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# Effectiveness Of Oral Curcumin Administration On The Natural Mucosa Of Wistar Rats After Exposure To Electric Cigarettes Smoke

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## ABSTRACT

**Background**: Exposure to e-cigarettes in human bronchial epithelial cells was found to induce mucociliary airway dysfunction in vitro. Additionally, e-cigarettes were shown to reduce the viability of gingival epithelial cells and promote cell apoptosis or necrosis.

**Methods**: The experimental study (true experimental design) employed a control group and a treatment group, with simple randomization of 20 Wistar rats per group, resulting in a total of 40 Wistar rats in the study. Then histopathological examination was performed to assess tissue damage.

**Results**: Research resultsshowed that 400 mg curcumin provided effective protection against nasal mucosal damage caused by e-cigarette smoke exposure, by reducing the severity of epithelial disarrangement, erosion, inflammation, and epithelial metaplasia. However, mild to moderate histopathological changes still occurred, so additional approaches are needed for more optimal protection

**Conclusions**: It can be concluded that there is a relationship between the effectiveness of oral curcumin administration on the nasal mucosa of Wistar rats after exposure to electronic cigarette smoke.

**Keywords**: *Curcumin, Nasal Mucosa, Electronic Cigarettes, Wistar Rats..*

## 1. INTRODUCTION

Since their introduction to the U.S. market in 2007, e-cigarettes have seen a rapid increase in popularity. Their widespread use has raised significant public health concerns, particularly due to their addictive properties and high usage rates among adolescents and young adults. While proponents argue that e-cigarettes present a less harmful alternative to traditional smoking and may serve as a tool for smoking cessation, the respiratory effects of e-cigarette use remain difficult to fully comprehend. Case studies and the 2019 outbreak of e-cigarette and vaping-related lung injuries have further associated e-cigarette use with negative respiratory health consequences [1].

Exposure to e-cigarettes in human bronchial epithelial cells has been shown to cause mucociliary airway dysfunction in vitro. Additionally, e-cigarettes have been found to reduce the viability of gingival epithelial cells and promote cell apoptosis or necrosis. Upon use, e-cigarette aerosol enters the oral cavity, with some of it reaching the lungs, while the remainder is exhaled through the mouth and nose. The nasal tissue, which is covered by a layer of nasal epithelial cells, plays an active role in innate immunity in this region of the body [2].

The use of electronic cigarettes can lead to damage to the nasal mucosa, which may be treated through natural remedies aimed at reducing the inflammatory process in the nasal mucosa. Curcumin, a polyphenolic compound derived from the spice turmeric (Curcuma longa), possesses a variety of pharmacological and biological properties. It has been utilized for centuries in traditional Chinese medicine and Ayurveda for its anti-inflammatory effects. The effectiveness of curcumin has been shown to be comparable to ibuprofen in treating knee osteoarthritis (OA). In a study involving rheumatoid arthritis

patients, curcumin significantly improved walking time and reduced joint swelling, nearly matching the effects of phenylbutazone. Preclinical research in mice has demonstrated that curcumin is gastro-protective and acts as a potent anti-ulcer agent, safeguarding against gastric mucosal injury. Additionally, studies have confirmed that curcumin is effective in protecting against NSAID-induced gastric ulcers by inhibiting excessive acid secretion, thus preventing ulcer exacerbation. Clinical evidence supports the safety of curcumin for human use, with further preclinical studies reporting anti-bloating and weight loss effects associated with its use [3].

Curcumin, due to its chemical structure and the presence of hydroxyl and methoxy groups, is associated with various beneficial properties, including antioxidant, antimicrobial, anti-inflammatory, antiangiogenic, and antimutagenic effects. It is considered a potentially valuable supplement for supporting the treatment of Irritable Bowel Syndrome (IBS), particularly due to its antioxidant and anti-inflammatory properties, as well as its ability to modulate the gut microbiota. Moreover, curcumin interacts with multiple molecular targets, inhibiting the proliferation of inflammatory cells and angiogenesis, while acting as a chemopreventive agent. These effects are linked to the regulation of pro-inflammatory cytokines, nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), lipoxygenase, xanthine oxidase, and the reduction of malondialdehyde (MDA) levels [4].

Research conducted by Punagi et al., experiments on samples in the form of mice were exposed to cigarette smoke followed by curcumin for 28 days, with the aim of observing the inflammatory reaction and repair of the nasal cavity mucosa of mice. From the study, it was found that curcumin can reduce inflammation, erosion, epithelial damage and epithelial metaplasia in the nasal cavity mucosa of mice [5].

## 2. RESEARCH METHODS

The study was conducted in the Animal Experiment Laboratory and Research Unit of the Faculty of Medicine, UNHAS. The study was conducted from July 8, 2024 to August 4, 2024. The experimental study (true experimental design) utilized a control group and a treatment group with simple randomization. The Wistar rats were randomly assigned to either the control or treatment group, with the treatment group being exposed to electronic cigarette smoke. A total of 20 Wistar rats were used per group, resulting in 40 Wistar rats overall in the study. . Grouping was carried out randomly in 2 test groups. The research variables included electronic cigarette smoke as the independent variable and tissue damage (Inflammation, Erosion, Epithelial Disarrangment, Epithelial Metaplasia) as the dependent variable.

## 3. RESEARCH PROCEDURES

### Preparation of experimental animals

Experimental animals Wistar rats were kept in individual cages, cleaned every day. The temperature was 28-32℃ and there was sufficient air circulation and light. The study began by preparing 40 Wistar rats aged 3-4 months which were adapted for 7 days by providing standard feed and drink. A rhinoscopy examination was performed before treatment. Wistar rats that met the inclusion criteria were randomly grouped into 2 groups, each group consisting of 20 rats.

**Group I**

The exposure began by inserting 20 Wistar rats into the smoking chamber, then an electronic cigarette was installed on a pipe connected to an air pump. The installed cigarette was lit and the air pump was turned on, at the same time oxygen was also flowed into the smoking chamber at a speed of 0.5 ppm. The treatment of electronic cigarette smoke exposure was carried out using 10mg of vaping fluid every day. It was carried out for 28 days for this treatment group. Then the histopathological examination procedure was carried out.

**Group II**

The exposure began by inserting 20 Wistar rats into the smoking chamber, then an electronic cigarette was installed on a pipe connected to an air pump. The installed cigarette was lit and the air pump was turned on, at the same time oxygen was also flowed into the smoking chamber at a speed of 0.5 ppm. The treatment of electronic cigarette smoke exposure was carried out using 10mg of vaping fluid every day. Then 400mg of curcumin was given orally via a sonde. It was carried out for 28 days for this treatment group. Then the histopathological examination procedure was carried out.

### Histopathology Examination

- Wistar rats under anesthesia
- Rthe nasal cavity is cleaned, secretions are sucked out with suction
- Aseptic and antiseptic are performed. Rhinectomy begins by performing a Weber Ferguson incision from the medial canthus along the lateral wall of the nasal dorsum, taking tissue and placing it in a container containing 10% formalin. The tissue taken is at level II-III of the nasal cavity.

- In the staining process, the slides are successively dipped into xylol solution (1) for 15 minutes, xylol solution (2) for 15 minutes, xylol solution (3) for 15 minutes, then into alcohol successively with a concentration of 95% for 5 minutes, 70% alcohol for 5 minutes, into 50% alcohol for 5 minutes then dipped in running water for 1 minute, then the slides are dipped in eosin for 30 seconds, then running water then hematoxylin for 30 seconds then running water then 95% alcohol for 30 seconds, then dipped into xylol for 30 seconds and dripped with 1 drop of Entelan then covered with a cover glass.
- Examination under a microscope Binocular Microscope 107BN Xsz-107BN with a magnification of 40x10 for observation of the sample.

Data were analyzed using the Mann-Whitney statistical test. The results obtained were then presented in the form of tables and graphs. Data processing with a computerized system using the R studio application. The assessment of the results of the hypothesis test is stated as significant if $p < 0.05$.

## 4. RESULTS AND DISCUSSION

**Table 1 Description of nasal mucosal damage in Wistar rats**

| **Variables** | **Category** | **20 Wistar without Curcumin** | **20 wistar with 400mg Curcumin** |
|---|---|---|---|
| | | **n (%)** | **n (%)** |
| Epithelial Disorganization | There isn't any | 0 (0) | 0 (0) |
| | Light | 4 (20) | 12 (60) |
| | Currently | 13 (65) | 8 (40) |
| | Heavy | 3 (15) | 0 (0) |
| Erosion | There isn't any | 0 (0) | 2 (10) |
| | Light | 3 (15) | 13 (65) |
| | Currently | 10 (50) | 4 (20) |
| | Heavy | 7 (35) | 1 (5) |
| Inflammation | There isn't any | 0 (0) | 0 (0) |
| | Light | 0 (0) | 5 (25) |
| | Currently | 5 (25) | 14 (70) |
| | Heavy | 15 (75) | 1 (5) |
| Epithelial Metaplasia | There isn't any | 3 (15) | 2 (10) |
| | Light | 5 (25) | 18 (90) |
| | Currently | 10 (50) | 0 (0) |
| | Heavy | 2 (10) | 0 (0) |

In this study, exposure to e-cigarette smoke in Wistar rats without curcumin protection showed significant damage to the nasal mucosa. In the variable of epithelial disarrangement, 65% of rats experienced moderate disarrangement, and 15% experienced severe disarrangement. However, after being given a dose of 400 mg curcumin, the majority of rats (60%) only showed mild disarrangement, and none experienced severe disarrangement. This indicates that curcumin can protect the structure of the mucosal epithelium.

In the mucosal erosion variable, the group without curcumin showed moderate erosion in 50% of mice and severe erosion in

35% of mice. In contrast, after being given 400 mg of curcumin, 65% of mice only experienced mild erosion, and only 5% experienced severe erosion. This indicates that curcumin is able to protect the mucosa from further damage.

Inflammation measured in mice also showed significant improvement. Without curcumin, 75% of mice experienced severe inflammation and 25% experienced moderate inflammation. However, with 400 mg of curcumin, 70% of mice experienced only mild inflammation, and only 5% experienced severe inflammation. These anti-inflammatory effects of curcumin indicate that the compound is effective in reducing the inflammatory response triggered by exposure to e-cigarette smoke.

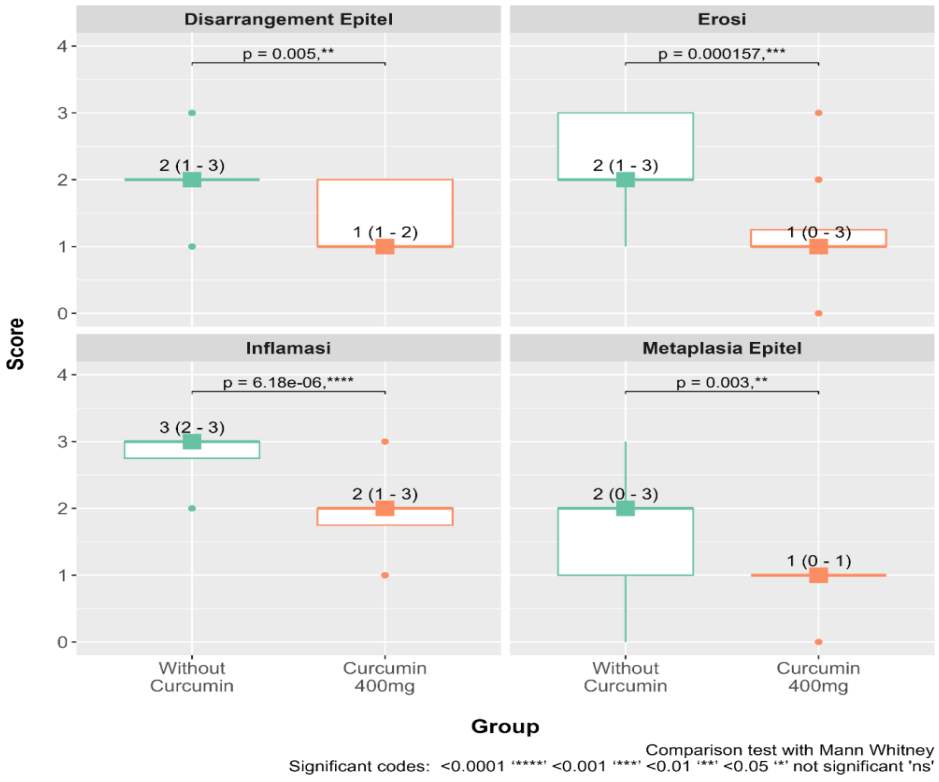
In the variable of epithelial metaplasia, the group without curcumin showed moderate metaplasia in 50% of mice and severe metaplasia in 10% of mice. In contrast, in the group given 400 mg curcumin, 90% of mice only experienced mild metaplasia, and no mice experienced moderate or severe metaplasia. This indicates that curcumin plays an important role in inhibiting the development of metaplasia and maintaining the normal structure of the nasal mucosa.

**Comparison of Treatment Without Curcumin and Curcumin 400mg**

In this study, a test was conducted to compare the protective effects of 400 mg curcumin dose against the control group (without curcumin) in Wistar rats exposed to e-cigarette smoke for 28 days. The statistical test used was Mann-Whitney, with a significance level determined to assess the difference between the two groups.

Figure 1. Protective and healing effects of curcumin on nasal mucosal damage in Wistar rats.

In the epithelial disarrangement variable, the group without curcumin had a median score of 2.0 with a range of 1.0–3.0, indicating quite severe epithelial disarrangement. In contrast, the group with 400 mg curcumin showed a median score of 1.0 with a range of 1.0–2.0, indicating improvement in epithelial structure. This difference was statistically significant with a p value = 0.005 (**).




In the mucosal erosion variable, the group without curcumin had a median score of 2.0 with a range of 1.0–3.0, while the group with 400 mg curcumin showed a decrease in the median score to 1.0 with a range of 0.0–3.0. This shows that curcumin is able to reduce the level of erosion significantly with a p value = 0.000157 (*). Furthermore, in the inflammation variable, the group without curcumin had a median score of 3.0 with a range of 2.0–3.0, indicating a severe level of inflammation. The group given 400 mg curcumin showed a decrease in the median score to 2.0 with a range of 1.0–3.0. This difference was statistically significant with a p value = $6.18 \times 10^{-6}$ (**), confirming the anti-inflammatory effect of curcumin.

In the epithelial metaplasia variable, the group without curcumin had a median score of 2.0 with a range of 0.0–3.0, indicating quite severe epithelial metaplasia. The group with 400 mg curcumin experienced improvement with a median score of 1.0

and a range of 0.0–1.0. This difference was significant with a p value = 0.003 (**), indicating that curcumin was able to significantly reduce the level of epithelial metaplasia.

Overall, the results of this study indicate that curcumin at a dose of 400 mg has a significant protective and healing effect on nasal mucosal damage in Wistar rats after exposure to e-cigarette smoke for 28 days. Curcumin has been shown to reduce epithelial disarrangement, erosion, inflammation, and epithelial metaplasia, so it can be a potential protective agent in preventing mucosal damage due to toxic exposure. However, mild to moderate histopathological changes still occur, so additional approaches are needed for more optimal protection.

The results of this study are in accordance with the results of a study conducted by Punagi et al (2015) which concluded that the administration of curcumin has a protective effect and reduces inflammation, epithelial erosion, epithelial disarrangement, and epithelial metaplasia in the mucosa of Wistar rats given tem cigarette smoke. In their study, curcumin was given at doses of 200 mg and 400 mg.

Erosion, metaplasia and epithelial disarrangement indicate a more severe inflammatory process of the nasal mucosa. In its action as an anti-inflammatory effect, curcumin as one of the active ingredients of turmeric can inhibit the formation of prostaglandins and suppress excessive cyclooxygenase enzyme activity in the nasal mucosa exposed to cigarette smoke [5],

Emiroglu et al (2017) also stated in their study that topical administration of curcumin at doses of 5 and 10 mg/ml can reduce the inflammatory response and significantly accelerate wound healing in an Albino mouse model experiencing nasal mucosal trauma [6].

Curcumin administered in dimethyl sulfoxide (DMSO) gel can significantly accelerate wound healing in mouse model samples, by improving various parameters related to the tissue repair process, such as reducing IL-6 levels, increasing collagen deposits and epithelialization, and modulating matrix metalloproteinase-9 (MMP-9) scores compared to controls receiving DMSO gel alone and groups receiving β-sitosterol ointment [7].

Reepithelialization is the process in which a wound is covered by newly formed epithelium. This occurs during the proliferative phase of wound healing, typically beginning 16-24 hours after the injury. The process involves the proliferation and migration of keratinocytes from the wound edges and skin appendages (such as sebaceous glands and hair follicles) to repair the epithelial damage and restore the skin's barrier function [7].

Curcumin is one of the active compounds contained in turmeric (Curcuma longa), which is a type of rhizome plant. Curcumin can accelerate fibroblast proliferation, collagen synthesis and maturation, has anti-allergic properties and antibacterial activity, so it can accelerate wound healing in a study conducted on the skin of Rattus norvegicus mice. Curcumin extract was given topically and it was found that the treatment group with topical curcumin extract had a significantly higher number of fibroblasts compared to the control group given tulle. In the wound healing phase, proliferation is the most important phase and lasts from day 4 to day 21 after trauma. In the proliferation phase, fibroblast activity will stop and prevent excessive wound healing, bridge keratinocyte migration, produce basic collagen fiber materials that will produce a lot of collagen which is important in wound healing [8].

Curcumin exhibits anti-inflammatory effects by specifically reducing the production of tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), which are key cytokines in regulating the inflammatory response. One of curcumin's significant actions is its ability to inhibit the activity of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), a transcription factor involved in the early stages of inflammatory reactions. Additionally, curcumin promotes the formation of granulation tissue, which supports re-epithelialization by providing a stable substrate for epithelial cells to migrate and close the wound. It has also been reported to enhance the synthesis of collagen and extracellular matrix, thus accelerating the wound healing process [9].

## 5. CONCLUSION

Oral curcumin 400 mg provided effective protection against nasal mucosal damage caused by e-cigarette smoke exposure, by reducing the severity of epithelial disarrangement, erosion, inflammation, and epithelial metaplasia.

## 6. RECOMMENDATION

The use of more samples so that observations for each group can be better and additional research time is needed to assess the effectiveness of curcumin more optimally

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