Archives of Biology and Engineering
An open access journal
eSciRes
ABE-1-101
Research Article

Protective Effect of *Malva sylvestris* Aqueous Extract against Loperamide - Induced Oxidative Stress in Rat Jejunum

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Abstract

Loperamide (LOP) is an antidiarrheal agent that works by slowing gastrointestinal transit and reducing intestinal secretions. The aim of the study is to evaluate the effect of loperamide consumption for five days on the intestinal oxidative balance, as well as the putative protective effect of *Malva sylvestris* aqueous extract (MSAE). Animals were divided into one normal control group and five experimental groups. LOP, LOP + various doses of MSAE (100, 200 and 400 mg/kg, *b.w*.), and LOP+yohimbine (2 mg/kg, *b.w. p.i.*), used as standard drug. Loperamide (3 mg/kg, *b.w. p.o*) was administered twice a day, for 5 days. Treatment with mallow extract or yohimbine protected against the lipid peroxidation, antioxidant enzymes activity depletion, the fall in the thiol group and reduced glutathione level as well as jejunal free iron and H_2O_2 overload induced by loperamide intoxication. Thereby, MSAE attenuates the pathogenicity of loperamide.

Keywords: Loperamide; *Malva sylvestris*; Yohimbine; Lipid peroxidation; Jejunum; Oxidative balance; Thiol group; Free iron

Introduction

The digestive tract comprises several organs. When we eat, we chew the food in our mouth, then they pass into the esophagus and then into the stomach where they are crushed, mixed, processed by various substances: enzymes and acids [1]. In the small intestine the essential phase of life takes place: intestinal absorption. The small intestine is an important organ, both by its size and surface area, as well as by its contribution to the endogenous synthesis of glucose [1,2] Foods (proteins, carbohydrates, trace elements, vitamins ...) will be transformed into energy. As regards nutrients, the absorption takes place mainly at the small intestine [1,3]. At the end, the ileum enters the colon and at this level, we have about 800 mL to 1 L of fecal fluid. The role of the colon is therefore to absorb water and some minerals [4]. Loperamide is a synthetic opiate derivative lacking central effects that acts as antidiarrheal by decreasing hydration of digestive contents and slowing down transit. Loperamide also exhibits calcium blocking and calmodulin inhibitory effects [5-7].

Oxidative stress is an imbalance between the generation of reactive oxygen species and the body's ability to neutralize and repair oxidative damage [8]. Free radicals are molecules with one or more unpaired electrons are very unstable and react quickly with other components, trying to capture the electron necessary for stability [8,9]. The excessive production of free radicals causes direct lesions of biological molecules such as oxidation of DNA, proteins, lipids and carbohydrates, but also secondary lesions due to the cytotoxic and mutagenic nature of the released metabolites, especially during the oxidation of lipids [10].

Malva sylvestris L. (Malvaceae family) is a hairy plant, from 30 to 60 cm in height, with a stem often spread out and crenelated leaves of a shape similar to those of ivy, the flowers are pink-purple with darker veins on the petals.

Mallow is biennial, but may be perennial by underground buds [11,12]. The mallow flowering occurs between May-June and September [13]. Numerous studies on the use of medicinal plants have demonstrated the importance of *M. sylvestris* in the traditional world medicine as a medicated feed. The mallow was used as a mild laxative, a tonic liver cleanser against heartburn [14-16].

Accordingly, the present study was designed to evaluate the putative protective effect of mallow (*Malva sylvestris L.*) aqueous extract against oxidative stress induced by loperamide exposure and the mechanism involved in such protection.

Materials and Methods

Chemicals

Epinephrine, bovine catalase, butylated hydroxytoluene (BHT), 2-Thio-barbituric acid (TBA), yohimbine and trichloroacetic acid were from Sigma chemicals Co (Germany). All other chemicals used were of analytical grade.

Plant collection and MSAE preparation

Mallow (*Malva sylvestris L.*) leaves were collected during March, 2016 from the area of Béja (North-West of Tunisia) and identified by the laboratory of taxonomy in the Faculty of Sciences of Tunis (FST)-Tunisia. The Voucher specimens (No. MSB01) has been deposited with the herbarium of the Higher Institute of Biotechnology of Béja. The Mallow leaves were dried in an incubator at 40°C during 72 hours and powdered in an electric blender (MOULINEX Ovatio 2, FR). The leaves powder was then dissolved in

distilled water and incubated at room temperature for 24 h in a shaking bath. Sample was centrifuged at 10 000 g for 10 min and the supernatant was lyophilized, aliquoted and stored at -80°C until use.

Animals

Adult male Wistar rats (weighing 200-220 g, 15 weeks old and housed five per cage) were purchased from Pasteur Institute of Tunis and used in accordance with the local ethics committee of Tunis University for the use and care of animals and in accordance with the NIH recommendations [17]. They were provided with standard food (BADR, Utique, TN) and water ad libitum and maintained in animal house under controlled temperature (22 ± 2°C) with a 12/12 h light–dark cycle.

Loperamide induced-oxidative stress in rats

Oxidative stress was induced in the animals by oral administration of 1 mL loperamide (3 mg/kg body weight in 0.9% sodium chloride for 5 days) at 09:00 and at 18:00 h, while the control rats were administered with the normal saline only [4,18].

The rats were divided into half a dozen groups of 10 animals each. Groups 1 and 2 served as controls and had a physiological solution (NaCl, 0.9%, *p.o.*). Groups 3, 4 and 5 were treated with various doses of MSAE (100, 200 and 400 mg/kg, *b.w. p.o*) daily, one hour after loperamide administration during the experiments, and the latter group was treated with yohimbine (2 mg/kg, *b.w. p.i.*), used as standard drug. At the end of experiments, the animals were sacrificed and the distal portions of the jejunum for each animal, were removed and cut longitudinally, then cleaned with physiological saline to remove fecal residues and homogenised in phosphate buffer saline. After centrifugation at 10,000 g for 10 min at 4°C, supernatant was used for biochemical determination of protein, -SH groups, reduced glutathione (GSH), free iron, H_2O_2 and MDA levels as well as antioxidant enzyme activities.

Biochemical estimations

Lipid peroxidation determination: The lipid peroxidation was determined by MDA measurement according to the double heating method [19]. Briefly, aliquots from small intestine, liver and lung tissues homogenates were mixed with BHT-trichloroacetic acid (TCA) solution containing 1% BHT (w/v) dissolved in 20% TCA (w/v) and centrifuged at 1000 g for 5 min at 4°C. Supernatant was blended with solution containing (0.5 N HCl, 120 mM TBA buffered in 26 Mm Tris) and then heated at 80°C for 10 min. After cooling, the absorbance of the resulting chromophore was determined at 532 nm. MDA levels were determined by using an extinction coefficient for MDA-TBA complex of $1.56 \times 105\ M^{-1}cm^{-1}$.

Non-enzymatic antioxidants measurement

The total concentration of thiol groups (-SH) was performed according to Ellman's method [20]. Briefly, homogenates of tissues were mixed with 800 µL of 0.25 M phosphate buffer (pH 8.2) and 100 µL of 20 mM EDTA, and the optical density was measured at 412 nm (A1). Then, 100 µL of 10 mM DTNB were added, incubated during 15 min and the absorbance of the sample was quantified at 412 nm (A2). The thiol groups concentration was calculated from A1 to A0 subtraction using a molar extinction coefficient of 13.6 $\times$ 103 $M^{-1}cm^{-1}$. The results were expressed as µmo of thiol groups per mg of protein.

GSH was estimated in small intestine, liver and lung tissues by the method of Sedlak and Lindsay [21]. Briefly, 500 µL of tissue homogenate prepared in 20 mM EDTA, (pH 4.7) were mixed with 400 µL of cold distilled water and 100 µL of 50% TCA. The samples were shaken using vortex mixer and centrifuged at 1200 g during 15 min. Following centrifugation, 2 mL of supernatant were mixed with 400 µL of 400 mM Tris–buffer (pH 8.9) and 10 µL of 10 mM DTNB. The absorbance was read at 412 nm against blank tube without homogenate.

Antioxidant enzymes activities assays

The activity of SOD was determined using modified epinephrine assays [22]. At alkaline pH, superoxide anion O_2- causes the autoxidation of epinephrine to adenochrome; while competing with this reaction, SOD decreased the adenochrome formation. One unit of SOD is defined as the amount of the extract that inhibits the rate of adenochrome formation by 50%. Enzyme extract was added to 2 mL reaction mixture containing 10 µl of bovine catalase (0.4 U/µl), 20 µL of epinephrine (5 mg/mL) and 62.5 mM of sodium carbonate/bicarbonate buffer pH 10.2. Changes in absorbance were recorded at 480 nm.

CAT activity was assayed by measuring the initial rate of H_2O_2 disappearance at 240 nm [23]. The reaction mixture contained 33 mM H_2O_2 in 50 mM phosphate buffer pH 7.0 and CAT activity was calculated using the extinction coefficient of 40 $mM^{-1}cm^{-1}$ for H_2O_2.

The activity of GPx was quantified following the procedure of Flohé and Günzler [24]. Briefly, 1 mL of reaction mixture containing 0.2 mL of small intestine, liver or lung supernatants, 0.2 mL of phosphate buffer 0.1 M pH 7.4, 0.2 mL of GSH (4 mM) and 0.4 mL of H_2O_2 (5 mM) was incubated at 37°C for 1 min and the reaction was stopped by the addition of 0.5 mL TCA (5%, w/v). After centrifugation at 1500 g for 5 min, aliquot (0.2 mL) from supernatant was combined with 0.5 mL of phosphate buffer 0.1 M pH 7.4 and 0.5 mL DTNB (10 mM) and absorbance was read at 412 nm. The activity of GPx was expressed as nmol of GSH consumed/min/mg protein.

H_2O_2 determination: The tissues H_2O_2 level was performed according to Dingeon et al. [25]. Briefly, in the

presence of peroxidase, the hydrogen peroxide reacts with p-hydroxybenzoic acid and 4-aminoantipyrine leading to a quantitative formation of a quinoneimine which has a pink color detected at 505 nm.

Iron measurement: Tissues non haem iron were measured colorimetrically using ferrozine as described by Leardi et al. [26]. Briefly, the iron dissociated from transferrin-iron complex by a solution of guanidine acetate and reduced by ascorbic acid reacts with ferrozine to give a pink complex measured at 562 nm.

Protein determination: Protein concentration was determined according to Hartree [27] which is a slight modification of the Lowry method. Serum albumin was used as standard.

Statistical analysis

The data were analyzed by one-way analysis of variance (ANOVA) and were expressed as means ± standard error of the mean (S.E.M.). The data are representative of 6 independent experiments. All statistical tests were two-tailed, and a p value of 0.05 or less was considered significant.

Results

Effects of MSAE and loperamide on lipid peroxidation

The inhibition of intestinal secretion by loperamide intoxication produced a significant increase in jejunal MDA content compared with the normal group. *M. sylvestris* aqueous extract (100, 200 and 400 mg/kg, *b.w. p.o*) treatment for 5 days significantly decreased MDA content as compared with loperamide group. Yohimbine (2 mg/kg, *b.w. p.i.*), also significantly protect ($P<0.001$) against jejunal MDA overload induced by loperamide (Figure 1).

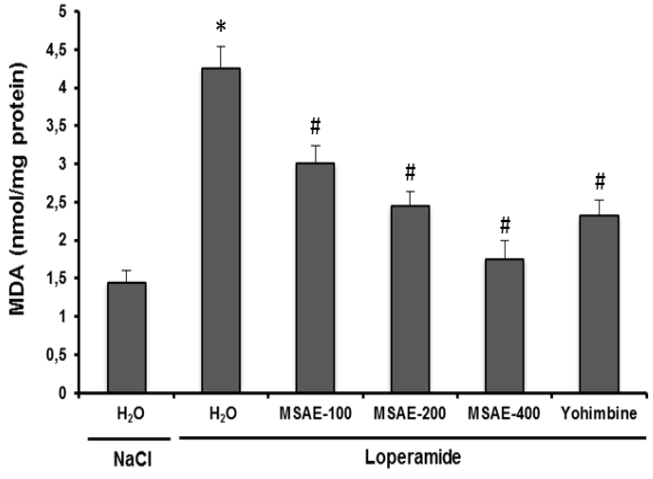

Figure 1: Effects of *Malva sylvestris* aqueous extract (MSAE) and yohimbine on jejunal MDA level during loperamide intoxication. Animals were treated with various doses of MSAE (100, 200 and 400 mg/kg, *b.w., p.o.*), reference molecule (yohimbine, 2 mg/kg, *b.w., i.p.*) or vehicle (NaCl 0.9%) after loperamide (Lop, 3 mg/kg *b.w., p.o.*) intoxication. $^{*}p<0.05$ compared to control group and $^{\#}p<0.05$ compared to loperamide group.

Effects of MSAE and loperamide on antioxidant enzymes activities

As depicted in Figure 2, loperamide intoxication significantly decreased intestinal antioxidant enzyme activities as SOD (A), CAT (B), and GPx (C). While MSAE treatment significantly reversed all loperamide-induced antioxidant enzymes depletion in a dose-dependent manner. Yohimbine, an competitive antagonist of selective α-2 adrenergic receptors, also exhibited the same protection.

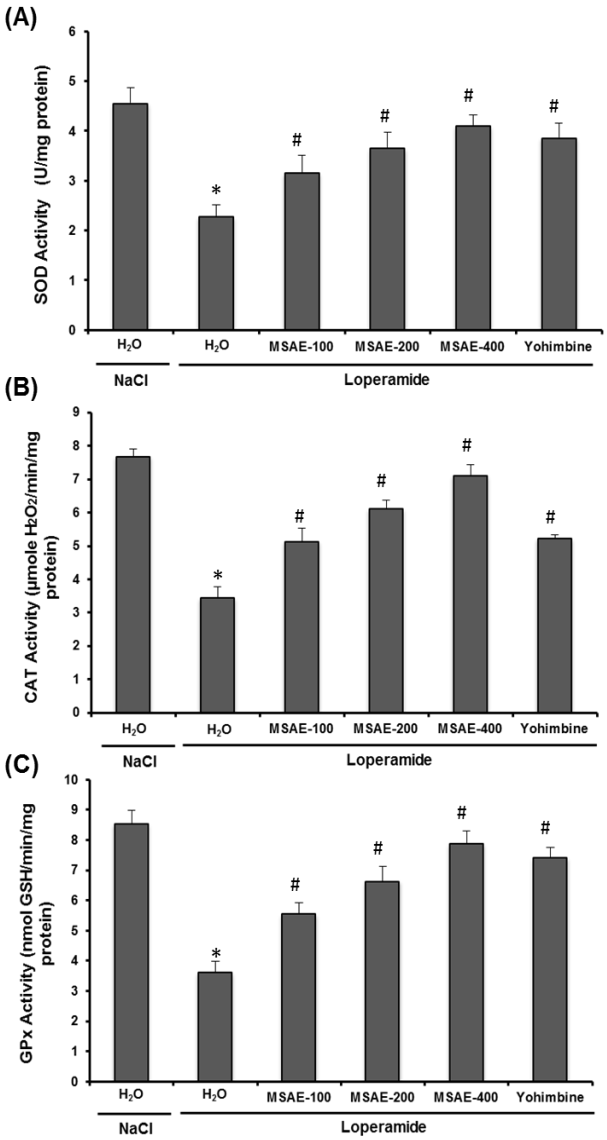

Figure 2: Effects of *Malva sylvestris* aqueous extract (MSAE) and yohimbine on jejunal antioxidant enzyme activities: SOD (A), CAT (B) and GPx (C) during loperamide intoxication.

Animals were treated with various doses of MSAE (100, 200 and 400 mg/kg, *b.w., p.o.*), reference molecule (yohimbine, 2 mg/kg, *b.w., i.p.*) or vehicle (NaCl 0.9%) after loperamide (Lop, 3 mg/kg *b.w., p.o.*) intoxication. $^{*}p<0.05$ compared to control group and $^{\#}p<0.05$ compared to loperamide group.

Effects of MSAE and loperamide on sulfhydryl groups and reduced glutathione levels

Loperamide-induced intoxication and oxidative stress resulted in decreased jejunal sulfhydryl groups and reduced glutathione levels in comparison with normal. Treatment with M. sylvestris aqueous extract (100, 200 and 400 mg/kg, *b.w. p.o*) for 5 days produced a significant increase in intestinal -SH groups and GSH levels compared to loperamide intoxicated group. Rats treated with yohimbine (2 mg/kg, *b.w. p.i.*) also showed the significant protection (Figure 3).

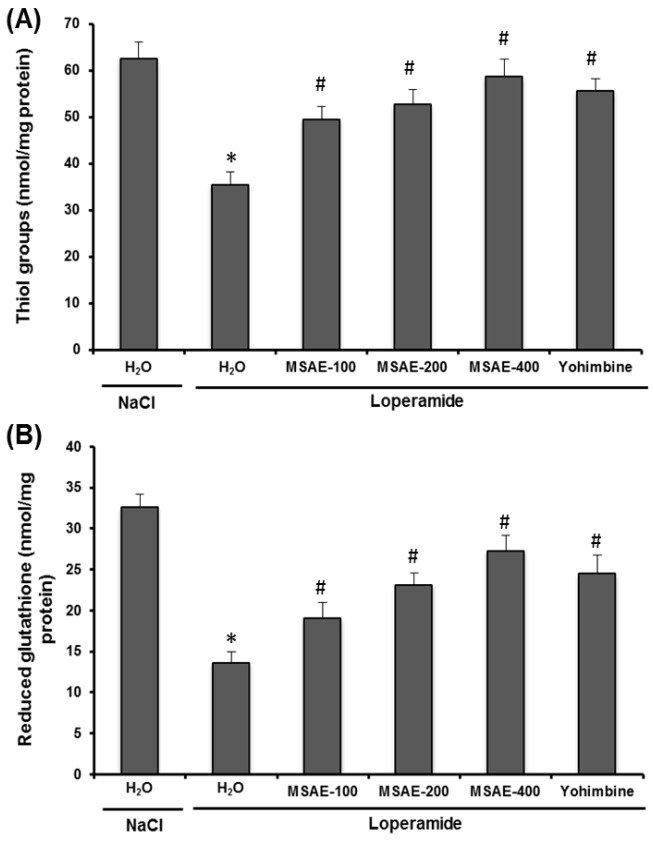

Figure 3: Effects of *Malva sylvestris* aqueous extract (MSAE) and yohimbine on jejunal sulfhydryl groups (A) and reduced glutathione (B) levels during loperamide intoxication. Animals were treated with various doses of MSAE (100, 200 and 400 mg/kg, *b.w., p.o.*), reference molecule (yohimbine, 2 mg/kg, *b.w., i.p.*) or vehicle (NaCl 0.9%) after loperamide (Lop, 3 mg/kg *b.w., p.o.*) intoxication. $^{*}p<0.05$ compared to control group and $^{\#}p<0.05$ compared to loperamide group.

Effects of MSAE and loperamide on intestinal H_2O_2 and free iron levels

In the present study, we also examined the effect of loperamide and MSAE on jejunal H_2O_2 (Figure 4A) and free iron (Figure 4B) levels. In fact, these two compounds are the constituents of the Fenton reaction, who is involved in the hydroxyl radical production. Loperamide per se significantly increased H_2O_2 and free iron levels in the jejunal tissues. While MSAE and yohimbine treatment significantly and does-dependently protected against loperamide-induced intracellular mediator disturbances.

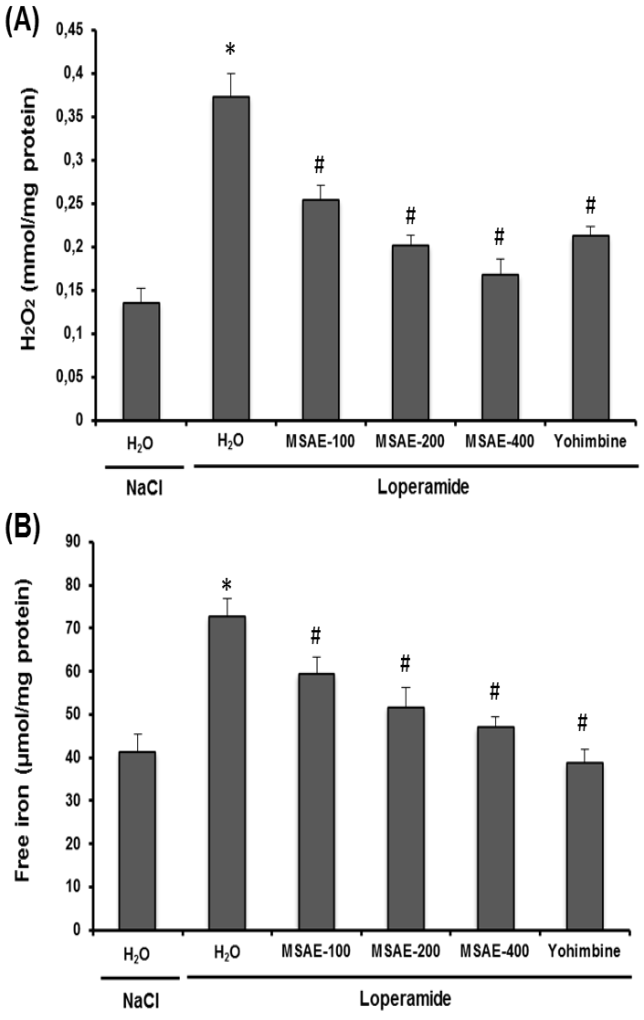

Figure 4: Effects of *Malva sylvestris* aqueous extract (MSAE) and yohimbine on jejunal H_2O_2 (A) and free iron (B) levels during loperamide intoxication. Animals were treated with various doses of MSAE (100, 200 and 400 mg/kg, *b.w., p.o.*), reference molecule (yohimbine, 2 mg/kg, *b.w., i.p.*) or vehicle (NaCl 0.9%) after loperamide (Lop, 3 mg/kg *b.w., p.o.*) intoxication. $^{*}p<0.05$ compared to control group and $^{\#}p<0.05$ compared to loperamide group.

Discussion

The aim of the present study is to evaluate the effect of loperamide on jejunal redox status, as well as the protective effect of mallow aqueous extract.

Normally, oral fluid intakes exceed fecal losses, the digestive tract behaving in a resultant manner with respect to the internal hydroelectrolytic movements, as an absorption system. Several pumps (cation and anions exchangers) and secretion proteins exist on the apical or basolateral surface of the enterocytes. Various agonists and antagonists of these pumps direct the resultant of the exchanges towards the secretion. This leads to a state of intestinal hypersecretion [1]. Several drugs have been used in this case, the best known is loperamide. Indeed, loperamide is an antidiarrheal drug; it is a structural analogue of opiates. It has an anti-secretory activity by increasing the hydro-electrolytic flow of the intestinal lumen towards to the plasma pole of the enterocyte, with reverse flow reduction. It also causes a slowing of the colonic transit with an increase in segmental contractions [5-7,28,29]. However, loperamide is a double-edged a weapon, to be used with caution. Possible side effects are usually mild and temporary. Some people may have constipation, drowsiness, abdominal discomfort, dizziness, tiredness, dry mouth, nausea and vomiting [30-32]. In this context, we have shown in this study that taking loperamide for 5 days causes a jejunal oxidative stress state.

In fact, loperamide intoxication has influenced the jejunal redox balance by inducing lipid peroxidation which is manifested by an increased levels of MDA, decrease in non-enzymatic antioxidants levels such as sulfhydryl groups and reduced glutathione as well as deleterious effects on the antioxidant enzymes activity such as superoxide dismutase, catalase and glutathione peroxidase. The induction of intestinal oxidative stress was chemically caused by several agents, like aspirin [33], castor oil [34], acetic acid [35] and ethanol [36].

A state of oxidative stress is characterized by an imbalance between the production of reactive oxygen species (ROS) and the level of antioxidant defense systems of the cell, in favor of ROS [37]. ROS may have different cellular sources, the most important of which is mitochondria [38]. The excessive production of free radicals causes direct lesions of biological molecules (oxidation of DNA, carbohydrates, lipids, proteins), but also secondary lesions due to the cytotoxic and mutagenic character of the metabolites released especially during lipids oxidation [38,39]. However MSAE treatment significantly backed all loperamide-induced jejunal oxidative stress to near control levels. The most of the antioxidant defenses are the micronutrients that oppose the action of the ROS and participate in the recycling of endogenous antioxidants, and which represent cofactors essential for the proper functioning of enzymatic systems such as glutathione peroxidase or superoxide dismutase [40].

In the other hand, we have shown that taking loperamide for five days leads to iron and hydrogen peroxide overload in the jejunum tissues. In addition, the Fenton reagent (a mixture of Fe^{2+} and H_2O_2) is one of the most active systems for the oxidation of organics in water. This reactivity is due to the generation of hydroxyl radicals [41,42]. The hydroxyl radicals are the most damaging ROS of oxidative stress, due to their extreme reactivity.

Hydroxyl radicals attack all biological materials (DNA, proteins, lipids...). They are powerful oxidants which react according to three modes of action: Either by pulling off an electron, or by tearing off a hydrogen atom, or by adding to the double bonds of the biomolecules [37]. However, *M. sylvestris* aqueous extract has strongly inhibited the jejunal overload of hydrogen peroxide and free iron, which results in inhibition of the hydroxyl radical production. The MSAE free iron chelation and H_2O_2 scavenging activities can be attributed to its richness in antioxidants molecules such as delphinidin, apigenin, malvidin, malvin, myricetin, quercetin and kaempferol [4,13].

Conclusion

This study has shown that aside the known adverse effects on loperamide, It also acts negatively on the intestinal oxidative balance by causing of oxidative damages that has been attenuated by *Malva sylvestris* aqueous extract, due to its antioxidant properties.

Ethical Consideration

All procedures on animals in this study were compiled with the NIH recommendations for the use and care of animals.

Acknowledgements

Financial support of the Tunisian Ministry of Higher Education and Scientific Research is gratefully acknowledged. Financial disclosures: None declared.

Competing Interests

The authors declare that they have any competing interests.

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Received date: July 21, 2017; **Accepted date:** August 30, 2017; **Published date:** September 05, 2017

Citation: Jabri MA, Hajji N, Wannes D, Marzouki L, Sebai H (2017) Protective Effect of Malva sylvestris Aqueous Extract against Loperamide - Induced Oxidative Stress in Rat Jejunum. *Arch Biol Eng* 1(1): 101.