

results of this measurement were standardised by dividing by protein.

Determination of MDA

MDA levels are determined by the method described by Ohkawa [8]. Accordingly, thiobarbituric acid and MDA form a coloured complex. The absorbance of this complex is measured at high temperature (95 °C), using spectrophotometry and at a wavelength of 532 nm. The MDA concentration in the tissue was measured in µmol/g protein.

Assessment of tGSH

In the measurement environment, 5.5'-dithiobis (2-nitrobenzoic acid) (DTNB) was a disulfide chromogen readily reduced by compounds with sulfhydryl groups. The yellow colour was obtained. This colour was measured spectrophotometrically (at a wavelength of 412 nm) [9]. The tGSH concentration in the tissue was determined in µmol/mg protein.

Evaluation of TOS and TAS

Special kits (Rel Assay Diagnostics, Turkey) are available to use this method developed by Erel [10, 11]. TAS level in the tissue was measured as mmol Trolox equivalent/g protein, and TOS level in the tissue was measured as µmol H_2O_2/g protein.

NF-ĸB analysis

The NF-ĸB levels were determined using the rat-specific NF-ĸB sandwich enzyme-linked immunosorbent assay (ELISA) kit (SunRed, 201-11-0288). The NF-ĸB concentration in the tissue was calculated in µg/g protein.

Histopathological examination

A necropsy was performed on the lung tissues of the rats. The tissues were placed in a 10% buffered formalin solution. Subsequently, the samples were embedded in paraffin blocks, exposing them to routine follow-up processes. Sections of 5 µm were taken from the blocks and placed on slides. After applying hematoxylin and eosin (H&E) staining, they were analysed under a light microscope. The interstitial areas were evaluated semi-quantitatively to determine if there was hyperplasia of the mononuclear (MN) cell infiltration and bronchial-associated lymphoid tissue (BALT), with 0 representing normal, 1 representing mild, 2 representing moderate and 3 representing severe.

Statistical analysis

After determining the differences between the groups using the ANOVA method, analysis was performed with the Tukey test. All statistical analyses carried out by SPSS (SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp.) were performed using statistical software. Kruskal Wallis or Mann-Whitney U-tests were used to determine the difference between the groups. and a *p*-value of < 0.05 was considered statistically significant

RESULTS

MDA and tGSH levels

MDA levels in the lung tissue of the AG group were found to be increased compared to the HG group, and a statistically significant difference was found between the two groups ($p < 0.001$). However, the MDA level was lower in the TAG group than in the AG group ($p < 0.001$). Moreover, MDA levels in the TAG group were similar to those in the HG group. There was no significant difference between TAG and HG groups regarding MDA levels ($p = 0.109$).

The AG group was found to have a lower tGSH level than the HG group, and there was a significant difference between the two groups ($p < 0.001$). The TAG group was found to have a higher tGSH level than the AG group. There was a statistically significant difference in the tGSH level between the AG and TAG groups ($p < 0.001$). The MDA and tGSH levels of the groups and the differences between the groups are shown in Figure 1.

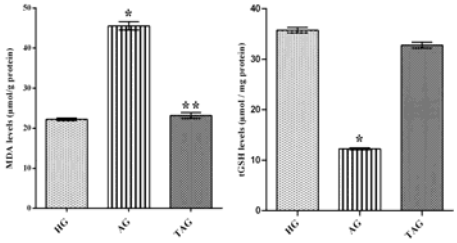

Figure 1: MDA and tGSH levels in rat lung tissues. *$p < 0.001$ according to HG and TAG; **$p = 0.109$ according to HG

TOS and TAS

When the TOS and TAS levels of the animals in the AG group were compared with those in the HG group, the AG group was found to have a higher TOS level and a lower TAS level than the HG group. There was a statistically significant

difference in TOS and TAS levels between the HG and AG groups ($p < 0.001$). In the TAG group, it was observed that the TAX administration prevented the possible damage of the ACL on the oxidative balance. A significant difference was found between the AG and TAG groups regarding TOS and TAS values ($p < 0.001$). Furthermore, when the TOS levels of the TAG and HG groups were compared, the difference in TOS levels between the two groups was statistically insignificant ($p = 0.213$). Figure 2 shows the differences between the TAS and TOS levels of the groups.

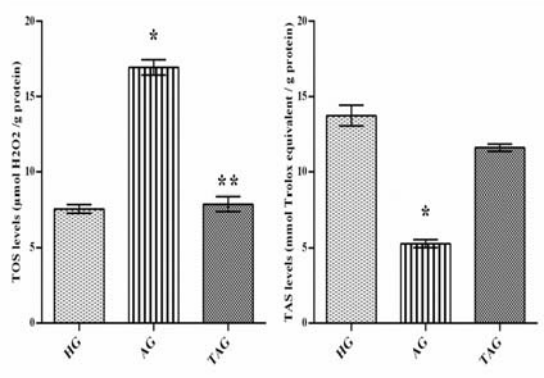

Figure 2: TOS and TAS levels in rat lung tissues. *$p < 0.001$ according to HG and TAG, **$p = 0.213$ according to HG

NF-ĸB levels

As shown in Figure 3, it was determined that NF-KB level increased in the AG group compared to the HG group, and the increase in the NF-ĸB level was prevented by administering TAX. There was a statistically significant difference between the NF-ĸB levels of the AG group and the NF-ĸB levels of the HG and AG groups ($p = 0.001$).

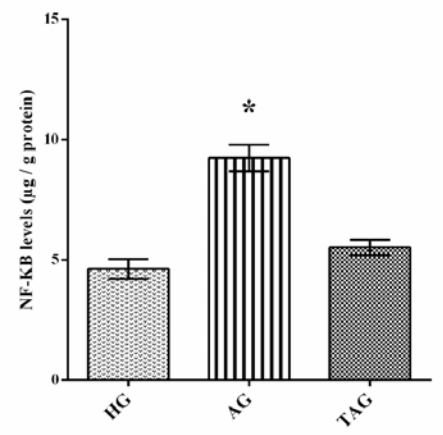

Figure 3: NF-ĸB levels in rat lung tissues. *$P < 0.001$ according to HG and TAG

Histopathological findings

Histopathologically, lung tissues of HG group had a normal appearance (Figure 4). When the histological sections of the AG group were examined, intense MN cell infiltration and severe BALT hyperplasia were discovered in the interstitial areas (Figure 5 A and C). In contrast, when the histological sections of the TAG group were examined, MN cell infiltration and BALT hyperplasia were found to be at a mild level (Figures 5 B and D). When these histopathological findings were scored, a significant difference was found both between AG and HG groups ($p < 0.05$) and between AG and TAG groups ($p < 0.05$). Table 1 shows the histopathological scores of the groups.

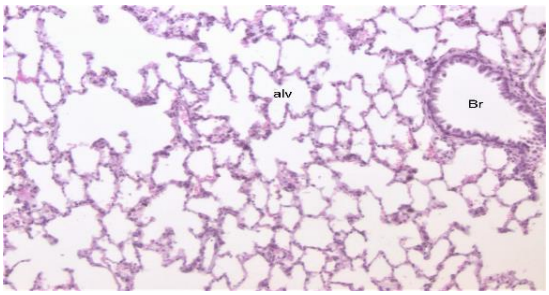

Figure 4: Histopathological image of HG. Br: Normal bronchiole structure, alv: Normal alveolar structure. (H&E x10)

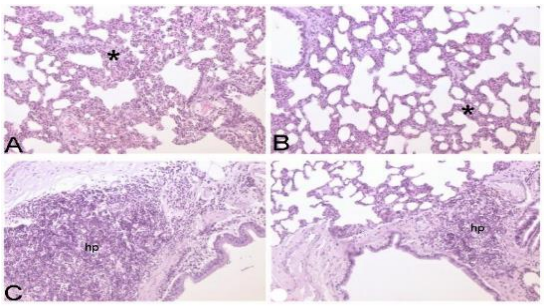

Figure 5: Histopathological image of AG and TAG. **A-** Dense MN cell infiltration (*) in lung section of AG **B-** Mild MN cell infiltration (*) in lung section of TAG **C-** Severe BALT hyperplasia (hp) in lung section of AG **D-** Mild BALT hyperplasia (hp) in lung section of TAG. (H&E x20)

DISCUSSION

Since the harmful effects of ACL on human health were first reported in the literature, experimental studies on the subject have increased. Recent studies have shown that the imbalance between antioxidant capacity and ROS production plays a crucial role in ACL-induced toxicity.

Table 1: Histopathological severity score

Groups	MN cell infiltration in interstitial areas	BALT hyperplasia
HG	0,16± 0,40[a]	0,33± 0,40[a]
AG	2,66± 0,51[b]	2,66± 0,51[b]
TAG	1,33± 0,51[c]	1,16± 0,40[c]

[a,b,c] *Different between groups (p < 0.05, Kruskal Wallis and Mann-Whitney U-test)*

Alturfan *et al.* proved that ACL causes oxidative stress in several tissues and has harmful effects on redox balance [3]. Excessive ROS production in the lungs has been known to cause cell membrane damage by inducing lipid peroxidation. Ghorbel *et al.* discovered a relationship between oxidative stress and ACL, as well as an increase in MDA levels [12]. In this study, tissue MDA levels of the AG group were high, which confirmed the previous studies. This increase indicated ACL-induced ROS formation in lung tissue.

Endogenous GSH and other antioxidants are known to neutralise excessive ROS in a controlled manner. GSH-like antioxidants are abundant and active in lung tissues. Batoryna *et al.* reported that ACL metabolism could induce redox imbalance in cells, affecting GSH [4]. A decrease in GSH levels occurs in the body due to ACL exposure through several metabolic pathways. GSH conjugates with ACL in tissues. This conjugation transforms ACL into a more reactive glycinamide (GA). Thus, ACL and GA are transformed into mercapturic acid metabolites, which are eliminated during the metabolism [13]. This study suggests that the ACL is conjugated, and therefore there is a decrease in tGSH levels.
Moreover, many oxidant and antioxidant molecules are formed in living organisms. It is easier to measure the total capacity of oxidant molecules and the total capacity of antioxidant molecules. For this purpose, TOS and TAS measurement methods were developed by Erel. [10, 11]. Several studies have shown that ACL causes an increase in TOS levels and a decrease in TAS levels [14]. However, no study has analysed TOS and TAS levels in ACL-induced lung injury. This study measured the TOS and TAS levels of the tissues in a lung injury and discovered that ACL administration resulted in an increase in TOS and a decrease in TAS. This situation revealed that ACL causes serious problems in the redox balance of the lungs.

The inflammatory response is another event that causes cell injury in a living organism. It has been stated that there is a relationship between inflammation and oxidative stress and that oxidative stress can increase inflammation [15]. As is known, inflammation is a complex process that involves proinflammatory cytokines. NF-ĸB directs the transcription of genes encoding proinflammatory cytokines. The importance of the NF-ĸB signalling pathway has been demonstrated in studies that used lipopolysaccharide to induce inflammatory lung injury [16]. A study that used ACL to induce neurotoxicity demonstrated that the NF-ĸB signalling pathway was triggered by oxidative stress [17]. In this regard, studies in which ACL was used to induce inflammation in the lung demonstrated an increase in proinflammatory cytokine levels, but the NF-ĸB levels were not measured. This study suggests that the ACL triggers inflammation through the NF-ĸB signalling pathway.

Histopathological findings of ACL-associated lung injury, such as interalveolar septal thickening [18] and peribronchial intense inflammation [19], have been reported in the literature. One of the most exciting studies examined the lung tissue sections of newborn rats with maternal ACL administration [20]. In the study mentioned, interstitial thickening occurred because of ACL administration. The same study also defined dilated occluded blood vessels, bronchial epithelial hyperplasia, and MN cell infiltration. In parallel with the literature, interstitial thickening was found in the lung tissues of the AG group in this study. It was also discovered that this thickening was due to MN cell hyperplasia.

Additionally, BALT hyperplasia was shown in this study. BALT is the mucosal lymphoid tissue adjacent to the central airways in some mammalian species. However, this tissue develops as a secondary lymphoid organ in other mammals. Their structures and functions change when mucosal surfaces are exposed to antigens and microorganisms. After pulmonary inflammation, innate cells are activated and produce cytokines and chemokines that stimulate inflammatory cells [21]. The BALT hyperplasia of the AG group in this study was quite prominent. This finding can be explained by the prolonged exposure of rats to the ACL.

Many experimental studies have been conducted on TAX, a flavonoid. TAX has been noticed to have neuroprotective and hepatoprotective effects and the ability to protect cells by

activating the antioxidant enzyme system. TAX prevented an increase in oxidant parameters and a decrease in antioxidant parameter levels in a model that created a lung injury [22]. The results in this study have similarities with the results in the literature. The MDA levels of the TAG group were as low as those of the HG group. This study showed that TAX had a strong antioxidant effect when the TAS and TOS levels were evaluated.

When the literature was reviewed, TAX was discovered to inhibit the NF-ĸB pathway in a cerebral ischemia-reperfusion model, osteoclastogenesis models and a diabetic nephropathy model. Chen et al. indicated that TAX inhibited the NF-ĸB signalling pathway in the lung inflammatory response [22]. The results of this study demonstrated that the administration of TAX significantly reduced the tissue NF-ĸB levels, and the results are consistent with those in the literature.

Histopathological analysis of the study by Chen *et al.* revealed that TAX reduced alveolar septal thickening, alveolar cell distortion, vascular occlusion, and edema [22]. In addition to these findings, Unver et al. reported that TAX prevented widespread alveolar septal fibrosis and polymorphic leukocyte infiltration [23]. Furthermore, TAX was found to significantly reduce tissue fibrosis scores in a pulmonary fibrosis model [24]. In this study, alveolar septal fibrosis was not detected, but alveolar septal thickening was detected. Inflammatory cell infiltration was shown to cause this thickening, which was alleviated by TAX. Additionally, TAX administration was found to reduce the BALT hyperplasia caused by ACL exposure in this study.

CONCLUSION

The findings of this study show that ACL-induced injury in rats is relieved by TAX. TAX may also help to prevent lung injury induced by ACL. The chronic lung damage caused by acrylamide and the effect of taxifolin on this chronic damage is unknown, and therefore requires further investigation. Regular use of taxifolin may be recommended, especially in people who are known to have had intense contact with acrylamide. But clinical trials are first required to ascertain its benefit and safety.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. OFD, BE and RM conducted a literature review. OFD and HS were involved in the protocol development and ethical approval process. OFD, BE, HS and FO prepared the draft text of the article. MO made histopathological examination of the lung, contributed to the statistical analysis and writing of the article. TAC conducted the biochemical examination of the tissues and contributed to the writing of the article. OFD, BE and BS made the final writing of the article. BE, RM and FO conducted statistical analysis. All authors have read the article and approved for publication.

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