*Archives of Pharmaceutical Sciences Ain Shams University 2025; Vol. 9(1): 194-208*

OPEN ACCESS

Clinical Pharmacy

Review Article

# The Protective Role of Statins against 5-Fluorouracil- induced Oral Mucositis in Colorectal Cancer Patients-Narrative Review

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## ABSTRACT

Oral mucositis (OM) is one of the most frequent complications affecting colorectal cancer (CRC) patients receiving 5-fluorouracil (5-FU). According to recent studies, the release of inflammatory cytokines like tumor necrosis factor-alpha (TNF-alpha) and the generation of reactive oxygen species (ROS) may play a significant role in the development of mucosal injury and progression of OM. Statins have been reported to have pleiotropic effects including anti-inflammatory and antioxidant activity. Hence, they might play a protective role against 5-FU-induced OM. This review aims to discuss the evidence from preclinical and clinical studies regarding the potential benefits of statins in this area. The Egyptian Knowledge Bank, Google Scholar, and PubMed databases were searched for published preclinical and clinical articles describing the anti-inflammatory antioxidant activity of statins and their potential role in the prevention of 5-FU-induced OM from English sources. Research was performed using different keywords: such as, "pathophysiology of 5-FU-induced oral mucositis", "inflammatory cytokine and 5-FU-induced oral mucositis", "oxidative stress and 5-FU-induced oral mucositis", "pleotropic effect of statins OR (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors)", "statins in 5-FU-induced oral mucositis". Relevant resources were extracted using source source-pulling method of the references. Multiple studies have proven the anti-inflammatory and antioxidant properties of statins as demonstrated in different inflammatory disorders models such as cardiovascular, renal, and pulmonary diseases. It has been shown that statins can inhibit nuclear factor kappa-B (NF-KB) which consequently inhibits the subsequent cascade of inflammatory cytokines release such as TNF-alpha in addition to the reduction of ROS such as malondialdehyde (MDA). The effects of various types of statins on mucositis in animal and human models have been investigated and the results were promising. Statins could be a potential candidate for the prevention of OM through their pleiotropic effects. Further additional clinical studies are required to provide evidence about the potential therapeutic benefits of statins in the prevention of 5-FU-induced OM in CRC patients.

**Keywords:** *Colorectal cancer; 5-FU; oral mucositis; TNF alpha; statins; pleiotropic effect.*

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Citation | Lotfy RS, Shawki MA, Aboelhassan R, El Wakeel LM, 2025. The Protective Role of Statins against 5-Flourouracil- induced Oral Mucositis in Colorectal Cancer Patients-Narrative Review. Arch Pharm Sci ASU 9(1): 194-208
DOI: 10.21608/aps.2025.342950.1211

**Print ISSN**: 2356-8380. **Online ISSN**: 2356-8399.

**Received** 24 December 2024. **Accepted** 03 January 2025.



**Published by**: Ain Shams University, Faculty of Pharmacy

## 1. Introduction

### 1.1. Colorectal cancer

Colorectal cancer (CRC) is reported to be the third most frequent type of cancer in the world and is considered one of the leading causes of cancer-related deaths for both sexes **[1].** It accounts for 9.4% of deaths that occur in cancer patients **[2].** In Egypt, it is reported that CRC represents about nearly 3.9% of total malignant

solid tumors **[3]**.

Pathogenesis of CRC has several phases. It begins with the formation of a dysplastic lesion then the formation of the adenomatous polyp and is terminated by the development of invasive cancer **[4]**. The most widely used classification for CRC origin consists of three pathways: Chromosomal instability (CIN), Microsatellite instability (MSI), and serrated pathways which may have some overlapping features **[5]**.

#### 1.1.1.Chromosomal instability pathway

Chromosomal instability can be observed in about 65-70% of sporadic CRC cases **[6]**. It is associated with a mutation in the adenomatous polyposis coli gene (APC), TP53, KRAS, PI3KCA, etc. which stimulate the development and progression of adenomatous cells. This pathway is associated with worsened outcomes and poorer prognosis than those with MSI **[4]**.

#### 1.1.2.The microsatellite instability pathway

Microsatellite instability occurs due to dysfunction of one or more of the mismatch repair (MMR) genes (MLH1, PMS2, MSH2, MSH6) **[7]**. Lynch syndrome which is one of the most common causes of hereditary cancer, is commonly associated with dysfunction of MMR proteins. It accounts for 3% of all CRCs and up to 15% of gene MMR dysfunction **[8, 9]**.

#### 1.1.3.Serrated polyp pathway

Approximately, 15 to 30% of all CRCs arise from neoplastic serrated polyps. This pathway is characterized by genetic mutation of KRAS or BRAF which stimulates the activation of the mitogen-activated protein kinase (MAPK) pathway **[10]**. It is associated with the worst prognosis **[4]**.

Over 70% of CRC cases are sporadic. However, several risk factors might contribute to the development of CRC **[11]**. Non-modifiable risk factors for CRC include male sex, type 2 diabetes, and inflammatory bowel disease (IBD)**.** Also, there are modifiable risk factors such as alcohol consumption, obesity, physical inactivity, smoking, and diet **[12–14]**.

Endoscopy is the main procedure for diagnosis of CRC **[15]**. It can detect polyps by investigating the inner wall of colon and for removal and biopsy **[16]**. Biopsy from colonoscopy or surgery is considered the gold standard for diagnosing colorectal lesions through histopathological examination for further classification and staging of tumor **[16, 17]**.

The treatment of CRC is usually a combination of local treatment strategies such as surgery or radiotherapy and systemic therapy including conventional chemotherapy, such as 5-FU-based chemotherapy, targeted therapy, and immunotherapy **[18]**. The management of CRC is hence a multi-modal approach that depends on tumor localization, extent, biology, and patient factors **[19]**.

### 1.2. 5-Fluorouracil

5-fluorouracil-based regimen is the standard chemotherapy protocol for the management of CRC in palliative and adjuvant settings **[20, 21]**. It is an antimetabolite that acts through the intracellular conversion into active metabolites that interfere with thymidine biosynthesis and affect DNA and RNA-mediated processes **[22]**.

The overall response rate to 5-FU in advanced CRC is limited to 10–15%. Although survival is reported to be improved after the addition of irinotecan and oxaliplatin to the 5-FU regimen **[23]**.

The 5-FU-based regimen is recommended in CRC stage III or stage II and is associated with high-risk factors for relapse except in positive biopsy for high microsatellite instability (MSI-H) or deficiency in DNA mismatch repair (MMR-D). For patients with Lynch syndrome, 5-FU-

based regimens are ineffective, and prior testing for MMR-D status is standard care **[22]**.

The use of 5-FU is limited by many side effects which include myelosuppression, dermatitis, cardiac toxicity, diarrhea, and mucositis. Gastrointestinal mucositis is considered a major complication in about 80% of patients receiving 5-FU and results in abdominal bloating as well as vomiting and diarrhea **[24]**.

### 1.3. 5-Fluorouracil-induced oral mucositis

#### 1.3.1. Epidemiology of 5-Fluorouracil- induced oral mucositis

Mucositis and stomatitis are the most frequent adverse effects in patients receiving chemotherapy **[25]**. It was reported that the incidence of OM was higher in patients receiving a 5-FU-based regimen than those receiving any other regimen of chemotherapy by about 20% **[26]**. The incidence of OM with 5-FU of grades 1 and 2 is nearly 93% **[27]**, while more than 15% of patients receiving 5-FU develop grades 3 to 4 of OM. Oral mucositis can result in dose reduction or discontinuation of therapy **[28]**.

Development and severity of OM are increased by several patient factors such as smoking, poor oral hygiene, dental health, younger age, female gender, nutritional status, and neutrophil counts before initiation of treatment **[29–32]**. Also, the dose, method of infusion of 5-FU, and concomitant chemotherapy may affect the grade of OM **[31, 33–35]**. For instance, more frequent low-dose infusions are less toxic to the host than less frequent higher doses **[33]**. The prevalence of mucositis in patients undergoing standard-dose chemotherapy is approximately 40%, and this ratio exceeds 50% in high-dose 5-FU protocols **[36]**. In addition, 5-FU infusion was reported to have better safety than bolus 5-FU **[34]**. Moreover, the addition of folinic acid to 5-FU increases the risk of OM despite increasing the efficacy of 5-FU. Concomitant use of chemotherapy may affect the development of mucositis where the risk of OM increases when the intensity of therapy increases **[31, 35]**.

## 2. Methods

### 2.1. Data Sources and Searches

The Egyptian Knowledge Bank, Google Scholar, and PubMed databases were searched for published preclinical and clinical articles relevant to the selected criteria. Searches were supplemented by a reference list review of relevant articles. Research was performed using different keywords such as, “pathophysiology of 5-FU-induced oral mucositis”, “inflammatory cytokine and 5-FU-induced oral mucositis”, “oxidative stress and 5-FU-induced oral mucositis”, “pleotropic effect of (statins OR 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors)”, “statins in 5-FU-induced oral mucositis”. Relevant resources were extracted using source source-pulling method of the references.

The inclusion criteria were preclinical and clinical articles describing the anti-inflammatory and antioxidant activity of statins and their potential role in the prevention of 5-FU-induced OM from English-language publications.

## 3. Results

### 3.1. Pathophysiology of 5-Fluorouracil-induced oral mucositis

The development of OM comprises five stages; initiation of the injury, signaling, amplification of the inflammatory responses, tissue ulceration, and healing **[37]**. The mucosal injury occurs through direct DNA damage. This leads to a series of activations of enzyme and transcription factors which results in the upregulation of genes coding for pro-inflammatory cytokines such as TNF-alpha, interleukin -1 beta (IL-1β), and interleukin -6

(IL-6) **[38]**. These cytokines recruit immune cells to the injured mucosa. The immune cells produce more cytokines and inflammatory mediators causing amplification of the inflammatory response **[39, 40]**. The released TNF-alpha activates MAPK that sustains the activity of nuclear factor kappa B (NF-κB) and augments the production of more pro-inflammatory cytokines and infiltration of the oral mucosa with inflammatory cells **[39, 41, 42]**. The inflammatory cells such as neutrophils, macrophages, and lymphocytes contribute to the development of ulceration and disruption of the mucosal barrier promoting bacterial invasion for further secondary infection **[39]**. Finally, stimuli from the submucosal extracellular matrix and mesenchyme promote the healing process and result in the proliferation of the epithelial layer and cell differentiation **[39,41]**. The healing process is initiated when the pro-inflammatory response subsides spontaneously or with treatment **[43]**.

On another side, tissue damage, and mitochondrial dysfunction lead to the generation of ROS as a result of activating signaling pathways **[43, 44]**. These are highly reactive molecules such as hydrogen peroxide, superoxide, and hydroxyl radicals. Leading to an imbalance between prooxidants and antioxidants **[45]**. Excessive production of ROS seriously affects the homeostasis of the body by inducing tissue injury and triggering a cascade of inflammatory pathways **[42, 46]**. They activate the NF-kB pathway and IL-6 and cause amplification of the inflammatory response in oral mucosa **[40]**. This cascade of inflammatory pathways results in mucosal ulceration; a main sign of clinical presentation of OM **[47]**.

### 3.2. Clinical presentation and severity assessment of 5-Fluorouracil-induced oral mucositis

Oral mucositis has a negative impact on the patient's quality of life (QOL). It can be manifested by different symptoms such as pain, erythema, and inflammation of the oral mucosa which consequently affect the ability to chew, swallow, eat, and drink leading to alterations in nutritional status. Severe mucositis can lead to interruptions and delays in the treatment **[48]**. It can increase the risk of systemic sepsis. It may require dose reduction of chemotherapy or even treatment cessation, which in consequence affects the patients' survival **[48]**. Oral mucositis can increase mortality by about 40 % **[49]**.

Assessment of OM is recommended regularly due to changes in severity over time **[39]**. The severity is usually graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). These criteria grade the adverse events of OM from Grade I to Grade IV, with increasing severity based on patient manifestation and clinical findings **[29]**. Grade I OM is usually asymptomatic or with mild symptoms while grade II is associated with moderate pain or ulcer that does not interfere with oral intake, but the patient requires a modified diet **[37]**. Grade III is considered medically significant. It is associated with pain and interferes with oral intake. Grade IV is life-threatening and requires hospitalization and urgent interventions **[50]**.

### 3.3. Management of 5-Fluorouracil-induced oral mucositis

Management of OM pain is essential to improve the QOL of patients receiving chemotherapy **[30]**. Uncomplicated mucositis is considered asymptomatic and does not require more than supportive care such as viscous lidocaine, diet modification, and avoiding rough food, alcohol, and tobacco. Normal saline or sodium bicarbonate solutions can be used to relieve pain **[29]**. In severe mucositis, an opioid analgesic like fentanyl is recommended to relieve pain **[51]**. Hospital admission may be needed for

systemic analgesics administration, intolerability of oral intake, and management of secondary infections. Patient-controlled analgesia with morphine may be used to manage the pain in hospitalized patients **[29]**.

Oral cryotherapy using ice chips in the mouth 30 min before receiving a bolus of 5-FU infusion chemotherapy is recommended for OM prevention **[52]**. It shows high activity in decreasing the incidence and severity of OM **[53]**. Palifermin is the only drug approved by the United States Food and Drug Administration and the European Medicines Agency for the prevention of OM**.** It is an intravenous recombinant human keratinocyte growth factor that acts by promoting proliferation, differentiation of epithelial cells, and stimulation of cytoprotective mechanisms **[54, 55]**. It decreases the incidence and severity of severe grades of OM **[56]**. Other preventive measures include oral zinc supplements for the prevention of OM **[51]**.

Up till now, there is no definite standard agent proven for the treatment or prevention of 5-FU-induced OM, and the management is based only on palliative and supportive protocols with uncertain clinical outcomes **[57]**. Hence, additional strategies are needed for discovering effective agents for prevention of OM.

### 3.4. Statins

Statins are a category of drugs that are used to lower cholesterol. Statins reduce the intracellular synthesis of cholesterol via reversible inhibition of (HMG-CoA) reductase; the rate-limiting enzyme in the cholesterol biosynthesis pathway **[58, 59]**. In addition to the lipid-lowering effect of statins, they exert many other activities such as improvement of endothelial dysfunction, stabilization of atherosclerotic plaques, antioxidant properties, and inhibition of inflammatory responses. Moreover, they have immunomodulatory actions and apoptotic and antiproliferative effects. These effects are attributed to the pleiotropic effects of statins **[60, 61]**.

The non-lipid lowering effect of statins is stimulated through the inhibition of the protein isoprenylation process which is responsible for mevalonate downstream via a cascade of cellular responses **[62]**.

#### 3.4.1. The anti-inflammatory effect of statins

The anti-inflammatory effect of statins depends on the inhibition of both “classical” (HMGCoA–Mevalonate–FPP–cholesterol) and “non-classical” (HMGCoA– Mevalonate–FPP–kinase) pathways **[63]**. This effect is based on inhibition of proliferation and aggregation of the inflammatory cells **[64]**.

Mevalonic acid, synthesized by HMG-CoA reductase, is the precursor of numerous metabolites such as the isoprenoid intermediates, farnesyl pyrophosphate (FPP), and geranyl pyrophosphate (GGPP) **[65]**. These metabolites are essential for the attachment of GTPases like RhoA, Rac, and Ras to the cell membrane **[66]**. Rho proteins stimulate the expression of the inflammatory cytokines while the Ras proteins regulate cell proliferation and hypertrophy and the Rac regulates the generation of ROS **[62]**. Inhibition of mevalonate pathway may affect cytokine production and reduce inflammation by decreasing the production of these metabolites **[66]**. Additionally, statins stimulate the synthesis of Nitric oxide (NO) through nitric oxide synthase (NOS). Nitric oxide is considered an important protective factor in the endothelium that could eliminate free oxygen radicals and affect inflammatory reactions **[64]**. Moreover, statins inhibit the activity of NF-κB; prevent it from entering the nucleus, and consequently reduce the inflammatory factors expression **[64]**.

The anti-inflammatory effect of statin has

been proven in previous animal studies. A preclinical study conducted on male mice treated with mevastatin, showed a significant increase in the levels of endothelial nitric oxide synthase (eNOS) mRNA and protein **[67]**. Another experimental model revealed that the pretreatment of mice with pravastatin and simvastatin is associated with a significant reduction in leukocyte number in endotoxin-induced acute lung injury and a significant decrease in TNF-alpha level **[68]**.

The results of clinical studies came in accordance with the studies of animal models. It was previously reported that the patients receiving high doses of rosuvastatin before percutaneous coronary intervention (PCI) had various positive outcomes. The level of inflammatory markers such as vascular cell adhesion molecule-1 (VCAM-1), and matrix metalloproteinase-9 (MMP-9) was significantly lower in the patients who received rosuvastatin **[69]**. Also, receiving atorvastatin combined with remote ischemic pre-conditioning (RIPC) in animal and human models showed a synergistic cardioprotective effect against ischemia as a result of a significant reduction in the levels of TNF-alpha, cardiac troponin I (cTnI) (in patients) and IL-6, and CRP (in rabbits) concurrently with increase in the level of protective NO **[70]**. Peled et al reported that pre-heart transplantation statin therapy is associated with a lower incidence of primary graft dysfunction after surgery due to the immunomodulatory and anti-inflammatory effect of statins **[71]**.

In addition, statins play an important role as anti-inflammatory agents in several disorders such as pulmonary fibrosis**,** atherosclerosis, chronic heart failure, sepsis, COVID-19, diabetic nephropathy, gastric cancer, Alzheimer's disease, bone disorders, and autoimmune diseases **[61,72]**.

### 3.4.2. The antioxidant effect of statins

Statins antioxidant activity is exerted through the inhibition of some pro-oxidant enzymes such as NADPH oxidase. Also, they reduce the synthesis of the highly reactive compound MDA resulting from lipid peroxidation of polyunsaturated fatty acids. Moreover, they upregulate antioxidant enzymes such as catalase, glutathione peroxidase (GPx), and superoxide dismutase (SOD) **[73]**.

The intrinsic activity of statins was tested in vitro showing anti-hydroxyl radical antioxidant activity with simvastatin and anti-peroxyl radical antioxidant activity with fluvastatin. **[74]**. In an animal model, the antioxidant activity of statin was proven through different mechanisms. Statins promote the activation of the antioxidant defense protein heme oxygenase-1(HO-1) in endothelial cells via HO-1 promoter; a target site of statins **[75]**. Another study demonstrated that atorvastatin decreased oxidative stress through direct inhibition of platelet Nox2; a marker of NADPH oxidase activation **[76]**.

Similarly, clinical trials confirmed the potential activity of statins as antioxidants. In end-stage renal disease patients treated with statins a significant elevation in selenium levels was observed, which binds to the active sites of glutathione peroxidase (GSH-Pxs) promoting an antioxidant defense role **[77]**.

Taking into consideration the previously mentioned pathogenesis of OM and the anti-inflammatory and antioxidant activity of statins, they have been suggested as a potential preventive strategy against OM in CRC patients.

### 3.4.3. Animal evidence of statins use in oral mucositis

A summary of the preclinical studies that provide evidence regarding statin use in chemotherapy-induced OM and oral toxicity is

presented in **Table 1**.

**Table 1. Summary of the experimental studies demonstrating the effect of statins on mucositis**

| Study | Statin agent | Animal model | Findings |
|---|---|---|---|
| **[78]** | Atorvastatin | Thirty-six male mice treated with intraperitoneal 5-FU to develop mucositis | -Atorvastatin showed the lowest diarrhea score, reduced intestinal permeability, down-regulation of inflammatory cytokines (IL-6, IL-1B, and TNF).<br>-Histopathological: Atorvastatin showed significant restoration of the mucosa.<br>-Atorvastatin reduced the loss of goblet cells at all doses |
| **[79]** | Atorvastatin | Ninety-six male adult hamsters were induced to develop mucositis by the administration of 5-FU. | Atorvastatin showed intestinal permeability reduction, and downregulation of inflammatory markers, such as Tlr4, MyD88, NF-κB, TNF-alpha, IL-1β, and IL-6 dose-dependent.<br>Atorvastatin showed upregulation of the mRNA transcript levels of MUC2, ZO-1 and tight junction proteins as occludin enhancing the epithelial barrier function and reducing the intestinal permeability. |
| **[80]** | Atorvastatin | Thirty -two male Wistar rats treated with chemotherapy to induce mucositis | No dissolution of epithelial layer in addition to modulation of serum level of TNF-alpha after atorvastatin administration. |
| **[81]** | Atorvastatin | Fifty adult albino rats were induced by irinotecan for OM | Atorvastatin showed a decrease in the expression of NF-κB mRNA and proteins, an increase in Nrf2 gene expression, and an increase in immunohistochemical and molecular gene expression of Ki-67 and antiapoptotic Bcl-2 levels. |
| **[82]** | Rosuvastatin | Twenty-four Wister-albino rats were treated with intraperitoneal cyclophosphamide. | -Histological effect: Rosuvastatin significantly decreased the inflammatory infiltration and edema cyclophosphamide-induced tongue lesion.<br>-Biochemical effect: Rosuvastatin decreased the expression of oxidative stress marker; MDA. |
| **[83]** | Simvastatin | Twelve Wistar rats were treated with 5-FU | Histopathological: Improvement of cytotoxicity signs via reduction of necrotic cell numbers and inflammation.<br>-Biochemical: Simvastatin showed lower levels of TNF-alpha expression and IL-6. |

Note: MDA, malondialdehyde; CPT-11, irinotecan.

A previous study conducted on mice to investigate the role of atorvastatin on improvement of 5-FU induced-intestinal mucositis; suggested that atorvastatin exerted anti-inflammatory and protective effects on mucosa. This was associated with a reduction in intestinal permeability and inflammatory infiltration and downregulations of some inflammatory mediators such as Tlr4, MyD88, NF-κB, TNF-alpha, IL-1ß, and IL-6. Also, atorvastatin enhanced the production of mucin 2 (MUC2), and ZO-1 and occluding tight junction proteins which helped to improve epithelial barrier function **[78]**. Another animal trial reported that administration of atorvastatin showed a significant reduction in 5-FU mucosal damage and inflammation in hamsters. Also, histopathological analysis of mucosal tissue revealed decreased production of TNF-alpha and IL-1β in the atorvastatin group **[79]**.

Campos et al reported that histopathological examination of the mucosa in Wister rats after induction of OM and treatment with atorvastatin revealed that no epithelial dissolution occurred in addition to the preserved thin lining layer of mucosa with mild diffuse inflammatory infiltrates. Moreover, modulation of serum level of TNF-alpha was detected after treatment with

atorvastatin. These results suggested that atorvastatin could inhibit the production of TNF-alpha **[80]**. Also, histopathological analysis of albino rats' tongues after administration of atorvastatin revealed a remarkable attenuation of irinotecan-induced OM. Atorvastatin was supposed to initiate the anti-apoptotic, anti-oxidant, and anti-inflammatory gene expression showing a significant decrease in NF-κB protein and gene expression **[81]**.

Rosuvastatin showed a protective effect from cyclophosphamide-induced-tongue toxicity. Histological investigation of the rats′ tongue revealed reduced inflammatory infiltration, and edema in the rats treated with rosuvastatin. This was attributed to the reduction of the levels of oxidative stress markers; MDA with rosuvastatin **[82]**.

Also, Simvastatin administration after treating Wistar rats with 5-FU showed a reduction in necrosis and inflammation of gastrointestinal tissues in histopathological analysis. The biochemical analysis revealed lower TNF-alpha expression and serum IL-6 levels **[83]**.

Hence, statins could be considered as a protective agent for the inner endothelium and mucosa and consequently, they could be used to control ulceration of the oral mucosa.

### 3.4.4. Clinical evidence of statins uses in oral mucositis

A study reported that the administration of atorvastatin mucoadhesive tablets showed a significant reduction in the wound size of aphthous stomatitis with minor susceptibility to recurrence. In addition, atorvastatin demonstrated a significant reduction of pain associated with aphthous stomatitis **[84]**.

The clinical trials evaluating the effect of statins on the development of OM in cancer settings were controversial. Ala et al. proved that the administration of atorvastatin mouthwash during radiotherapy for head and neck cancer patients was associated with a significant reduction in the incidence and severity of OM. Additionally, the intensity of pain was much lower in the statin group **[85]**. Moreover, the administration of lovastatin in head and neck cancer patients who received doxorubicin and ionizing radiation treatment promoted a protective effect on keratinocytes from cytotoxic agents **[86]**.

On the contrary, Karbasizade et al. demonstrated that intestinal and gastric cancer patients who received atorvastatin with 5-FU showed no added beneficial outcome when compared with placebo regarding the severity of OM **[87]**. The same was observed for lovastatin administration in addition to conventional radiation which showed no significant response regarding the incidence of OM in head and neck squamous cell carcinoma patients **[88]**.

The clinical trials discussing the statins' use in the management and prevention of OM are summarised in **Table 2**.

## Conclusion

Several previous studies have reported that statins may play a potential role in the prevention and amelioration of OM whether in animal or human models. Statins were suggested to have anti-inflammatory effect and antioxidant effects as a result of their pleiotropic effects. They could play an effective in protecting against mucosal damage in chemotherapy-induced OM. Further clinical studies are needed to investigate statin therapy as a therapeutic candidate for the prevention and management of OM in cancer patients.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Recommendations

It is recommended to conduct clinical trials to investigate the potential benefit of different types of statins on the severity of 5-FU-induced OM in CRC patients and other types of cancers and to upgrade to larger phase studies.

**Table 2. Summary of the clinical studies demonstrating the effect of statins on mucositis**

| Statin | Model | Enrollment | Concomitant therapy | Findings | Ref. |
|---|---|---|---|---|---|
| Atorvastatin 10-mg mucoadhesive tablets during the first 24 hours after the occurrence of aphthous lesions | Aphthous stomatitis | Forty-four patients | ---------- | Less size of the ulcer.<br>Relief pain. | **[84]** |
| Atorvastatin mouthwash 1% 3 times a day during the radiotherapy period | Head & Neck cancer | Thirty patients | Radiotherapy | Less severe grades of mucositis with atorvastatin. | **[85]** |
| Lovastatin | Head & Neck cancer | ---------- | Doxorubicin and IR treatment, | Protection of keratinocytes from the cytotoxic and genotoxic effects of IR and Doxorubicin through attenuation of pro-toxic DNA damage-related responses of keratinocytes. | **[86]** |
| Atorvastatin 10 mg daily until 2 weeks after chemotherapy sessions | Intestinal and gastric cancer | One hundred and twenty patients | 5-FU | No significant difference from the placebo regarding the incidence and severity of OM. | **[87]** |
| Lovastatin 80 mg daily in conjunction with chemoradiotherapy | Head & Neck cancer | Thirty-five patients | conventional radiation therapy | No significant difference from the placebo regarding the incidence.<br>Severe mucositis (Grade 3) is reported more in the lovastatin group. | **[88]** |

Note**:** IR, ionizing radiation.

## Declarations

### Ethics Approval and Consent to Participate

Not applicable.

### Consent to Participate

Not applicable.

### Consent for publication

Not applicable.

### Availability of the data and Material

All data generated or analyzed during this study are included in this published article in the main manuscript**.**

### Competing interests

The authors declare that there is no conflict of interest.

### Funding

No funding source was received.

### Author contribution

Alaa Amin has collected the data for the All authors have read and approved the final - manuscript.

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