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Research Article

Methyl Jasmonate Ameliorates Liver Oxidative Stress Associated with Acetic Acid-Induced Ulcerative Colitis in Wistar Rats

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Abstract: Ulcerative colitis is the most common type of inflammatory bowel disease, with many extra manifestations. Reports have shown that over 30% of IBD patients presents with various liver disease. This study was carried out to investigate the effects of *Methyl jasmonate* (MEJ) in the reversal of liver oxidative stress associated with ulcerative colitis in a rat-model of ulcerative colitis. Fifteen male Wistar rats were used for this study and divided into 3 groups (n=5). Groups 1 (Control) and 2 (Colitis) were administered 1% ethanol three days before colitis induction. While, group 3 (MEJ + COL) received MEJ dissolved in 1% ethanol three days prior to colitis induction. Colitis was induced by administration of 2ml 4% acetic acid (v/v) intrarectally. The liver was collected six days post induction and protein concentration, myeloperoxidase, catalase and superoxide dismutase were determined by spectrophotometry. Protein concentration and myeloperoxidase levels rises significantly while, catalase and superoxide dismutase activities decreased significantly following colitis induction. *Methyl jasmonate* significantly decrease myeloperoxidase and increase catalase and superoxide dismutase activities in the liver compared to colitis group. Thus, in this study *Methyl jasmonate* was proven effective in reversing the oxidative stress in liver associated with ulcerative colitis and could be considered as an effective therapeutic agent in the treatment of inflammatory bowel diseases extra manifestations.

Keywords: ulcerative colitis, inflammatory bowel disease, liver toxicity, methyl jasmonate, antioxidants.

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1. Introduction

The most prevalent form of inflammatory bowel disease (IBD), ulcerative colitis, is an idiopathic chronic inflammatory disease of the colon that affects and erodes its innermost lining, leading to the formation of small sores (or ulcers), which are typically accompanied by bleeding (Gisbert & Chaparro, 2019). The condition can affect people of all ages, although it is most prevalent in those in their mid-thirties, and older men are more likely to be diagnosed than their female counterparts are (Danese et al., 2018).

Although there is no known cause for ulcerative colitis specifically, there are a number of unknown factors that may play a role in its onset. A basic genetic component, an aberrant immunological response, microbiotic and environmental variables, etc. are a few examples of such components (Danese et al., 2018). Its

pathogenesis has also been linked to autoimmune disease (Danese et al., 2018; Liu & Polk, 2018). Normally, the immune system of the human body causes inflammation to fight an infection or illness, and the inflammation would subside once the threat was removed. However, in individuals with ulcerative colitis, the inflammation typically lasts for a long time after the immune system has completed its task. This is because the body keeps injecting white blood cells into the lining of the large intestine, leading to ulcers and chronic inflammation (Liu & Polk, 2018).

According to studies (Gaspar et al., 2021; Harbord et al., 2016; Omayone et al., 2023), 50% of patients develop extra-intestinal signs such as metabolic bone disease, arthropathy, neurologic, ophthalmic, dermatological, pulmonary, urological, and hepatobiliary problems. The majority of IBD patients' extra-intestinal symptoms are hepatobiliary problems, which affect about 30% of patients (Gaspar et al., 2021). Primary sclerosing cholangitis (PSC) and small-duct primary sclerosing cholangitis (small-duct PSC) are two conditions that share a pathophysiology with inflammatory bowel disease (IBD) (Navaneethan & Shen, 2010; Uko et al., 2012). Their clinical trajectories don't necessarily correspond with disease activity, and in other circumstances, they may be unrelated to the severity of gastrointestinal inflammation (Navaneethan & Shen, 2010).

Jasmonic acid, cis-jasmonate, and methyl jasmonate (MeJA), which have anti-inflammatory potential and structural resemblances to prostaglandins, make up the majority of the jasmonates family of fatty acid-derived cyclopentanones (Cesari et al., 2014). In response to biotic and abiotic stressors, they also function as signaling molecules (Raviv et al., 2013). Numerous investigations on the jasmonate family's effects on mammalian cells, notably their cytotoxic activity against cancer cells, have been conducted as a result of their anti-inflammatory properties (Cesari et al., 2014; Raviv et al., 2013). However, it has been demonstrated by numerous studies that methyl jasmonate has a greater anticancer potential in comparison to the other jasmonates. As a result, it has recently come to the attention of researchers as a promising drug in the amelioration of cancer (Cesari et al., 2014). Other investigations shown that methyl jasmonate can prolong the lives of mice who have lymphoma (Fingrut & Flescher, 2002) or that have been injected with multiple myeloma cells (Klippel et al., 2012).

Methyl jasmonate has also been claimed to have anti-oxidant properties; studies have shown that it can significantly reduce hepatic ROS content, restore hepatic GSH/GSSG levels, and reduce inflammatory parameters in compromised biological systems (Sá-Nakanishi et al., 2018). Medical researchers are concerned about the most typical types of liver complications that emerge from IBD-related illnesses because they have been known to lead to hepatic failure or death of sufferers (Faubion Jr et al., 2001). The liver may experience negative consequences from drugs used to treat IBD symptoms, such as sulfasalazine, thiopurines, and methotrexate (Dubinsky et al., 2002; Teo & Tan, 2006). By evaluating the liver's antioxidant status, this study aims to determine the role of methyl jasmonate in the treatment of hepatic problems brought on by acetic acid-induced ulcerative colitis.

2. Materials and Methods

Drugs and Chemicals

While methyl jasmonate was acquired from Sigma-Aldrich in the United States, acetic acid was purchased from LOBA Chemie in India.

Experimental design

For the investigation, fifteen (15) male Wistar rats weighing between 140g and 200g were employed. The animals were bought and kept in the animal house at the Federal University of Technology in Akure's Department of Physiology. They had two (2) weeks of acclimatization and unrestricted access to rat food and water. Five (3) groups were created from the animals. The animals were cared for in accordance with the Laboratory Animal Care and Use Guide (Albus, 2012).

Animal Groupings

Group 1: Control group (n=5), was given 1% ethanol being the vehicle used for the dissolving *Methyl jasmonate*.

Group 2: Colitis group (n=5), also received 1% ethanol and thereafter induced with ulcerative colitis.

Group 3: MEJ + COL group (n=5), received *Methyl jasmonate* and was induced with ulcerative colitis.

Methyl jasmonate and ethanol administration

Three days before employing acetic acid to induce colitis, the corresponding groups were given intraperitoneally (IP) doses of methyl jasmonate (50 mg/kg) and ethanol (1%) respectively. Based on the findings of earlier research, MJ was prepared, and the dose was used (Aluko & Umukoro, 2020).

Induction of colitis

A 2mL intrarectal injection of 4% (v/v) acetic acid in 0.9% sodium chloride was used to induce colitis. A soft, flexible catheter that was put into the anus up to a length of 8cm was used. To prevent the acid from being expelled, the rats were kept in a head-down position for 30 seconds while this was being done under a light ketamine anesthetic (Omayone & Olaleye, 2021).

Preparation of liver tissues for biochemical assay

Six days after the induction of colitis, the animals were slaughtered, and the livers were harvested. They were blotted and weighed after being rinsed in ice-cold normal saline. They were homogenized using a Teflon homogenizer in 4 liters of ice-cold 0.1M tris KCl buffer, pH 7.4. The resultant homogenates underwent a ten-minute centrifugation at 10,000 g and 4 °C. The supernatants were gathered and utilized to estimate the antioxidant enzymes.

Oxidative stress marker assay

With a small modification, the Biuret method as published by Gornal et al. (1949) was used to determine the protein concentrations of the individual samples. The reagent was given potassium iodide to stop the Cu 2+ ions from precipitating as cuprous oxide. The method of (Misra & Fridovich, 1972) was used to determine the degree of SOD activity. The method described by Kim et al. (2012) was used to measure the activity of myeloperoxidase (MPO). The procedure of (Claiborne, 2018) was followed in the determination of the catalase activity assay. The technique is based on the decrease in absorbance at 240 nm seen as catalase breaks down hydrogen peroxide.

3. Results

Effects of Methyl jasmonate on Protein concentration and Myeloperoxidase (MPO) level in liver following acetic acid induced ulcerative colitis

Protein concentration significantly increased in the colitis and MEJ+ COL groups after the induction of colitis when compared to the control group (figure 1). In terms of protein content, there was no discernible change between the colitis and MEJ+ COL groups. Figure 2 shows that when colitis was induced, myeloperoxidase was considerably higher in the colitis group than in the control group. Comparative to the colitis group, methyl jasmonate considerably lowers MPO levels, bringing them back to normal.

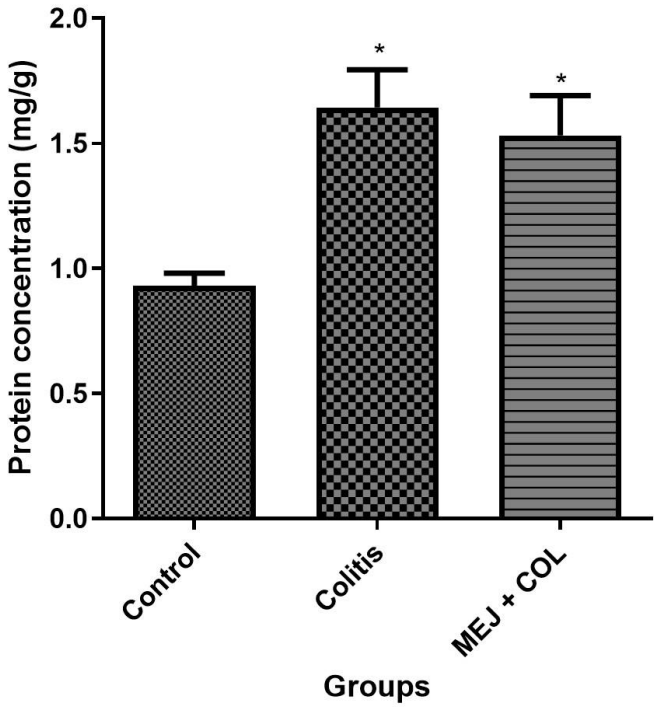

Figure 1. Effect on *Methyl jasmonate* Protein concentration of the liver in acetic acid induced colitis

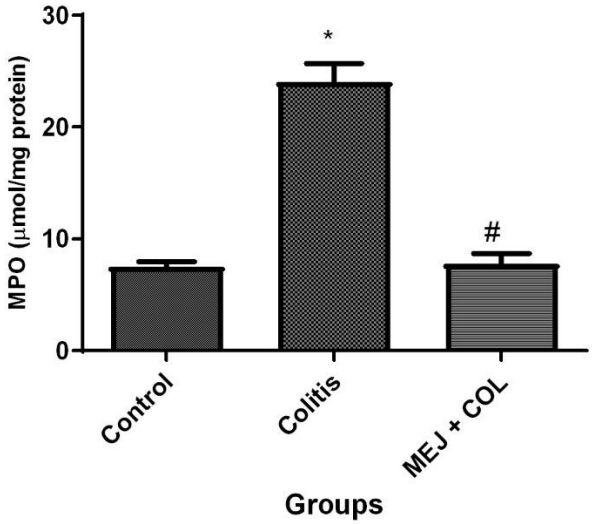

Figure 2. Effect on *Methyl jasmonate* myeloperoxidase of the liver in acetic acid induced colitis

Effects of Methyl Jasmonate on Catalase (CAT) and Superoxide Dismutase (SOD) expression in Indomethacin-treated Colitis Rats

The control group had much higher antioxidant status than the other groups, according to the results of the evaluation of antioxidant levels. There was no discernible difference between the colitis group and MEJ + COL according to CAT (Figure 3). But when compared to the colitis group, methyl jasmonate dramatically increases SOD levels (Figure 4).

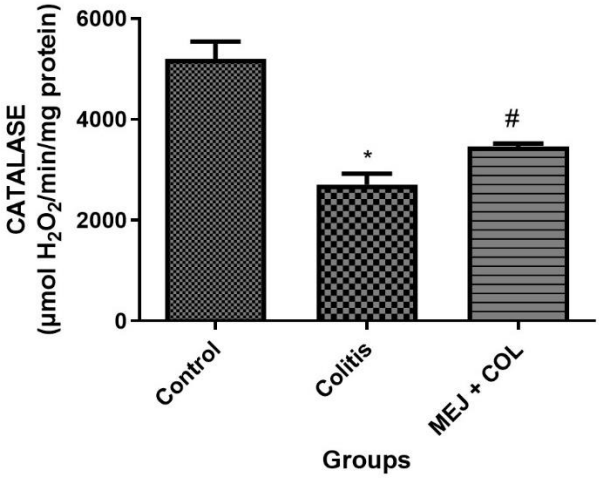

Figure 3. Effect on *Methyl jasmonate* on catalase activity in the liver following acetic acid induced colitis

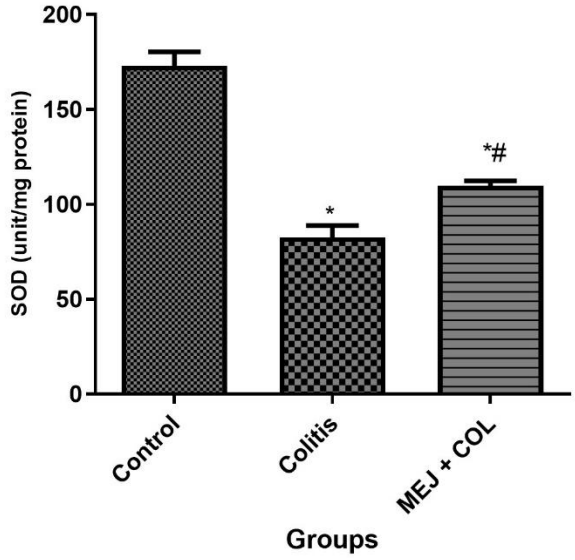

Figure 4. Effect on *Methyl jasmonate* superoxide dismutase activity in the liver post acetic acid induced colitis

4. Discussion

The colonic mucosa becomes inflamed in ulcerative colitis (UC), a chronic intestinal illness. The most common symptoms of UC are diarrhea, blood in the stool, and on rare instances, stomach pain. Weight loss, anemia, and fever are further potential adverse effects. According to Loftus et al. (2005), 2–7 people out of 100,000 are expected to develop UC each year. According to Hanauer (2006), UC is to blame for about 20,000 hospital admissions and 250,000 doctor visits each year in the US.

Methyl jasmonate's effects on liver antioxidant status after acetic acid-induced ulcerative colitis were assessed in this study. The study's findings demonstrated that the additional manifestation of ulcerative colitis caused oxidative stress in the liver. This was supported by the fact that myeloperoxidase levels increased in the colitis group relative to the control group while catalase and superoxide dismutase activity were depleted. According to Rensen et al. (2009), myeloperoxidase (MPO) is a lysosomal protein that is abundantly expressed in neutrophils and is involved in the production of reactive oxygen species. According to Hansberry et al. (2017), MPO is typically utilized as a reliable biomarker to evaluate the severity of the disease when it comes to inflammatory bowel disease (IBD). According to earlier studies, patients with active inflammatory bowel disease (IBD) had significantly higher MPO levels than those with inactive IBD or those without the condition. When evaluating the effectiveness of a therapy, MPO levels are utilized as an indicator of the caliber of the response (Hansberry et al., 2017). Therefore, the fact that Methyl Jasmonate administration significantly reduced MPO levels in this trial suggests that it is effective in treating IBD and accompanying symptoms.

The findings of this study also demonstrated that acetic acid-induced ulcerative colitis and indomethacin treatment both increased protein expression levels. However, the administration of methyl jasmonate was able to somewhat reduce the levels of protein expression that were normally increased by the administration of indomethacin. This is consistent with research (Yi-Han et al., 2020) that point to the effectiveness of methyl jasmonate in treating IBD cases of inflammation and its symptoms, including higher protein expression levels.

Additionally, this study demonstrated that the MEJ + COL group's levels of the antioxidant enzymes catalase (CAT) and superoxide dismutase (SOD) were increased by the effects of methyl jasmonate. The colitis group's enzyme activity were significantly reduced after receiving acetic acid treatment, although methyl jasmonate was effective in undoing this impact. This is also consistent with other research on the effects of methyl jasmonate, which demonstrates that MJ enhances antioxidant defense system and improves ROS scavenging (Farooq et al., 2016; Omayone et al., 2023; Umukoro et al., 2017).

Both plant and animal research have reported on the therapeutic properties of MJ. Methyl jasmonate can be used to encourage the synthesis of natural compounds with therapeutic qualities in some plant species, increasing those plants' positive impacts on human health (Reyes-Daz et al., 2016).

According to Sayyari et al. (Sayyari et al., 2011), MJ treatment increases the bioactive chemicals in pomegranates, enhancing antioxidant activity. A similar effect was noted for blackberries (Wang et al., 2008). In addition to increasing antioxidant activity due to increased activity of antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), ascorbate peroxidase (APX), among others, the application of MJ on various fruit crops via vapor, dipping, or spraying increases the concentrations of antioxidant compounds like anthocyanins and other phenolic metabolites. In animal research, it has been demonstrated that MJ lowers inflammation and oxidative stress in the brains of rats with arthritis and rats subjected to acetic acid-induced ulcerative colitis (Pereira-Maróstica et al., 2019; Omayone et al., 2023).

5. Conclusion

As a result of this investigation, methyl jasmonate has been shown to be efficient in reversing the oxidative stress in the liver linked to ulcerative colitis and may be used as a therapeutic agent for further manifestations of inflammatory bowel illnesses.

Authorship Contribution

Author TPO conceived the idea of the work and designed the study. Both authors were involved in the experimental procedures, data collection, data analysis and statistical analysis. Author IPO wrote the first draft of the manuscript. Both authors revised the manuscript and agreed on the final draft submitted to the journal.

Conflict of Interests

All authors disclosed there is no conflict of interest.

Ethical consideration

The study was approved by the ethical committee for animal studies of the Federal University of Technology Akure.

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