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RESEARCH ARTICLE

PHYTOCHEMICAL ANALYSIS, PEPTIC ULCER CURATIVE, ANTIOXIDANT AND MEMBRANE STABILIZATION POTENTIAL OF THE EXTRACT OF *CALLITRIS ROBUSTA* VAR. *MICROCARPA*

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ABSTRACT

Callitris robusta var. *microcarpa* (CRM) contains phytochemicals used to treat diverse ailments. This study was aimed at investigation of the phytochemicals in *C. robusta* var. *microcarpa* (CRM) that have antioxidant potential for curative of various gastrointestinal disorders. Chromatographic and multifaceted biochemical assays were carried out as shown in the body of the work. The results showed that CRM has a better gastrointestinal protection and ulcer healing potential when compared with cimetidine. A significant reduction of the ulcers scores and protection was observed. CRM helps to maintain the integrity of the stomach mucosa by minimizing oxidative damage through the reduction of ROS levels. Histological screening of the tissues showed viable muscularis-propria wall mucosal lining cells, and no abnormalities. CRM demonstrated an increase in membrane stability, suggesting its potential to reinforce membrane integrity. This study provides information on therapeutic uses of CRM as a natural antioxidant for gastrointestinal protection.

KEYWORDS

Callitris robusta var. *microcarpa* (CRM), antioxidant, gastrointestinal, ulcer healing, membrane stabilization.

1. INTRODUCTION

Africa is greatly enhanced by range of herbal medicinal plants with ethnopharmacological qualities that are frequently utilised in various traditional medical systems. Plant secondary metabolites are very valuable products from an economic perspective. The majority of people globally preferred the use of alternative medicine as their primary source of healthcare (Evbuomwan et al., 2023; Ololade et al., 2024). *Callitris robusta* var. *microcarpa* (*Cupressaceae*) is a medicinal tree locally used to treat inflammation, skin problems etc (Kochti et al., 2023). Gastrointestinal disease such as stomach ulcer is associated with osteoporosis include early onset of disease, malabsorption, and maldigestion of nutrients necessary for bone health and maintenance (eg, calcium, vitamin D), as well as the impact of glucocorticoids (Katz et al., 2010). A bacterial infection can cause chronic inflammation of the stomach, and duodenum mucosa thereby decrease absorption of calcium and production of inflammatory mediators in the bones. Peptic ulcer disease may be accompanied by dietary restrictions calcium intake is negatively influenced. Inflammation of gastric and duodenal mucosa as well as alkali used may significantly decrease calcium absorption (Merlotti et al., 2022; Xu et al., 2023). There is paucity of scientific report on the medicinal properties of *C. robusta* var. *microcarpa*. Therefore, this study aimed at investigating the synergistic potential of the secondary metabolites in the aerial of *C. robusta* var. *microcarpa* (CRM) for healing of gastrointestinal problems, such as various ulcer ailments.

2. MATERIALS AND METHODS

2.1 Identification of the Sample and Extraction Process

The plant was grown as an ornament in Abuja, Nigeria, where the sample was collected. It was identified and authenticated as *Callitris robusta* var. *microcarpa* (Benth) FM Baley. Voucher specimen was deposited at the Arboretum of the University of Medical Sciences, Ondo, Nigeria with number UNIMED PBTH 0188. The sample was extracted according to the previous method used by (Ololade et al., 2024a).

2.2 Phytochemical Analysis

The phytochemicals in the extract of CRM were examined using a Shimadzu GC-MS-QP2010 Plus (Japan). The analysis conditions were established in accordance with Salemcity et al. 2024.

2.3 Experimental Animals and Biochemical Protocols

Thirty male albino rats, weighing between 100±10 grams, were purchased from the University of Lagos' animal house and the rats were kept in good environmental condition as prescribed by ethical condition. After two weeks of acclimatization to the animal house environment, these rats were divided into five (5) groups of Six (6) rats each.

Group I – Control (Ethanol as vehicle); Group II– CRM extract only; Group III – indomethacin only (100 mg/kg b.w.) (14 days); Group IV – CRM extract+ Indomethacin (200 mg/kg b.w.) (14 days) and Group V - Cimetidine + Indomethacin (1 mL/kg b.w.). The gastroprotective potential of CRM was assessed using the indomethacin-induced peptic ulcer model as used with minor modifications by (Alfadil et al., 2024).

The following biochemical assays were determined according to previous methods used by El Azab et al., 2024; Ololade et al., 2024. Bovine serum

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albumin was used as a standard method to determine the samples' total protein concentration. Alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST), malondialdehyde (MDA), superoxide dismutase (SOD). By evaluating the rate at which hydrogen peroxide breaks down at 240 nm, catalase (CAT), reduced glutathione (GSH) (Onifade et al., 2020; Hammid, 2024). In the histological analysis, the slices were stained with hematoxylin and eosin (H and E) dye (Ololade et al., 2024a). The *in vitro* molecular stabilization potential on associated secondary osteoporosis was carried out as previously described by (Zohora et al., 2024).

2.4 Ethical Approval

The University ethical committee approved and evaluated this study before any data were collected, and also ensured that all areas of animal experimentation were done in line with the highest ethical standards.

2.5 Statistical Analysis

All values were expressed as the mean ± S.E.M. of triplicate. Data were analyzed using one-way ANOVA followed by the Duncan multiple range test for analysis of biochemical data using SPSS (16.0). Values were considered statistically significant at $P < 0.05$.

3. Results and Discussion

Table 1: GC-MS Screened Phytochemicals in the Aerial Extract of *Callitris robusta* var. *microcarpa* (CRM)

Compound	Retention Index	Percentage Composition
α-furfuryl alcohol	885	0.40
β-butyrolactone	766	1.00
Cyclohexanone	891	1.20
2-hydroxy-gamma-butyrolactone	1013	0.96
β-propylene glycol	805	0.40
4,5-dimethyl-1,3-dioxol-2-one	975	0.35
2,5-dimethyl-4-hydroxy-3(2H)-furanone	1022	0.10
1-ethyl-2-pyrrolidinone	1020	0.36
4-ethyl-3-methyl-4-penten-2-one	856	0.40
Hydroxymethylcyclopropane	664	0.30
α-amino-*γ*-butyrolactone	1030	1.30
3,5-dihydroxy-6-methyl-2,3-dihydro-4H-pyran-4-one	1269	0.37
Catechol	1122	0.80
Coumaran	1036	0.35
5-hydroxymethylfurfural	1163	0.40
Resorcinol	1122	0.70
p-vinylguaiacol	1293	0.58
α-l-rhamnopyranose	1522	0.59
glucopyranoside, O-*α*-D-glucopyranosyl	4506	0.48
(R)-4-hydroxy-*α*-methyl-benzenepropanol	1475	0.40
α-methylglucoside	1714	2.85
N-(5-hydroxy-7-oxabicyclo[4.1.0]hept-2-yl)acetamide	1479	10.80
4-((1*E*)-3-hydroxy-1-propenyl)-2-methoxyphenol	1653	0.70
4-O-methylhexopyranose	1714	73.00
17-hydroxy-1,17-dimethyl-(1α5α17β)-androstan-3-one	2213	0.27
Percentage Total		**99.06**

The extract of *Callitris robusta* var. *microcarpa* (CRM) have twenty-six (26) components with percentage composition of 99.06%, including sugars, furan derivatives, phenolics, and other bioactive substances, according to the GC-MS study. The most abundant phytochemical was 4-O-methylhexopyranose (73.00%). These substances have been linked to mucoprotective, antibacterial, anti-inflammatory, and antioxidant qualities—all of which are critical in the treatment of stomach ulcers. The bioactive chemicals found in this study are pertinent for therapeutic investigation because ulcers are typified by oxidative stress, inflammation, and microbial infections.

The key compounds relevant to ulcer treatment include: 4-O-methylmannose (67.82%). This methylated sugar derivative, which is the most prevalent, has mucoprotective and immunomodulatory properties. According to studies, the formation of protective layers over the stomach mucosa by sugars such as 4-O-methylmannose may lessen irritation and aid in the healing process (Cherrada et al., 2024). These substances also lessen oxidative stress, a major contributor to ulcer etiology, and scavenge free radicals. By neutralizing reactive oxygen species (ROS), its antioxidant action reduces mucosal damage and promotes stomach repair (Chaudhary et al., 2023). 1R-4-*trans*-acetamido-2,3-*trans*-cyclohexanol (10.81%), the anti-inflammatory qualities of this cyclohexanol derivative are essential for controlling the inflammation brought on by stomach ulcers (Metuge et al., 2024). It may lessen mucosal inflammation and stop more damage by blocking inflammatory mediators including prostaglandins and cytokines. *p*-vinylguaiacol (0.58%) is a potential gastroprotective, antidiabetic, antimicrobial and anticancer polyphenol metabolite from ferulic acid for chemotherapy-resistant colon cancer cells (Luo et al., 2021; Markowska et

al., 2025). *p*-vinylguaiacol also have antibacterial and antioxidant properties, this phenolic molecule may help manage bacterial infections and oxidative stress, which are factors in the development of ulcers. In addition to suppressing *H. pylori* colonization in the stomach mucosa, it suppresses free radicals (Sah et al., 2023). Catechol (0.37%), a phenolic compound is well-known for its potent antibacterial and antioxidant qualities. According to study, these characteristics are crucial for lowering oxidative stress and managing *Helicobacter pylori,* a bacteria linked to the development of ulcers (Han et al., 2022). By scavenging ROS and inhibiting bacterial growth, catechol may help restore the mucosal barrier. Hydroquinone (0.43%), is another strong antioxidant found in the extract. It can lessen mucosal damage by lowering oxidative stress in the stomach environment. Lipid peroxidation, which worsens tissue damage during ulcer development, is inhibited by hydroquinone (Yeerbao et al., 2026). 5-hydroxymethylfurfural (5-HMF) (0.35%), in models of ulcers, this furan derivative has shown cytoprotective and anti-inflammatory effects (Vera et al., 2021). By increasing the synthesis of stomach mucus and decreasing inflammatory cytokines, it forms a barrier that protects against enzymatic and acidic attacks.

The concentration of serum glutamic-oxaloacetic transaminase (SGOT) is presented in Figure 1. SGOT level reduced significantly ($p<0.05$) in CRM alone (171.03±24.36) and CRM + Indomethacin (164.17±4.87) when compared with the control group (203.90±31.95). An insignificant decrease ($p>0.05$) was observed in the indomethacin only (200.73±16.20) in comparison with control group (203.90±31.95). Marked increase ($p<0.05$) was observed in CM + Indomethacin (210.27±40.24). Serum glutamic oxaloacetic transaminase (SGOT), also known as aspartate aminotransferase (AST), is an enzyme that reflects peptic function (Rahma et al., 2020). Elevated SGOT levels indicate tissue damage, especially in the mucosa legion, where the enzyme is released into the bloodstream during cellular injury. In peptic ulcer studies, SGOT levels can signal tissue damage as a result of oxidative stress or the toxicity of ulcer-inducing agents like ethanol and NSAIDs such as indomethacin. When indomethacin is combined with CRM extract, SGOT levels dropped significantly to as compared to indomethacin only group, indicating a protective effect of the plant extract. The substantial reduction in SGOT levels suggests that CRM extract mitigates the mucosa damage caused by indomethacin, likely through its antioxidant properties that neutralize ROS and reduce oxidative stress (Ansari et al., 2025). This finding suggests that the plant extract not only protects the mucosa but also has systemic benefits (Anwar et al 2025). This reduction in both SGPT and SGOT levels suggests that CRM extract has a protective effect on the mucosa preventing damage typically associated with ulcer formation.

ALP level was significantly increased ($p<0.05$) in the Indomethacin-induced group (337.80±125.65) when compared with the control group (292.70±10.11). There was significant reduction ($p<0.05$) in the administered CRM only (150.73±33.28), CRM + Indomethacin (98.77±8.97) compared to the CM + Indomethacin (160±5.10) Figure 1. Alkaline phosphatase (ALP) is an enzyme found in many tissues, including the liver, bones, kidneys, and digestive system (Swetha et al., 2025). Elevated ALP levels are often associated with liver damage, bone disorders, or bile duct obstruction and as well be an indicator of tissue damage, particularly involving the liver or other systems that may be affected by ulcer-induced stress or the side effects of medications (Gish et al., 2025). Indomethacin is known for its ulcerogenic effects, primarily targeting the mucosa, but it can also contribute to systemic oxidative stress, affecting other tissues, mucosa (Abu-Baih et al., 2025). The elevated ALP level in indomethacin only indicates stomach tissue injury or inflammation which may result in indomethacin-induced oxidative stress. This significant reduction indicates that CRM extract offers substantial protection against peptic damage caused by indomethacin. The decrease in ALP suggests that the plant extract may effectively neutralize reactive oxygen species (ROS) and reduce oxidative stress, leading to less mucosa tissue damage (Gulcin, 2025). The gastro-protective effect of CRM extract is further supported by this dramatic decrease in enzyme levels, demonstrating its potential role in preventing both peptic and systemic side effects of NSAIDs (Ololade et al., 2025d).

The result for Total Bilirubin (TBIL) for statistical analysis in Figure 1 showed that there was significant reduction ($P<0.05$) in the induced rat with indomethacin alone (1.96 ±0.31) when compared with the control group (ethanol as vehicle) (17.03±0.08). The pre-treated rat administered with the plant extract (CRM extract + Indomethacin) showed a significant ($P<0.05$) decrease (13.62±2.54) in comparison to CRM only group (16.46±1.90) and control group (ethanol as vehicle) (17.03±0.08). All other experimental groups except indomethacin only however have enhanced significant values ($p<0.05$) when compared with the group given standard drug (CM + Indomethacin) (9.27±3.23). Enhanced values observed in pre-treated plant extract groups suggest that CRM extract helps to protect the stomach tissues from oxidative damage and inflammation caused by indomethacin, allowing for partial recovery of normal bilirubin production and processing as against hypobilirubin initiated in indomethacin only. The plant extract's antioxidant and anti-inflammatory properties likely reduce mucosal damage, enabling better maintenance of normal bilirubin levels (Mittal et al., 2025).

Urea level for induced indomethacin only group (7.03±0.08) of rats in Figure 2, shows significant reduction ($P<0.05$) as compared to the control which is the vehicle (7.28±0.58). The pre-treated group administered with plant extract, CRM + Indomethacin (4.62±0.03) was significantly reduced ($P<0.05$) when compared to the CM + Indomethacin group (9.17±0.68), the control group (7.28±0.08) and the CRM extract alone group (7.66±0.75). When the stomach is exposed to excessive acid and intense pepsin activity, gastrointestinal toxicity of non-steroidal anti-inflammatory drugs (NSAIDs), and toxic substances like alcohol use, it is the most common gastrointestinal disorder ever reported (Sohail et al., 2023). Ethanol consumption is known to affect gastrointestinal function due to its ability to induce oxidative stress, which can lead to mucosa damage (Chung et al., 2025). The mildly increased urea level reflects ethanol's systemic toxicity, potentially stressing mucosa. Urea as a biochemical function in gastrointestinal tract, is the main nitrogenous waste product of protein catabolism. Elevated urea levels in the bloodstream, a condition known as hyperuremia, can signal increased protein breakdown (Laville et al., 2022). Urea levels can reflect the systemic impact of ulcer-inducing agents such as ethanol and nonsteroidal anti-inflammatory drugs (NSAIDs) like indomethacin. It also indicates potential oxidative stress or inflammation affecting multiple organs (Rahimi et al., 2025). This significant decrease suggests that the plant extract plays a protective role in reducing systemic oxidative stress and potentially preserving gastrointestinal function in the presence of indomethacin. The reduced urea level could indicate less protein breakdown and reduce the activities of pepsin and hydrochloric acid causing damage to the membrane, likely due to the antioxidant effects of CRM, which neutralizes free radicals and reduces inflammation (Yigit et al., 2025).

From Figure 2, the Creatinine level of the control rat group (vehicle as ethanol) (63.67±2.41) shows significant increase ($P<0.05$) as compared to the induced rat group of Indomethacin alone group (56.09±2.12). The pre-treated group of rats administered with plant extract (CRM + Indomethacin) (52.45±2.42) was significantly decreased ($p<0.05$) when in contrast with the standard (CM + Indomethacin) (61.85±2.73), CRM group only (78.22±5.78). Ethanol consumption is known to induce oxidative stress which causes damage to mucosa by promoting inflammation and damaging the mucus tissues (Metro et al., 2022). The observed creatinine level suggests that ethanol disrupts lining causing a mild increase in creatinine levels. Creatinine is a waste product generated from muscle metabolism and excreted by the kidneys. In ulcer studies, creatinine levels can provide insights into how ulcer-inducing agents like ethanol and NSAIDs (such as indomethacin) stomach lining function, and whether potential treatments offer gastroprotective effect (Ávila et al 2025). The combination of indomethacin with CRM results in a further reduction in creatinine levels to 52.45. This suggests that the plant extract has a protective effect on gastrointestinal function when co-administered with indomethacin. CRM extract likely exerts its protective effect through its antioxidant properties, which help to neutralize free radicals and reduce inflammation in the stomach lining thereby improving mucus layer and reducing creatinine levels (Nabil et al., 2021). The reduction in creatinine highlights the potential of CRM extract to mitigate the systemic side effects of NSAIDs like indomethacin.

From the statistical result obtained for triglyceride level in Figure 2, it was observed that there were slightly significant differences from all the groups. Slight increase was observed in Indomethacin induced only group (0.82±0.05) when compared with the control group (0.75±0.05). The Pre-treated group given plant extract, CRM + Indomethacin (1.15±0.09) had marked increment ($P<0.05$) when compared with the control group (0.75±0.05), Indomethacin only group (0.82±0.05) and rats administered with reference drug, CM + Indomethacin group (0.80±0.16). Slight significant was observed CRM + Indomethacin (1.15±0.09) in comparison to the group with plant extract alone CRM only (1.07±0.14). Triglycerides (TRIG) are a type of fat found in the blood, and their levels can provide insights into metabolic health, liver function, and lipid metabolism (Yuan et al., 2025). In ulcer studies, triglyceride levels can indicate how various

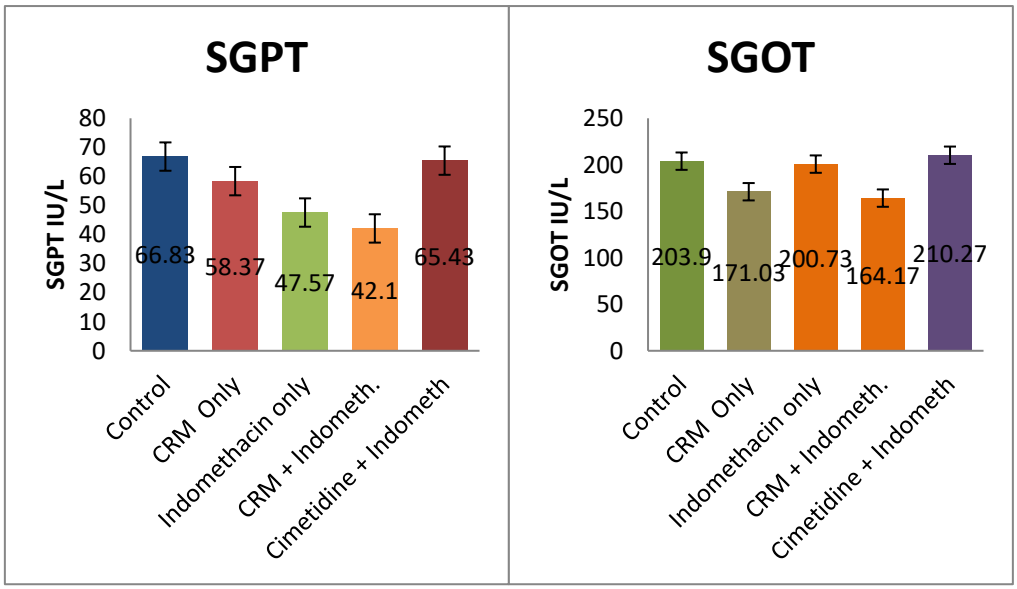
treatments affect lipid metabolism, oxidative stress, and overall energy balance in the body. This elevation suggests that while investigated sample CRM may offer protective effects in terms of peptic and renal health, it may also influence lipid metabolism when combined with indomethacin. The higher triglyceride level could be attributed to the synergistic effect of the plant extract and indomethacin, leading to altered energy utilization or fat storage (Yang et al., 2024). Indomethacin is an NSAID that can disrupt lipid metabolism by increasing oxidative stress and causing gastrointestinal damage to the stomach. The modest increase in triglycerides may indicate some metabolic disturbance caused by indomethacin, but it remains relatively low, suggesting that the impact on lipid metabolism is minimal in this acute phase (Shaik et al., 2023; Ajayi et al., 2024).

Figure 2, reveal cholesterol level of all experimental albino rat groups. Significant reduction (P<0.05) was noticed in induced group of rats with indomethacin alone (1.40±0.11) in comparism with the control group (1.98±0.18) and the rat given plant extract alone, CRM group (2.11±0.18). The pre-treated group administered with plant extract, CRM + Indomethacin (1.46±0.09) indicates significant reduction when compared with the standard drug, CM + Indomethacin group (1.71±0.04) and the plant extract alone (CRM) group. Cholesterol (CHOL) is a crucial lipid involved in cell membrane structure, hormone production, and other metabolic functions. It is also a marker of metabolic health, and its levels can indicate how treatments for ulcers may affect lipid metabolism. In ulcer research, cholesterol levels can shed light on the systemic effects of ulcer-inducing agents and potential therapeutic interventions. Sample CRM has been shown to have gastro-protective and antioxidant properties, which can contribute to better regulation of lipid metabolism and cholesterol levels (Guo et al., 2024; Kök et al., 2025). Although the cholesterol level remains lower in CRM+ Indomethacin group than in the control group, the slight increase of CRM + Indomethacin over Indomethacin only indicates a protective effect of the plant extract on lipid metabolism. Ethanol is known to cause oxidative stress and mucosal damage, which can disrupt lipid metabolism over time (Tsermpini et al., 2022). However, in the control group (1.98±0.18), the cholesterol level remains stable, suggesting that short-term ethanol exposure has not yet significantly altered cholesterol metabolism.

In High Density Lipoprotein Level (HDL) in Figure 3, there was significant reduction (P<0.05) in the induced Indomethacin group (0.89±0.14) when compared to the control group (ethanol as vehicle), (1.69±0.28). There was slight increment in CRM + Indomethacin group (0.93±0.04) when compared with Indomethacin only group (0.89±0.14). It was discovered that the pre-treated rats given the plant extract, CRM + Indomethacin group (0.93±0.04) showed significant reduction (p<0.05) in HDL level when compared with the group of rats given reference drug, CM + Indomethacin group (1.47±0.12) and plant extract alone, CRM only group (1.69±0.28). High-density lipoprotein (HDL) is an important lipoprotein involved in reverse cholesterol transport, carrying cholesterol from the tissues to the liver for excretion (von Eckardstein et al., 2023). HDL is often referred to as "good" cholesterol because higher levels are associated with a reduced risk of cardiovascular disease. In ulcers studies, changes in HDL levels could reflect alterations in lipid metabolism induced by oxidative stress or the treatments applied to alleviate the ulcer. Although HDL remains below the level observed in the control group, the slight increase suggested that CRM may provide some protective effects against the lipid peroxidation induced by indomethacin (Deng et al., 2025; Ololade et al., 2025d). The plant extract likely helps modulate oxidative stress and inflammation, preserving HDL to a certain extent, although not enough to fully restore it to normal levels.

Furthermore, in Figure 3 the statistical result obtained in Albumin (ALB) level, it was observed that Indomethacin only group (28.60 ±1.96) had slight reduction when compared with control group (29.87±1.15). Pre-treated rat given plant extract, CRM + Indomethacin group (27.23±0.53) lowered than Indomethacin only group. The healthy rat given the plant extract, CRM group alone has significant increase (P<0.05) in albumin level (36.37±1.37) as compared to the remaining groups which are statistically the same. However, the pre-treated rat given plant extract, CRM + Indomethacin group (27.23±0.53) was slightly significantly (p<0.05) reduced when compared to the group administered with standard drug, CM + Indomethacin (30.73 ±0.35) and also in the induced indomethacin group (28.60 ±1.96). Albumin (ALB) is a vital protein synthesized by the liver, playing a key role in maintaining osmotic pressure and transporting various substances in the blood, including hormones, drugs, and waste produts. In peptic ulcers studies, changes in albumin levels may reflect alterations in protein metabolism, liver function, and the body's inflammatory response to ulcerative damage (Wu et al., 2024). Slight reduction was noticed in albumin levels of CRM + Indomethacin group when compared to indomethacin-alone group. This suggests that while CRM extract offers some protection against indomethacin-induced peptic damage, it does not completely counteract the impact of indomethacin on protein metabolism and liver function. The plant extract likely reduces oxidative stress and inflammation to some extent, but the persistent damage from indomethacin may still impair albumin production (Wahnou et al., 2026).

The protein result obtained in Figure 3 shows that there was significant reduction (P<0.05) in the induced indomethacin group only (59.97 ±0.98) when compared to control group (ethanol as vehicle) (76.33 ±2.17) and the plant extract alone, CRM group (87.87±4.9). The ulcerated group of rats administered with plant extract, CRM + Indomethacin group (61.77 ±5.77) shows significant reduction (P<0.05) when compared with the standard drug (CM + Indomethacin) group (67.43±2.30), but in contrast to induced Indomethacin only which is reduced to (59.77±0.98). This decline is likely due to the damage induced by indomethacin, which can lead to protein loss through the gastrointestinal tract and a decrease in protein synthesis due to inflammation. Indomethacin disrupts the mucosal barrier, triggering ulcer formation and systemic inflammation, which may impair the body's ability to produce and maintain normal protein levels. The plant extract's antioxidant and anti-inflammatory properties may mitigate some of the ulcer-induced damage, allowing for a slight recovery in protein synthesis (Abdul-Majeed and Al-Atrakji, 2025).



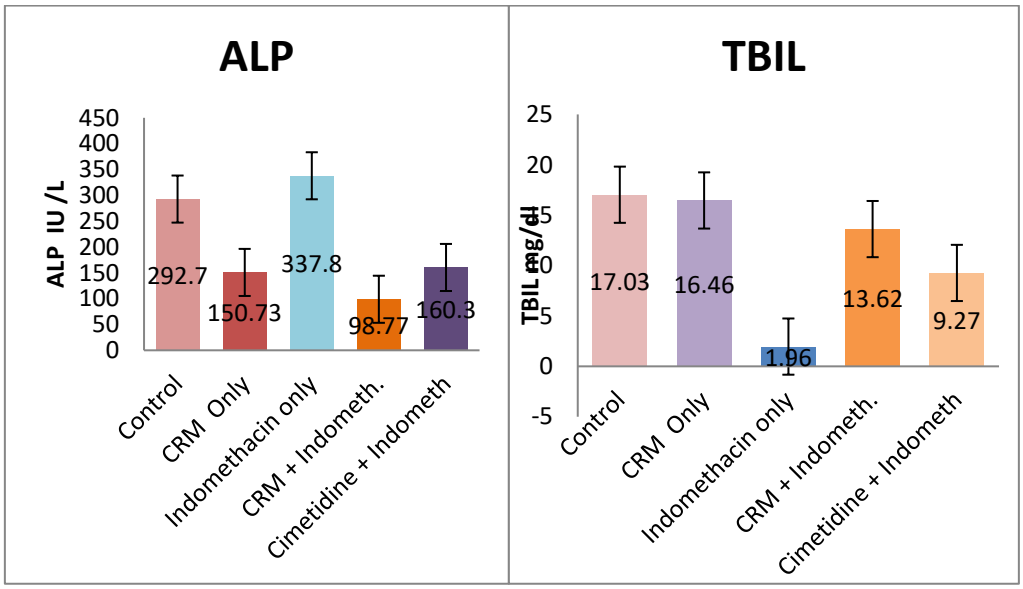


Figure 1: Gastro-specific enzymes – SPGT, SGOT, ALP and TBIL

alkaline phosphate, TBIL- total bilirubin in indomethacin induced ulcer rats. Values were expressed as mean ± SEM. Differences were considered significant at $p<0.05$

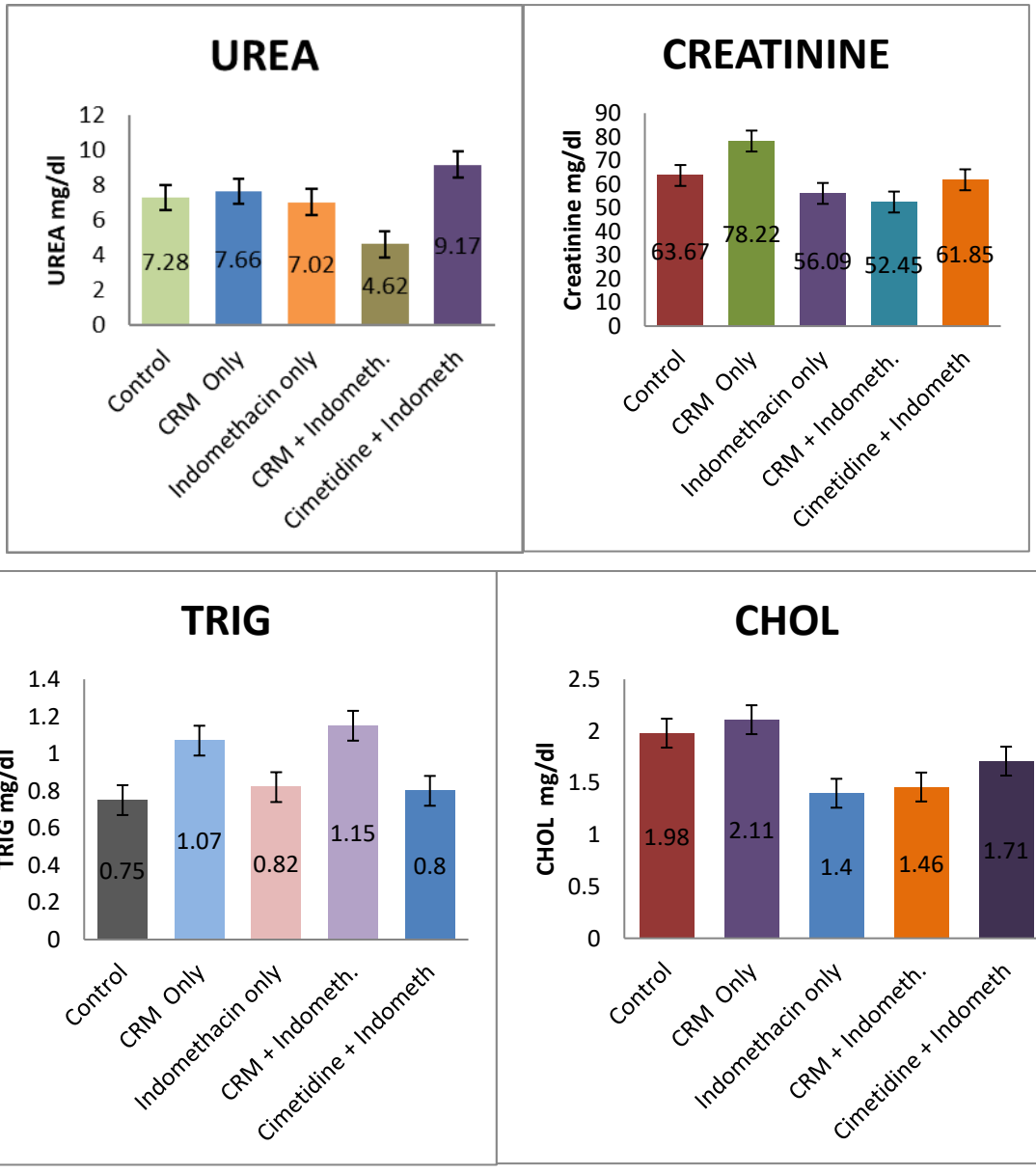


Figure 2: Urea, Creatinine, Triglyceride and Cholesterol. Values were expressed as mean ± SEM. Differences were considered significant at $p<0.05$.

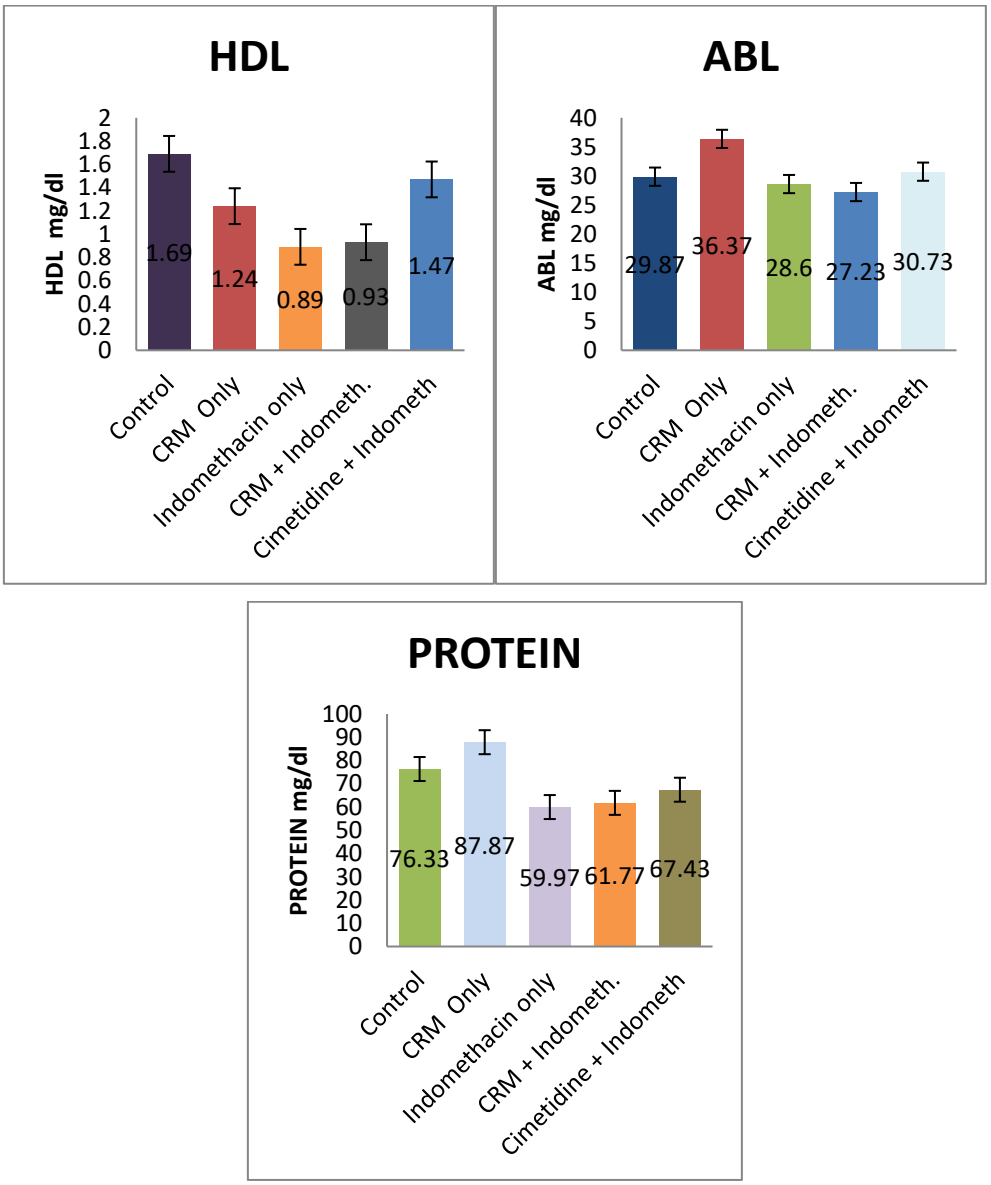


Figure 3: HDL (high density lipoprotein). Albumin and Protein. Values were expressed as mean ± SEM. Differences were considered significant at p<0.05

The induced group with indomethacin alone (0.38±0.40) slightly increased in reduced Glutathione (GSH) level compared to the control group (0.36±0.02). The GSH level of ulcerated group of rat given plant extract CRM + indomethacin (0.35±0.02) was slightly reduced when compared with indomethacin group alone (0.38±0.04) and standard drug group which is (0.38±0.00) which has same value. The plant extract group alone (0.31±0.03) was significantly (P<0.05) reduced as compared to the control group (0.36±0.02) and indomethacin alone in Figure 4. The group treated with CRM extract alone has a slightly lower GSH level of 0.31±0.03. CRM extract, known for its antioxidant properties, may initially deplete GSH levels due to its detoxification activity or its role in modulating ROS (Abdel-Raheem, et al., 2010). This reduction might reflect the body's immediate response to oxidative stress caused by the plant extract, as the antioxidant mechanisms are being upregulated to protect the mucosa. The GSH level, while slightly lower, suggests that CRM extract is engaging the antioxidant defense but may require further boosting of GSH over time. However, many plant extracts, including those from *Callitris* species, contain bioactive compounds like flavonoids, which can have varying effects on oxidative stress depending on the dose and context. From the result above, GSH level in indomethacin only group has higher level than plant treated group i.e. CRM + indomethacin, Indomethacin, a nonsteroidal anti-inflammatory drug (NSAID), is known to cause oxidative stress by inhibiting prostaglandin synthesis and damaging the mucosa (Mohamed et al., 2019). Despite this, the increased GSH level suggests that the body is mounting an adaptive response to counteract the oxidative damage. The elevation in GSH may reflect the activation of compensatory antioxidant pathways, as GSH is vital in detoxifying the ROS generated by indomethacin-induced ulcers.

Superoxide dismutase (SOD) level of indomethacin group alone (0.61±0.06), slightly higher than the control group (0.60±0.04). The ulcerated group administered with plant extract, CRM + Indomethacin (0.37±0.02) was significantly (P<0.05) reduced as compared with the group treated with standard drug Cimetidine + Indomethacin (0.50±0.02), the plant extract (CRM) alone (0.51±0.07) and indomethacin alone (0.61±0.06) Figure 4. Indomethacin is an NSAID known to cause mucosal damage by increasing oxidative stress and inhibiting prostaglandin synthesis (Głowacka et al 2023). Despite the oxidative stress associated with indomethacin, the relatively unchanged SOD level suggests that the enzyme is being upregulated to counteract the ROS generated by the drug. However, this upregulation may not be sufficient to prevent oxidative damage, as indomethacin is a potent inducer of ulcers. The combination of indomethacin with CRM results in a significantly reduced SOD level of 0.37. This suggests that CRM may provide antioxidant protection through non-SOD pathways, such as increasing levels of other antioxidants like glutathione (GSH) or catalase (CAT), as seen in other studies on plant extract. The low SOD level could also reflect a suppression of oxidative stress by CRM extract, reducing the need for SOD activity. Despite the reduced SOD activity, the plant extract may help mitigate the oxidative damage caused by indomethacin through its direct antioxidant effects.

The Catalase (CAT) level in Figure 4 of indomethacin group alone (4.15±0.41), was significantly (P<0.05) lower than the control group (4.51±0.23). The ulcerated group given the plant extract CRM + Indomethacin (3.79±0.20) has significant (P<0.05) reduction when compared with induced indomethacin group alone and the control group. In contrast, the CAT level in the administered standard drug group (3.06±0.07) activity significantly reduced when compared to the group treated with plant extract, indomethacin group and the control group. The reduction observed in indomethacin group alone in comparison to the control group suggests that indomethacin causes oxidative stress but not to the same extent as ethanol. CRM extract, known for its antioxidant

properties, may be reducing ROS production, leading to a decreased demand for CAT activity. The lower CAT level suggests that the plant extract effectively modulates oxidative stress, lowering the overall oxidative burden and reducing the necessity for high CAT levels. When CRM extract is co-administered with indomethacin, CAT activity decreases further to 3.79±0.20 level. This result suggests that the antioxidant properties of CRM extract reduce the oxidative stress caused by indomethacin, thereby lowering the need for high CAT activity. The plant extract likely complements the body's endogenous antioxidant defenses, reducing ROS levels and thus the demand for CAT. This moderate CAT level reflects a balance where oxidative damage is being controlled, and the need for antioxidant enzyme activity is reduced.

The Malondialdehyde (MDA) level in the induced indomethacin group (2.26±0.16) showed significant (P<0.05) increase as compared to the control group (1.85±0.09). The ulcerated group given plant extract, CRM + indomethacin (2.76±0.26) indicates that there was a significant (P<0.05) increase in MDA level when compared with standard drug (1.78±0.20) and the indomethacin group alone and CRM alone (1.83±0.06) in Figure 4. Malondialdehyde (MDA) is a biomarker of lipid peroxidation, indicating oxidative damage to cell membranes. Elevated MDA levels reflect increased oxidative stress and tissue damage, while lower MDA levels suggest a reduction in lipid peroxidation and oxidative injury (Cordiano et al 2023). In peptic ulcers, MDA serves as an indicator of the extent of oxidative damage within the mucosa. In this group, where CRM extract was used to pre-treat indomethacin induced rats, the MDA level rises to 2.76±0.26, which is unexpectedly higher than indomethacin alone. This may indicate that while CRM extract has antioxidant properties, the dose or timing of administration might not be sufficient to fully counteract the oxidative stress induced by indomethacin. This could also suggest a complex interaction between the plant extract and indomethacin, where the combination might not fully prevent the lipid peroxidation effects of indomethacin at certain stages of ulcer development.

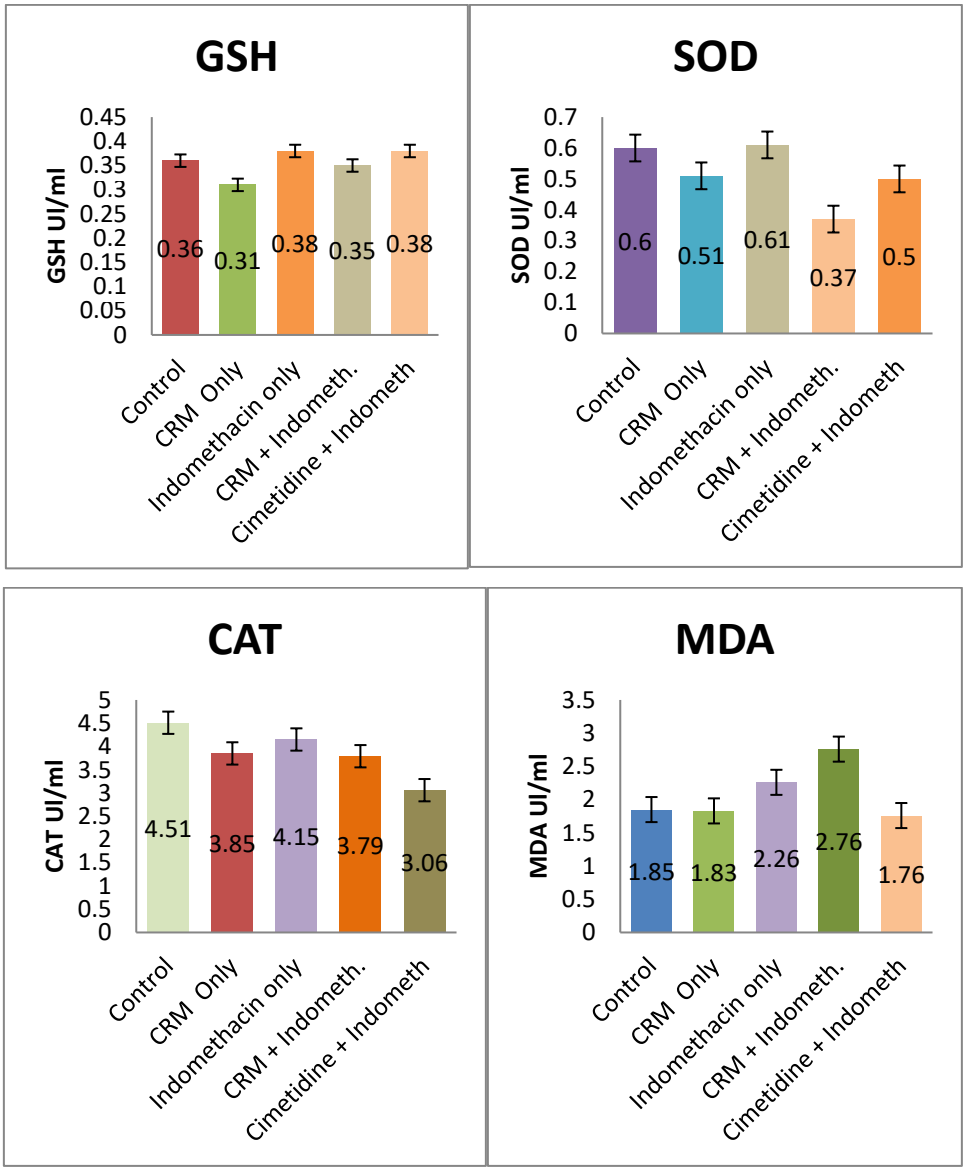


Figure 4: GSH- Glutathione-S-transferase, SOD- Superoxide dismutase, CAT- Catalase, MDA-Malondialdehyde, Showing Antioxidants and oxidative stress markers Values were expressed as mean ± SEM. Differences were considered significant at p<0.05

Table 2a: Ulcer index score

Experimental Group	Treatments
A	70% ethanol (vehicle)
B	CRM alone
C	Indomethacin alone
D	CRM+Indomethacin
E	100 mg/kg bw cimetidine + Indomethacin

Table 2b: Ulcer Score		
Group	**Average ulcer values/ index**	**Percentage protection**
A	0	100%
B	0	100%
C	5	75.6%
D	1	95.1%
E	20.5	0%

Group A (Control: 70% ethanol) – Ulcer Index: 0; Percentage Protection: 100%, Group B (CRM alone) – Ulcer Index: 0; Percentage Protection: 100%, Group C (Indomethacin alone) – Ulcer Index: 5; Percentage Protection: 75.6%, Group D (CRM + Indomethacin) – Ulcer Index: 1; Percentage Protection: 95.1%, Group E (Cimetidine + Indomethacin) – Ulcer Index: 20.5; Percentage Protection: 0%.

These results in tables 2a and 2b show that, in comparison to the groups treated with cimetidine and indomethacin alone, CRM extract alone and CRM in combination with indomethacin considerably ($p<0.05$) reduce the ulcer index. Crucially, the group that received both indomethacin and CRM extract had a lower ulcer index of 1, which is equivalent to a 95.1% protection rate, indicating that the combination has the ability to provide protection.

CRM extract's capacity to lessen peptic ulcers is consistent with recent research that indicates antioxidant-rich plant extracts can stop ulcers from developing by lowering oxidative stress and boosting the defenses of the stomach mucosa. Flavonoids and phenolics, two bioactive substances found in CRM extract, have been demonstrated to scavenge free radicals and lessen oxidative stress in peptic tissue, shielding the mucosa from harm caused by NSAIDs (Rathod et al., 2023).

Because it inhibits the manufacture of prostaglandins, the nonsteroidal anti-inflammatory medicine (NSAID) indomethacin is known to cause ulcers. By encouraging mucus and bicarbonate secretion and boosting mucosal blood flow, prostaglandins are essential for preserving the stomach mucosal barrier (Ko et al., 2025). Indomethacin breaks down this barrier of defence by preventing the generation of prostaglandins, which leaves the stomach mucosa more susceptible to damage. However, by counteracting this process through its antioxidant activities, the administration of CRM extract in addition to indomethacin dramatically lowers the ulcer index as compared to indomethacin alone (Group C), which had an ulcer index of 5 with only 75.6% protection.

Curiously, Group E, which had 0% protection, had the highest ulcer index score of 20.5 when cimetidine and indomethacin were combined. In certain situations, cimetidine, an H2-receptor antagonist, effectively prevents ulcers by decreasing the production of stomach acid. Cimetidine, however, did not prevent the stomach mucosa from being harmed by indomethacin in this investigation. This result may indicate that the ulcerogenic effects of indomethacin, which go beyond acid secretion to include direct oxidative damage to peptic tissues, cannot be reversed by acid suppression alone. In contrast, CRM extract appears to enhance mucosal defense through its antioxidant qualities in addition to providing a buffering effect against peptic acidity.

According to studies, anti-ulcer medications' effectiveness in treating NSAID-induced ulcers frequently rests on their capacity to help the stomach mucosa rebalance its defensive and aggressive components. Maintaining appropriate prostaglandin levels, antioxidant defenses, and mucus production—all crucial for mucosal integrity—is part of this equilibrium (Ko et al., 2025). The ability of CRM extract to target several pathways of stomach protection beyond simple acid suppression may be the cause of the high protection rate seen in the group who received treatment.

Recent research highlights the potential of extracts rich in polyphenols and flavonoids to offer gastro-protection against stomach ulcers brought on by NSAIDs. By preventing oxidative damage and strengthening mucosal defence, *Sphaeranthus senegalensis*, which has antioxidant components identical to those of CRM extract, was shown to have considerable gastro-protective effects in reducing ulcer formation (Sudi et al., 2021). These investigations support the findings of CRM extract, indicating that its bioactive substances are useful in lessening the ulcer-causing effects of indomethacin.

Furthermore, the recent research on CRM extract supports the gastroprotective function of other plant-based substances, which have been demonstrated to function through pathways other than acid suppression. The congruence of these results suggests that the protective effect seen in CRM extract might belong to a larger class of plant-based treatments that provide a comprehensive strategy for preventing stomach ulcers.

4. HISTOPATHOLOGY

A comparison of tissue integrity and damage between experimental groups is shown by the histopathology slides (Plate 1). These images display the stomach's typical histological architecture, including a healthy muscularis propria, an intact mucosal lining, and no discernible tissue erosion or inflammatory infiltration. This suggests that the plant extract is non-toxic to the stomach mucosa under normal circumstances, as neither the control nor CRM extract alone caused any discernible gastrointestinal damage. CRM extract helps to maintain the integrity of the stomach mucosa by minimizing oxidative damage through the reduction of ROS levels. Research indicates that by preventing the synthesis of pro-inflammatory cytokines and enzymes, including cyclooxygenase and lipoxygenase, which mediate the inflammatory response in stomach tissues, polyphenols and flavonoids decrease inflammatory pathways (Al-Khayri et al., 2022). By lowering the infiltration of inflammatory cells seen in the histopathological examination, CRM anti-inflammatory qualities may help avoid significant tissue damage.

Significant histological abnormalities, such as severe inflammatory infiltrates, mucosal gland erosion, and villi destruction, are shown on these images. This is in line with the well-known ulcerogenic effects of indomethacin, a nonsteroidal anti-inflammatory medicine (NSAID) that raises stomach acidity and decreases mucus production by blocking prostaglandin synthesis. By promoting the secretion of mucus and bicarbonate, prostaglandins help to preserve the integrity of the mucosa; yet, when they are inhibited by indomethacin, the mucosa becomes more vulnerable to damage (Sohail et al., 2023). Furthermore, with only minor inflammation and little to no erosion of the stomach mucosa, the group treated with both CRM extract and indomethacin showed noticeably less tissue damage than the group treated with indomethacin alone. This implies a gastroprotective action of CRM extract, most likely because of its anti-inflammatory and antioxidant qualities, which aid in reducing inflammation and oxidative stress brought on by indomethacin. However, by lowering the production of stomach acid, cimetidine, an H2-receptor antagonist, is frequently used to treat and prevent ulcers. However, when paired with indomethacin, the cimetidine-treated group in this study displayed severe histological damage, including mucosal erosion and inflammatory infiltration. This result might indicate that cimetidine's acid suppression alone is not enough to lessen indomethacin's ulcer-causing effects. In addition to increasing stomach acidity, NSAIDs like indomethacin can produce oxidative stress and decreased mucus production, which may not be entirely addressed by acid suppression alone (Park et al., 2024).

CRM extract, on the other hand, showed a protective effect that goes beyond acid suppression. This is consistent with earlier research on antioxidant-rich natural extracts, which indicates that their complex defensive processes provide benefits over traditional acid suppressants in the treatment of ulcers brought on by NSAIDs (Sudi et al., 2021). The results highlight CRM potential as an adjuvant therapy to traditional anti-ulcer treatments, especially in situations when the use of NSAIDs is required.

4.1 Photomicrographs of stomach tissues of male albino rats

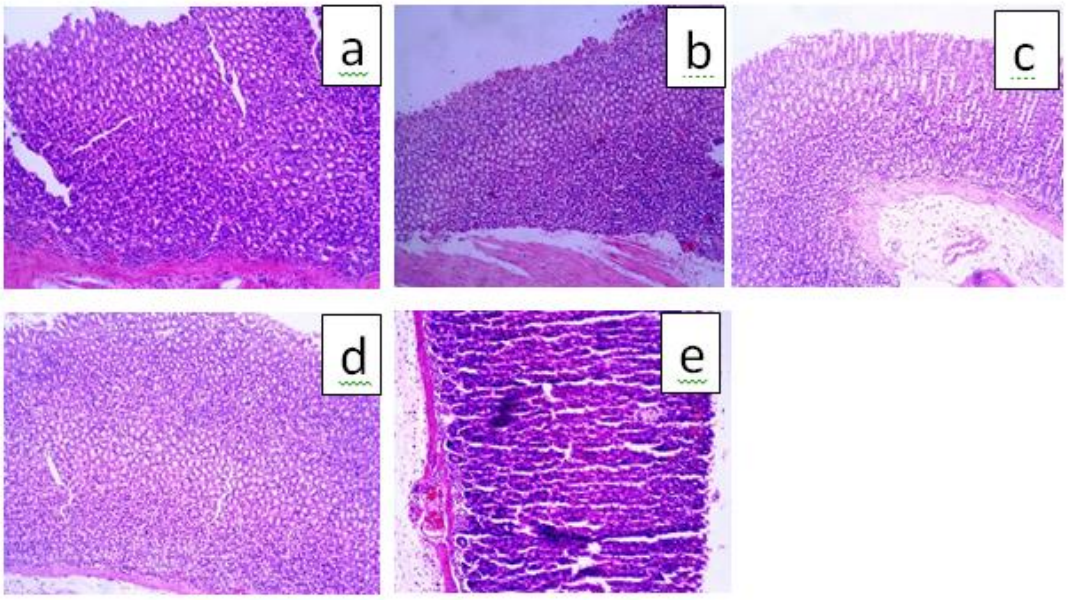


Plate 1: Showing histological sections of stomach tissues (a) Control (b) CRM extract alone (c) Indomethacin only (d) CRM alone + Indomethacin (e) CM + Indomethacin H andE X100

4.2 Membrane Stabilization Profile of *Callitris robusta* var. *microcarpa* (CRM) on Secondary Osteoporosis Associated Stomach Ulcer

This study also evaluated the membrane stabilization profile of the extract of *Callitris robusta* var. *microcarpa* (CRM) and its potential in treating secondary osteoporosis-associated stomach ulcers. The membrane stability profiles of CRM, as shown in Figure 5, highlight its potential in preserving cellular integrity. The study compared CRM with alendronate, a standard osteoporosis drug, to assess their membrane-stabilizing effects. The CRM extract showed a more pronounced, concentration-dependent increase in stability, indicating enhanced cellular integrity protection. At 1–200 µg/mL; CRM and alendronate demonstrated equivalent membrane-stabilizing potential; 200–400 µg/mL; CRM significantly outperformed alendronate, showcasing higher membrane stability. The extract of *CRM* exhibited significant, dose-dependent membrane-stabilizing activity, reducing erythrocyte hemolysis in hypotonic solutions. This suggests that the extract acts by preventing the release of intracellular lysosomal constituents and inflammatory mediators, which are crucial in preventing gastric mucosa breakdown. Furthermore, the extract showed potential in mitigating gastric lesions, likely by strengthening the mucosal barrier through decreased permeability, acting in tandem with its antioxidant properties. This finding suggests that CRM could be a more effective alternative for protecting membrane integrity, which is vital in mitigating the side effects associated with standard osteoporosis treatments and protecting against secondary conditions like stomach ulcers. While effective, alendronate is known to cause gastrointestinal side effects, including esophageal and gastric ulceration, because it is a topically caustic drug that impairs mucosal healing. High membrane stability is crucial for maintaining gastric mucosa integrity, reducing the risk of ulcers, and preserving overall cellular health in patients managing osteoporosis. This suggests that CRM may offer superior membrane protection, a crucial factor in osteoporosis management and renal health (Jarusriwanna et al., 2024; Wang et al., 2025). The results indicate that *CRM* extract possesses significant membrane-stabilizing and anti-inflammatory activity, which likely contributes to its gastroprotective effect in models of secondary osteoporosis-associated stomach ulcers. It is a potential candidate for developing natural therapeutic agents for managing ulcers in osteoporotic conditions. This is as a result of phytochemicals in CRM integrating into the membrane, reinforcing its structure and reducing cell lysis. Key findings from recent studies indicate that membrane-stabilizing agents act by reducing lipid peroxidation, stabilizing lysosomes, and increasing prostaglandin E_2 levels (Tsermpini *et al*., 2022; Ydyrys et al., 2023; Zhang et al., 2024). Secondary osteoporosis is frequently associated with increased risk of gastric ulceration, often due to chronic inflammation, stress, and medication-induced impairment of the mucosal barrier. Membrane stabilization of erythrocytes and lysosomal membranes is a key mechanism for managing inflammatory conditions and protecting against tissue degradation (Selvin et al., 2022; Hosein-Woodley et al., 2024).

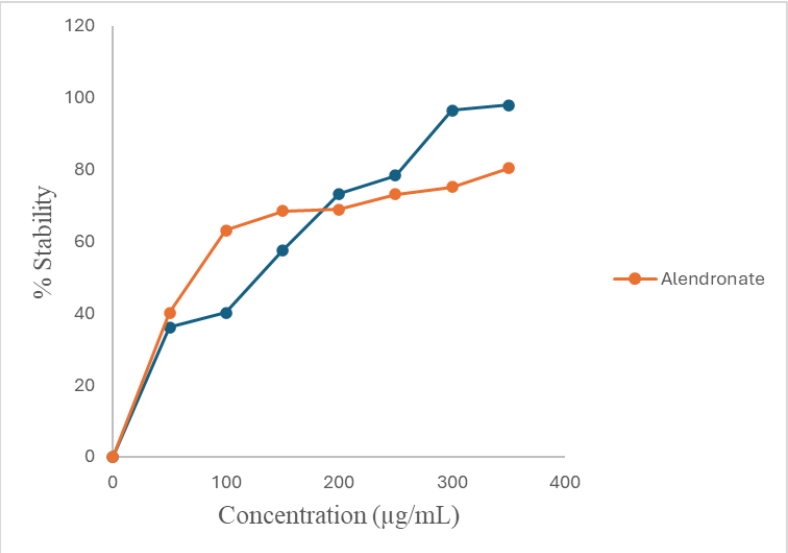


Figure 5: Membrane Stabilizing Profiles of CRM and Alendronate (Standard Drug) Extracts on Stressed and Perturbed Human Erythrocytes. Each value represents the Mean (triplicate) ± SEM.

5. Conclusion

The study showed that CRM could be a viable natural product for the treatment of stomach ulcers. Histopathological evidence of decreased inflammation and mucosal damage suggested that CRM treats the underlying pathophysiology of stomach ulcers in addition to their symptoms. Incorporating CRM could improve therapeutic outcomes, particularly for individuals at high risk of gastrointestinal problems, given the high prevalence of ulcers linked to prolonged NSAID usage. This study provides compelling evidence for the superior membrane stability of CRM compared to alendronate at higher concentrations. These findings showed that CRM holds promise as a more stable and potentially more effective therapeutic agent.

Conflict of interest

We declare no conflict interest.

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