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Gastroprotective Activity of CaMn2O4 NP's

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Abstract

The chemical calcium manganese oxide ($CaMn_2O_4$), which has many different biological uses, is investigated for its gastroprotective characteristics in this research. Peptic ulcers and other gastrointestinal diseases are common and need safe and efficient treatments. There is a constant need to find new drugs since existing therapies have a lot of limits and negative effects. This study uses a battery of in vivo and in vitro tests to look at $CaMn_2O_4$'s potential as a gastroprotective agent. Animal models of generated gastric lesions showed that the chemical significantly reduced ulcer development and stomach mucosal damage, demonstrating its effectiveness. Improved mucosal integrity and reduced inflammation were found in histological investigation, which points to the presence of anti-inflammatory and cytoprotective mechanisms. Furthermore, antioxidant tests showed that $CaMn_2O_4$ might reduce oxidative stress, an important component in the development of ulcers. Additional research into the mechanisms of action and therapeutic uses of $CaMn_2O_4$ is warranted in light of these results, which suggest that it might be a good candidate for the creation of novel gastroprotective medicines..

Keywords: Gastroprotective agents • $CaMn_2O_4$ • Gastroprotective activity • Peptic ulcer

Introduction

Many things, including stress, medicine, infections, and poor eating habits, may damage or disrupt the gastrointestinal (GI) tract. Gastritis, peptic ulcers, and damage to the stomach mucosa may result from these disruptions. Research into potential chemicals that might prevent or alleviate these disorders, known as gastroprotective agents, has been going on for quite some time. Biological activity, such as antioxidant, anti-inflammatory, and antibacterial capabilities, have been shown by metal oxides, among several other substances examined. The possible gastroprotective effects of one such chemical, calcium manganese oxide (CaMn2O4), have attracted a lot of interest. The unusual structure and chemical characteristics of CaMn2O4 make it a possibility for therapeutic use in preserving the stomach mucosa. Examining the mechanisms of action, effectiveness in experimental models, and potential for development as a medicinal agent, this introduction seeks to dive into the gastroprotective activity of CaMn2O4. The development

of innovative therapies for gastrointestinal illnesses, which may improve patient outcomes and quality of life, can be facilitated by gaining a better knowledge of the function of CaMn2O4 in gastroprotection (Meagher, 1999).

One of the most common gastrointestinal disorders, gastric ulcers may have many different causes. Factors that may lead to the development of stomach ulcers include stress, smoking, alcohol use, sepsis, trauma, Helicobacter pylori, and both steroidal and non-steroidal anti-inflammatory medicines. Injuries to many tissues, including the digestive system, are thought to be caused in large part by oxygen-derived free radicals, according to a lot of research (Hamburger, 1991).

Although some theories have been put up on occasion, the exact biochemical changes that occur during the development of ulcers remain unclear. Ulcers may form as a result of stress-induced changes in stomach motility, mast cell degranulation, and prostaglandin levels. Equally important in experimental stomach damage caused by ischemia and reperforation, hemorrhagic shock, and ethanol treatment are free radicals produced from oxygen (Choudhary, 2015).

Damage to the stomach mucosa may result from reactive oxygen species produced by arachidonic acid metabolites, platelets, macrophages, reduction in non-protein sulfahydral concentration, and regulation of the nitric oxide system. Pain and inflammation caused by rheumatologic abnormalities are treated with a multitude of medicines, including nonsteroidal anti-inflammatory drugs (NSAIDs), by older individuals. When people use NSAIDs, they increase their risk of developing gastritis type C, erosions, petechiae, ulcers, complications from ulcers, and damage to both the small and large intestines (Zhang, 2022).

Since the small intestine does not contain any cells that secrete acid, NSAIDs caused mucosal damage apart from the acid. Thus, traditional acid-reducing treatments like proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RAs) should not be the only pharmaceuticals used to treat small intestine mucosal damage caused by nonsteroidal anti-inflammatory drugs (NSAIDs) (Santos, 2018).

The gastric ulcer regimen typically consists of H2RAs and proton pump inhibitors. Diarrhoea, rash, and discomfort are frequent adverse effects of these, however. Furthermore, significant organ systems such as the genitourinary, cardiovascular, central nervous system, and others have been linked to negative effects of H2RAs. An extra risk of "acid rebound phenomenon" upon treatment termination is associated with their companion PPIs, in addition to the adverse effects on key organ systems such as the cardiovascular system, central nervous system, ear, nose, and stomach. While there are a variety of mucosal protective agents on the market, including carbenoxolone sodium, sucralfate, and prostaglandin analogues, each has its own set of advantages and disadvantages, and there are also antisecretory medications, antimuscarinic agents, and proton pump inhibitors (PPIs) to consider.

Cellular proliferation, migration, and differentiation are essential steps in the healing process of peptic ulcers, which include restoring the structures of the epithelium and the connective tissue underneath. This is not possible with the standard anti-ulcer treatment plan, which mostly comprises H2RAs and PPA. Antioxidant treatment alone, rather than in conjunction with other treatments, is the primary emphasis of the current investigation. Herbal remedies have received a lot of media attention as of late. There is a lot of evidence from animal experiments that medical treatment extracts are safer than manufactured medications. This is one of the main benefits of herbal medications. The anti-ulcer effects of newly discovered drugs and compounds are investigated using ulcer models caused by variables that contribute to ulcer etiopathogenesis.

The incidence of ulcers may be increased by certain variables, such as stress, alcohol use, and the use of certain anti-inflammatory medicines. Stress ethanol-induced gastric injury has been linked to reactive oxygen species (ROS). Enzymes like catalase, endogenous glutathione (GSH), superoxide dismutase (SOD), and glutathione S-transferase (GST) reduce reactive oxygen species

(ROS), which harm tissues. An enormous public health concern, peptic ulcer disease has an extremely high incidence rate throughout the world and is the most prevalent illness affecting the upper gastrointestinal tract. Between 8 and 11 percent of women and 11 to 14 percent of men will have peptic ulcers at some point in their lives. In the United States, duodenal ulcers afflict between 4–10% of the population, whereas gastric ulcers affect about 0.03%–0.05%. Of all peptic ulcers, about 80% are duodenal ulcers, while the rest are gastric ulcers. Although stomach ulcers often begin between the ages of 45 and 55, duodenal ulcers typically manifest in adults between the ages of 20 and 50. Among American adults, 14% use indigestion medicine at least twice weekly, and 44% suffer from heartburn at least once a month.

A peptic ulcer now causes 14.2 out of 10,000 American hospitalisations, down from 25.2% in 2000. The peptic ulcer mortality rate has dropped from 3.5 per 100,000 to 1.1 per 100,000 because of the development of accurate diagnostic techniques and several antiulcer medications. The development of a stomach ulcer might be influenced by mucosal ischemia. It is well-known that prostaglandins promote mucosal cell repair and regeneration by increasing blood flow, bicarbonate production, and mucus secretion. Therefore, gastritis and stomach ulcers may develop in the presence of their shortage, which may be brought on by the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or other insults. Decreased bicarbonate or mucus secretion, on the other hand, might be caused by other factors. There are subgroups of gastric ulcer patients that have these problems. New therapeutic formulations at the nanoscale level are now widely used. The biological, chemical, and physical characteristics of nanoparticles (NPs) are distinct. Among the most promising nanomaterials, AgNPs have antibacterial, anti-inflammatory, antifungal, and antiviral properties, making them effective against a wide range of microorganisms. Several studies have shown that NPs may effectively cure a variety of skin conditions, including pemphigus, toxic epidermal necrolysis, chronic ulcers, and burns. Therefore, the purpose of this work was to use a variety of in vivo methodologies to assess the biological impacts of mineral nanoparticles, such as Ca2MnO4 and CaMn2O4 NPs (Yadav, 2020).

Methods

Experimental details

The sex-neutral albino Wistar rats (150-200 gm) were purchased from Sainath agency in Musheerabad for this study. The rats were kept in an environment with a 12-hour light/dark cycle, 25°C, and a regular pellet meal with water available at all times. The rats were fasted for 48 hours after a 7-day acclimatisation period in the lab. In order to perform the studies, prior consent was sought from the institutional ethics committee (1567/PO/Re/S/11/CPCSEA). The animals went without food for 24 hours before the trial, although water was available to them at all times.

Drugs

This antiulcer evaluation made use of Ca2Mno4 and CaMn204 nanoparticles.

Chemicals

- Toffer’s reagent (Dimethylaminoazobnzene)
- Phenolphthalein
- Alcian blue dye
- Diethyl ether
- Anesthetic ether

- Sodium Hydroxide (NaOH)
- Hydrochloric acid
- Sucrose
- Sodium acetate
- Magnesium chloride (MgCl2)
- Formalin

The analytical grade chemicals and reagents were sourced from authorized agents/suppliers.

Model Of Pylorus-Induced Ulcers Via Ligation

One hour before pyloric ligation (PL), all medications were taken orally. All of the injections mentioned above ranged in volume from 0.2 to 0.4 ml. The procedure for pylorus ligation was somewhat modified from that described by Shay et al. (1945). In order to prevent coprophagy, rats were housed in cages with elevated mesh bottoms and fasted for 36 hours before surgery. Anesthesia was administered by intravenous ketamine hydrochloride at a dosage of 45 mg/kg. A tiny incision was made midline, below the xiphoid process, to open the abdomen. The pyloric part of the stomach was carefully located, gently elevated, and sutured so as not to entrap the pylorus or cut off blood flow. Sutures were used to seal the abdominal wall after the stomach was carefully restored. After the surgery, the animals were fasted for four hours without food or drink before being killed. By inserting a ligature at the esophageal end, the whole stomach was dissected out. By removing it from its surrounding tissues and organs, the stomach and all of its contents may be extracted in one piece. Volume, pH, total and free acidity, stomach wall mucus content, ulcer score, and ulcer index were determined after centrifugation at 3000 rpm for 10 minutes.

Gastric volume and pH

Researchers measured the volume of the liquid that remained after centrifugation. Gastric juice pH was tested using a pH metre that had a 2.0-4.5 and 5.0-8.5 pH range, with a 0.5 difference between the two.

Total and free acidity

To determine the total and free acidities, a volume of 5 ml of diluted gastric juice was titrated with 0.01N NaOH using phenolphthalein and toffer's reagent, respectively, until a persistent pink hue and canary yellow colour were noticed. Clinical units of acidity were defined as the volume of 0.01N NaOH base needed to titrate 100 mL of stomach secretion or pH.

Acidity was express as:

$$\text{Total acidity} = \frac{\text{volume of NaOH}^{*}}{0.1}\ \text{Normality}\ ^{*}100\ \text{mEq/L}$$

Ulcer Score

The methodology outlined by Wilhelmi and Menasse-Gadyni (1972) was used to determine the occurrence and severity of ulcers. Ulcers were defined as necro-haemorrhagic patches with a diameter larger than 2 mm. The following is the grading system.

- 0.5- Minute, sporadic, punctuate lesions
- 1- Several small lesions
- 2- One large extensive lesion, or multiple moderate sized lesions
- 3- Several large lesions.

Ulcer Indexes

$$\text{Ulcer index} = \frac{10}{X}$$

$$\text{where, } X = \frac{\text{total mucosal area}}{\text{total ulcerated area}}$$

Gastric Wall Mucous Content

The gastric wall mucus content was measured using a slightly modified version of the technique reported by Corne et al. (1974). After the stomach was opened along its larger curvature, it was weighed and submerged in 10 ml of a solution containing 0.1% Alcian blue in 0.16 M sucrose/0.05 M sodium acetate, with a pH of 5.8, for a duration of 2 hours. The excess dye was then washed away in two separate rinses with 0.25 M sucrose solutions (15 minutes and 45 minutes apart). After 2 hours of being shaken every 30 minutes, the residual dye complexed with the stomach mucus was removed using 0.5M $MgCl_2$. The spectrometer was used to determine the optical density of the water phase at 605 nM after shaking the blue extract with diethyl ether in equal amounts. The absorbance of each solution was used to determine the different dye concentrations and weights (in milligrammes) using a standard curve. Next, the dye's weight was multiplied by the stomach's weight.

Results

Modulation of PL-Induced Ulcers in Rats by Nanoparticles of Ca_2Mno_4 and $CaMn_2O_4$

The outcomes for rats with Pylorus-induced ulcers, as seen in the ulcer score and ulcer index, are shown in Table 1. Ulcer score, free acidity, and total acidity were all markedly decreased after pretreatment with ranitidine, Ca2Mno4, and CaMn204 Nanoparticles.

Table 1. Effect of JMEE on PL induced ulcer indicating ulcer score, free acidity and total acidity.

Groups	Volume of gastric juice	PH	Total acidity	Free acidity	Ulcer score	Ulcer index
Normal control	---	----	----	----	0.0	0.0
Pathological control	12.25 ± 1.03	3.60 ± 0.195	132.75 ± 2.32	61.50 ± 1.25	2.50 ± 0.28	0.90 ± 0.05
Positive control (Ranitidine 30 mg/kg)	6.00 ± 0.70***	6.10 ± 0.26***	93.25 ± 1.49***	37.0 ± 1.87***	0.50 ± 0.12***	0.17 ± 0.07***
Ca2Mno4 NP's 200 mg/kg	6.87 ± 0.42***	4.92 ± 0.11***	110.75 ± 2.68***	50.50 ± 1.55***	1.50 ± 0.28***	0.47 ± 0.01***
CaMn2o4 NP's 200 mg/kg	5.57 ± 0.21***	5.90 ± 0.12***	99.00 ± 1.29***	42.0 ± 1.08***	1.25 ± 0.25***	0.32 ± 0.01***

The data was analysed using two-way ANOVA followed by Tukey multiple comparisons. The values shown are the mean ± SEM (n=6). The significance level for all comparisons was set at P<0.001.

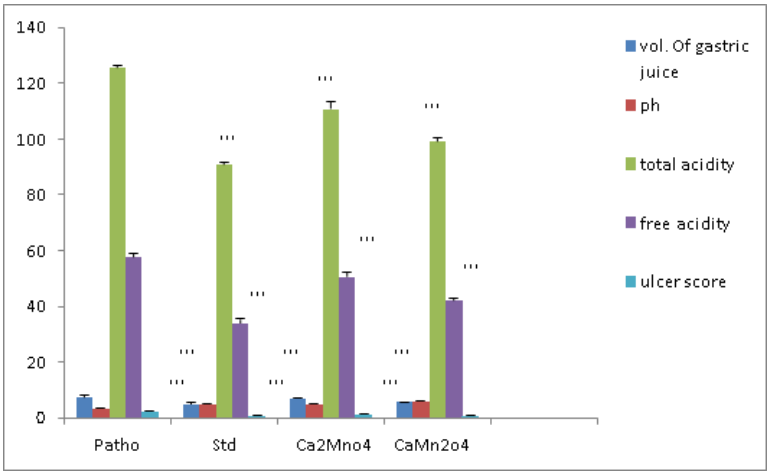

Figure. 1 Effect of Ca2Mno4 and CaMn204 NP's on PL induced ulcer indicating ulcer score, PH, volume of gastric juice and free acidity and total acidity.

The data was analysed using a two-way ANOVA followed by Tukey HSD multiple comparisons. The values shown are the mean ± SEM (n=6). All comparisons were deemed significant when P<0.001.

Figure 2. Control

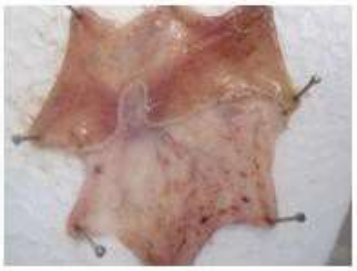

Figure 3. Standard

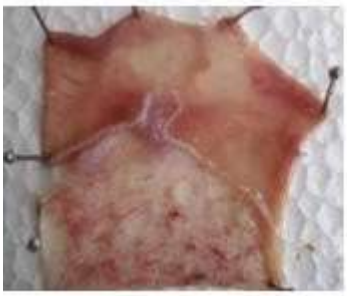

Figure 4. Ca2Mn04 NP's 200mg/kg

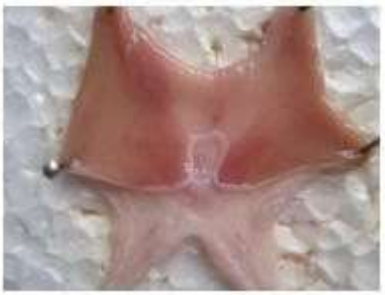

Figure 5. CaMn204 NP's 200mg/kg

Details

Figure 2: Illustrative picture showing severe ulcers in opened stomach of control PL induced model in rat.

Figure 3: Illustrative picture showing open stomach of rat pretreated with ranitidine (30 mg/Kg, p.o.). The severity of ulceration is reduced by pretreatment when compared to control PL induced ulcer in rat.

Figure 4: Illustrative picture showing open stomach of rat pretreated with Ca2Mno4 (200 mg.kg, p.o.).

Figure 5: Illustrative picture showing open stomach of rat pretreated with CaMn204 (200 mg/kg, p.o.).

Histopathology of stomach

After 19 hours after pyloric ligation, the gastric mucosa of a rat exhibits congestion, erosion, haemorrhage, and necrosis (a). Rat gastric wall after pyloric ligation and ranitidine (30 mg/kg) treatment (b). The histological architecture of the stomach wall in rats

treated with Ca2Mno4 & CaMn2o4 Nanoparticles (200 mg/kg) and undergoing pyloric ligation seems almost normal (c and d). In comparison to (a), the necrotic alterations here are somewhat minor.

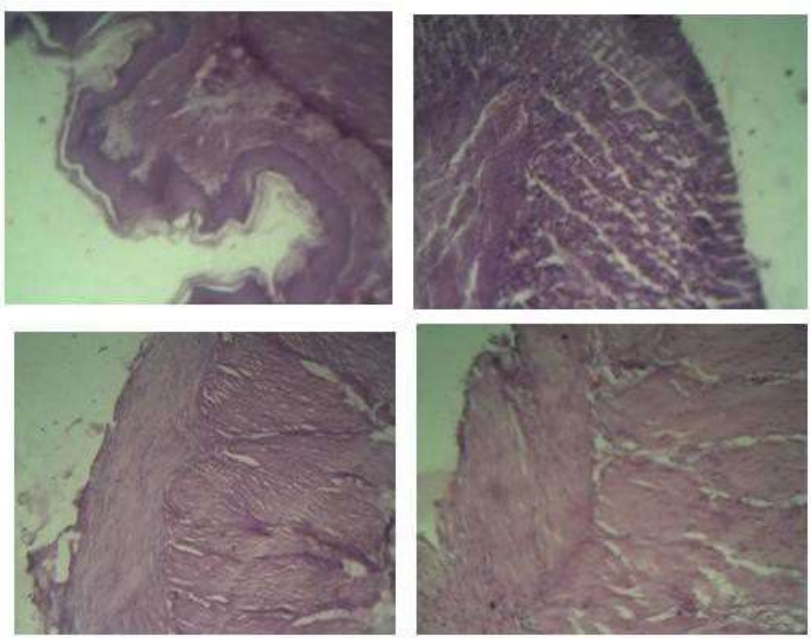

Figure 6. Histological evidence of protective effect of Ca2Mno4 and CaMn204 NP's on PL induced ulcer in rats

Conclusion

Finally, CaMn2O4 shows great promise as a treatment for gastric lesions and improving gastrointestinal health due to its gastroprotective action. Antioxidant characteristics, which aid in neutralising dangerous free radicals and reducing oxidative stress in stomach tissues, are believed to be the compound's mode of action. Another possible explanation for $CaMn_2O_4$'s preventive actions against ulcerogenic chemicals is its capacity to strengthen mucosal defence systems. The exact pathways involved should be further understood, dosing regimens should be optimised, and the safety and effectiveness of the chemical in long-term clinical settings should be investigated in future studies. In conclusion, $CaMn_2O_4$ shows great promise as a potential novel gastroprotective treatment.

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