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Rosuvastatin protects against methotrexate- induced oral mucositis in rat model

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Abstract

Methotrexate is an antineoplastic agent employed in chemotherapy. Currently, inflammation of the oral mucosa (oral mucositis) is considered one of the most severe negative effects of anticancer treatment. The aims of this research to examine the effects of rosuvastatin on rat oral mucositis produced by methotrexate. 30 adult albino male rats were randomly allocated into 3 groups (n=10). The healthy control group was orally given normal saline for 15 days. The methotrexate, rosuvastatin+ methotrexate groups were administered methotrexate (80 mg/kg) intraperitoneally on the day 8. The rosuvastatin+ methotrexate group received oral rosuvastatin (20 mg/kg) once daily for 14 days. Cheek tissue specimens were obtained for histopathological evaluation, and biochemical assessment of tissue homogenates. Treatment with rosuvastatin significantly reduced malondialdehyde (MDA), and tumor necrosis factor alpha (TNF-α) compared with the methotrexate group ($p<0.05$), while boosting interleukin-10 (IL-10) activity. Furthermore, it significantly improved histopathological scores in methotrexate-induced alterations. Rosuvastatin had significant tissue -protective effects via antioxidant, and anti-inflammatory mechanisms in a rats model of methotrexate evoked mucositis. These results support its potential as an adjunct therapy in the prevention of oral stomatitis.

Keywords: Methotrexate, oral mucositis, rosuvastatin.

Introduction

Methotrexate may induce detrimental effects on specific tissues, although its established anticancer, anti-inflammatory, and immunosuppressive properties (1). Despite its therapeutic efficacy, substantial data demonstrates that methotrexate induces cytotoxic effects, including oxidative damage, and cellular death (2). Research by (3) demonstrates that the negative effects of methotrexate stem from its capability of a free radicals and apoptotic pathways activation. The synergistic impact of methotrexate with agents with inhibitory effects on inflammatory and oxidative stress may alleviate its detrimental effects (4). Chemotherapy agents target and eliminate rapidly proliferating cells in several anatomical regions, including the gastrointestinal tract and oral cavity (5, 6). The primary sign of mucositis is the emergence of reactive oxygen species (ROS). These facilitate the secretion of pro-inflammatory mediators. This injures the mucosa, induces infection, and results in cellular death. Oral mucositis leads to either cessation or reduction of the

therapeutic dosage (7, 8). Consequently, numerous investigations have been undertaken to avert mucositis; at present, there is no specific pharmaceutical intervention for mucositis accessible in clinical practice.
Statins are categorized as inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase. Lamb (9) asserts that they are employed to manage hypercholesterolemic disorders linked to hypertension. The primary advantages of statins, in addition to their ability to reduce cholesterol, are linked to their anti-inflammatory properties. Rosuvastatin is a leading member of this class. Recent medical research has mostly focused on the antihyperlipidemic properties of rosuvastatin, as well as its antioxidant and anti-inflammatory benefits. Prior research has shown that rosuvastatin possesses an antioxidant effect on hepatic, renal dysfunction, and gastropathy. However, it is yet unclear if it can protect against the harmful effects of methotrexate on the oral mucosa (10).

Materials and Methods

Ethical Approval

The research received approval from the institutional animal ethics committee at the College of Dentistry, University of Mosul. (UoM.Dent/A, L12/22).

Preparation of drugs

During experiment, rosuvastatin was prepared immediately prior to administration. The Methotrexate dosage of 80 mg/kg was employed as oral mucositis-provoked model (11, 12).
The estimated medication (rosuvastatin) was formulated as suspension in distilled water. The rosuvastatin dosage of 20 mg/kg was established according to a prior study (13).

Preparation of animals

Rats were housed in individual, sanitized polypropylene cages featuring wire-mesh bases to inhibit licking or physical contact between them. The rats inhabited a controlled environment with a 12-hour light/dark cycle and a temperature range of 22 to 25 degrees Celsius. The structure itself had a ventilation facility that continuously circulated air, along with easy access to drinking water and food. We let the animals one week to acclimate to their new environment prior to commencing the experiment.

Grouping of animals

Thirty adult male Albino Wistar rats, weighing between 300 and 400g, were randomized into three groups, with ten rats in each group:
Group I (Normal Control): administered normal saline solution every day for 15 days.
Group II (induction, methotrexate) received an intraperitoneal injection of methotrexate at a dosage of 80 mg/kg on the 8th day of the experiment.
Group III (protective, rosuvastatin+methotrexate): administered rosuvastatin (20 mg/kg orally once daily for 14 days: 7days prior to induction and 7 days subsequent to induction).

On day 15, the rats were killed with a mixture of Ketamine (50 mg/kg) + Xylazine (5 mg/kg). The oral tissue was excised and subjected to histopathology and biochemical analysis. The processing of tissue samples produced a homogenate suitable for bioindicator study.

Measurement of oxidative, inflammatory, and anti-inflammatory markers

Cheek mucosal tissues were rapidly excised, rinsed with cold phosphate-buffered saline, homogenized, and centrifuged at 10,000 × g for 15 min at 4°C. The supernatant was used for biochemical analysis. MDA levels were measured using the Thio barbituric acid-reactive substance method and expressed as nmol/mg protein at 532 nm (14). Oxidative stress parameters were assessed using commercial kits according to the manufacturer's instructions. Cytokine levels (TNF-α, IL-10) were measured in rat cheek mucosal homogenates using sandwich ELISA according to the manufacturer's protocol. Absorbance was read at 450 nm and concentrations were determined from standard curves.

Histopathological Examination

Tissue specimens from all rats' groups were fixed in 10% neutral buffered formalin for histological examination. Small fragments were rinsed with tap water, dehydrated through graded ethanol (70–100%), cleared in xylene, and embedded in paraffin at 55–60°C (15-18). Paraffin blocks were prepared and sectioned, and sections were mounted on slides coated with egg albumin using a water bath. Hematoxylin and eosin (H&E) staining was performed following standard steps including deparaffinization, rehydration, hematoxylin staining, differentiation, eosin counterstaining, and dehydration (19-22).
All sections were examined blindly by a histopathologist and graded according to a modified scoring system (23).
Grade 0, normal tissue architecture without vascular dilation or inflammatory changes;
Grade 1, mild vascular congestion with partial re-epithelialization and minimal mononuclear infiltration;
Grade 2, moderate congestion with epithelial hydropic degeneration and mixed inflammatory infiltrates accompanied by focal hemorrhage, edema, and small ulcerations;
Grade 3, severe vascular dilation with extensive inflammation, hemorrhage, edema, abscess formation, and marked ulceration.

Statistical Analysis

One-way ANOVA, then the Tukey's post hoc test, was utilized to compare mean values among groups. The Kruskal–Wallis test for non-parametric data, followed by Mann–Whitney U tests for pairwise comparisons. Results are expressed as mean ± standard deviation (SD) for parametric data and as median for non-parametric data". A significance level of $p < 0.05$ was used for all statistical analyses (24).

Results

Impact of examined agents on oxidative and pro-inflammatory biomarkers

A significant increase in MDA and TNF-α was observed following methotrexate treatment when compared with the vehicle control rats ($P < 0.05$). Meanwhile, combined administration of rosuvastatin with methotrexate significantly mitigated this elevation relative to the methotrexate group ($P < 0.05$), as indicated in Figure. 1, 2.
In contrast, IL-10 showed a significant reduction in the methotrexate-treated rats compared with the vehicle control group ($P < 0.05$). Co-treatment with rosuvastatin significantly reversed this alteration and produced higher IL-10 values than those recorded in the methotrexate group ($P < 0.05$), as shown in Figure 2.

Impact of examined agents on histopathological assessment

Figures. 3A and 3B illustrate that the histological examination of the control group's rat cheek tissue reveals normal architecture, encompassing the mucosa (A), submucosa (B), and muscles (C), with minimal edema (D). In the induction methotrexate group, rat cheek tissue exhibits inflammatory cells infiltration in the submucosa (A), accompanied by atrophy and necrosis of skeletal muscle (B) and hyaline degeneration (C), with intervening spaces oedema (D), yielding a score of 3 (3–3), in contrast to the normal group (D), yielding a score of 3 (3–3), in contrast to the normal group ($p<0.001$; Figure 4A, 4B). The most favorable results for the histology analyses were noted in the rosuvastatin + methotrexate group. The results indicated preserved mucosa (A) submucosa (B) and edema present between muscle fibers (C), yielding a score of 1 (1–1), in contrast to the methotrexate group ($p<0.01$, Figure 5A, 5B).

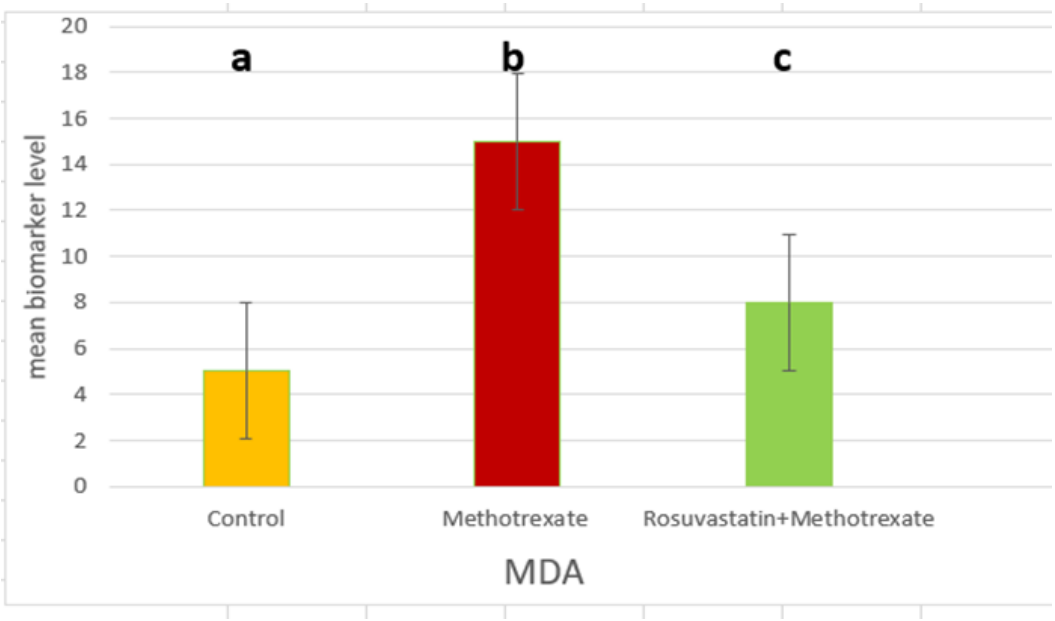

Figure. 1: Effects of evaluated drugs on oxidative stress indicators. Data are presented as mean ± standard deviation. Comparison denoted by letters; distinct letters indicate a substantial difference. The concentration of MDA was quantified as nmol/mg. MDA refers to malondialdehyde

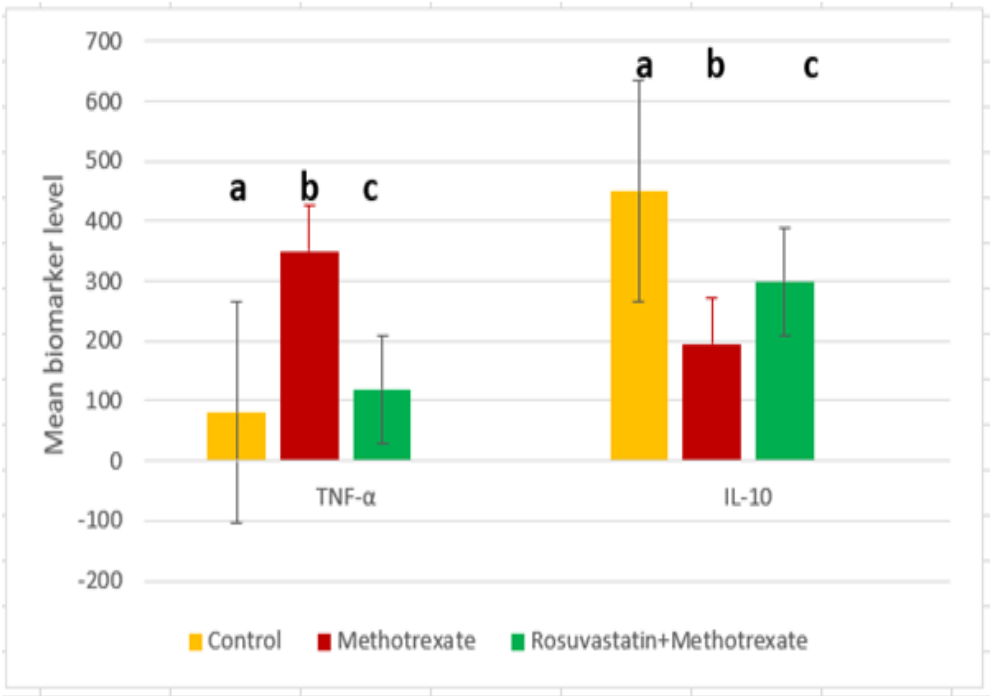

Figure (2) Effects of evaluated drugs on pro-inflammatory and anti-inflammatory indicators. Data are presented as mean ± standard deviation; Comparisons are indicated by letters; differing letters signify a significant difference. The concentrations of TNF-α, and IL-10 were measured in picograms per gram of protein. TNF-α: tumor necrosis factor-alpha; Interleukin-10 (IL-10).

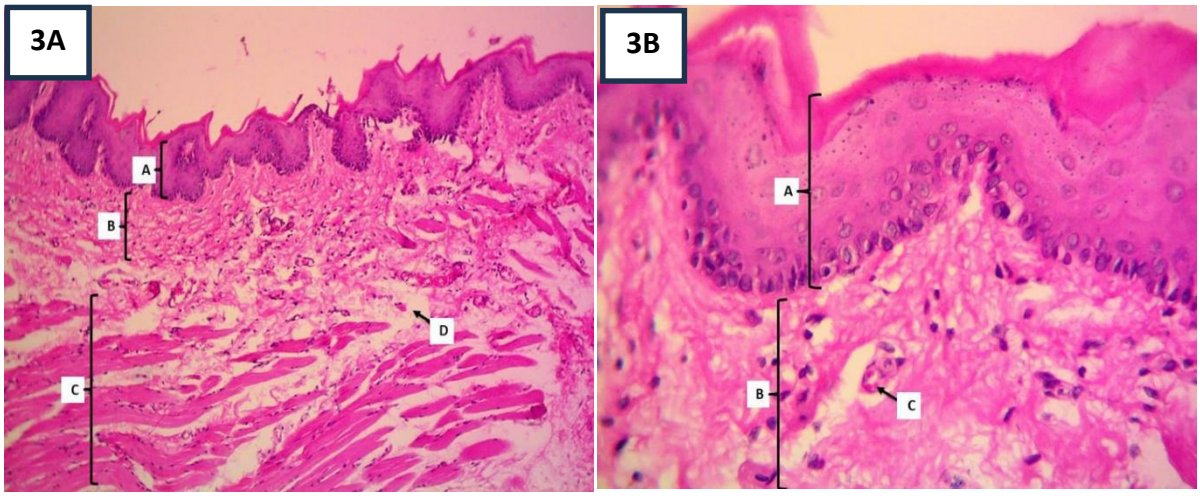

Figure 3: A, B: Effect of investigated agents on histological alterations in buccal mucosa from the control group (H&E 100X, 400X)

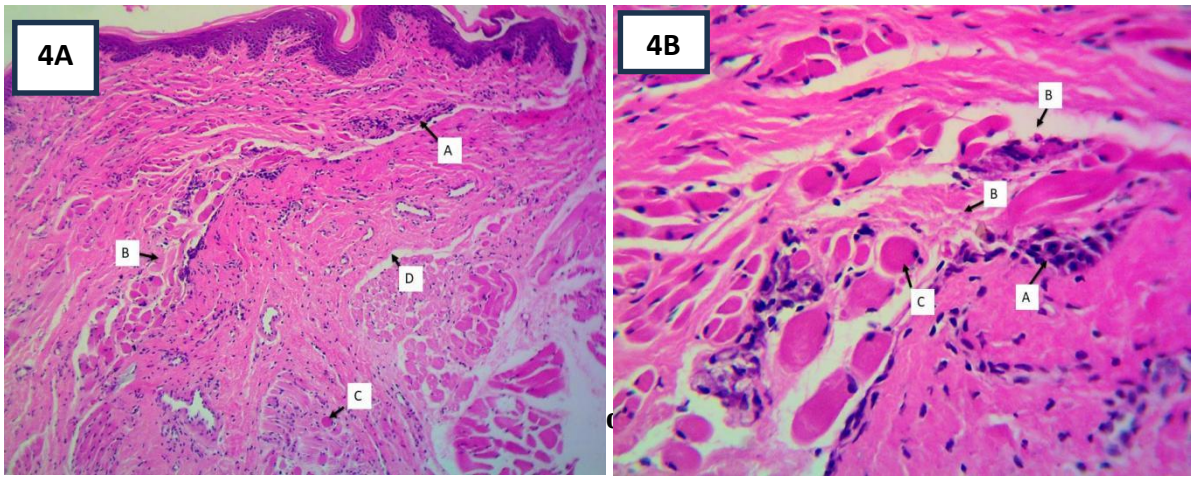

Figure 4: A, B: Effect of investigated agents on histological alterations in buccal mucosa from the methotrexate group (H&E 100X, 400X)

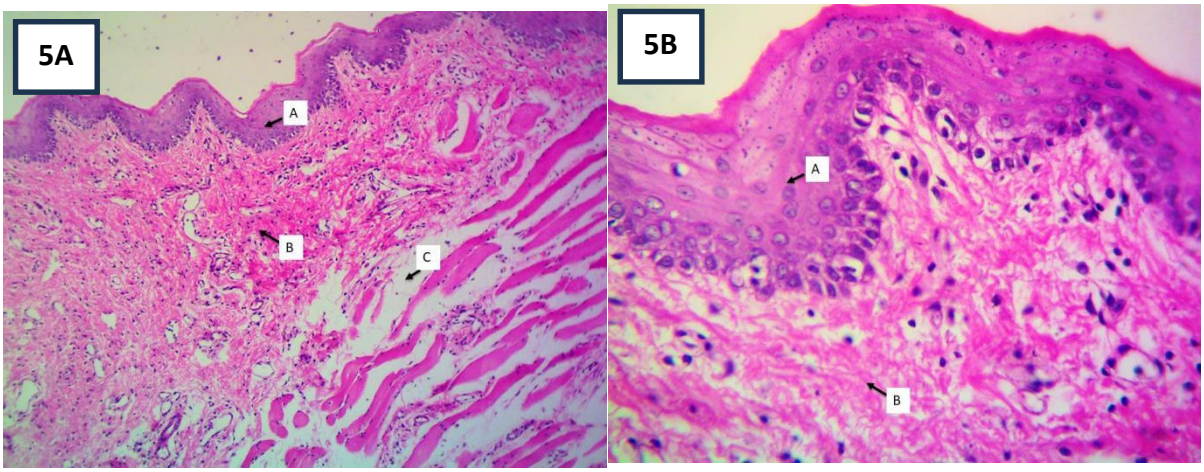

Figure 5: A, B: Effect of investigated agents on histological alterations in buccal mucosa from the rosuvastatin+methotrexate group (H&E 100X, 400X)

Discussion

The current work demonstrates that methotrexate induced oral mucositis, as demonstrated by markedly increased levels of MDA, TNF-α and decreased level of IL-10 compared with vehicle control group. The findings of this research align with previous study indicating that methotrexate -evoked tissue deterioration is associated with elevated expression of inflammatory indicators (25-27). Previous models of chemotherapy-induced oral mucositis, such as those using cisplatin and 5-florouracil, as well as investigations into radiotherapy-evoked mucositis, have revealed reduced antioxidant capacity and elevated MDA levels, highlighting the pivotal role of oxidative stress in mucosal damage (28-30. MDA is a harmful byproduct generated from lipid peroxidation triggered by ROS (31, 32). Consequently, MDA represents a commonly measured and

robust marker of oxidative stress in contemporary times (33). The free radicals generated by methotrexate metabolism interact with the cell membrane, leading to membrane rupture and the release of substantial amounts of antioxidant mediators into the blood. This affects the typical level of the scavenger enzymes in the serum and signifies a harmful effect of methotrexate on cellular health (34). Sikder *et al.,* (2020) (35) reported the potent antioxidant properties of rosuvastatin in rats administered CCl4 to cause liver fibrosis., Rosuvastatin therapy elevated reduced glutathione levels and restored compromised superoxide dismutase (SOD) activity. Moreover, in streptozotocin - provoked diabetic rats, Heeba et al. (36) showed the nephroprotective effects of rosuvastatin, which seem to be a precursor to antioxidant, and anti-inflammatory properties of rosuvastatin. The anti-inflammatory, and anti-lipid properties of rosuvastatin were evaluated of following treatment at different doses. Furthermore, it was found that rosuvastatin elevated plasma nitrate concentrations and enhanced endothelial nitric oxide synthase expression (37). Furthermore, Arafat *et al.,* (2021) (38) additionally recorded the antioxidant and anti-inflammatory effects of statins on the lingual mucosa in response to irinotecan-induced mucosal damage.

The current literature indicated an association between oxidative stress and inflammation. Research demonstrates that ROS, which cause oxidative stress, substantially modulate inflammation (39). Mitochondrial ROS are posited to function as signaling molecules that initiate the synthesis of pro-inflammatory cytokines (40). A study investigating the relationship between oxidants and pro-inflammatory cytokines demonstrated reduced levels of GSH and enzymatic antioxidants in tissue with raised quantities of LPO, IL-1β, TNF-α, and IL-6 (41). The biochemical findings from buccal tissue samples corresponded with the histology results obtained in our investigation. Intraperitoneal dosing of methotrexate adversely impacted the histology of the rat cheek mucosa, leading to considerable atrophy and necrosis of skeletal muscles. The modification of the histological architecture of the buccal mucosa suggests that the initiation of oral mucositis predominantly stems from damage to the submucosal layer, potentially preceding disruption to the superficial epithelium. (42). Endothelial cell injury associated with reduced secretion of growth factors from keratinocytes, which may contribute to dysregulated mucosal epithelial cell proliferation. (43, 44). The rosuvastatin may have facilitated the restoration of histological damage in oral tissues caused by methotrexate, owing to its antioxidant and anti-inflammatory consequences. Moreover, other study reported that rosuvastatin exhibited a significant therapeutic effect on all degenerative and atrophic symptoms induced by cyclophosphamide in the lingual mucosa (13, 45). Research demonstrates that reactive oxygen species and several pro-inflammatory cytokines play a role in the onset of mucositis. (13, 46). The findings support our hypothesis that rosuvastatin may be essential in protecting the methotrexate-induced model of oral mucositis.

Conclusion

The results indicated that methotrexate induces inflammatory response, and oxidative stress in rats. Rosuvastatin significantly mitigates these adverse effects, demonstrating its usefulness as anti-inflammatory and antioxidant agent. These results support its potential as an adjunct therapy in the prevention of oral stomatitis.

Declarations

Acknowledgment

The authors acknowledge the College of Dentistry, University of Mosul, for its facilities and continuous support.

Ethics statement

The research obtained authorization from the institutional animal ethics committee held at the College of Dentistry, University of Mosul. (UoM.Dent/A, L12/22).

Availability of Data and Materials

The datasets utilized and examined during the present research are accessible from the corresponding author subsequent to valid inquiry.

Competing Interests

There are no conflicts of interest to declare.

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Authors' Contributions

WMA designed the study, performed the laboratory assays & the statistical analysis, and **NSA** wrote the manuscript and was responsible for patient recruitment and sample collection.

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