ANTI-ULCEROGENIC ACTIVITY OF LEAF EXTRACT OF *CAPPARIS CARTILAGINEA DECNE* ON ETHANOL AND INDOMETHACIN- INDUCED PEPTIC ULCERS IN WISTAR RATS

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Anti-Ulcerogenic Activity of Leaf Extract of *Capparis Cartilaginea Decne* on Ethanol and Indomethacin- Induced Peptic Ulcers in Wistar Rats

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DECLARATION

This thesis is my original work and has not been presented for the award of a degree in any other University.

Signature……..Date……..

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This thesis has been submitted for examination with our approval as university supervisors.

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DEDICATION

This work is dedicated to my husband, my children, my siblings and my parents for giving me an easy moment during my studies.

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LIST OF ABBREVIATIONS

CO_2	Carbon Dioxide
DMSO	Dimethyl Sulfoxide
FELASA	Federation of European Laboratory Animal Science Association
H.pylori	Helicobacter Pylori
KEMSA	Kenya Medical Supplies Authority
NICE	National Institute for Health and Care Excellence
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
OECD	Organization of Economic Cooperation and Development
PPI	Proton Pump Inhibitor
SAFARI	Small Animal Facility for Research and Innovation
WHO	World Health Organization

ABSTRACT

Peptic ulcer disease is a non-malignant, mucosal lesion of the stomach or duodenum, in which pepsin and hydrochloric acid plays a major pathogenic role. The purpose of this study was to determine the anti-ulcerogenic effect of *Capparis cartilaginea decne* on peptic ulcers induced by ethanol and indomethacin in Wistar rats of female species. A laboratory-based true experimental study design was employed. Fresh leaves *of Capparis Cartillaginea decne* were subjected to methanol extraction, and the extract was dissolved in 5% DMSO. Qualitative phytochemical screening of the *Capparis cartillaginea decne* extract was also conducted. Forty five animals were divided into nine groups. Treatment groups were given omeprazole 20mg/kg +ethanol 70% 0.5ml/100mg; omeprazole 20mg/kg+ indomethacin 30mg/k; ethanol+ 200mg/kg extract; indomethacin+ 200mg/kg extract; ethanol+ 400mg/kg extract; and indomethacin+ 400mg/kg extract. The control groups were given indomethacin only 30mg/kg; ethanol 70% 0.5ml/100mg and normal saline 2ml. These were administered through oral gavage for 14 days. Results were analyzed using SPSS software version 21. Groups' comparison was done using one-way ANOVA. Results are expressed as Mean ± SEM and presented using tables and bar graphs. Flavonoids, tannins, alkaloids, steroids, and saponins were detected in the methanol extract upon phytochemical screening. Animals ulcerated with ethanol 70% 0.5ml/100mg and treated with 400mg/kg of extract caused a significant ulcer inhibition ($p=0.003$), with corresponding significant reduction in mean gastric juice output ($p=0.001$) and mean total acidity ($p=0.001$). There was also significant ulcer inhibition ($p=0.001$), with significant reduction in mean gastric juice output ($p=0.003$), mean total acidity ($p=0.003$) and significant increase in mean pH value ($p=0.001$) in animals ulcerated with indomethacin 30mg/kg and treated with extracts at 400mg/kg. We conclude that methanol leave extract of *Capparis cartillaginea decne* had ulcer inhibition against gastric ulcers induced by ethanol and indomethacin. The extract also caused reduction in mean total acidity, mean gastric juice output and increased the mean pH value. We recommend further studies involving molecular characterization of the phytochemicals of *Capparis cartillaginea decne* that exert these actions.

CHAPTER ONE

INTRODUCTION

1.1 Background

Peptic ulcer disease is a benign, mucosal lesion of the stomach whereby acid and pepsin are the major causes in the injury (Guidelines, 2005). The mucosal defect caused by peptic ulcers reaches the muscularis mucosa and sometimes, beyond. Life threatening complications can occur, including bleeding, perforated peptic ulcers, obstruction and malignancy. These complications may necessitate surgery, and if untreated, can cause death (Abdelwahab and Abourehab, 2017). A study in Europe showed an increase in cases of peptic ulcer disease due to non-steroidal anti-inflammatory drugs use over 10 years period of study(Diego *et al.*, 2015). Alcohol consumption has been linked with the risk of non-steroidal anti-inflammatory drugs (NSAID) associated upper gastrointestinal tract bleeding (Strate, 2016).

Peptic ulcer disease affects about 5% of the global population (Monitor, 2016). There are many scientific advancement in management of peptic ulcers, but there remains a clinical setback largely due to *H.pylori* infection and an increased use of non-steroidal anti-inflammatory drugs (Adinortey *et al*., 2013) . Nowadays, there are two main approaches for managing peptic ulcers: the first approach is to reduce the gastric acid secretion and another approach is to reinforce the gastric mucosal protection (Chandra *et al.*, 2015).

Acid and pepsin play an important role in peptic ulcer formation when *Helicobacter pylori*, NSAIDs or other uncommon factors like radiation, stress, chemotherapy and vascular insufficiency disrupt normal mucosal defense and healing mechanisms (Kumar *et al.,* 2019). The gastric-mucosal defense includes several mechanisms, which allow the mucosa to resist exposure to damaging factors; this includes bicarbonates, prostaglandins and mucosal blood flow (Laine *et al*., 2008). Non-steroidal anti-

inflammatory drugs cause mucosal damage by recruiting circulating neutrophils and causing endothelial adhesion through inhibition of prostaglandin biosynthesis (Whittle, 2002). The adhered neutrophils cause clogs in the micro vascular causing local decrease of mucosal blood flow and significant release of tissue damaging factors including proteolytic enzymes and leukotriene's, which lead to severe degrees of mucosal damage (Jimenez *et al.*, 2004)

The WHO traditional medicine strategy 2014-2023 aims to support member states in developing proactive policies and implementing action plans that will strengthen the role traditional medicine plays in keeping populations healthy (WHO, 2013). A study in Elgeyo-Marakwet County, Kenya on medicinal plants used in that community showed that the villagers reported the use of a plant *Capparis cartilaginea decne*, locally known as "*chepteretwo*" in the treatment of peptic ulcers (Korir *et al.,* 2015).

1.2 Statement of the Problem

The prevalence of peptic ulcer globally is estimated to be 5% (Monitor, 2016). Lifelong likelihood of developing peptic ulcers is 10% for males and 4% for females (Kumar *et al.,* 2008). In the United States of America, four million people were reported to have peptic ulcers in 2002 and three hundred and fifty thousand cases were reported to be diagnosed annually (Sandler RS *et al.,* 2002). In Nigeria, out of 1084 patients who had an endoscopy, 28.7% had upper gastrointestinal bleeding, 32.8% being due to peptic ulcer disease (Ugiagble *et al.*, 2016). In Kenya, out of 3,147 patients who had an endoscopy at Aga Khan University hospital, Nairobi County, 9.8% had duodenal ulcers, while 8.5% had gastric ulcers. At St Mary's hospital, Nakuru County, out of 6,110 patients who had an endoscopy 9.5% had duodenal ulcers and 1.9 % had gastric ulcers (Makanga & Nyaoncha, 2010). In Kenya, heavy episodic drinking (alcohol consumption of 60 or more grams of pure alcohol) has been shown to have a prevalence of 12.6% (Kendagor *et al*., 2015). Human studies have shown peptic ulcers occur upon consumption of brews with ethanol content of more than 10% (Zion, 2002). NSAIDs are one of the most commonly prescribed classes of medication for pain and

inflammation and prevalence of use is as high as 96% in general practice setting (Wongrakpanich *et al.,* 2018). Recommendations by NICE guidelines CG17, for treatment of peptic ulcer following use of NSAIDs, use proton pump inhibitors, example omeprazole 20mg once daily for eight weeks (NICE, 2020). Omeprazole in Kenya costs 10 shillings per capsule, and 150 shillings per vial for intravenous administration (KEMSA, 2017). This makes it hard for the low-income earning Kenyans to access the drug. The complications associated with peptic ulcer disease also increase the cost of management and could be fatal. It is therefore paramount to come up with an affordable medication for the prevention and treatment of peptic ulcers.

1.3 Justification

With the increasing prevalence of peptic ulcers, heavy episodic drinking coupled with high incidence of non-steroidal anti-inflammatory drugs used, there is a need to search for ways of preventing and treating peptic ulcers. This is especially important to the low-income earning Kenyans who are unable to buy conventional medicines available in the market. A study done by Korir *et al*., (2015) on medicinal plants used by the Marakwet community in Kenya, reported the plant *Capparis cartilagenia decne* locally known as "chepteretwo" was reported to cure peptic ulcers when the leaves were chewed. There are no experimental scientific studies done to prove this claim. This study aimed to scientifically validate the claims on the anti-ulcer effects of *Capparis cartilaginea decne*.

1.4 Research Questions

1. What are the phytochemical compounds present in *Capparis cartilaginea decne* plant?
2. What is the acute oral toxicity of leaves extract of *Capparis cartilaginea decne* in Wistar rats?
3. What are the gastric secretion parameters (gastric acid output, pH of gastric juice, and total acidity) on all groups of Wistar rats in the study?

4. What is the ulcer inhibition activity of leaves extract of *Capparis cartilaginea decne* on peptic ulcers induced by ethanol and indomethacin in Wistar rats?

1.5 Broad Objective

To determine the anti-ulcerogenic effect of *Capparis cartilaginea decne* leave extracts on peptic ulcers induced by ethanol and indomethacin in female Wistar rats.

1.6 Specific Objectives

1. To determine the phytochemical compounds present on the leave extract of *Capparis cartilaginea decne*.
2. To determine acute oral toxicity of the leave extract of *Capparis cartilaginea decne* in Wistar rats.
3. To determine the effect of leaves extract of *Capparis cartilaginea decne* on gastric juice output, pH of gastric juice, and total acidity.
4. To determine the anti-ulcerogenic activity of leaves extract of *Capparis cartilaginea decne* on peptic ulcers induced by ethanol and indomethacin in Wistar rats.

1.7 Hypothesis

1.7.1. Null hypothesis

H_o: The leave extracts of *capparis cartillaginea decne* have no anti-ulcerogenic effect on peptic ulcers induced by ethanol and indomethacin in Wistar rats.

1.7.2. Alternative hypothesis

H_1: The leave extracts of *capparis cartillaginea decne* have anti-ulcerogenic effect on peptic ulcers induced by ethanol and indomethacin in Wistar rats

CHAPTER TWO

LITERATURE REVIEW

2.1 Physiology of the human stomach

The stomach has a capacity of 1000-1500ml, and making it the most dilated part of the gastrointestinal tract in an adult. The main function of the stomach is to mix food with mucus, pepsin and acid, which is then released at a controlled rate to the duodenum as chyme for absorption (Daniels and Allum, 2011). 2500Ml of gastric juice is released daily. The juice contains various substances and enzymes, whose role is to help in protein digestion, destroy ingested bacteria, stimulate the flow of pancreatic and biliary juices, and also allow the necessary pH for protein pepsin to begin its action of protein degradation (Guidelines, 2005). The pH of gastric acid is between 1.5-3.5, a level maintained by the proton pump H^+/K^+ ATPase (Elaine *et al.,* 2018). Components of gastric juice include the following:

- Hydrochloric acid (HCl) from parietal cells.
- Pepsinogens – pepsins from chief cells.
- Lipase.
- Intrinsic factor from parietal cells.
- Mucus from neck cells.

2.2 Pathophysiology of Peptic Ulcer Formation

The mechanism of gastric mucosal defense includes several local, neuronal and hormonal factors, which allow the stomach lining to resist damage by destructive factors (Laine *et al.,* 2008). The local mechanism of gastric mucosa defense includes mucus, bicarbonates, epithelial cells, mucosal blood flow, sensory innervation and prostaglandins (Fornai, Pisa, and Antonioli, 2011). The function of prostaglandins is to stimulate bicarbonate and mucus secretion which neutralizes the pH of gastric juice produced deep in the gastric pits before reaching the surface of the stomach mucosa

(Zatorski, 2017). Under normal conditions, there is a physiologic balance existing between the gastric acid secretion and gastric mucosal defense system. Mucosal injury occurs when the balance between aggressive and protective factors is disrupted (Jimenez *et al.*, 2004). Diverse factors such as alcohol consumption, stressful life, use of non-steroidal anti-inflammatory drugs, *H. pylori* infection and smoking, contribute to the formation of gastric ulcers.

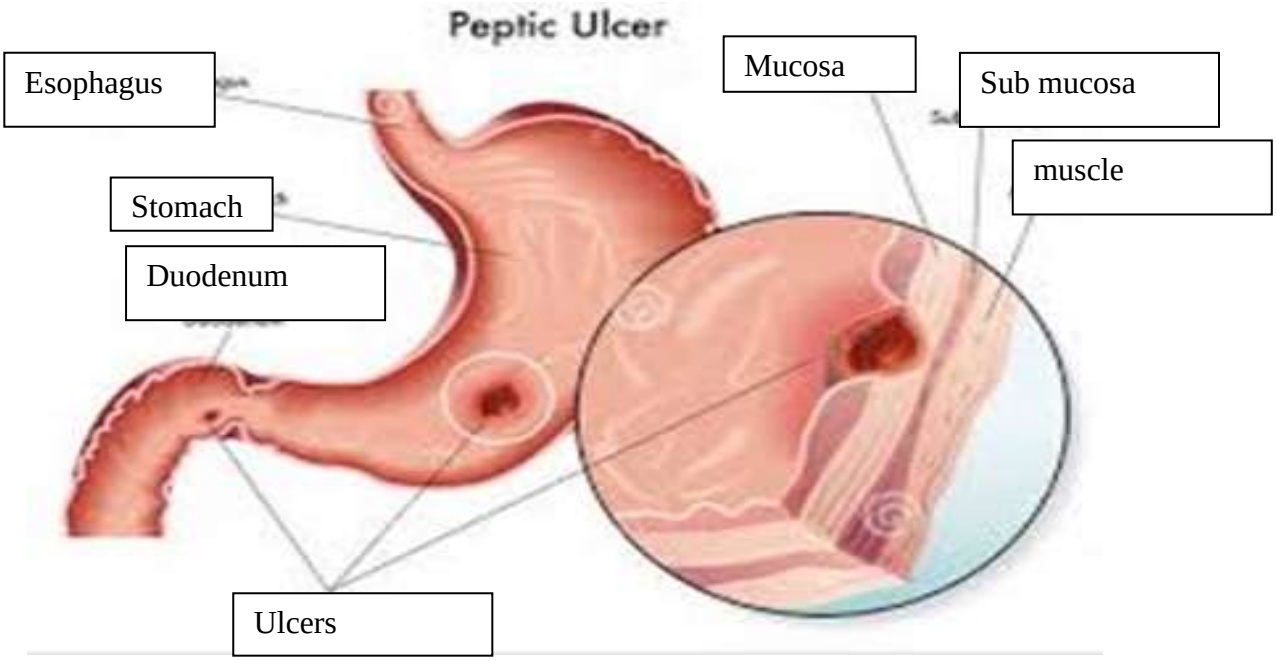


Figure 2.1: Anatomical sites of Gastric and Duodenal ulcers.

Figure 2.2: Endoscopic appearance of gastric ulcers (Rubel , 2012)

2.2.1 Pathophysiology of ethanol in ulcer induction.

Ethanol destroys gastric mucosa by damaging the protective layer in the stomach and reduces the mucosal blood flow and mucus production. These factors lead to an exacerbated inflammatory response (Augusti *et al.*, 2014). Ethanol increases activity of xanthine oxidase and also triggers an imbalance in the cellular antioxidant process, by causing the release of superoxide anions and hydroperoxyl free radicals, hence increasing oxidative stress in tissues (Adinortey *et al.*, 2013).

Absolute ethanol is highly corrosive to the gastric mucosa and its mechanism of action on rats involves superficial necrosis of gastric mucosa (Oates & Hakkinen, 1988).

2.2.2 Pathophysiology of indomethacin in ulcer induction.

Indomethacin is a non-steroidal anti-inflammatory drug and it is known to cause gastric damage by inhibiting cyclo- oxygenase (COX-1 and COX-2), the enzymes responsible for production of prostaglandins, prostacyclin's and thromboxane's that act as protection to the gastric mucosal lining against injury (Schellack & Shellack, 2015).

NSAIDs disrupt the layer of surface-active phospholipids on the mucosal surface, independent of the effects on prostaglandin synthesis. Such action renders the mucosa less able to resist damage induced by luminal acid (Adinortey *et al*., 2013).

2.3 Signs and Symptoms of Peptic Ulcer Disease

The disease is characterized by complains of (Fashner *et al*., 2015):

- Dyspepsia.
- Epigastric discomfort or pain.
- Burning sensation in epigastrium
- Gastrointestinal bleeding, perforation or gastric malignancy in complicated cases.

2.4 Pharmacological Treatment of Peptic Ulcer Induced By non-steroidal anti-inflammatory drugs and Ethanol.

The table below shows the various conventional methods of treating peptic ulcers. Their mechanism of action and adverse effects.

Table 2.1: Mechanism Of Action And Adverse Effects Of The Most Commonly Used Anti-Ulcer Treatment Options

Drug.	example	Mechanism of action	Adverse effects
Proton Pump Inhibitors (PPIs)	Omeprazole, Lansoprazole, Rabeprazole, Esomeprazole, Pantoprazole	Inhibition of the gastric H+/K+-ATPase (proton pump) enzyme system	• Headache • Abdominal pain • Diarrhea • Nausea • Vomiting • Constipation • Flatulence • VitaminB12 deficiency • Osteoporosis
Cytoprotective Agents	Misoprostol Sucralfate	Stimulate mucus production and enhance blood flow throughout the lining of the gastrointestinal tract	• Diarrhea • Abdominal pain • Headache • Constipation
Potassium-Competitive Acid Blocker	Vonoprazan	Inhibits H+, K+-ATPase in gastric parietal cells at the final stage of the acid secretory pathway	• Nasopharyngitis • Contusion • Diarrhea • Upper respiratory tract inflammation • Eczema • Constipation • Back pain
Antacids	Aluminum hydroxide	Increases gastric pH to greater than four, and inhibits the proteolytic activity of pepsin	• Nausea • Vomiting • Hypophosphatemia • Chalky taste • Constipation • Abdominal cramping • Diarrhea • Electrolyte imbalance • Magnesium hydroxide Causes osmotic retention of fluid
H2 Receptor Blockers	Cimetidine Famotidine Nizatidine Ranitidine	Blocking the action of histamine at the histamine H2 receptors of parietal cells	• Headache • Anxiety • Depression • Dizziness • Cardiovascular events • Thrombocytopenia

Source: (Kuna *et al.*, 2019)

2.5 *Capparis cartilaginea decne*

Capparis cartilaginea decne belongs to the family Capparaceae, genus capparis and the species cartillaginea decne. It is distributed throughout warm regions. In Kenya, this plant is found in Elgeyo -Marakwet County, Turkana, Samburu, Masaai land and at the coast, on coral rocks or old ruins (Flora of Tropical East Africa, 2009). It is a spreading or scrambling shrub, 0.5 to 4m high, with solitary flowers in the upper leaf axils. All petals are white and it has fruits that are ovoid or ellipsoid shaped, up to 5 cm long, 3cm in diameter and red in color (Kamel & Abd, 2009). It is locally identified by different names, Maasai (Olatunde), Samburu (leachar), Turkana (Lokapilak), Marakwet (chepteretwo) (National museum of Kenya, 1994).

Traditionally the plant is used in wound treatment and stomach problems.

Figure 2.3: Plant capparis cartillaginea decne(plants of the world online)

2.5.1 Phytochemical constituents of Capparis cartilagenia decne

A study done in Japan identified phytochemicals such as carbohydrates, saponins, polyphenols, flavonoids, tannins, triterpenes, sterols, amino acid and protein in *Capparis cartillaginea decne* (Studies, 2016). The essential oil of *Capparis cartilaginea decne* was dominated by methyl isothiocyanate (31.81 %), isopropyl isothiocyanate (18.25 %), isobutyl isothiocyanate (5.40 %), 3-p-menthene (5.18 %), occidol (4.33 %), carissone (3.11 %) and ethyl isothiocyanate (2.55 %) (Sciences, 2012). In Yemen, a study on the leave extract of *Capparis cartillaginea decne* showed a potential source of bioactive compounds that have a role in anti-inflammation (Moharram *et a*l., 2017).

2.5.2 Flavonoids

Flavonoids are a diverse group of plant metabolites with over 10,000 compounds that have been identified up to date. However, only very few of them have been fully investigated. They have antioxidant, antiviral and antibacterial properties and also regulate gene expression and modulate enzymatic action (Pa & Koz, 2016).

2.5.3 Phenolic compounds

Phenolic compounds have been shown to be in most plants and have antioxidant activities, hence considered of health benefit to humans. Due to safety concerns and limitation in the use of synthetic antioxidants, natural antioxidants have become of interest to researchers (Shahidi & Ambigaipalan, 2015). Phenolic compounds also exert activity against degenerative and infectious diseases. They cause enzyme and or protein modulation or neutralization (Ozcan & Delikanli, 2014).

2.5.4 Tannins

Tannins possess antioxidant activities and radical scavenging activities. Experimental and clinical trials of the protective function of tannins can help in the development of modern drugs (Ghosh et al., 2015).

2.5.5 Geographical Variation of Phytochemical Constituent of Medicinal Plants

Environmental factors such as temperature, humidity, and light intensity influence the growth of a plant and its secondary metabolite production. Temperature stress has been shown to affect the secondary metabolites and other compounds which plants produce, which is the basis of their medicinal activity. Research has shown a plant collected at different geographical regions has varying phytochemical constituents (Nayeem & El-feky, 2017).

2.6 Omeprazole

Omeprazole is a proton pump inhibitor (PPI). It is a prodrug activated by acid. It inhibits gastric H+, K+- ATPase by covalent bonding at cysteine near the ion pathway. Because of the property of covalent bonds, its inhibitory activity lasts longer (Shin and Kim, 2013).

2.7 Indomethacin

Indomethacin is a non-steroidal anti-inflammatory drug that acts by inhibiting cyclooxygenase (COX) followed by multiple pathogenic events like increased intestinal permeability, infiltration of neutrophils and microcirculatory regulation, which plays a critical role in development of inflammation and ulcers. The chemical classification is an indole-acetic acid derivative with the chemical name 1- (p-chlorobenzoyl) 25-methoxy-2-methylindole-3-acetic acid (Bjarnason *et al*., 2017).

CHAPTER THREE

MATERIALS AND METHODS

3.1 Study Site

Capparis cartilaginea decne plant was collected from Elgeyo-Marakwet County in Kenya. Elgeyo-Marakwet county is located in the rift valley province. Total area is 3,049.7 km^2. The temperature ranges from a minimum of 12^0c to a maximum of 22^0c. Rainfall ranges annually from 800-2300mm high above sea level.

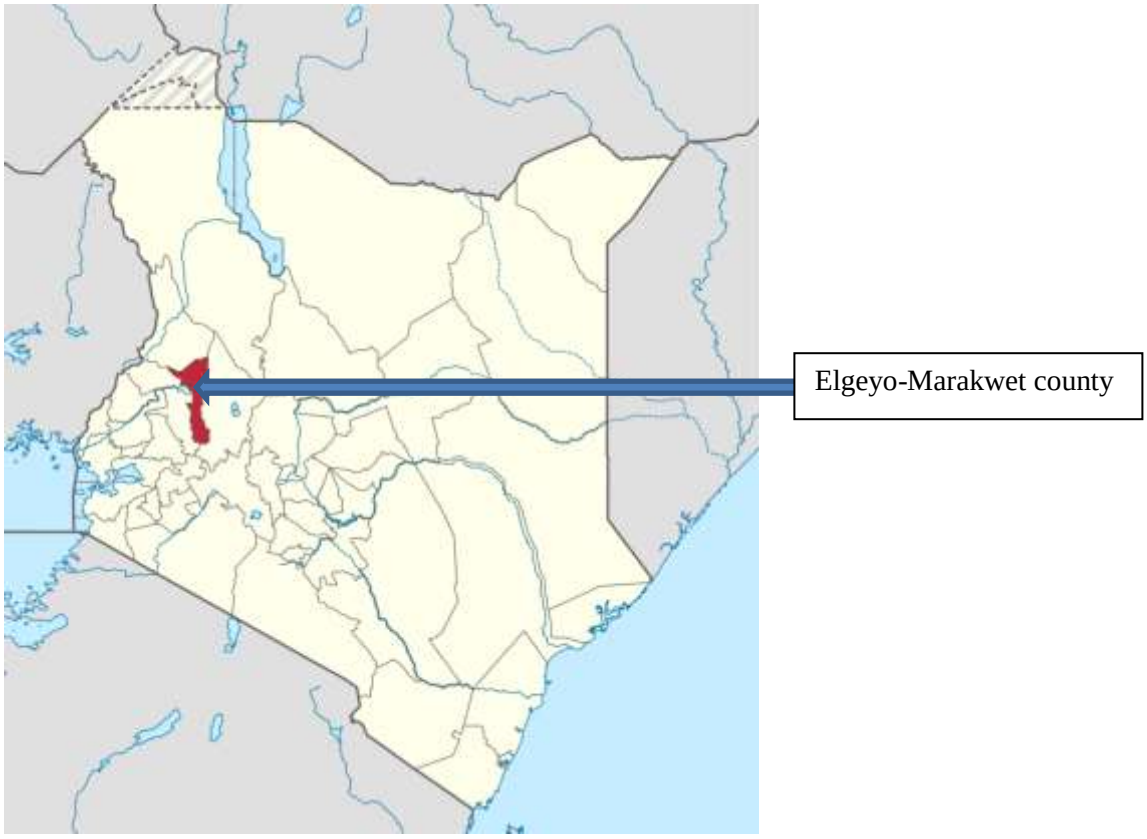


Figure 3.1: Map of Kenya, showing Elgeyo-Marakwet County (Wikipedia, 2018).

3.2: Study design

A laboratory based true experimental study was employed.

3.3 Experimental Animals

Female Wistar rats weighing 150-200 gm were used because this species of rats can be used for multipurpose experiments and also possess an increased tolerability to crude extracts. All rats were procured from the JKUAT's Small Animal Facility for Research and Innovation (SAFARI). They were kept in appropriate rodent cages (Material: plastic walls & floor and wired roof; Size: length-3 feet, width-2 feet, height-2 feet; Nest: wood dust) and had free access to approved food pellets (Mazuri® rat and mice food) and water ad libitum. Acclimatization period of two weeks was allowed before the commencement of the experiment.

3.4 Ethical consideration

Ethical conduct was observed at all times during the course of this study. Federation of European Laboratory Animal Science Association (FELASA) guidelines were adhered to as the principles of Replacement, Reduction and Refinement (3Rs of animal ethics) were observed (Nevalainen *et al.*, 1999). Ethical approval was sought from the JKUAT Institutional Ethics Review Committee (REF: JKU/2/4/896B) and animals were handled humanely. Animals were not used for any other purpose other than that indicated.

3.5 Sample Size Determination

Resource Equation method (Arifin, 2017)

$n = DF/k + 1$

Minimum $n=10/k+1$; Maximum $n=20/k+1$

That is $n=10/9+1=3$; $n=20/9+1= 4$

Minimum $N=\min n \times k= 27$

Maximum $N=\max n \times k =36$

Therefore, the number of animals should be between 27-36 animals; 3-4 animals per group.

DF-degree of freedom

n- Number of subjects per group

k- Number of groups

N-total number of subjects

3.6 Plant Collection and Authentication

Capparis cartilagenia decne plant was collected following identification of the plant among the Marakwet community through the guidance of a taxonomist, from the University of Eldoret. The branches of the plant that had already formed the fruit were harvested. They were placed in brown paper bags. A voucher specimen (Ref. MGBK/08/19/001) was deposited in the University Of Eldoret botany herbarium.

3.7 Preparation of Extracts of *Capparis cartillaginea decne*

Extraction was done with distilled water and methanol

3.7.1 Aqueous extraction

Aqueous extraction was done by hot maceration. 50g of the *Capparis cartillaginea decne* leave powder was added to 500 ml of distilled water in a 1litre flask then boiled for 15 minutes. The boiled mixture was then filtered using Whatman No. 1 filter paper, and the extract evaporated to a powder by use of a freeze dryer (BUCHI Lyovapor™ L-300). The lyophilized sample was kept at 4^{o}C as described by Wangia et al., 2016

3.7.2 Organic extraction

Organic extraction was done by cold maceration. 500ml of Methanol was added to 50mg of the capparis cartillaginea decne leave powder for 72 hours then the extract was concentrated by use of rotary evaporator (BUCHI Vac® V-500) at 45^0c then stored at 4^0C till the point of use as described by Wangia *et al*., 2017.

Figure 3.2: Rotary evaporator (BUCHI Vac® V-500)

3.7.3 Test for flavonoids

Ten percent (10%) ammonium hydroxide solution was added to *Capparis cartillaginea decne* aqueous and methanol extracts and the appearance of a yellow fluorescence color was indicative of the presence of flavonoids (Banu and Cathrine, 2015)**.**

3.7.4 Test for tannins

Presence of tannins was tested using the ferric chloride test, where 0.5 mL of 5% ferric chloride solution was added to 0.5mL of sample solution. Formation of dark green color indicated the presence of tannins.

3.7.5 Test for saponins

A quantity of 20mls of distilled water was added to 5 mLs of *Capparis cartillaginea decne* in a graduated cylinder then shaken vigorously for 15 minutes. Formation of foam that persisted for 15 minutes after shaking was indicative of the presence of saponins (Savithramma *et al.,* 2011).

3.7.6 Test for alkaloids

A quantity of 1ml of *Capparis cartillaginea decne* extract was added to a test tube and 2 drops of Mayer's reagent added. Formation of a white creamy precipitate was indicative of alkaloids (Banu and Cathrine, 2015).

3.7.7 Test for sterols

Salkowaski method was used where 1 ml of *Capparis cartillaginea decne* extract was put in a test tube and 0.5 ml of sulfuric acid, acetic anhydride and chloroform each added. A red coloration was indicative of the presence of sterols (Catherine, 2016).

3.7.8 Test for phenolic compounds

5ml of distilled water was added to 50 mgs of the extracts of *Capparis cartillaginea decne* and allowed to dissolve, a few drops of neutral 5% ferric chloride solution was put into the mixture. The presence of phenolic compound was indicated by the appearance of a dark green color. (Banu and Cathrine, 2015).

3.7.9 Terpenes –Liebermann-Burchard Test

Chloroform was added to the extract then the solution was filtered. A few drops of acetic anhydride was added to the filtrate. The solution was boiled and then cooled. Concentrated Sulfuric acid was slowly added along the sides of the test tube. The appearance of a brown ring at the junction indicated the presence of terpenes (Tiwari and Kaur, 2011).

3.7.10 Glycosides - Keller – Killian test

To 1 ml of 3.5% ferric chloride in acetic acid, 1mg of the extract was added, followed by a careful dropwise addition of 1.5 ml concentrated sulfuric acid by the sides of the test tube to form a separate bottom layer. A brown ring at the interface because of the presence of de-oxy sugar was characteristic of cardenolides, and pale green colour in the upper layer due to the steroid nucleus indicated presence of cardiac glycosides as described by Wangia *et al*., 2017.

3.7.11 Acute Toxicity Studies

Acute oral toxicity studies were done using organization of economic corporation and development's (OECD) guideline number 423 (OECD, 2001). A total of 12 rats were used for the whole oral toxicity study. Three female, nulliparous non-pregnant rats weighing 160 – 200 grams were used for each dose of the extract. The animals were randomly selected, marked with picric acid for identification and put in their cages for seven days to acclimatize to laboratory conditions. All the rats were fasted overnight before administration of the extract via gastric lavage but ad libitum access to water was allowed. Food was withheld 4 hours after administration of the extract. The extract was administered in 0.5ml of normal saline to all rats.

Individual rats were put in the observation chamber. They were observed intensively during the initial 30 minutes upto 4 hours after extract administration. Observation was carried out again after 24 hours then daily for 14 days. The observations included:

changes in skin and fur, eyes and mucous membranes, respiratory, circulatory, and autonomic and central nervous systems. They were monitored for tremors, convulsions, salivation, diarrhea, lethargy and sleep pattern.

The starting dose of the plant extract was 300mg/kg body weight using three rats. None of the animals died at 300mg/kg do so the procedure was repeated using 2000 mg/kg body weight of the extract. There was no mortality observed at 2000 mg/kg body weight dose. A control group composed of three rats were fasted overnight and given only 0.5ml of normal saline then observed and weighed like the rest of the test groups. All animals were weighed before fasting, at day zero, day one, day three, day seven and day fourteen.

At the end of the study, all the rats were humanely sacrificed by inducing hypoxia by use of CO2 from a compressed CO2 cylinder. The rats would be introduced to a clear chamber then CO2 introduced for 2 – 3 minutes, death was confirmed by ascertaining cardiac and respiratory arrest, fixed and dilated pupils. After euthanasia, the carcasses were incinerated.

3.8 Omeprazole preparation

Omeprazole was used as positive control. Pure molecules were obtained and dissolved in 5% dimethyl sulfoxide (DMSO) to make omeprazole solution. The prepared solution contained 20mg of omeprazole per 1 ml of 5% DMSO. This solution was then refrigerated at 4^0C for use on the experiment

3.9 Animal grouping and treatment

The animals were grouped as follows:

Group I- Control groups

Group I: Negative control: female Wistar albino rats administered with 0.5ml normal saline

Group 2: Baseline: female Wistar rats administered with 30mg/kg indomethacin.

Group 3: Baseline: female Wistar rats administered with ethanol 70% 0.5ml/100gm.

Group 4: Positive control: female Wistar rats administered with omeprazole 20mg/kg before ulcer induction with indomethacin 30mg/kg.

Group 5: Positive control: female Wistar rats administered with omeprazole 20mg/kg before ulcer induction with ethanol 70% 0.5ml/100gm

Group II – Interventional groups

Group 1: 200mg/kg c.c.d extract before ulcer induction with indomethacin 30mg/kg.

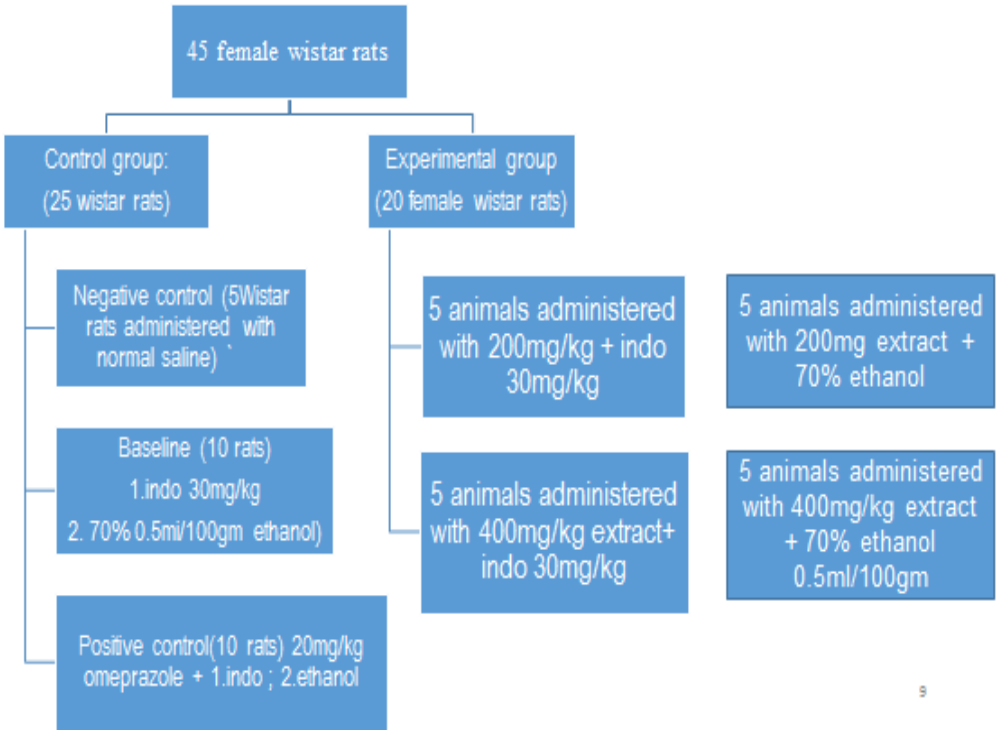
Group 2: 200mg/kg c.c.d extract before ulcer induction with ethanol 70% 0.5ml/100gm.

Group 3: 400mg/kg c.c.d extract before ulcer induction with indomethacin 30mg/kg.

Group 4: 400mg/kg c.c.d extract before ulcer induction with ethanol 70% 0.5ml/100gm.

Key: Indo-indomethacin c.c.d- ***capparis cartillaginea decne***

Treatment with omeprazole and methanol leave extract lasted for 14 days prior to ulcer induction. These were orally administred once daily using oral intubator with provision of food and water throughout the experimental period.



3.10 Ulcer Induction

Gastric ulceration was induced in the experimental animals by giving those 0.5 mL/100 g body weight of 70% solution of ethanol by oral gavage (Ineu RP *et al.*, 2013)

Ulcers induction by indomethacin was done by administering a single oral dose of 30mg/kg body weight of indomethacin tablets (Sayanti *et al.*, 2007).

3.10.1 Isolation of stomach and collection of gastric juice

On the fifteenth day (4 hours post ulcer induction) the animals were euthanized in the carbon-dioxide chamber. The stomachs were immediately removed and opened along the greater curvature and all gastric contents drained into a centrifuge tube.

3.10.1.1 Determination of pH and Volume of Gastric Secretion (Sisay and Jemere, 2020)

After the abdomen was opened the cardiac end of the stomach was dissected out and its content drained into a glass tube. The quantity of the digestive juice was measured after centrifugation at 2000 rpm for 10 minutes. From the supernatant, an aliquot (1 mL of each) was taken and diluted with 1 mL of water, and the pH of the fluid was measured using a pH meter.

3.10.1.2 Determination of Total Acidity (Wang *et al*., 2007)

1 mL digestive juice diluted with 9 mL of distilled water was taken into a 50 mL conical flask and two drops of phenolphthalein indicator were added there to and titrated with 0.01 N NaOH until a permanent pink color was observed. The quantity of 0.01 N NaOH consumed was noted. The entire acidity is expressed as mEq/L by the subsequent formula.

$$Total\ Acidity\ = \frac{V\ NaOH\ x\ N\ x\ 100 mEqlL}{0.1}$$

Where V is volume and N is normality

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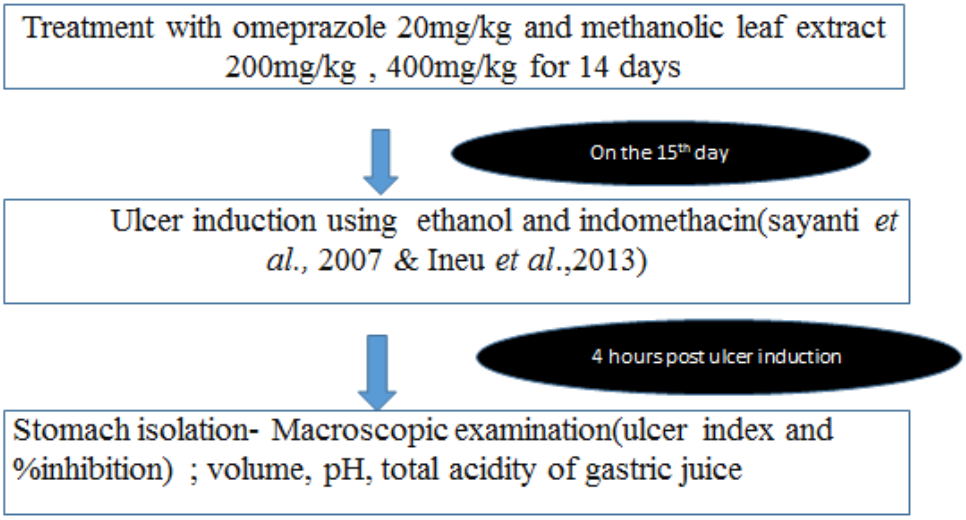

Figure 3.3: Summary of the protocol followed.

3.10.2 Quantification of ulceration

The dissected stomachs were gently rinsed with normal saline to remove any excess gastric content. Examination carried out macroscopically with a dissecting microscope. The ulcer score and ulcer index were calculated as shown below (M. Adinortey *et al.*, 2013).

Normal colored stomach- 0

Red coloration- 0.5

Spot ulcer- 1

Hemorrhagic streaks- 1.5

Deep ulcer- 2

Perforation-3

$$Ulcer\ index\ (UI) = \frac{total\ ulcer\ score\ per\ animal}{Number\ of\ animals\ ulcerated}$$

$$\%Ulcer\ inhibition = \frac{100 - \ U.I\ index\ in\ treated}{U.I\ in\ control} \times 100$$

3.11 Data Management and Analysis

Data was collected using check lists and data acquisition tables and analyzed using SPSS version 21(SPSS Inc. Chicago, IL) software. Shapiro Wilk's test and Levine's test were used to check for normality and homoscedasticity of data respectively. Groups were compared using one-way ANOVA and $P < 0.05$ was considered to be statistically significant. Post hoc statistical analysis by Tukey HSD test was performed to identify groups with significant differences. Results are expressed as Means ± SEM presented using tables.

CHAPTER FOUR

RESULTS

4.1 The percentage yield of *Capparis cartillaginea decne* leaves extract in different solvents

$$\text{Methanol \% yield} = 2.482 = \frac{2.48250}{50} \times 100 = 4.96$$

$$\textit{Aqueous \% yield} = 1.47 = \frac{1.4750}{50} \times 100 = 2.94$$

4.2 Phytochemical composition of *Capparis cartillaginea decne*

Phytochemical compounds of *Capparis cartillaginea decne* leaves extract of the different solvents (water and methanol) were screened. Presence of flavonoids, saponins and sterols, was detected as shown in Table 4.1.

Table 4.1: Phytochemical screening of *Capparis cartillaginea decne leaves.*

Phytochemical compound	Methanol extract	Aqueous extract
Flavonoids	++	++
Tannins	++	-
Phenols	++	-
Alkaloids	-	-
Saponins	++	+++
Sterols	++	-

Key '+' Mild presence, '++' Moderate presence, '-'absent

The aqueous extract screening revealed presence of flavonoids and saponins. Alkaloids, phenolic compounds, and sterols were absent. Methanol extraction yielded the highest number of different phytochemical compounds; saponins, flavonoids, sterols and

phenolic compounds. All solvents extract revealed absence of alkaloids. The methanol extract had the highest number of various phytochemical compounds.

The *Capparis cartillaginea decne* leaves methanol extract was therefore chosen as the ideal solvent for use in the rest of the study.

4.3 Acute oral toxicity studies

A starting dose of 300 mg/kg was administered to 3 female rats. All rats had normal breathing and were active following administration up to 24 hours and the entire 14 days of study. No mortality occurred at 300 mg/kg so three other rats were administered with 2000 mg/kg of the extract. All animals had normal breathing and were active following the extract administration up to 24 hours and the entire 14 days. No mortality occurred at 2000 mg/kg. A control group of three female rats were administered with 0.5 ml normal saline to serve as negative control. This group demonstrated normal breathing and normal activity throughout the fourteen days.Oral administration of *capparis cartillaginea decne* at even 2000 mg/kg did not cause any mortality or any clinical symptom of toxicity (Table 4.2). No gross pathology was observed from all organs in postmortem of the rats at the end of the study.

Table 4.2: Clinical symptom observation of rats treated with capparis cartillaginea decne leave methanol extract

Doses (Mg/kg)	Observation in time							Mortality	Mortality rate (%)
	Immediate	½ hour	1 hour	4 hours	24 hour	Day 7	Day 14		
300	Normal activity	Normal activity	Normal activity	Normal activity	Normal activity	Normal activity	Normal activity	0/3	0
2000	Normal activity	Normal activity	Normal activity	Normal activity	Normal activity	Normal activity	Normal activity	0/3	0
Control (Normal saline)	Normal activity	Normal activity	Normal activity	Normal activity	Normal activity	Normal activity	Normal activity	0/3	0

Table 4.3 and 4.4 show the mean body weights ±SEM of *capparis cartillaginea decne* extract treated rats compared to the negative control at fasting day, days 0, 1, 7 and day14. There was no significant difference between treated groups and the control group

Table 4.3: Weights change in treatment and control rats during the acute toxicity studies

Animals	Dose (mg/kg)	Fasting	Day 0	Day 1	Day 7	Day 14
Rat 1	300	182.72	170.26	180.57	184.55	192.20
Rat 2	300	186.75	161.77	184.55	195.70	202.30
Rat 3	300	181.76	172.61	182.41	185.64	190.40
Rat 4	2000	183.81	163.62	177.58	185.62	190.99
Rat 5	2000	169.68	156.68	164.24	172.08	174.76
Rat 6	2000	177.36	164.77	169.06	183.11	184.28
Rat 7	Saline 0.5ml	182.99	174.76	180.65	187.46	192.99
Rat 8	Saline 0.5ml	173.65	168.72	177.46	183.06	188.41
Rat 9	Saline 0.5ml	176.75	172.22	177.90	183.82	185.45
Mean	178.89	167.84	178.38	185.27	189.14	

Table 4.4: Mean Body Weights for Capparis Cartillaginea Decne Treated and Control Group for the Acute Oral Toxicity Study

C.Cartillaginea decne	**Fasting day**	**Day 0**	**Day 1**	**Day 7**	**Day 14**
Control	177.80.±2.747	171.90±1.751	178.67.±0.998	184.78±1.358	188.95.±2.193
300	183.74±1.529	168.21±3.292	182.51±1.150	188.63±3.549	194.97.±3.703
2000	176.95.±5.269	165.02±5.269	173.63.±4.713	180.27±4.159	183.34.±4.709
P value	0.275	0.639	0.393	0.365	0.270

Plate A was treated with buffered saline only. In comparison **plate B** shows the stomach lining of an ethanol treated rat. The ethanol caused extensive necrotic lesions of the stomach lining, covering almost the entire surface area of the stomach with mean ulcer index at (1.260±0.18). **Plate C** shows the stomach lining of the rat that was treated with

indomethacin only. It also shows extensive areas of ulceration with mean ulcer index of (1.400±0.14).

The **plate D** shows stomach lining of animals pretreated with extracts of *Capparis cartillaginea decne* at 200mg/kg before ulcer induction with ethanol. **Plate E** shows animals pretreated with 200mg/kg of extracts of *Capparis cartillaginea decne* before ulcer induction with indomethacin. There are minimal areas of erosion as evident by the ulcer index (0.42±0.07; 0.32±0.03) respectively, compared to indomethacin treated only (1.40±0.14) and ethanol treated only (1.26±0.18). The **plate F** shows animals pretreated with 400mg/kg of extracts of *Capparis cartillaginea decne* before ethanol administration. **Plate G** shows animals pretreated with 400 mg/kg of extracts of *Capparis cartillaginea decne* before administration of indomethacin. (Figure 4.4).

4.4 Macroscopic Appearance of stomach lining of experimental rats.

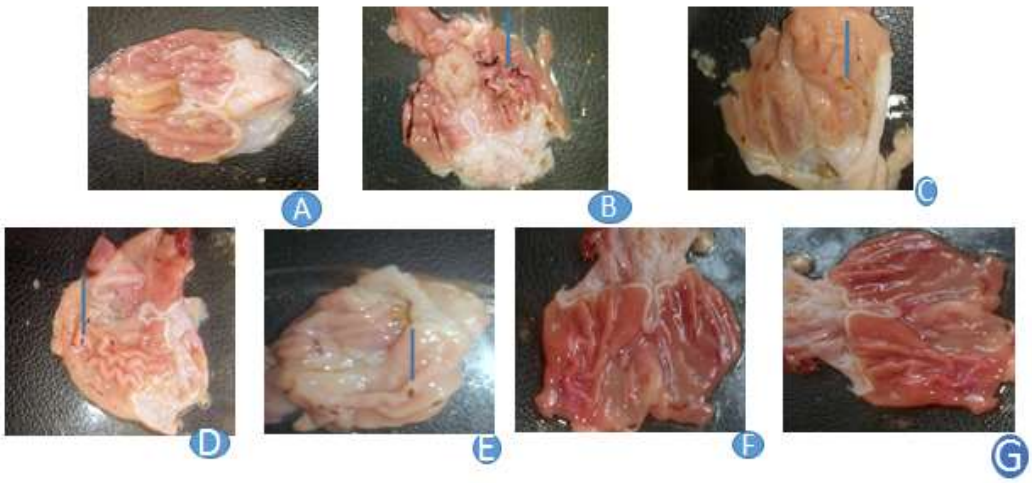

Plate 4.1: Macroscopic Appearance of stomach lining of experimental rats

Key*:* Arrow shows areas of ulceration

A-buffered saline only, B-Ethanol only treated, C-Indomethacin only treated, D-Ethanol+200mg/kg extract, E-Indomethacin+200mg/kg extract, F-Ethanol+400mg/kg extract, F-Indomethacin+ 400mg/kg extract

4.5. Mean ulcer index

Both Indomethacin and ethanol ulcerated animals s had high levels of the total surface area of the stomach mucosa ulcerated, with a mean ulcer index of (1.400±0.14; 1.260±0.18) respectively. Pretreatment with 200 mg of extracts of *Capparis cartillaginea decne* before induction of ulcers with indomethacin and ethanol (0.420±0.074; 0.320±0.059) respectively, significantly reduced the mean ulcer index indicating less total surface area of the stomach mucosa ulcerated. The mean ulcer index was further reduced with pretreatment with extracts at 400mg/kg (0.160±0.097; 0.280±0.054) before ulcer induction with indomethacin and ethanol respectively, signifying lesser total surface area of the stomach mucosa ulcerated. This was comparable to what happened when the experimental animals were pretreated with the drug omeprazole before ulcer induction with ethanol and indomethacin (0.140±0.03; 0.100±0.00) respectively.

4.6. Percentage inhibition of ulcer formation

Pretreatment of animals with 200 mg/kg of extracts of *Capparis cartillaginea decne* caused inhibition of ulcer development in indomethacin (79.25$\pm$2.10) induced ulcers and ethanol (70.20$\pm$3.20) induced ulcers. The percentage inhibition was better with pretreatment with extracts of *Capparis cartillaginea decne* at a dose of 400mg/kg before ulcer induction with ethanol (80.40$\pm$5.20) and indomethacin (84.88$\pm$4.50), respectively. This was comparable to total inhibition caused by pretreatment with the positive control (omeprazole 20mg/kg) before ulcer induction with indomethacin and ethanol. This showed that the extracts of the plant *Capparis cartillaginea decne* had the potential to

inhibit ulcer formation in indomethacin and ethanol induced ulcers. This effect seen is dose depended (Table 4.5).

Table 4.5: Mean percentage inhibition of treated groups in comparison to positive control

Parameter % inhibition	Positive Control 20mg/kg	200mg/kg extract	400mg/kg Extract	P value
Indomethacin	92.54±1.72[a]	79.25.±2.10[b]	84.88±4.50[a]	**0.003***
Ethanol	88.36.±5.40[a]	70.20±3.20[b]	80.40±5.20[a]	0.001*

4.7. Gastric Acid Output.

The groups that exhibited the highest volume of gastric acid output were animals treated with indomethacin only (M=3.14ml, SD=0.207) and ethanol only (M=2.72 ml, SD=0.148). Pretreatment with the 200mg/kg extracts of *Capparis cartillaginea decne* before ulcer induction with ethanol and indomethacin (M=2.25ml, SD=0.141) , (M=2.12ml, SD=0.142) respectivelly showed reduction in mean volume of gastric juice output.This was not stastistically different from the ulcerated control (p=0.08). The results were better with pretreatment with extracts of *capparis cartillaginea decne* at 400mg/kg (M=1.82, SD=0.192), (M=1.80, SD=0.158) before ulcer induction with ethanol and indomethacin respectively.This was stastically significant(p=0.001) compared to ulcerated animals (Table 4.6).

Table 4.6: Mean volume of gastric juice in treated groups in comparison to negative control and baseline.

Model	Negaticontrole	Baseline (Ulcerated)	200 mgkg	400 mgkg	P value
Indo	1.69+0.201	3.14+0.207[a]	2.12+0.142[a]	1.80+0.158[b]	0.001*
EtOH	21.69±0.201	2.72±0.148[a]	2.25±0.140[a]	1.82±0.192[b]	<0.003*

Key: Comparison between groups was performed in row.

a: indicates values that were significantly different ($p < 0.05$) from the negative control using ANOVA in Tukey test on post hoc.

b: indicates values that were significant different ($p < 0.05$) from the ulcerated control using ANOVA in Tukey test on post hoc t –test

4.8 The pH value

From the results in Table 4.7, Indomethacin ulcerated rats (M=2.20, SD=0.158) and ethanol ulcerated rats (M=2.22, SD=0.19) had lower pH. This shows that the indomethacin and ethanol treatment to experimental rats has ability to lower the pH and make it more acidic. Pretreatment with 200mg/kg of extracts of *Capparis cartillaginea decne* before ulcer induction with indomethacin(M=3.12, SD=0.210) and ethanol (M=3.21,SD=0.436) caused the pH to rise up and become less acidic. The results were much better with pretreatment of the animals with 400mg/kg of extracts of *Capparis cartillaginea decne* before ulcer induction with ethanol(M=4.64, SD=0.230) and indomethacin(M=4.82, SD=0.311). This showed that the plant had potential to rise the pH of gastric juice and make it less acidic. This was similar to pretreatment with standard drug omeprazole before ulcer induction with indomethacin(M=5.02,SD=0.526) and ethanol(M=5.18 SD=0.466) which also caused an increase in pH of gastric juice.

Table 4.7: Mean pH of treated groups in comparison to negative control and baseline

Model	Negaticontrole	Baseline (Ulcerated)	200 mgkg	400 mgkg	P value
Indo	2.93±0.445	2.20±0,158[a]	3.12±0.210[a]	4.82±0.311[b]	0.001
EtOH	2.93±0.445	2.22±0.192[a]	3.21±0.436[a]	4.64±0.230[b]	<0.001

Key: Comparison between groups was performed in row.

a indicates values that were significantly different ($p < 0.05$) from the negative control using ANOVA in Tukey test on post hoc

b indicates values that were significant different ($p < 0.05$) from the ulcerated control using ANOVA in Tukey test on post hoc t –test

4.9 Total Acidity

From the table 4.8, indomethacin ulcerated rats (M=88.64 mEq/L, SD=1.71) and Ethanol ulcerated rats (M=88.64 mEq/L, SD=2.17) had the highest total acidity levels. This showed that ulcer induction with indomethacin and ethanol caused an increase in both dissociated and undissociated hydrogen ions. Pretreatment with extracts of *Capparis cartillaginea decne* at 200mg/kg before ulcer induction with ethanol(M=80.12mEq/L, SD=3.12) and indomethacin (M=70.22mEq/L, SD=4.12) caused a decrease in total acidity. There was even more decrease in total acidity compared to the ulcerated animals only, after pretreatment with extracts of *Capparis cartillaginea decne* at 400mg/kg before ulcer induction with ethanol(M=68.12mEq/L, SD=2.19) and indomethacin (M=61.44mEq/L, SD=2.42). This was similar to what was seen in animals pretreated with standard drug omeprazole before ulcer induction with ethanol (M=54.19 mEq/L, SD=5.32) and indomethacin(M=55.26mEq/L, SD=3.77) respectivelly.

Table 4.8: Mean total acidity of treated groups in comparison to negative control and baseline

Model	Negaticontrole	Baseline (Ulcerated)	200 mgkg	400 mgkg	P value
Indo	81.74±2.14	88.64±0,1.71[a]	70,22±4.12[a]	61.44±2.42[b]	0.001
EtOH	81.74±2.14	88.64±2.17[a]	80.12±3.12[a]	68.12±2.19[b]	<0.001

Key: Comparison between groups was performed in row.

a indicates values that were significantly different ($p < 0.05$) from the negative control using ANOVA in Tukey test on post hoc

b indicates values that were significant different ($p < 0.05$) from the ulcerated control using ANOVA in Tukey test on post hoc t –test

CHAPTER FIVE

DISSCUSION, CONCLUSION AND RECOMMENDATION

5.1. Discussion

5.1.1. Phytochemical compounds of leave extracts of Capparis cartillaginea decne

This study was able to establish presence of tannins, sterols, phenolic compounds and saponins in the extracts of *Capparis cartillaginea decne*. This is in agreement with studies done in Yemen (Moharram et al., 2017) and Japan (Science, 2012). These metabolites are effective as anti-oxidants, anti-inflammatory and also regulate gene expression (Pa and Koz, 2016). The acute toxicity studies revealed that the plant extract was safe in rats at a limit dose of 2000 mg/kg. The findings concur with those posted by Al-Goufi et al., 2018.

5.1.2 Effect of methanol leave extracts of capparis cartillaginea decne on gastric juice output, pH value, and total acidity

Control of gastric acid secretion is the cornerstone in management and prevention of peptic ulcers (Fornai *et al*., 2011). Analysis of gastric contents is performed to study the normal function of the stomach and the effects of disease upon them. Biochemical analysis of gastric secretions and mucosal integrity for stomach is usually employed to ascertain its status following administration of pharmacological agents (Biplab *et al.,* 2011). The accomplishment of pharmacological treatments in preventing or healing ulcers may not depend only on the inhibition of acid secretion, but also on the enhancement of mucosal protective factors (Lapa *et al.,* 2007). The pH gives an idea of the level of acidity which has been linked to the pathogenesis of gastric damage in experimental animals (Lullmann *et al.,* 2000).

Ethanol and indomethacin administration caused significant decreased pH ($p<0.05$). It also caused a significant increase in gastric volume ($p<0.05$). This may be attributed to

either free radicals formation or inhibition of prostaglandin synthesis by indomethacin. Decreased prostaglandin level has been attributed to impaired gastro protection and increased gastric acid secretion which are important events in the etiology of mucosal ulceration (Sabiu *et al.,* 2015). There was also notable significant ($p<0.05$) increase in total acidity. This could be explained by the fact that ethanol increases acid secretion principally by stimulating the secretion of gastrin a hormone that modulates acid production (Edy, 2002). These findings are in agreement with submissions by Sabiu *et al.,* (2015).

5.1.3 Effect of methanol leave extracts of capparis cartillaginea decne on ulcer inhibition.

The study observed that ethanol and indomethacin administration to experimental animals caused macroscopic lesions to gastric tissue such as loss of normal color, petechial, spot ulcers and hemorrhagic streaks (plate B and C). The ulcer index was significant ($p<0.05$) and was further able to illustrate the macroscopic differences seen.

The surface of gastric mucosa is covered by a layer formed by mucus gel, bicarbonate anions and surfactant phospholipids (Fornai *et al.,* 2011).The mucus-mucosa interface, an unstirred layer is capable of maintaining an environment with a near pH value of seven (Allen and Flemstrom, 2005). Indomethacin, a non-steroidal anti-inflammatory drug, interferes with cyclo-oxygenase pathway which leads to production of prostonoids. This disruption interferes with the effectiveness of mucus-bicarbonate barrier (Russel, 2001).

Pretreatment of the animals with the extract *Capparis cartillaginea decne* before ulcer induction with indomethacin and ethanol caused significant ($p>0.05$) ulcer inhibition. The effects were best at high doses (400mg/kg) of extracts of *Capparis cartillaginea decne* compared to the lower dose of 200mg/kg. This could be attributed to the medicinal attributes of phytochemical compounds of the plant *Capparris cartillaginea decne*. These compounds (tannins, phenolic compounds, saponins, sterols and

flavonoids) have been cited to have anti-inflammatory and antioxidant activity (Ozcan and Delikanli, 2014). They have also been shown to possess ability to scavenge for free radicles and regulate mucosal membrane permeability thereby countering the effect of indomethacin and ethanol on gastric acid secretion and consequently inhibition against gastric ulceration. This is in agreement with the submissions of (Boligon *et al.,* 2014) and (Abebaw *et al.,* 2017) where gastro protective potential of plant extracts against ulcerated rats was associated with their bioactive secondary metabolite.

Since omeprazole is a proton pump inhibitor, then the effect produced by the extracts of *Capparis cartillaginea decne* might have perhaps mimicked its mechanism of action by modifying cells in mucosal lining of stomach against excess acid secretion hence the results seen in animals pretreated with extracts of *Capparis cartillaginea decne* before ulcer induction with indomethacin and ethanol comparable to animals pretreated with the drug omeprazole before ulcer induction with indomethacin and ethanol.

5.2 Conclusions

1. Extracts of *Capparis cartillaginea decne* have high margin of safety in experimental animals in doses of 2000 mg/kg body weight.
2. The leaf extracts of *Capparis cartillaginea decne* contained the compounds tannins, saponins, phenolic compounds, sterols and flavonoids.
3. Leaf extract of *Capparis cartillaginea decne* produces ulcer inhibition against ethanol and indomethacin induced ulcers in the experimental animals in a dose dependent manner.
4. This protection was most likely due to the antioxidant and anti-inflammatory phytochemicals the plant *Capparis cartillaginea decne* contained.
5. The leaf extract of *Capparis cartillaginea decne* also showed significant gastric acid volume reduction and a rise in pH, thus reducing the risk of ulcer formation caused by indomethacin and ethanol. These provide strong interest in developing natural drug that produce the desired antiulcer effect without the undesired effect of synthetic drugs.

5.3 Recommendations

The study recommends further studies involving;

1. Further studies to establish the specific compound(s) and possible mechanism of action in ulcer inhibition.
2. Further studies on sub-acute and chronic oral toxicity of *Capparis cartillaginea decne*
3. Further studies on quantitative analysis of Capparis cartillaginea decne methanolic leave extract phytochemical components

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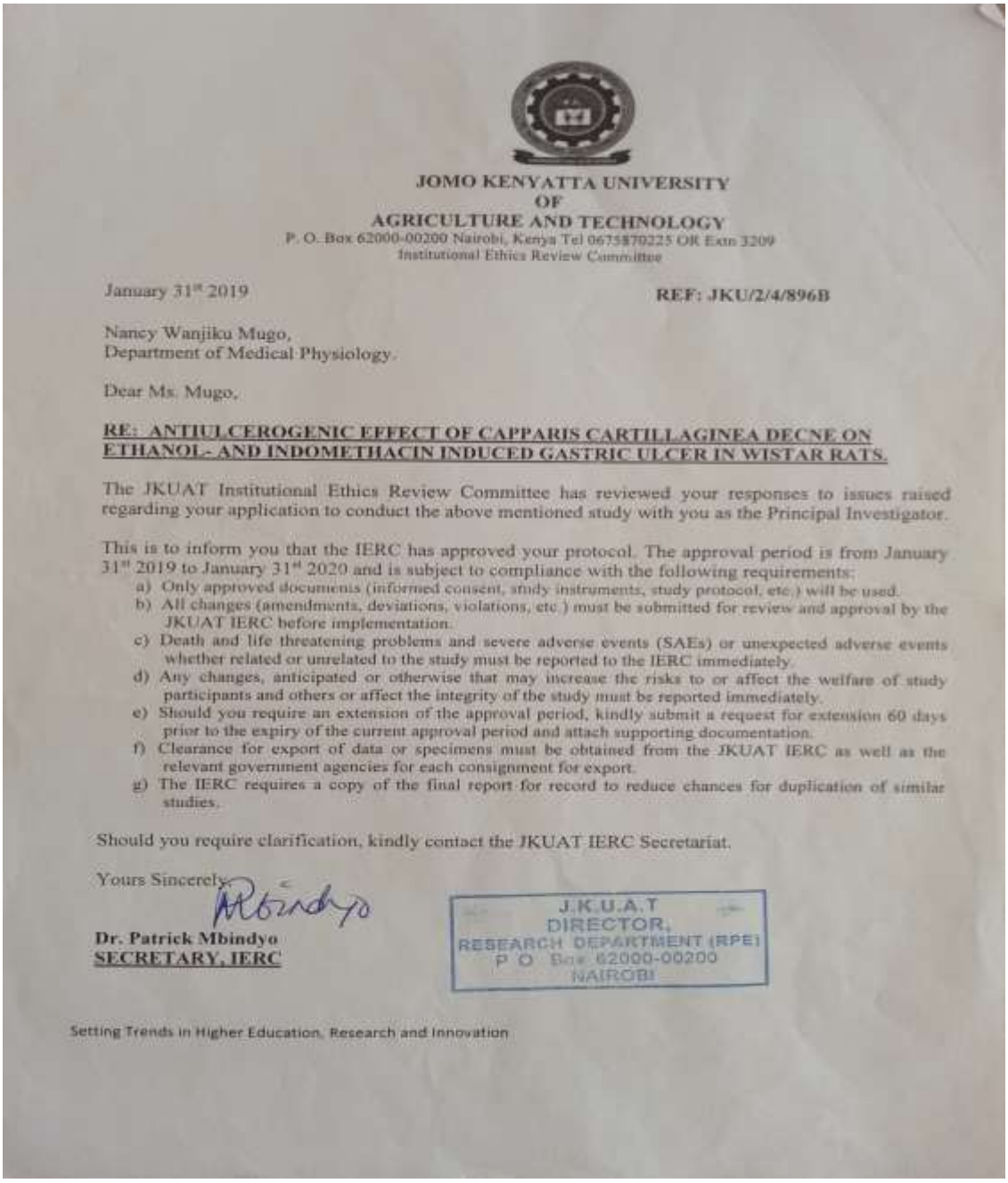
APPENDICES

Appendix I: Ethical approval from JKUAT



JOMO KENYATTA UNIVERSITY
OF
AGRICULTURE AND TECHNOLOGY
P. O. Box 62000-00200 Nairobi, Kenya Tel 0675870225 OR Extn 3209
Institutional Ethics Review Committee

January 31st 2019

REF: JKU/2/4/896B

Nancy Wanjiku Mugo,
Department of Medical Physiology.

Dear Ms. Mugo,

RE: ANTIULCEROGENIC EFFECT OF CAPPARIS CARTILLAGINEA DECNE ON ETHANOL- AND INDOMETHACIN INDUCED GASTRIC ULCER IN WISTAR RATS.

The JKUAT Institutional Ethics Review Committee has reviewed your responses to issues raised regarding your application to conduct the above mentioned study with you as the Principal Investigator.

This is to inform you that the IERC has approved your protocol. The approval period is from January 31st 2019 to January 31st 2020 and is subject to compliance with the following requirements:

a) Only approved documents (informed consent, study instruments, study protocol, etc.) will be used.
b) All changes (amendments, deviations, violations, etc.) must be submitted for review and approval by the JKUAT IERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the IERC immediately.
d) Any changes, anticipated or otherwise that may increase the risks to or affect the welfare of study participants and others or affect the integrity of the study must be reported immediately.
e) Should you require an extension of the approval period, kindly submit a request for extension 60 days prior to the expiry of the current approval period and attach supporting documentation.
f) Clearance for export of data or specimens must be obtained from the JKUAT IERC as well as the relevant government agencies for each consignment for export.
g) The IERC requires a copy of the final report for record to reduce chances for duplication of similar studies.

Should you require clarification, kindly contact the JKUAT IERC Secretariat.

Yours Sincerely,

Mbindyo

Dr. Patrick Mbindyo
SECRETARY, IERC

J.K.U.A.T
DIRECTOR,
RESEARCH DEPARTMENT (RPE)
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Setting Trends in Higher Education, Research and Innovation

Appendix II: Publication

International Journal of Research in Medical Sciences *Mugo NW et al. Int J Res Med Sci. 2020 Oct;8(10):3445-3448* www.msjonline.org pISSN 2320-6071 | eISSN 2320-6012

Original Research Article

Antiulcerogenic effect of *Capparis cartillaginea decne* on indomethacin induced gastric ulcer in wistar rats

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ABSTRACT

Background: Peptic ulcer disease is a non-malignant, mucosal lesion of the stomach or duodenum. The mucosal defect reaches the muscularis mucosa and sometimes, beyond causing life threatening complications, including haemorrhage, perforations, gastrointestinal obstruction and malignancy.

Methods: The animals were pre-treated with omeprazole 20 mg/kg and 300 mg/kg of *Capparis cartillaginea decne* orally for 14 days. On the 15th day, ulcers were induced using indomethacin 30 mg/kg and 4 hours post ulcer induction, they were sacrificed. Ulcer index, pH, total acidity and volume were determined.

Results: Extensive lesions were seen in indomethacin ulcerated rats with mean ulcer score of (1.260±0.18). In comparison, there were minimal areas of erosion on animals pre-treated with omeprazole (0.14±0.025) and plant extracts (0.280±0.097). Indomethacin-induced ulcer treated animals showed the highest volume of gastric juice output (3.14±0.21 ml), whereas the animals pre-treated with omeprazole had lower gastric juice output (2.20±0.2 9ml). This was comparable to animals pre-treated with the plant extract (1.80±0.13 ml). The pH was high in animals pre-treated with omeprazole (5.02±0.53). This was also seen in animals pre-treated with the extract (4.82±0.31). This was in comparison to the low pH seen in indomethacin ulcerated animals (2.20±0.16). Indomethacin-induced ulcer treated animals showed high levels of total acidity (88.64±1.71 mEq/L). Whereas the animals pre-treated with omeprazole had lower total acidity (55.26±3.77 mEq/L), which was also mirrored in animals pre-treated with the plant extracts (61.44±2.42 mEq/L).

Conclusions: The extracts of *Capparis cartillaginea decne* showed anti-ulcer effect on indomethacin induced ulcers in Wistar rats.

Keywords: Indomethacin, Omeprazole, *Caparris cartillaginea decne*, Peptic ulcers

INTRODUCTION

Peptic ulcer disease is a non-malignant, mucosal lesion of the stomach or duodenum in which pepsin and acid plays a major pathogenic role.1 The mucosal defect caused by peptic ulcers reaches the muscularis mucosa and sometimes, beyond. It is usually associated with life threatening complications, including haemorrhage, perforations, gastrointestinal obstruction and malignancy. The life- threatening complications may necessitate surgery, and if untreated, can cause death.2

Acid and pepsin plays an important role in peptic ulcer formation when Helicobacter pylori, NSAIDs or other uncommon factors like radiation, stress, chemotherapy and vascular insufficiency disrupt normal mucosal defence and healing mechanisms.3 The mechanism of gastric-mucosal defence includes several local and neuro-hormonal protective factors, which allow the mucosa to resist exposure to damaging factors. This includes bicarbonates, prostaglandins and mucosal blood flow.4 Non-steroidal anti-inflammatory drugs cause mucosal damage by recruiting circulating neutrophils and causing