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# **Role of Oxidative/Nitrosative Stress in Diarrhea and Constipation**

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Kaïs Rtibi, Hichem Sebai and Lamjed Marzouki

Additional information is available at the end of the chapter

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## **Abstract**

Oxidative/nitrosative stress, a pervasive condition of increased amounts of reactive and nitrogen species, is responsible for a variety of degenerative processes in some human diseases such as gastrointestinal affections. Diarrhea is one such infection that has long been recognized as one of the most important health problems in developing countries. Constipation is a delay or difficulty in evacuating the stool. In this respect, several studies were performed and have shown that the diarrhea pathophysiology and constipation were accompanied by accumulation of biomarkers of oxidative/nitrosative stress as well as the depletion of antioxidant system. In this chapter, we discuss about the recent advances that propose a major role of oxidative/nitrosative stress on diarrhea pathogenesis and constipation.

**Keywords:** oxidative/nitrosative stress, reactive and nitrogen species, diarrhea pathogenesis

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## **1. Introduction**

Reactive oxygen species (ROS)/reactive nitrogen species (RNS) are produced as the by-products of the normal metabolic mechanism in all aerobic organisms [1]. The augmentation of oxidative/nitrosative stress normally describes a situation in which cellular antioxidant capacities are incapable to scavenge the ROS and RNS engendered as a result of massive generation of ROS/RNS, loss of antioxidant defenses, or both. The ROS/RNS cause disruptions in the cellular macromolecules such as the oxidative degradation of lipids, DNA lesion and proteins alteration [2].

Constipation is defined as infrequent or difficult evacuation of feces leading to water absorption, hardening of stool in colon, and excessive straining. This gastrointestinal disorder is a risk factor of colorectal cancer [3].

Diarrhea is usually a result of gastrointestinal infection, which can be induced by various microorganisms such as viruses, bacteria, and parasites. Despite different pathophysiological changes in different types of diarrheas, there are four major mechanisms responsible for this gastrointestinal disruption in electrolyte and water exchange, that is, elevated luminal osmolarity, increased electrolyte secretion, decreased electrolyte absorption, and accelerated intestinal motility [4].

Therefore, the objective of this chapter is to discuss, based on the literature, the contribution of oxidative/nitrosative stress in gastrointestinal disorders such as constipation and diarrhea.

## 2. Oxidative/nitrosative stress and gastrointestinal disorders

Alterations in the digestive tract such as constipation and diarrhea are caused by many external agents and factors. These disturbances are accompanied by the installation of oxidative/nitrosative stress, which can cause various disruptions in gastrointestinal intestinal function (**Figure 1**).

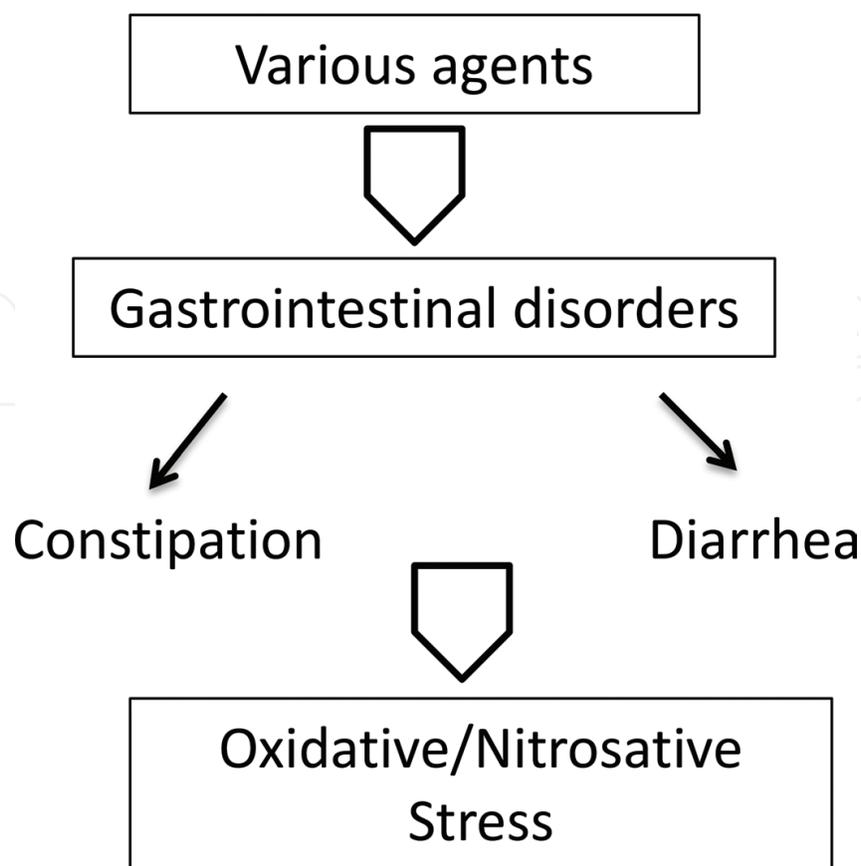
### 2.1. Oxidative stress and diarrhea

Many literature studies suggest the involvement of oxidative stress in the aggravation of diverse perturbations, including gastrointestinal infectious diseases produced by pathogens. These results indicate that Rotavirus induces a generation of ROS and deficiency in the reduced glutathione (GSH)/oxidized glutathione (GSSG) ratio [5]. Added to that, it has been shown also that diarrhea induced by bacterial infections was combined with an oxidative injury. Indeed, during the steps of salmonellosis, ROS are also generated which provokes a depletion of glutathione in intestinal epithelial cells [6].

Other researches have shown the implication of oxidative stress in castor oil-induced diarrhea. Therefore, recent studies have shown that acute administration of castor increased the formation of malondialdehyde (MDA) in the gastrointestinal tract mucosa indicating an increase in lipid peroxidation. This process presents a possible mechanism of tissue alteration by oxygen reactive derivatives [7, 8]. Furthermore, current findings showed that intestinal hypersecretion was also accompanied by  $H_2O_2$  generation in mucosal intestine.  $H_2O_2$  can lead to the formation of toxic ( $\cdot OH$ ) which oxidizes important cellular components and induces the depletion of glutathione. Oxidative damage of lipids provokes a membrane fluidity alteration, disruption in ion transport, loss of membrane integrity, and finally, cellular function disturbance [9].

Other studies reported that diarrhea was able to induce deleterious effects on the sulfhydryl ( $-SH$ ) group and generation of protein carbonyls. These effects can be explained by the proteins oxidation process, which leads to the dysfunction of many enzymes [10].

Enzymatic antioxidants including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) have an important role in the prevention of oxidative damage by reactive oxygen species. SOD plays a crucial action in dismutation of superoxide radicals to  $H_2O$  and oxygen. On the other hand, catalase protects the cells from toxic effects of ROS by transforming



**Figure 1.** Contribution of oxidative/nitrosative stress in gastrointestinal disorders including diarrhea pathophysiology and constipation pathogenesis.

$\text{H}_2\text{O}_2$  to  $\text{H}_2\text{O}$  and  $\text{O}_2$  [11]. In addition, glutathione peroxidase has a high affinity for hydrogen peroxide; it therefore allows for the removal of hydrogen peroxide, even when present at a low concentration. In this respect, numerous studies have reported that castor oil-induced diarrhea causes a depletion of antioxidant activities of SOD, CAT, and GPx, which explains the overproduction of ROS [12, 13].

## 2.2. Oxidative stress and constipation

On the other hand, several studies have reported an increased oxidative stress and imbalance in antioxidant enzymes following the administration of antineoplastic agents that induced the constipation. In this respect, the use of vinblastine was provoked by the installation of constipation which is associated with a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses in intestinal mucosal barrier. This mechanism was evaluated by lipid peroxidation, protein oxidation, and damaging actions on sulfhydryl groups. Disorders in the normal redox state of cells can induce toxic activities through the generation of free radical reactive oxygen species that induce cell injury and alter these cellular macromolecules [14]. These obtained results are in agreement with those found by Li et al. [15] who revealed that the level of MDA augmented in constipated rats. In addition, other previous reports indicate that chronic constipation can cause potential oxidative stress in children and depletion of antioxidant enzyme activities [16].

### 2.3. Nitrosative stress and diarrhea

The castor oil-induced diarrhea model and intestinal mucosal injury responses may involve the nitric oxide that caused an enhancement of epithelial layer permeability to calcium ions, leading to an accumulation of intracellular  $\text{Ca}^{2+}$  and improvement of calmodulin activation of NO synthetase action. At this level, the NO could cause the hypersecretion process in the small bowel. It was later proved in many research studies that NO and prostaglandins are strongly involved in the inflammatory pathway produced by castor oil [17].

### 3. Conclusion

These data clearly demonstrate the implication of oxidative/nitrosative stress in gastrointestinal disorders such as diarrhea and constipation.

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