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Gastroprotective Activity of $CaCr_2O_4$ NP's

Nagarjuna Rao Mamidipalli[1], Papireddy Tiyyagura[2], and K. Suresh Babu[1*]

[1]Faculty of Sciences, Lincoln University College, Malaysia.
[2]Faculty of Pharmacy, Lincoln University College, Malaysia.

Corresponding Author: K. Suresh Babu, Faculty of Sciences, Lincoln University College, Malaysia.

Abstract

These days, peptic ulcer is considered a global epidemic. Peptic ulcer instances have been on the increase due to the fact that people's stress levels and level of physical activity have been negatively impacted by contemporary, civilised lifestyles [1]. Stomach ulcers may occur in 3% to 10% of the population. Peptic ulcers are responsible for 15,000 deaths every year throughout the globe [2]. Approximately four million people in the United States are hospitalised every year as a result of pressure ulcer disease (PUD), and over 3.6 lakh new ulcer cases are recorded every year [3]. There is a 3:1 male-to-female ratio for duodenal ulcers and a 1.5:2.1 female-to-male ratio for stomach ulcers [4].

Keywords: Gastroprotective agents • CaCr2O4 • Gastroprotective activity • Peptic ulcer

Introduction

Peptic ulcers develop when the balance of protective and harmful substances in the gastrointestinal tract (GIT) is disturbed. In PUD, harmful factors dominate over protective ones in the gut[5].

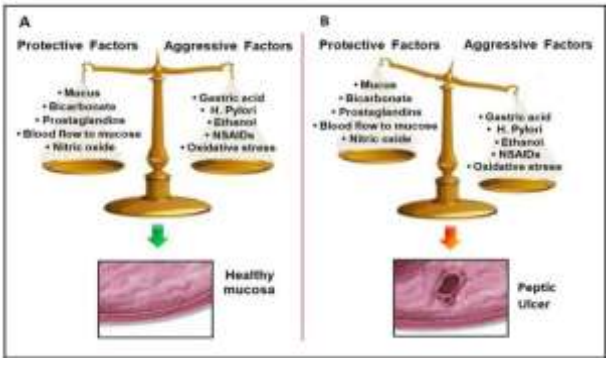

Figure 1. Factors involved in the pathological process of peptic ulcer.

Gastric mucosal protection

When it comes to preventing ulcers, the gastromucosal layer is very crucial. As a result, the stomach's layers are spared the acid. The close closeness of the mucosal lining cells and the epithelial cells helps to protect the stomach from acid attacks [6]. Prostaglandins promote wound healing by increasing bicarbonate synthesis, blood supply to damaged mucosal cells, and gastric mucus secretion. It is evident that prostaglandins possess cytoprotective properties[7,8,9,10].

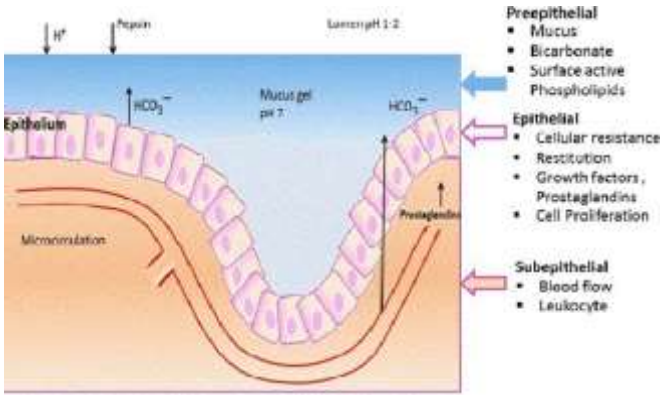

Figure 2. Factors associated with gastro mucosal defense and repair free radicals and their role in causing peptic ulcer.

Some researchers believe that ROS reactive oxygen species are crucial to the onset of acute stomach ulcers brought on by ethanol, experimental stress, or “nonsteroidal anti-inflammatory drugs” (NSAIDS). The amount of ROS released has an inverse relationship with the severity of gastritis in helicobacter pylori infections [11]. This capacity of the GIT to prevent ulcers by protecting the stomach mucosa is inhibited by these oxygen radicals. The creation of free radicals, such as OH, promotes oxidative damage when iron or copper ions are transferred to albumin, plasmin, or ferritin [12]. This is how these free radicals cause ulcers to fo rm.

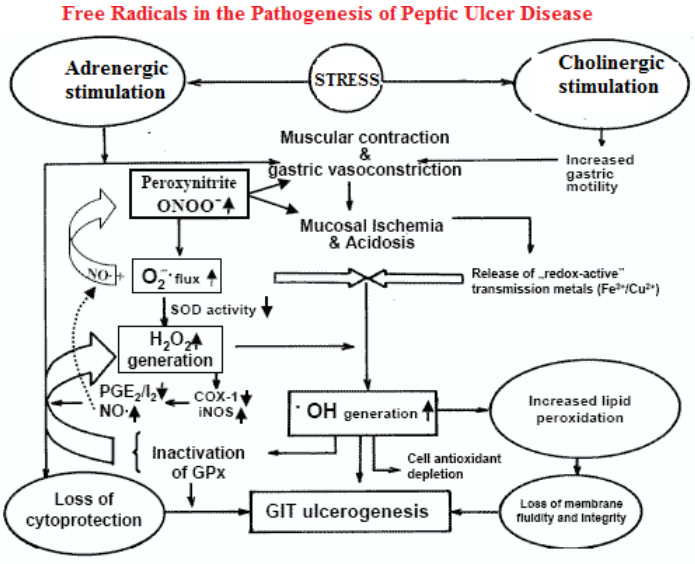

Figure 3. Free radicals in the pathogenesis of Peptic Ulcer

Although certain hypotheses have been advanced on occasion, the precise biochemical alterations that take place during ulcer formation are still unknown. Stress may alter stomach motility, mast cell degranulation, and prostaglandin levels, all of which can have an impact on ulcer development [13]. Free radicals produced by oxygen have also been shown to be involved in experimental stomach injuries induced by reperforation and ischaemia, hemorrhagic shock, and ethanol administration [14]. Damage to the stomach mucosa may result from a variety of sources, including reactive oxygen species generated by arachidonic acid metabolites, platelets, macrophages, decreased concentrations of non-protein sulfahydral, and changes to the nitric oxide system [15]. Many

medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), are used by older adults to alleviate pain and inflammation induced by rheumatologic disorders [16]. Some of the negative effects that may occur from using non-steroidal anti-inflammatory medicines (NSAIDs) include erosion, blisters [17].

Since small intestines do not contain any cells that release acid, the mucosal damage caused by NSAIDs was unrelated to the acid. Since conventional acid-reducing therapies, such as proton pump inhibitors and histamine 2 receptor inhibitors, might affect the small intestinal mucosa, nonsteroidal anti-inflammatory drugs (NSAIDs) should be considered with other pharmacological options [18]. Proton pump inhibitors and H2RAs are the usual components of an ulcer therapy program. Regrettably, they may sometimes cause nagging side effects including a rash, pain, and diarrhoea. In addition, the genitourinary, cardiovascular, and central nervous system systems have all been associated to H2RAs' detrimental effects [19]. The risk of "acid rebound phenomenon" after treatment stops is increased when they are used with proton pump inhibitors (PPIs), [20]. In addition to antisecretory therapy like H2RAs, antimuscarinic drugs, and proton pump inhibitors, there are mucosal protective pharmaceuticals such carbenoxolone sodium, sucralfate, and prostaglandin analogues. However, each of these medications has its own limits and adverse effects. In order for peptic ulcers to heal, the underlying connective tissues and epithelial layers must reconcile. Cells migrate, differentiate, and proliferate during this process [21].

This is not possible with the present standard of care for ulcer treatment, which mostly comprises H2RAs and PPA. The current investigation primarily looks at antioxidant treatment alone, not in conjunction with other methods. The media has recently given herbal remedies a lot of attention. Research on animals regularly shows that therapeutic treatment extracts are safer than manufactured medications. The primary benefit of using herbal therapies is this. Ulcer models based on ulcer aetiology features are developed. Ulcers are more likely to occur in people who are already under a lot of stress, who drink excessively, or who take certain medicines, such as NSAIDs. With a high incidence rate worldwide, peptic ulcer disease is the most frequent condition affecting the upper gastrointestinal tract. It has been a major setback in terms of health. The lifetime prevalence of peptic ulcers is 8 –11% in women and 11–14% in males. Gastric ulcers affect 4- 10% of Americans, and 3- 5% of people with peptic ulcers also have duodenal ulcers. Although the majority of stomach ulcers begin between the ages of 45 and 55, duodenal ulcers often manifest in people between the ages of 20 and 50. Among American adults, 14% use medicine for indigestion at least twice weekly, and 40% have heartburn at least once a month. Peptic ulcer-related hospitalizations in the United States have decreased from 25.2% to 14.2%.

The peptic ulcer mortality rate has decreased from 3.5 per 100,000 to 1.1 per 100,000 due to the availability of more antiulcer drugs and more accurate diagnostic procedures. Gut ulcer formation may be impacted by mucosal ischaemia. It is well-known that prostaglandins contribute in mucosal cell repair and regeneration by increasing blood flow, bicarbonate synthesis, and mucus secretion. As a result, NSAIDs and other irritants may lead to vitamin deficiencies, which in turn can induce gastritis and stomach ulcers. However, decreased bicarbonate or mucus production might have other causes. These problems manifest in subgroups of stomach ulcer patients. Novel pharmaceutical compositions that operate at the nanoscale are finding extensive usage in modern medicine. The unique physical, chemical, and biological characteristics shown by nanoparticles (NPs) are really remarkable. Because of their high antibacterial activity against a variety of microbes, anti-inflammatory, antifungal, and antiviral properties, AgNPs are among the most promising nanomaterials. Numerous studies have shown that NPs have potential in treating a variety of skin conditions, including pemphigus, toxic epidermal necrolysis, chronic ulcers, and burns.

Methods

Experimental details

For this study, researchers contacted Sainath Agency in Musheerabad to get male and female albino Wistar rats, which range in weight from 150 to 200 gm. A standard pellet diet was also provided to them. Following a week of acclimation to the environment,

the rats were subjected to a 48-hour period of starvation. The study could not proceed without the proper institutional ethics committee's consent ((1567/PO/Re/S/11/CPCSEA). Even though the animals were instructed to fast for 24 hours before the experiment, they were given free approach to water. The research was place at the animal facilitation facility's experimental room at Hyderabad's Marri Laxman Reddy Institute of Pharmacy in Dundigal.

Drugs

The ranitidine sample was acquired from the Hyderabad laboratory of Dr. Reddy as a gift. Nanoparticles of Ca_2Mno_4 and $CaMn_20_4$ were used in this assessment for their antiulcer properties.

Chemicals

- Conical flasks (Titration flask)
- Micro burettes
- Volume measuring glass tubes
- 10ml, 50ml beakers
- Glass cylinders
- Centrifuge tubes
- Droppers
- Wattman filter paper
- Desiccators for anesthesia
- Distilled water
- Weighing Machine

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

Pylorus-ligation induced Ulcer model

Rats were divided into five groups (n=6 in each group).

- Group I: Negative control (normal saline 1 ml)
- Group II: Positive control (normal saline 1 ml)
- Group III: Pylorus ligation + Ranitidine (30 mg/kg, orally)
- Group IV: Pylorus ligation + $NiCr_2O_4$ NP's (200 mg/kg, orally) Group V: Pylorus ligation + $CaCr_2O_4$ NP's (200 mg/kg, orally)

Each medicine was administered orally one hour before to pyloric ligation (PL). For the ones already stated, the injection volumes varied between 0.2 and 0.4 ml. The technique for ligating the pylorus was somewhat altered from that which was detailed by Shay et al. (1945). In order to avoid coprophagy during surgery, rats were fasted for 36 hours and kept in cages with high mesh bottoms.

Gastric volume and pH

The amount of liquid inside the supernatant was quantified. Using a pH meter with a 2.0-4.5 and 5.0-8.5 range, with a 0.5 difference, the stomach fluids' pH levels were determined.

Total and free acidity

A micro burette was used to titrate 5 ml of diluted gastric juice with 0.01N NaOH, using phenolphthalein and toffer's reagent as indicators. It was necessary to wait until a canary yellow hue was seen for free acidity and a persistent pink hue for total acidity before proceeding. The amount of 0.01N NaOH base required to titrate 100 mL of stomach output was used to establish the clinical units of acidity.

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

Ulcer score

The incidence and grading of ulcers was done according to the method described by Wilhelmi and Menasse-Gadyni (1972). Necro-hemorrhagic spots greater than 2 mm diameter was taken as ulcer. These are graded as follows:

- 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

Ulcer index was determined by method of Ganguly and Bhatnagar

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

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

Gastric wall mucous content:

A significantly altered version of the method outlined by Corne et al. (1974) was used to quantify the quantity of mucus on the stomach wall. Afterwards, the stomach is prepared by opening it along its major curvature, weighing it, The extra dye was then rinsed off with two 0.25 M sucrose solutions, one applied every 15 minutes and the other every 45 minutes. Any remaining dye complexed with the stomach mucous was washed away with 0.5M $MgCl_2$ after 2 hours of shaking every 30 minutes. The optical density of the water phase at 605 nM was detected using the spectrometer after adding

equal amounts diethyl ether and shaking the blue extract. Using a standard curve to compare the absorbance of each solution, we were able to calculate the various dye concentrations and weights (in milligrams). The outcome was obtained by dividing the dye's weight by the stomach's weight.

Results

Nanoparticles of $CaCr_2O_4$ and Their Impact on Rats with PL-Induced Ulcers. In an ideal of ulcers affected by pylorus ligation, antiulcer effectiveness of $CaCr_2O_4$ nanoparticles was evaluated at doses of Two hundred mg/kg.

Impact on Ulcer Table

Using 200 mg/kg of $CaCr_2O_4$ considerably decreased the ulcer index by increasing the percentage of protection against ulcers to 76.0±1.12. The results are shown by the T.No.1.

Impact on Gastric quantity

In comparison to the control group, the quantity of gastric juice was significantly decreased by 200 mg/kg of $CaCr_20_4$. Table 2 shows that ranitidine at a dose of 10 mg/kg significantly reduced the volume of stomach contents.

Impact on Available Acidity & Total Tartness

At a dose of 600 mg/kg, $CaCr_20_4$ significantly decreased acidity (free and total) ($p<0.01$), which was comparable to the effect of the conventional medicine ranitidine (10 mg/kg) on rats ($p<0.01$). The outcomes may be shown in table 2.

Table 1. Effect of $CaCr_2O_4$ Nanoparticles on Pylorus ligation ulcer model in rats

Treatment	Dose (mg/kg)	Ulcer index	% ulcer inhibition
Control	10 m/kg	1.25 ± 0.15	-
$CaCr_2O_4$NP′s	200	0.3 ± 0.36	$76.0 \pm 1.12^{**}$
Ranitidine	10	0.00	$100 \pm 0.42^{***}$

Results are expressed in Mean ± SEM. One way ANOVA with *P<0.05, **P<0.01, ***P<0.001 by using Tukey- kramer multiple comparison test.

Table 2: Effect of $CaCr_2O_4$ Nanoparticles on Antisecretory parameters

Treatment	Dose (mg/kg)	Gastric volume (m/100 g)	**pH**	Free acidity (mEg/L/**l00**)	Total acidity (mEg/L/**l00**)
Control	10ml/kg	2.64 ± 0.11	1.45 ± 0.31	61.26 ± 4.3	80.76 ± 3.5
$CaCr_2O_4$ NP′s	200	$1.82 \pm 0.33^{*}$	$2.85 \pm 0.43^{**}$	$38.26 \pm 3.68^{**}$	$42.15 \pm 2.47^{**}$

Ranitidine	10	$1.61 \pm 0.06^{**}$	$4.31 \pm 1.62^{**}$	$21.64 \pm 3.6^{**}$	$32.18 \pm 3.1^{**}$

Results are expressed in Mean ± SEM. One way ANOVA with *P<0.05, **P<0.01, ***P<0.001 by using Tukey-kramer multiple comparison test.

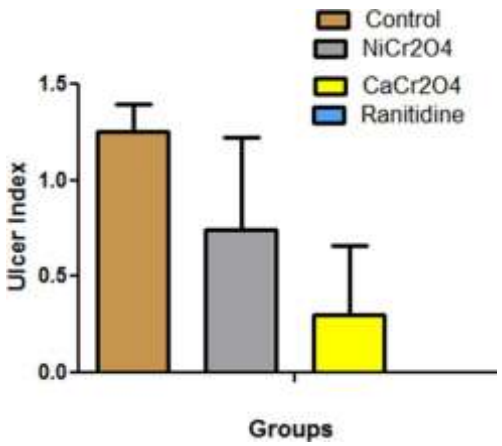

Figure 4. Effect of $CaCr_2O_4$ Nanoparticles on ulcer index in pylorus ligation induced ulcer model in rats

Figure 3. Morphological appearance of gastric ulcers in pylorus ligation induced stomach ulcers in rats

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