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Is tannic acid a promising option in local treatment of nasal diseases?

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Abstract. – OBJECTIVE: We investigated the effects of tannic acid on viability and proliferation of nasal cells after topical application. It was also evaluated whether tannic acid served as an alternative treatment agent.

MATERIALS AND METHODS: Collected primary nasal epithelium from healthy people who had undergone septoplasty operations were incubated in cell culture. Following the implementation of 2.5 μM tannic acid in cultured cells, both the number of total cells and their viability were measured using the trypan blue assay, while proliferation was assessed through the XTT method. The XTT method, which involves using "2,3-bis-(2-methoxy-4-nitro-5-sulphophenyl)-2H-tetrazolium-5-carboxanilide", is a reliable means of determining cellular toxicity.

RESULTS: XTT experiment results showed that there was no harm was detected to nasal cells after tannic acid's topical implementation. There were no significant changes in cell proliferation; moreover, no matter what the doses were. Additionally, no cytotoxic effects were detected on nasal cells primary culture at "the end of the 24 hours of implementation". There was no side effect of it, either.

CONCLUSIONS: According to the research, the application of tannic acid topically did not result in any harmful effects on the nasal cell culture. Tannic acid's potential anti-inflammatory properties and its ability to decrease Th2-related cytokines suggest that it may be beneficial for patients with rhinosinusitis or allergic rhinitis, pending confirmation through clinical trials. Additionally, if clinical trials confirm its effectiveness, tannic acid may be useful in healing wounds for patients undergoing septorhinoplasty.

Key Words:
Tannic acid, Nasal cells, Cytotoxic effect, Cell viability.

Introduction

Tannic acid is a polyphenolic compound known as a substance in the form of light yellow-brown powder, flake, or spongy mass obtained from plants. It is anticarcinogenic, antioxidant, antimutagenic, antimicrobial, antiallergic, and anti-inflammatory[1-3], but there is no information about its relationship with nasal diseases yet.

Tannins are polyphenolic compounds[4,5] and are generally found in the roots, wood, bark, leaves, and fruits of plants like almonds, grapes, cacao, walnut, tea, and cranberry. Since ancient times, some Asian countries, such as China, have used tannins as astringents, antidiarrheal, anti-hemorrhage agents[6], anti-carcinogens[7,8], and antimicrobials. Recently, they have been used in industry for coloring the materials like textiles and leather[9] and mining[10].

Hydrolyzable and condensed tannins are the groups of tannins in terms of their features[5]. Hydrolyzable tannins are decomposable in water and esters of gallic acid or ellagic acid with a sugar core. Gallotannin is one of the most known hydrolyzable tannins. Acids or enzymes also hydrolyze glucose into monomeric products[11]. Tannins are known to have priceless pharmacological features which are suitable for health. Plants with rich plant extracts have many positive effects in clinical trials[12], such as green tea, grapes, and cocoa.

Tannic acid is a mixture of plant-derived polyphenolic compounds. Gallic acid and pentagalloyl glucose have the most prosperous components with bovine serum albumin, and are commercially used[13]. Tannins have antibacterial properties[14]; moreover, bacteria modulate gene expression actively in response to tannins[15,16], and currently, they have been stated[17] to have antibiofilm properties. Pentagalloyl glucose and ellagic acid are pointed to inhibit biofilm formation in *S. Aureus*[18-20].

The study aims at defining tannic acid's impact on nasal cells' viability and proliferation. The

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objective was to investigate the potential use of tannic acid as an alternative way to treat patients with nasal diseases. The research was performed to see if there is any harmful effect on the nasal cells after applying tannic acid topically to the nasal epithelial cells.

Materials and Methods

This research has been conducted by the Medical Biology and Otorhinolaryngology Departments of Eskisehir Osmangazi University, Faculty of Medicine. Before starting the study, the volunteers signed a consent form to allow the use of their tissue samples for scientific reasons. Then, the nasal epithelium was collected from their healthy tissues and removed routinely as a part of surgery (septorhinoplasty). The collected mucosa samples were transferred to the Medical Biology Laboratory, Faculty of Medicine, Eskisehir Osmangazi University, in preservative conditions, appropriate for cell culture.

Just after tissues were brought to the laboratory in penicillin-containing transport solution, they were dissected into smaller bits in a sterile petri dish. Then the pieces of tissues were processed with trypsin, and incubated at 37°C for 10 minutes with 5% carbon dioxide. They were then transmitted into sterile centrifuge tubes, which included a washing solution. 4 ml of solution that included Dulbecco's Phosphate Buffered Saline was put in, and they were transmitted to trypsin/EDTA solution (Sigma-Aldrich, St. Louis, USA) in centrifuge tubes (Corning, New York, USA) and centrifuged at 1,000 rpm. Following the centrifugation process, the supernatant was separated, and 4 ml of solution were put into the pellet to bind at the base and washed twice. The pellet remaining at the base was taken into T25 petri dishes (Corning, NY, USA), including DMEM medium consisting of 1% Penicillin-streptomycin solution, and placed in a 37°C CO_2 incubator.

Tissue specimens included a mixture of epithelial and fibroblast cells. To be able to decrease the number of invasive fibroblast cells holding the petri dish faster, the culture was incubated with trypsin/EDTA solution for 4 minutes at 37°C; after the cells reached 80% majority at the bottom, fibroblasts – which stuck to the petri dish surface – stayed stuck to the base with no effect of trypsinization phases. Then, the culturing of epithelial cells separated from the medium by trypsinization continued.

Afterward, the remaining pellet was transmitted to T25 petri dishes with DMEM medium and put into a 37°C CO_2 incubator. Then, the cells were grouped as control and experimental cells to deal with tannic acid. After the cells at the base got 80% majority, culture was implemented. 2.5 µM of tannic acid was also implemented in the cells. Viability was defined *via* trypan blue assay, and proliferation was defined *via* XTT[3,21].

Viability of the Cells

Once the necessary amount of the cells was attained in the flask, they were collected using trypsin. The cells' essential amounts were prepared for measurement *via* the Neubauer slide using trypan blue staining. Counting was done regarding total cell, viability, and proliferation[22].

Proliferation Assay

Evaluating cellular toxicity, XTT (2,3-bis-(2-methoxy-4-nitro-5-sulphophenyl)-2H-tetrazolium-5-carboxanilide) analysis could be utilized. To check the proliferation, 96-well plates were formed for the cells. All wells filled with 50 µl from 5 ml of reaction buffer solution, including 100 µl of activation solution. Then they were transfered into the wells containing 100 µl fresh DMEM medium. Proliferation analysis was done *via* a test of absorbance at 450 nm by a Microplate Spectrophotometer (Bio-Tek HTX Synergy, VT, USA)[23,24].

Results

The XTT experiment showed that after the implementation of tannic acid, there was no harm to the nasal cells. To reach this conclusion, research was first conducted to determine non-lethal concentrations of tannic acid in primary nasal cells. The cells were initially treated with tannic acid at concentrations of 25, 50, and 100 µM, but these concentrations were found to be too high. The IC50 concentration of tannic acid was determined as 2.5 µM among the 2.5, 5, and 10 µM concentrations applied afterward. The substance was not cytotoxic to the culture of primary nasal cells after 24 hours of administration of 2.5 µM tannic acid (Figure 1). In addition, it was also determined that this concentration applied to the cells did not reduce the percentage of viability of the cells (Figure 2). Also, cell viability persisted for a considerable amount of time following treatment. As tannic acid does not harm normal cells when used

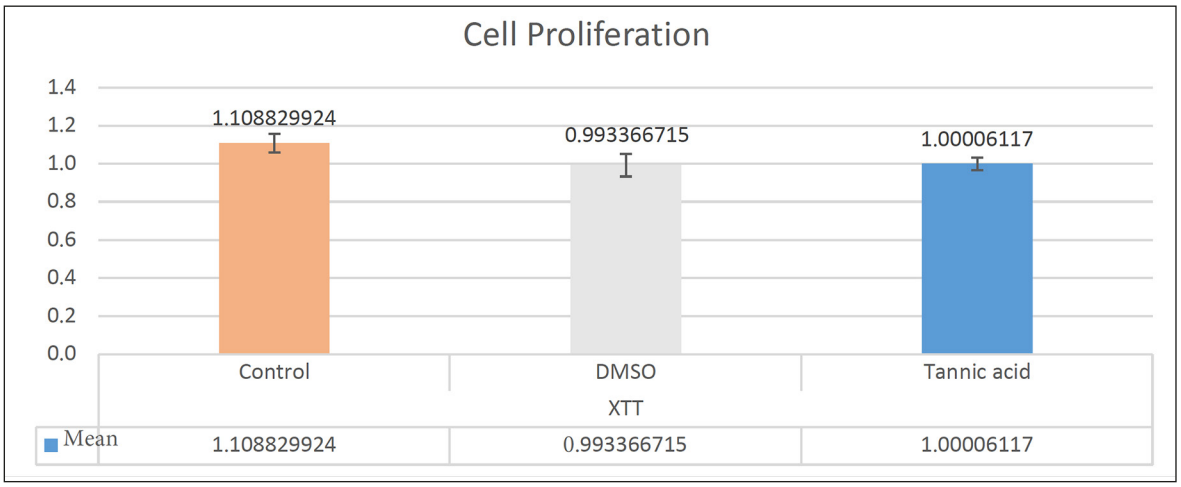

Figure 1. XTT was used to measure the effects of nasal cells exposed to tannic acid and DMSO for 24 hours in terms of cell proliferation.

at the proper concentration, these encouraging results regarding the viability and proliferation of cells suggest that tannic acid has the potential to be used as an alternative active ingredient in the topical treatment of nasal disorders. However, for the tannic acid component to be clinically applicable, these laboratory findings need to be further deepened by clinical studies.

Discussion

Tannic acid is a polyphenolic compound mainly made of gallotannins[13]. It is a mixture of plant-derived polyphenolsin light yellow-brown powder, flake, or spongy mass obtained from plants. Since ancient times, it has been used to precipitate proteins from solution[25] and as a guarding plant against bacterial and fungal infections[26]. They are believed to be the agents of a great taste of tea or wine[27,28].

Payne et al[18] stated that drinks, including tannin, such as green tea, were proved to be less methicillin-resistant. They[18] stated that tea inhibited *S. Aureus* biofilm development, and they concluded that drinking tea reduced *S. Aureus*, and commonly consumed polyphenolic ingredients, such as tannins, affect *S. Aureus* surface colonization.

We found that tannic acid works against HIV, herpes simplex virus, and Noroviruses[29-31]. In addition, studies[32] trying to prove the use of tannic acid to prevent and inhibit the contagion of SARS-CoV-2 emphasize that the results are optimistic. The number of studies[29,33] confirming the antibacterial activity of tannic acid on Gram-positive and Gram-negative bacteria is increasing.

The function of deactivating cancer cells has made tannic acid indispensable for researchers. Mhlanga et al[34] reported that tannin has become the most crucial study item in recent years because it not only induces cell apoptosis through

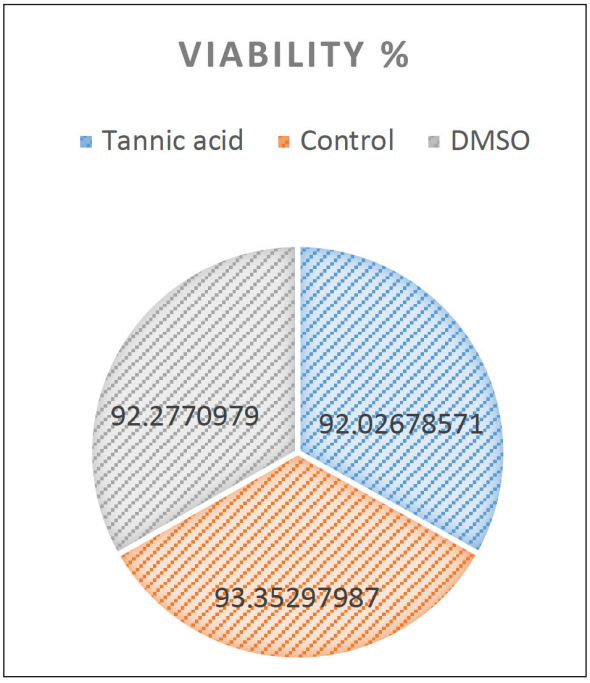

Figure 2. Results of the trypan blue assay were used to measure the effects of nasal cells exposed to tannic acid and DMSO for 24 hours in terms.

DNA fragmentation on hepatocellular carcinoma of the liver, but also induces oxidative stress and neutralizes them[34]. Studies conducted by Sp et al[35] investigated the mechanism of apoptosis in embryonic carcinoma cells point to promising findings for tannin[35]. It is proven[33,36] by more and more studies that tannic acid is a powerful fighter against cancer.

This research is about the effect of tannic acid on the vitality and proliferation of nasal cells. It aims to determine whether it is possible to use tannic acid to treat nasal diseases. When applied topically, we tried to determine whether tannic acid has a detrimental effect on nasal epithelial cells.

The XTT experiment study reveals that culture of nasal cells had no damage after the topical application of tannic acid and DMSO used as the solvent of tannic acid. No significant change was detected in the proliferation of culture of cells, independently by the doses. The application showed no cytotoxic effect on the culture of cells after 24-hour application. Also, cell viability had no adverse effect after the medication.

The complex link between the inflammatory process and the microbiota of the sinuses in chronic rhinosinusitis, an inflammatory disease of the sinonasal mucosa, is not fully understood yet. At this point, the role of bacteria has been determined[33,37,38] more clearly. If the symptoms suddenly progress more strongly and are accompanied by purulence in the sinuses, this is associated with a bacterial infection. Then, the need for antibiotic use is determined[33,37,38]. There is no other method for treatment in the formation of antibiotic resistance[39]. In other words, the need for different therapeutic modalities arises[33].

A formalin-induced paw edema model was applied to detect the anti-inflammatory effects of T.A. The edema inhibition rate of tannic acid proved the ability of tannin to prevent edema by reducing the MPO (myeloperoxidase) enzyme activity. However, its effect on the molecular mechanism has yet to be fully clarified[40]. Since most epidemiological data show the positive effects of tannin on skin inflammation and injuries, it has been shown[4] that using tannin can be a preventive factor for chronic diseases.

Ultraviolet B (UVB) is known as the most harmful medical wave. Studies[41] show that the use of tannin reduces the ornithine decarboxylase activity and UVB-induced DNA synthesis due to UVB. As a result, tannin is recommended against UVB radiation. The use of tannin also counteracts the adverse effects of UVB irradiation due to increased production of the proinflammatory cytokine IL-18 and increased "mRNA expression in HaCaT cells". Regular tannins decreased other inflammatory mediators such as IL-1, IL-6, tumor necrosis factor-α cyclooxygenase-2, and prostaglandin E2[42].Tannin-induced nanoparticles (AgNPs) also downregulate the production of IL-6 and IL-8 by TNF-triggered keratinocytes, enabling them to have immunomodulatory properties[43]. Detailed studies[4,44] show that tannic acid protects against UVB radiation in the retinal pigment epithelium.

Eczema (atopic dermatitis) is a chronic skin condition that causes dry, scaly, patchy lesions on the skin and intense itching. Itching of the skin causes red raised spots, thickened skin, and open cuts on the skin surface. The use of tannin for dermatitis helps to soothe the symptoms and heals the wounds and spots by inhibiting the expression of vascular endothelial growth factor (WEGF)[45]. The use of tannin alleviates specific symptoms and has a significant impact on inhibiting the infiltration of inflammatory cells in some illnesses, such as parakeratosis, acanthosis, and dermatitis[4].

Wounds heal due to a complex dynamic process consisting of many successive stages[46,47]. The repair process is not regular (routine wound healing requires hemostasis, inflammation, proliferation, and remodeling stages are impaired). The use of tannin is highly effective in the treatment of minor wounds and burns, sunburns, acne, dandruff, and eczema decreasing Th2-related cytokine expression[48] and upregulating the expression of growth factors[49]. It was reported[50] that TA decreased NO production and showed anti-inflammatory activity. It has been shown[51] that topical application of antioxidant-containing compounds will be beneficial for wound healing and the protection of tissues from oxidative damage. Tannin, a medicinal plant that provides coagulation, inflammation, collagen production, and epithelial formation and has antifungal, antibacterial, and antioxidant effects, draws attention.

Conclusions

The research showed no cytotoxic effect on the culture of nasal cells after applying topically implemented tannic acid. Taking tannin's anti-inflammatory effects and Th2-related cytokine decline into consideration, it is possible that tannic acid will be applied to rhinosinusitis or allergic

rhinitis patients if clinical trials will confirm this. Moreover, it will be good for healing wounds in patients having septorhinoplasty, if other clinical trials will confirm this.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Ethics Approval
This is a cell-culture study. Ethics committee approval was not needed.

Informed Consent
Human primary nasal epithelium was obtained from healthy tissue removed routinely as part of surgery (septorhinoplasty) from individuals who gave written consent for their tissue to be used in scientific research.

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Authors' Contribution
Marwan Alqunaee: Planning, designing, literature survey, active intellectual support, submission. Nuray Bayar Muluk: Planning, designing, literature survey, interpretation of the results, active intellectual support, writing. Didem Turgut Cosan: Planning, designing, data collection, literature survey, interpretation of the results, active intellectual support. Cemal Cingi: Planning, designing, literature survey, data collection, interpretation of the results, active intellectual support, English editing.

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